Exercise after a Bladder or Kidney Cancer Diagnosis

by

Fernanda Zane Arthuso

A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Faculty of Kinesiology, Sport and Recreation
University of Alberta

ABSTRACT

Bladder and kidney cancer are among the eight most common cancers in Canada. Cancer and its treatments affect patient functioning and quality of life. Exercise interventions help many patients with cancer improve health-related fitness, treatment-related side effects, quality of life, and possibly survival; however, limited research has been conducted in patients with bladder and kidney cancer. The overarching goal of this dissertation is to generate new knowledge in the field of exercise oncology in two common, yet understudied genitourinary cancers - bladder and kidney cancer.

Chapter 1 reviews bladder and kidney cancer statistics, pathophysiology, staging, and treatments. Briefly, bladder cancer is classified as muscle-invasive bladder cancer (MIBC) or non-muscle-invasive bladder cancer (NMIBC). MIBC is managed by chemotherapy in combination with bladder-removal surgery. NMIBC is treated with transurethral resection of the bladder tumor followed by induction adjuvant intravesical therapy. Renal cell carcinoma (RCC) is the most common type of kidney cancer. The primary treatment for localized RCC is kidney-removal surgery.

Study 1 (Chapter 2, Paper 1) retrospectively investigated the associations of pre-surgical body mass index (BMI) with bladder cancer outcomes in 488 patients treated with radical cystectomy. Cox regression were used to estimate the hazard ratio (HR). The HR for overweight during the first 63 months was 0.66 (95% CI 0.49–0.90, p=0.008), whereas it was 1.41 (95% CI 0.89–2.23, p=0.14) after 63 months. Although not statistically significant, a similar pattern was observed for obese patients. These data suggest that the obesity paradox in bladder cancer patients treated with radical cystectomy may be short-lived.

Study 2 (Chapter 3, 4, and 5, Papers 2, 3, and 4) was a randomized controlled trial. The Bladder cancer and exeRcise trAining during or after intraVesical thErapy (BRAVE) trial evaluated the feasibility and safety of high-intensity interval training (HIIT) in NMIBC patients during or after intravesical therapy. Secondary aims were 1) to assess the preliminary efficacy of HIIT on cardiorespiratory fitness and physical functioning, and 2) to explore the motivational outcomes, perceived benefits and harms, and perceived barriers to exercise. Patients scheduled to receive intravesical treatment or on surveillance after intravesical treatment for NMIBC were randomly assigned to usual care (UC, n=8) or HIIT (n=13). The HIIT group performed thrice-weekly, supervised HIIT at 75-95% of peak cardiorespiratory fitness (VO_{2peak}) for 12 weeks. In 24 months, 21 out of 129 eligible participants (16.3%) were randomized. Median exercise attendance was 100%, VO_{2peak} increased from baseline to 12 weeks by 1.2 ml/kg/min in the HIIT group but was not significantly higher than the UC group (p=0.33). Compared to the UC group at 12 weeks, the HIIT group significantly improved six-minute walk distance (p=0.034) and time in the 8-foot up-and-go (p=0.039). The HIIT group reported that the exercise was meaningfully ($d \geq 0.33$) more enjoyable, elicited higher confidence, and was less difficult than anticipated. Compared to the UC group post-intervention, the HIIT group reported meaningfully lower motivation, lower confidence, and higher difficulty to exercise on their own for the next 6 months. The most common perceived benefits of HIIT included cardiovascular endurance and physical functioning. The most common exercise barriers were being too busy/having limited time. Despite limited accrual, the BRAVE trial demonstrated that HIIT during or after intravesical therapy was feasible and safe for NMIBC patients and resulted in significant improvements in several indicators of

physical functioning. Moreover, HIIT was more motivating than anticipated with many perceived benefits and few perceived harms or barriers, however, it appeared to reduce confidence and motivation to exercise on their own over the next 6 months.

Study 3 (Chapter 6, Paper 5) was a scoping review of physical activity in kidney cancer patients. A comprehensive search identified 17 articles from nine independent studies, including one cross-sectional study (n=8 articles), one randomized controlled trial (n=2 articles) and seven cohort studies (n=7 articles). Due to limited evidence, no conclusions can be drawn from current research on the role of physical activity in patients with kidney cancer.

Chapter 7 discusses the strengths and limitations of the dissertation and proposes future directions for research. In summary, this dissertation provides novel findings and important future directions for research examining how exercise could benefit patients with bladder and kidney cancer and ultimately be incorporated into the standard clinical care.

PREFACE

This dissertation is an original work designed, planned, performed and interpreted by Fernanda Zane Arthuso under the supervision of Dr. Kerry S. Courneya. Study 1 entitled "A retrospective analysis of the associations between body mass index and bladder cancer recurrence and survival" received research ethics approval from the Health Research Ethics Board of Alberta-Cancer Committee (HREBA.CC-20-0294) on August 11, 2020. Study 2 entitled "Feasibility and Efficacy of High-Intensity Interval Training in Bladder Cancer Patients Undergoing Intravesical Therapy: a randomized controlled trial" received research ethics approval from the Health Research Ethics Board of Alberta-Cancer Committee (HREBA.CC-20-0184) on July 14, 2020 and from the Northern Alberta Clinical Trials and Research Centre (NACTRC PRJ37630) on November 17, 2020. Study 3 entitled "Physical Activity in Patients with Kidney Cancer: A Scoping Review" do not require ethical approval because of the nature of the research.

Chapter 2 (Study 1) of this dissertation has been published as "Arthuso, F. Z., Fairey, A. S., Boulé, N. G., & Courneya, K. S. (2022). Associations between body mass index and bladder cancer survival: Is the obesity paradox short-lived?. *Canadian Urological Association journal = Journal de l'Association des urologues du Canada*, *16*(5), E261–E267. https://doi.org/10.5489/cuaj.7546". I conceived and designed the study, analyzed and interpreted the data, and wrote the first draft of the manuscript. AS Fairey collected and managed the data. KS Courneya, AS Fairey, and NG Boulé made important contributions to the conception and design of the study, data analyses and interpretation. All authors revised the manuscript critically for important intellectual content and approved the final manuscript.

Chapter 3 (Study 2) of this dissertation has been published as "Arthuso, F. Z., Fairey, A. S., Boulé, N. G., & Courneya, K. S. (2021). Bladder cancer and exeRcise trAining during intraVesical thErapy-the BRAVE trial: a study protocol for a prospective, single-centre, phase II randomised controlled trial. BMJ open, 11(9), e055782. https://doi.org/10.1136/bmjopen-2021-055782". I conceived and designed the study and wrote the first draft of the manuscript. KS Courneya, AS Fairey, and NG Boulé contributed to the conception and design of the study, manuscript revision and editing. All authors approved the final manuscript.

Chapter 6 (Study 3) of this dissertation has been published as "Arthuso, F. Z., & Courneya, K. S. (2022). Physical Activity in Patients with Kidney Cancer: A Scoping Review. Clinical genitourinary cancer, 20(5), e369–e379. https://doi.org/10.1016/j.clgc.2022.04.003". I conceived and designed the study, reviewed the literature, conducted data abstraction and synthesis, and wrote the first draft of the manuscript with input from KS Courneya at all stages of the process. KS Courneya contributed to the conception and design of the study and revised the manuscript critically for important intellectual content.

ACKNOWLEDGMENTS

I would like to express my sincere gratitude to my supervisor Dr. Kerry Courneya for giving me the opportunity to work under his supervision and for the incredible support and mentorship. Dr Courneya's discipline, ethics, and kindness are just a few of the numerous qualities I will follow as an example in my career. I must say that Dr Courneya provided me with an outstanding training environment and access to a variety of learning opportunities that I will always be grateful for. Under Dr. Courneya's supervision, I had the opportunity to collaborate on very high-quality research projects, including large multinational trials that will shape the field of exercise oncology. The opportunities and the exceptional guidance Dr. Courneya provided, led me to excel as a researcher. I am capable now of conducting high-quality research that will answer important questions for cancer patients. I will be eternally grateful for the professional and personal growth under Dr. Courneya's supervision. I could not have obtained better training as a Ph.D. student anywhere else.

My sincere gratitude to the members of my committee, Dr. Normand Boulé and Dr. Adrian Fairey, for generously sharing their precious time to review my work, provide thoughtful feedback, and for being supportive throughout the entire duration of my graduate studies. I also would like to extend my gratitude to Dr. Carla Prado for serving on both my candidacy and final examination. I am very appreciative of your thoughtful insights and questions. Thank you to Dr. Daniel Galvão for serving on my final examining committee and for the supportive feedback provided. To Dr. Jeffrey Johnson, thank you for serving on my candidacy examining committee. I am also grateful to Dr. Niels-Erik Jacobsen and Dr. Lucas Dean for their support recruiting patients for my trial.

My heartfelt gratitude goes to all the participants in my trial. I was very fortunate to have the most incredible, fun, and dedicated study participants. Thank you all for your time and commitment. This dissertation would not have been possible without your contribution. Thank you for trusting in this research project and my work, and for allowing me to be part of your journey. Stay strong and be BRAVE!

I also would like to acknowledge and thank the funding agencies and scholarships that supported my training and work. Specifically, the Government of Alberta for the Alberta Graduate Excellence Scholarship, the University of Alberta Graduate Students'

Association for the Graduate Student Research Assistant Award and the Martha Piper Award, the Faculty of Kinesiology, Sports and Recreation for the Graduate Tuition Award, and the Faculty of Graduate Studies and Research for the Doctoral Recruitment Scholarship. Thank you to the Alberta Cancer Foundation for funding my doctoral project entitled "Feasibility and preliminary efficacy of high-intensity interval training in bladder cancer patients receiving intravesical therapy: A randomized controlled trial" through the Alberta Cancer Clinical Trials–Provincial Investigator-Initiated Trial Competition.

I would like to thank my colleagues in the Exercise Oncology Research Laboratory (former Behavioral Medicine Laboratory) who I have had the pleasure of working with: Ki-Yong An, Myriam Filion, Stephanie Ntoukas, Spencer Allen, Don-Woo Kang, Andria Morielli, Stephanie Wharton, and Diane Cook. Thank you all for the assistance with ethics application, grant writing, data collection, exercise testing, and exercise supervision. Thank you for your kindness and friendship. I would like to extend my gratitude to the practicum students Matthew Steventon and Kasi Jain who have assisted with exercise testing, supervision, and data imputation.

I would like to express my sincere gratitude towards my family. Thank you to my wonderful parents Marcos and Celia, and my incredibly supportive siblings, Debora and Rodrigo. I love you all so much. Thank you for always being by my side, for supporting my education, and above all, for your love and encouragement.

A special thank to my beloved husband, Alexsandro (aka Moreno). You are such a blessed soul, you have the gift to awaken the best of what is inside of those around you. You trusted in my potential more than I did and encouraged me to pursue a Ph.D. at the University of Alberta. You kept me strong even when you were still in Brazil. We overcame the anxiety and fear of the pandemic, the closure of the borders between Canada and Brazil, the three years in a long-distance relationship, the challenges with immigration, and many others that only we know. Thank you for being open to restarting your life by my side, and for being my source of stability amidst so much uncertainty, for always surprising me and making me laugh. I love you.

Above all, I thank God, who made everything possible.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

BCG	Bacillus Calmette-Guerin
BCSS	Bladder Cancer Specific Survival
BMFC	Behavioural Medicine Fitness Center
BMI	Body Mass Index
CES-D	Center for Epidemiologic Studies Depression
CI	Confidence Intervals
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CRF	Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EORTC	European Organization for Research and Treatment of Cancer
FASN	Fatty Acid Synthase
GLTEQ	Godin Leisure-Time Exercise Questionnaire
HIIT	High Intensity Interval Training
HEBRA-CC	Health Research Ethics Board Of Alberta-Cancer Committee
HR	Hazard Ratio
HRQoL	Health-Related Quality Of Life
IARC	International Agency for Research on Cancer
ISI	Insomnia Severity Index
KC	Kidney Cancer
MeSH	Medical Subject Headings
MET	Metabolic Equivalent
MIBC	Muscle Invasive Bladder Cancer
NAC	Neoadjuvant Chemotherapy
NAUC	Northern Alberta Urology Centre
NMIBC	Non-Muscle Invasive Bladder Cancer
OR	Odds Ratio
OS	Overall Survival
PA	Physical Activity
PAR-Q+	Physical Activity Readiness Questionnaire For Everyone Questionnaire

PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews
RC	Radical Cyctectomy
RCC	Renal Cell Carcinoma
SFT	Senior's Fitness Test
SPIRIT	Standard Protocol Item for Randomised Trials
TPB	Theory of Planned Behavior
TURBT	Transurethral Resection Of The Bladder Tumour
UC	Usual Care
VO_{2peak}	Peak Oxygen Consumption

CHAPTER 1. INTRODUCTION

1.1 Background

Urologic cancers comprise cancers of the urinary tract and the male reproductive organs. The most common urologic cancers are prostate, bladder, and kidney cancer [1, 2]. Bladder and kidney cancers are cancers of the urinary tract predominantly diagnosed in older individuals, affecting men two and three times more often than women [1]. Bladder and kidney cancers are respectively ranked as the fifth and the eighth most common cancers in Canada [1], and the ninth and the fourteenth most common cancers worldwide [2]. In 2023, it is estimated a total of 13,400 new cases of bladder cancer and 8,600 new cases of kidney cancer, accounting together for 9.2% of all new cases of cancer in Canada [1]. Approximately 2,600 bladder cancer and 1,900 kidney cancer deaths were estimated in 2023, corresponding to 5.2% of the total deaths by cancer in Canada [1]. The 10-year survival rate is 66% for bladder cancer and 64% for kidney cancer [1].

Despite being amongst the most prevalent urologic cancers, patients with bladder and kidney cancers are an understudied population. In 2022, research on the disparity of the global distribution of urologic clinical trials identified 3,331 active trials in urologic malignancies of which approximately 62% were in prostate cancer, 20% in bladder cancer, and 18% in kidney cancer [3]. Disparities in research, whether due to differences in research focus, funding, patient recruitment, or trial access, can lead to unequal understanding and advancements of cancer treatment and management across different cancer types.

The exercise oncology field, which investigates the role of exercise after a cancer diagnosis, is rapidly evolving and providing evidence on the safety, feasibility, and

efficacy of exercise on a diverse range of patient-reported outcomes, health-related outcomes, and cancer outcomes [4, 5]. The advancements in the field contributed to developing physical activity and exercise guidelines [5-8]. However, the majority of research supporting the publicly available guidelines is based on the most common cancer types, including breast, prostate, lung, and colorectal cancers [6-8], with little or no supporting evidence of exercise on bladder and kidney cancers. There is an urgent need to address these cancer patient groups to inform targeted exercise interventions and ensure that bladder and kidney cancers patients have access to the benefits that exercise may provide across the cancer continuum. This document is a paper-based dissertation in exercise oncology with the overarching goal of generating new knowledge in the field of exercise oncology in two common, yet understudied, cancer groups - bladder and kidney cancer.

1.2 Bladder cancer

Bladder cancer is classified as muscle-invasive bladder cancer (MIBC) or non-muscle-invasive bladder cancer (NMIBC) depending on the tumor penetration into the layers of the bladder wall [9]. The degree of the tumor invasiveness and tumor grade determines the risk profile for bladder cancer recurrence and progression, as well as the treatment options [9]. For a detailed description of bladder cancer and its treatment, please see Appendix A.

Briefly, MIBC is managed by neoadjuvant or adjuvant systemic chemotherapy in combination with radical cystectomy (i.e., bladder removal) or trimodal treatment, which includes transurethral resection of the bladder tumor (TURBT), radiation treatment, and chemotherapy [9]. Patients with very high-risk NMIBC also have cystectomy as the

preferred treatment approach. Radical cystectomy is a major surgery with high morbidity and mortality rates, the 90-day complications rate following surgery is 58.5% (range 36.1%–80.5%) and the 90-day mortality rate is 4.7% (range 0.0%–7.0%) [10].

The primary treatment for intermediate and high-risk NMIBC is TURBT followed by induction adjuvant intravesical immunotherapy (i.e., bacillus calmette-guerin) or chemotherapy (i.e., mitomycin or gemcitabine) [9]. Treatment regimen vary depending on the medication being administered but usually consists of weekly instillations for six weeks. NMIBC has a high rate of recurrence (15-40%) and progression (1-10%) that may lead to MIBC [11]. Therefore, NMIBC patients may receive adjuvant maintenance therapy for one year if intermediate-risk disease and up to three years if high-risk NMIBC [9, 12].

Bladder cancer and its treatment often leads to side effects that adversely affect patient functioning and quality of life [13, 14]. Observational studies have reported an association between increased physical activity levels with better health-related quality of life [15-17] and a protective effect of exercise on physical health status in bladder cancer patients [18]. For a detailed review of observational studies and exercise intervention trials in bladder cancer patients, please see Appendix B. In summary, there is limited, but growing evidence suggesting that physical activity and exercise may be feasible and beneficial for a subgroup of bladder cancer patients [19-21]. Research to date have focused on bladder cancer patients treated with radical cystectomy due to the high morbidity and mortality rates, and the potential benefits of exercise in the pre- and post-surgical setting on cardiorespiratory fitness and quality of life [21-26].

Bladder cancer is often diagnosed among those in their 70s [27]. Age-related changes and comorbidities affect bladder cancer prognosis [28, 29]. Some studies have suggested that obesity is a predictor of clinical outcomes and survival rates in bladder cancer patients treated with radical cystectomy. However, the findings are inconsistent across the literature [30-33]. Higher body mass index (BMI) has been linked to a worse prognosis in some studies [30, 34], whereas other studies found that individuals with higher BMI have better bladder cancer prognosis [32, 33, 35], a phenomenon known as the obesity paradox. For a brief review of obesity on bladder cancer patients, please see Appendix C. Understanding the association between BMI and survival in bladder cancer patients is essential to improve bladder cancer management and inform future exercise interventions. A chapter of this thesis is dedicated to investigating the associations between BMI and bladder cancer outcomes.

Patients with NMIBC have received substantially less attention, as we can observe by the literature comprising two reviews on exercise and physical activity interventions among individuals with bladder cancer [19, 20]. This observation is important because it indicates that despite NMIBC being the most common type of bladder cancer (70-75% of newly diagnosed patients), it is an understudied patient group in the exercise oncology field. It is currently unknown if patients with NMIBC are able and motivated to exercise during or after their therapy and if exercise is safe, beneficial or harmful. Therefore, research addressing this knowledge gap is urgently needed before making clinical recommendations. A randomized controlled trial named Bladder cancer and exeRcise trAining during or after intraVesical thErapy (BRAVE) trial, was developed to examine the safety, feasibility, and preliminary efficacy of exercise in

patients with NMIBC during or after intravesical therapy. The BRAVE trial comprises the main focus of this dissertation and is presented in detail in three chapters containing the study protocol, and primary and secondary outcomes.

1.3 Kidney cancer

Treatment for kidney cancer is based on histology, tumor size, location, and spread. The most common type of kidney cancer (85%) is renal cell carcinoma (RCC), with less common types including papillary, chromophobe, translocation, and collecting duct tumors [36]. The primary treatment for non-metastatic kidney cancer is partial nephrectomy (i.e., kidney-sparing surgery) or radical nephrectomy (i.e., kidney-removal surgery). If clinically indicated, patients can be treated with ablative techniques (e.g., extreme heat or cold on the tumor and surrounding tissue), or undergo active surveillance. Depending on the cancer stage and grade, patients with kidney cancer may receive adjuvant immunotherapy (i.e., pembrolizumab) or targeted therapy (i.e., sunitinib). Although surgery is the main treatment option, it can potentially result in reduced kidney function or kidney failure leading to dialysis or kidney transplantation and increased risk of cardiovascular diseases and mortality [37, 38].

Kidney cancer, along with its treatments, places a considerable strain on patients, with psychosocial and physical challenges that may affect their well-being, quality of life, and survival [39-41]. More specifically, declines in the physical component score of quality of life from pre- to post- kidney cancer diagnosis were significantly associated with a 10% increased risk of death in a population based-cohort study [40]. This emphasizes the importance of physical health on kidney cancer prognosis. Physical activity and exercise interventions positively impact health-related fitness outcomes,

patient outcomes, and treatment outcomes after a cancer diagnosis [5-8]. Evidence has been compiled in many systematic reviews and meta-analysis across many cancer groups, informing public guidelines [5-8]. A systematic approach of the literature is important to synthesize knowledge, identify gaps in the existing research, inform clinical practice, and provide justification to funding agencies the need for further research in a specific area [42, 43]. No study to date, however, have conducted a systematic approach to map evidence on physical activity and exercise interventions after a kidney cancer diagnosis. A chapter of this thesis addresses this important issue and presents a scoping literature review of physical activity and kidney cancer.

1.4 Objectives

Objective 1: To investigate the association between body mass index and bladder cancer outcomes in muscle-invasive bladder cancer patients treated by radical cystectomy.

Objective 2: To examine the safety, feasibility, and preliminary efficacy of exercise in non-muscle invasive bladder cancer patients during or after intravesical therapy.

Objective 3: To examine the motivational outcomes, perceived benefits and harms, and perceived barriers to exercise during or after intravesical therapy in patients with non-muscle invasive bladder cancer.

Objective 4: To conduct a scoping review of physical activity and kidney cancer, report current findings, delineate strengths and limitations, and provide key recommendations for future research.

1.5 Overview of the Dissertation

The dissertation consists of seven chapters, including this brief introduction. **Chapter 2** (Paper 1) examines the association of pre-surgical body mass index with bladder cancer outcomes in patients treated with radical cystectomy. **Chapter 3** (Paper 2) reports the rationale and protocol for the BRAVE trial. **Chapter 4** (Paper 3) examines the feasibility, safety, and the preliminary efficacy of the BRAVE trial on cardiorespiratory fitness and physical functioning. **Chapter 5** (Paper 4) explores the effects of the BRAVE trial on motivational outcomes, perceived benefits and harms, and perceived barriers to exercise during or after intravesical therapy. **Chapter 6** (Paper 5) provides a scoping review of physical activity and kidney cancer, aiming to summarize current findings, delineate strengths and limitations, and provide key recommendations for future research. **Chapter 7** reflects on the overall findings, strengths, and limitations of this dissertation, and discusses practical implications and future directions

1.6 References

1. Canadian Cancer Statistics Advisory Committee, et al., *Canadian Cancer Statistics 2023.* 2023, Canadian Cancer Society: Toronto, ON.

2. Ferlay J, et al. *Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer.* 2024 March 4, 2024]; Available from: https://gco.iarc.who.int/today.

3. Choksi, A.U., et al., *The disparities in clinical trials addressing urologic conditions among lower-income countries.* 2023: *Front. Urol*.

4. Jones, L.W. and C.M. Alfano, *Exercise-oncology research: past, present, and future.* Acta Oncol, 2013. **52**(2): p. 195-215.

5. Ligibel, J.A., et al., *Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline.* J Clin Oncol, 2022. **40**(22): p. 2491-2507.

6. Campbell, K.L., et al., *Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable.* Med Sci Sports Exerc, 2019. **51**(11): p. 2375-2390.

7. Hayes, S.C., et al., *The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management.* J Sci Med Sport, 2019. **22**(11): p. 1175-1199.

8. Rock, C.L., et al., *American Cancer Society nutrition and physical activity guideline for cancer survivors.* CA Cancer J Clin, 2022. **72**(3): p. 230-262.

9. National Comprehensive Cancer Network [NCCN], *NCCN Clinical Practice Guidelines on Oncology: Bladder Cancer, Version 1.2024*. 2024.

10. Maibom, S.L., et al., *Short-term morbidity and mortality following radical cystectomy: a systematic review.* BMJ Open, 2021. **11**(4): p. e043266.

11. Kamat, A.M., et al., *Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group.* J Clin Oncol, 2016. **34**(16): p. 1935-44.

12. Lamm, D.L., et al., *Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study.* J Urol, 2000. **163**(4): p. 1124-9.

13. Nayak, A., J. Cresswell, and P. Mariappan, *Quality of life in patients undergoing surveillance for non-muscle invasive bladder cancer-a systematic review.* Transl Androl Urol, 2021. **10**(6): p. 2737-2749.

14. Clements, M.B., et al., *Health-related Quality of Life for Patients Undergoing Radical Cystectomy: Results of a Large Prospective Cohort.* Eur Urol, 2022. **81**(3): p. 294-304.

15. Karvinen, K.H., et al., *Associations between exercise and quality of life in bladder cancer survivors: a population-based study.* Cancer Epidemiol Biomarkers Prev, 2007. **16**(5): p. 984-90.

16. Gopalakrishna, A., et al., *Physical activity patterns and associations with health-related quality of life in bladder cancer survivors.* Urol Oncol, 2017. **35**(9): p. 540.e1-540.e6.

17. Chung, J., et al., *Modifiable lifestyle behaviours impact the health-related quality of life of bladder cancer survivors.* BJU Int, 2020. **125**(6): p. 836-842.

18. Koelker, M., et al., *Impact of exercise on physical health status in bladder cancer patients.* Can Urol Assoc J, 2023. **17**(1): p. E8-E14.

19. Bessa, A., et al., *Is there a role for physical activity interventions in the treatment pathway of bladder cancer? A scoping review of the literature.* BMJ Open Sport Exerc Med, 2021. **7**(1): p. e000951.

20. Rammant, E., et al., *A systematic review of exercise and psychosocial rehabilitation interventions to improve health-related outcomes in patients with bladder cancer undergoing radical cystectomy.* Clin Rehabil, 2018. **32**(5): p. 594-606.

21. Briggs, L.G., et al., *Prehabilitation Exercise Before Urologic Cancer Surgery: A Systematic and Interdisciplinary Review.* Eur Urol, 2022. **81**(2): p. 157-167.

22. Jensen, B.T., et al., *Exercise-based pre-habilitation is feasible and effective in radical cystectomy pathways-secondary results from a randomized controlled trial.* Support Care Cancer, 2016. **24**(8): p. 3325-31.

23. Porserud, A., A. Sherif, and A. Tollbäck, *The effects of a physical exercise programme after radical cystectomy for urinary bladder cancer. A pilot randomized controlled trial.* Clin Rehabil, 2014. **28**(5): p. 451-9.

24. Minnella, E.M., et al., *Multimodal Prehabilitation to Enhance Functional Capacity Following Radical Cystectomy: A Randomized Controlled Trial.* Eur Urol Focus, 2019. **7**(1): p. 132-138.

25. Kaye, D.R., et al., *The Feasibility and Impact of a Presurgical Exercise Intervention Program (Prehabilitation) for Patients Undergoing Cystectomy for Bladder Cancer.* Urology, 2020. **145**.

26. Taaffe, D.R., et al., *Efficacy and Feasibility of Presurgical Exercise in Bladder Cancer Patients Scheduled for Open Radical Cystectomy.* Med Sci Sports Exerc, 2023. **55**(7): p. 1123-1132.

27. National Institute of Health and National Cancer Institute. *Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Bladder Cancer*. Cancer Stat Facts: Bladder Cancer. 2023 March 4, 2024]; Available from: https://seer.cancer.gov/statfacts/html/urinb.html.

28. Burg, M.L., et al., *Frailty as a predictor of complications after radical cystectomy: A prospective study of various preoperative assessments.* Urol Oncol, 2019. **37**(1): p. 40-47.

29. Qin, F. and J. Wu, *Impact of sarcopenia on outcomes of bladder cancer undergoing radical cystectomy: A systematic review and meta-analysis.* Scott Med J, 2024: p. 369330241234690.

30. Chromecki, T.F., et al., *Obesity is associated with worse oncological outcomes in patients treated with radical cystectomy.* BJU Int, 2013. **111**(2): p. 249-55.

31. Bachir, B.G., et al., *Effect of body mass index on the outcomes of patients with upper and lower urinary tract cancers treated by radical surgery: results from a Canadian multicenter collaboration.* Urol Oncol, 2014. **32**(4): p. 441-8.

32. Bi, H., et al., *Impact of Body Mass Index and Pretreatment Hemoglobin Level on Prognosis Following Radical Cystectomy for Bladder Cancer in Males and Females.* Urol Int, 2020. **104**(1-2): p. 28-35.

33. Psutka, S.P., et al., *Mortality after radical cystectomy: impact of obesity versus adiposity after adjusting for skeletal muscle wasting.* J Urol, 2015. **193**(5): p. 1507-13.

34. Dabi, Y., et al., *Impact of body mass index on the oncological outcomes of patients treated with radical cystectomy for muscle-invasive bladder cancer.* World J Urol, 2017. **35**(2): p. 229-235.

35. Kwon, T., et al., *Obesity and prognosis in muscle-invasive bladder cancer: the continuing controversy.* Int J Urol, 2014. **21**(11): p. 1106-12.

36. National Comprehensive Cancer Network [NCCN], *NCCN Clinical Practice Guidelines on Oncology: Kidney Cancer, Version 2.2024*. 2024.

37. McKiernan, J., et al., *Natural history of chronic renal insufficiency after partial and radical nephrectomy.* Urology, 2002. **59**(6): p. 816-20.

38. Huang, W.C., et al., *Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study.* Lancet Oncol, 2006. **7**(9): p. 735-40.

39. Ames, S.C., et al., *Quality of life of patients undergoing surgical treatment for newly-diagnosed, clinically localized renal cell carcinoma.* J Psychosoc Oncol, 2011. **29**(6): p. 593-605.

40. Bhandari, N.R., et al., *Association of Health-Related Quality of Life with Overall Survival in Older Americans with Kidney Cancer: A Population-Based Cohort Study.* Healthcare (Basel), 2021. **9**(10).

41. O'Dea, A., et al., *Identifying the unmet supportive care needs of people affected by kidney cancer: a systematic review.* J Cancer Surviv, 2021.

42. Tricco, A.C., et al., *PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation.* Ann Intern Med, 2018. **169**(7): p. 467-473.

43. Swartz, M.K., *The PRISMA statement: a guideline for systematic reviews and meta-analyses.* J Pediatr Health Care, 2011. **25**(1): p. 1-2.

CHAPTER 2: PAPER 1

Associations between body mass index and bladder cancer survival: is the obesity paradox short-lived?

A version of this paper has been published.

Arthuso, F. Z., Fairey, A. S., Boulé, N. G., & Courneya, K. S. (2022). Associations between body mass index and bladder cancer survival: Is the obesity paradox short-lived?. *Canadian Urological Association journal = Journal de l'Association des urologues du Canada*, *16*(5), E261–E267. https://doi.org/10.5489/cuaj.7546

2.1 Abstract

Introduction: We investigated the associations of pre-surgical body mass index with bladder cancer outcomes in patients treated with radical cystectomy. **Methods:** We retrospectively analyzed data from 488 bladder cancer patients treated with radical cystectomy between 1994 and 2007 and followed-up until 2016. Cox regression with step function (time-segment analysis) was conducted for overall survival because the proportional hazard assumption was violated. **Results:** Of 488 bladder cancer patients, 155 (31.8%) were normal weight, 186 (38.1%) were overweight, and 147 (30.1%) were obese. During the median follow-up of 59.5 months, 363 (74.4%) patients died including 197 (40.4%) from bladder cancer. In adjusted Cox regression analyses, body mass index was not significantly associated with bladder cancer-specific survival for overweight (HR=0.79; 95% CI: 0.57 to 1.10; p=0.16) or obese (HR=0.76; 95% CI: 0.52 to 1.09; p=0.13) patients. In the Cox regression with step function for overall survival, the time-interaction was significant overall (p=0.020) and specifically for overweight patients (p=0.006). In the time-segment model, the HR for overweight during the first 63 months was 0.66 (95% CI: 0.49–0.90, p=0.008) whereas it was 1.41 (95% CI: 0.89–2.23, p=0.14) after 63 months. Although not statistically significant, a similar pattern was observed for obese patients. **Conclusions:** Our findings suggest that overweight and obese bladder cancer patients had better outcomes within the first five years after radical cystectomy; however, there were no differences in longer-term survival. These data suggest that the obesity paradox in bladder cancer patients treated with radical cystectomy may be short-lived.

Keywords: body mass index; cystectomy; obesity; survival; urinary bladder neoplasms.

2.2 Introduction

Bladder cancer is the fifth most common cancer in Canada [1] and the tenth most common cancer worldwide [2]. Radical cystectomy is the main treatment for muscle invasive bladder cancer and high risk non-muscle invasive bladder cancer [3]. Although bladder cancer survival has increased slightly, [4] bladder cancer remains the eighth most common cause of cancer mortality in Canada[1]. The 90-day mortality rate after radical cystectomy ranges from 3.2%-7.5% [5, 6] and the five-year relative survival rate ranges from 16% to 55% depending on the tumor stage [7].

Overweight and obesity are potential risk factors for developing bladder cancer because fat mass is related to inflammatory processes, alterations in sex hormone metabolism, abnormal levels of insulin and insulin-like growth factor, adipokine pathways, and microenvironment perturbations that contribute to tumor cell growth and proliferation [8, 9]. The association of obesity with bladder cancer survival, however, is much less clear. Some studies have reported that higher body mass index (BMI) is associated with a worse prognosis [10, 11] whereas other studies have found no association [12, 13]. Conversely, some studies have reported that higher BMI is associated with better survival in bladder cancer patients, [14-16] a phenomenon known as the obesity paradox.

Obesity may be linked to cancer treatment-related symptoms, treatment tolerance and response, recurrence, and long-term survival. Understanding the association between obesity and survival in bladder cancer patients after radical cystectomy may improve prognosis and guide bladder cancer management. The purpose of the present study was to

investigate the association of pre-surgical BMI with bladder cancer outcomes in patients treated with radical cystectomy.

2.3 Materials and Methods

After institutional review board approval (Health Research Ethics Board of Alberta (HREBA) – Cancer Committee #20-0294), we analyzed an existing database of bladder cancer patients undergoing radical cystectomy from the Northern Alberta Urology Centre in Edmonton, Canada. The data set was collected retrospectively and included bladder cancer patients undergoing radical cystectomy between 1994 and 2007 and followed-up for mortality outcomes until 2016. The primary exposure of interest was BMI defined as weight in kilograms divided by the square of height in meters (kg/m^2). BMI was measured objectively during a clinical visit prior to radical cystectomy and was recorded in the patient electronic medical record. Eligible patients had to have a measure of BMI recorded in the data set.

The primary outcomes were length of hospitalization, 90-day mortality, bladder cancer-specific survival (BCSS), and overall survival (OS). Length of hospitalization was the number of days hospitalized from the time of radical cystectomy until discharge. 90-day mortality was assessed as death from any cause within 90 days of the radical cystectomy. BCSS was defined as the time from radical cystectomy to the date of death from bladder cancer or last follow-up if the patient had not died of bladder cancer. If the patient died of other causes, the event was censored at the time of death. OS was determined as the time from radical cystectomy to the date of death from any cause. Patients who were still alive were censored at the date of last follow-up.

Patients were categorized as normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), or obese (≥30 kg/m^2). Descriptive statistics were used to summarize the data overall and by BMI category. Missing values for covariates (<3%) were replaced with the mean for continuous variables and the mode for categorical variables. Univariable associations between BMI and clinicopathologic variables were assessed using Pearson chi-square for categorical variables and ANOVA for continuous variables. Life tables were used to obtain median survival time overall and by BMI category. Kaplan-Meier curves were used to describe survival probabilities of OS by BMI category. Log-rank tests were used to assess differences in unadjusted survival probabilities by BMI category.

Proportional hazard assumption was verified graphically using the log minus log plot and considered valid if the curves run in parallel. Cox proportional model was used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for 90-day mortality and BCSS. We observed evidence of non-proportionality for OS, indicating that the effect of a fixed baseline covariate (i.e. BMI) may change over time [17]. Therefore, a Cox regression with a step-function (time-segment analysis) was applied to explore the time varying coefficient [17, 18]. Two separate analyses were conducted based on a split of the median survival time [18]. All the survival analyses were adjusted for established prognostic factors including age, sex, cancer subtype (urothelial vs non-urothelial), lymphovascular invasion, tumor grade, pathologic T stage, pathologic N stage, and adjuvant chemotherapy. All tests were 2-sided and statistical significance was set at $p<0.05$. All analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA).

2.4 Results

A total of 508 patients were initially available in the data set. Twenty patients were excluded from the analyses due to missing data on weight or height (n=6), implausible BMI (n=4), and being underweight (n=10). The final sample included 488 bladder cancer patients who underwent radical cystectomy and had a valid measure of BMI before surgery.

Table 2-1 summarizes the baseline demographic and disease characteristics of the bladder cancer patients overall and by BMI category. Mean age at diagnosis was 65.8 years, BMI was 27.7 kg/m^2, and 78.5% were males. Most patients were diagnosed with urothelial carcinoma (89.8%), high-grade tumors (88.5%), and ≥T2 stage (71.1%). Overall, 155 patients (31.8%) were normal weight, 186 (38.1%) were overweight, and 147 (30.1%) were obese. Sex differed among the BMI categories, with the overweight and obese groups having more men ($p<0.05$). Regarding disease profile, overweight and obese patients generally had a more favorable prognostic profile compared to normal weight patients including a significantly lower pathologic T stage ($p<0.05$).

Table 2-2 summarizes the treatment and survival outcomes of bladder cancer patients overall and by BMI category. Only 1% of patients underwent neoadjuvant chemotherapy. Surgical procedures did not vary among BMI categories; all women in the study underwent anterior exenteration and 98.2% of men had a radical cystoprostatectomy; 85.2% of patients had a standard lymph node dissection; and 77.7% had ileal conduit diversion. In the 30-day mortality analyses, overweight patients had a lower proportion of deaths compared to normal and obese patients ($p=0.039$) but the overall number of deaths was small (n=15; 3.1%).

Regarding our primary outcomes of interest, obese patients had a prolonged hospital stay compared to overweight patients (17.5±1.4 vs 13.2±1.3 days, $p<0.05$). After adjusting for prognostic factors, hospitalization remained significantly longer for obese versus overweight (17.8±1.4 vs 13.0±1.2 days; $p=0.010$) patients and became significantly longer for obese versus normal weight (17.8±1.4 vs 14.0±1.4 days; $p=0.036$) patients. In the 90-day mortality analyses, overweight patients had a lower proportion of deaths compared to normal and obese patients ($p<0.001$). The results remained statistically significant in the multivariable Cox regression analyses where overweight patients (HR=0.09; 95% CI: 0.02-0.38; $p=0.001$) were less likely to die within 90-days after radical cystectomy (Table 2-3).

During the median follow-up of 59.5 months (interquartile range, 13-144), 363 (74.4%) patients died including 197 (40.4%) from bladder cancer. Univariable analyses for bladder cancer-specific mortality showed that being obese was associated with improved BCSS ($p=0.011$). After adjusting for established prognostic factors in the multivariable Cox regression analyses (Table 2-3), the difference in BCSS was not significant for either overweight (HR=0.79; 95% CI: 0.57 to 1.10; $p=0.16$) or obese (HR=0.76; 95% CI: 0.52 to 1.09; $p=0.13$) patients. The supplementary Table 2-1 provides the multivariate analysis including all the covariates for the association of BMI with 90-day mortality, bladder cancer-specific mortality, and all-cause mortality.

Median OS for normal weight, overweight, and obese patients was 34.4, 88.5, and 70.8 months, respectively. The OS probability was not significantly different by BMI category (Figure 2-1). When assessing the proportional hazard assumption using the graphical model log-log plot, we observed evidence of non-proportional hazards among

the BMI categories for OS. The violation of the proportional hazard assumption indicates that the hazard is transient over time (i.e. time-varying coefficient) and may lead to biased effect estimates when follow-up is long. One method to address the non-proportionality is dividing the Cox model into time-intervals, therefore, we conducted two separate analyses split at the median survival of 63 months. In this analysis, BMI was included as a time-varying coefficient and the overall time-interaction was significant (p=0.020). More specifically, the interaction was significant for overweight (HR=2.13; 95% CI: 1.24–3.66; p=0.006) but not obese, although the interaction was in the same direction (HR=1.57; 95% CI: 0.87-2.82; p=0.13). In the time-segment model, the estimated HR for overweight during the first 63 months was 0.66 (95% CI: 0.49–0.90, p=0.008) whereas it was 1.41 (95% CI: 0.89–2.23, p=0.14) after 63 months. The estimated hazards ratio for obese during the first 63 months was 0.88 (95% CI: 0.64-1.20, p=0.42) whereas it was 1.38 (95% CI: 0.84–2.28, p=0.21) after 63 months (Table 2-3). We conducted a sensitivity analysis for all survival analyses that excluded non-urothelial cancers and found no meaningful differences compared to the overall analyses (data not shown).

2.5 Discussion

In this retrospective analysis of a previously established database, overweight and obese patients had a lower 90-day mortality rate and a better OS within the first five years of radical cystectomy. After five years, however, overweight and obese patients had an increased risk of all-cause mortality, resulting in no difference in longer-term OS. These data suggest that the obesity paradox in bladder cancer patients treated with radical cystectomy may be driven by a lower 90-day mortality rate and fewer early bladder

cancer-specific deaths and, therefore, short-lived. Our findings suggest a more nuanced interpretation of the obesity paradox for bladder cancer survival.

The role of BMI as a predictor of survival outcomes in bladder cancer patients varies considerably among studies [19, 20]. A recent systematic review and meta-analysis of BMI and survival in urothelial cancer patients treated with radical surgery reported that overweight was associated with better BCSS (HR=0.793; 95% CI:0.706-0.891; p<0.001) but worse OS (HR=1.125; 95% CI:1.018-1.244; p=0.021). Conversely, obesity was significantly associated with both worse BCSS (HR=1.138; 95% CI:1.028-1.261; p=0.013) and OS (HR=1.308; 95% CI:1.192-1.436; p < 0.001) [20]. This review noted substantial heterogeneity among the studies, although the source of the variance was not identified. One possible source of heterogeneity is that the review included Asian and Western-based studies with varying definitions of the BMI categories. Moreover, the studies had relatively short median follow-up times (from 21 to 64.1 months) making it difficult to compare the short-term and long-term survival experience of overweight and obese bladder cancer patients.

The obesity paradox appears to only hold during the first five years after radical cystectomy, when most deaths are due to surgical complications or bladder cancer, and then dissipates during further follow-up when most deaths are due to other causes. After five years, obesity appears to exert its usual negative association with survival. This unique finding in our study was prompted by a violation of the proportional hazard assumption in our data set, which indicated BMI as a time-varying coefficient for OS [21]. Assessment of the proportionality of hazards is a fundamental step for survival analyses using the Cox model. When the assumption is violated, a significant effect in the

early (or late) follow-up period may be missed [18]. The verification of this assumption, however, is not commonly reported in survival analysis of BMI in oncology, including investigations in bladder cancer [11-15, 22].

It is possible that our observation may provide another explanation of the inconsistency in the obesity paradox across different cancers. Petrelli et al. [23] observed that the association between obesity and cancer survival may differ based on cancer type. More specifically, these authors reported evidence of the obesity paradox in lung, renal, and metastatic melanoma cancers; all cancers that generally have higher rates of surgical complications and more cancer deaths that occur early in the cancer trajectory. Conversely, they noted that the traditional negative association of BMI with survival seemed to hold in patients with breast, colon, and uterine cancers; all cancers that generally have lower rates of surgical complications and fewer early cancer-specific deaths, where patients are more likely to die of other causes during longer-term follow-up.

Nevertheless, the obesity paradox, whether short-lived or not, should be interpreted with caution. Explanations in the literature include methodological biases, such as unmeasured confounding [24]. For instance, smoking status was not assessed in our study and it may confound the association between BMI and survival in bladder cancer patients. Other studies have suggested clinical and biological differences among BMI categories including body composition and tumor expression [24].

For example, in patients with clear cell renal cell carcinoma, another malignancy of the genitourinary tract, differences in gene expression pathways within the tumor microenvironment might be associated with the obesity paradox [25, 26]. Sanchez et al.

[25] reported that obese patients had significant tumor up-regulation angiogenic pathways in comparison to normal weight patients; therefore they were more likely to increase local drug delivery and benefit from therapy. Hakimi et al. [26] identified that fatty acid synthase (*FASN*) gene expression, an indicator of tumor aggressiveness and prognosis, differed by BMI categories. *FASN* was significantly upregulated in the normal BMI group and downregulated in the obese group, suggesting that the tumors of obese patients may be less aggressive than normal weight patients with renal cell carcinoma. [26] In our sample, overweight and obese patients had a more favorable prognostic profile compared to normal weight patients. The literature has conflicting findings, however, regarding the associations of BMI with tumor characteristics in bladder cancer patients and further investigation is needed [10, 22].

BMI as a measure of obesity is also questionable since it fails to distinguish body composition compartments among individuals in the same BMI range [27]. Psutka et al. [16] explored the association of BMI and fat mass index with OS in patients treated with radical cystectomy and urinary diversion. Increased BMI was associated with improved 5-year OS, however, obesity based on fat-mass index had no association. In addition, after adjusting for the presence of low skeletal muscle mass, the association disappeared [16]. Skeletal muscle mass is an important prognostic factor not assessed by BMI. Bladder cancer patients with lower skeletal muscle mass are at increased risk of early complications, cancer specific mortality, and all-cause mortality [28, 29]. Bladder cancer patients have a high prevalence of low skeletal muscle mass at diagnosis and post-treatment [30]. It is plausible that patients in the normal weight range might have lower muscle mass and, therefore, lower survival rates compared to overweight and obese

patients. Another possible explanation for better survival rates among overweight patients relates to the amount of subcutaneous fat. Cancer patients with higher subcutaneous adipose tissue experience longer survival than those with low subcutaneous fat [31]. The moderate amount of fat allows patients to survive weight losses that occur with treatment and may provide nutritional benefits [24, 32]. These explanations are only speculations, however, and further research is warranted.

Our study has important strengths and limitations. The strengths of our study include a sufficient sample size, the balanced distribution across the BMI categories, the relatively long follow-up time, and the verification of the proportional hazard assumption for the survival analysis. The limitations of our study include the exploratory nature of the analysis, the retrospective design of the study, the lack of data on potential confounders (e.g., smoking status, comorbidities), the use of BMI as the measure of obesity, and the measurement of BMI at only one time point. In addition, treatment has evolved since the completion of data collection (1994-2007) which may alter the association of obesity with survival. For example, our 90-day mortality rate of 12.3% is higher than that reported in the current literature, possibly due to changes in treatments and/or the likely higher rate of normal weight patients in our more dated sample. Finally, the generalizability of our results is limited only to patients treated with radical cystectomy. Future research should collect more sophisticated measures of obesity at multiple time points and check the proportional hazard assumption for a potential time-varying interaction with obesity. Moreover, other measures of health-related fitness besides body composition (e.g., cardiovascular fitness, muscular strength, physical

functioning) may also be important predictors of clinical outcomes in bladder cancer patients as they have been in breast cancer patients [33].

2.6 Conclusions

This exploratory analysis suggests that the obesity paradox in bladder cancer patients treated with radical cystectomy may only apply to postsurgical complications and bladder cancer deaths that typically occur early in the survival trajectory. With sufficient follow-up, the benefits of obesity on bladder cancer survival are reversed by an increased risk of other deaths, resulting in no long-term survival advantage for overweight/obese bladder cancer patients. Whether these associations were due to unmeasured confounding, limitations of BMI, or different tumor expression among the BMI groups is unknown. Well designed, prospective studies that include a direct measure of body composition and tumor expression pathways are warranted to understand if and how body composition is associated with survival outcomes in bladder cancer.

2.7 References

1. Brenner DR, Weir HK, Demers AA et al. Projected estimates of cancer in Canada in 2020. *CMAJ* 2020;192:E199-205.

2. International Agency for Research on Cancer. Estimated number of incident cases worldwide, both sexes, all ages. http://gco.iarc.fr/today/home Accessed July 28, 2021

3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines on Oncology: Bladder Cancer, 2021

4. Antoni S, Ferlay J, Soerjomataram I et al. Bladder cancer incidence and mortality: A global overview and recent trends. *Eur Urol* 2017; 71:96-108.

5. Zakaria AS, Santos F, Dragomir A. et al. Postoperative mortality and complications after radical cystectomy for bladder cancer in Quebec: A population-based analysis during the years 2000-2009. *Can Urol Assoc J* 2014; 8:259-67.

6. Yafi FA, Aprikian AG, Chin JL et al. Contemporary outcomes of 2287 patients with bladder cancer who were treated with radical cystectomy: a Canadian multicentre experience. *BJU Int* 2011; 108:539-45.

7. Surveillance & Reporting. The 2019 Report on Cancer Statistics in Alberta Edmonton: CancerControl Alberta,, Alberta Health Services; 2019. https://public.tableau.com/profile/cancercontrol.ab#!/vizhome/The2019ReportonCancerStatisticsinAlberta/Highlights?publish=yes. Accessed September 7, 2020

8. Sun JW, Zhao LG, Yang Y et al. Obesity and risk of bladder cancer: a dose-response meta-analysis of 15 cohort studies. *PLoS One* 2015; 10:e0119313.

9 Avgerinos KI, Spyrou N, Mantzoros CS. et al.: Obesity and cancer risk: Emerging biological mechanisms and perspectives. *Metabolism*, 92: 121, 2019

10. Chromecki TF, Cha EK, Fajkovic H. et al. Obesity is associated with worse oncological outcomes in patients treated with radical cystectomy. *BJU Int* 2013; 111: 249-55.

11. Dabi Y, Rouscoff Y, Anract J et al.: Impact of body mass index on the oncological outcomes of patients treated with radical cystectomy for muscle-invasive bladder cancer. *World J Urol* 2017; 35:229-35.

12. Hafron J, Mitra N, Dalbagni G et al. Does body mass index affect survival of patients undergoing radical or partial cystectomy for bladder cancer? *J Urol* 2005; 173:1513-7.

13. Bachir BG, Aprikian AG, Izawa JI et al. Effect of body mass index on the outcomes of patients with upper and lower urinary tract cancers treated by radical surgery: results from a Canadian multicenter collaboration. *Urol Oncol* 2014; 32: 441-8.

14. Gierth M, Zeman F, Denzinger S et al. Influence of body mass index on clinical outcome parameters, complication rate and survival after radical cystectomy: Evidence from a prospective European multicentre study. *Urol Int* 2018; 101:16-24.

15. Bi H, Huang Y, Wang G et al. Impact of body mass index and pretreatment hemoglobin level on prognosis following radical cystectomy for bladder cancer in males and females. *Urol Int* 2020; 104: 28-35.

16. Psutka SP, Boorjian SA, Moynagh MR et al. Mortality after radical cystectomy: impact of obesity versus adiposity after adjusting for skeletal muscle wasting. *J Urol* 2015; 193:1507-1513.

17. Zhang Z, Reinikainen J, Adeleke KA et al. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med* 2018; 6:121.

18. Schemper M. Cox analysis of survival data with non-proportional hazard functions. *The Statistician* 1992; 41:455-65.

19. Ornaghi PI, Afferi L, Antonelli A et al. The impact of preoperative nutritional status on post-surgical complication and mortality rates in patients undergoing radical cystectomy for bladder cancer: a systematic review of the literature. *World J Urol* 2020; 39:1045-81.

20. Yang Z, Bai Y, Hu X et al. The prognostic value of body mass index in patients with urothelial carcinoma after surgery: A systematic review and meta-analysis. *Dose Response* 2020; 181559325820979247, 2020

21. Lee L, Shih JH. An introduction to survival analysis. In: Principles and practice of clinical research, 2018, 373-381.

22. Kwon T, Jeong IG, You D et al. Obesity and prognosis in muscle-invasive bladder cancer: the continuing controversy. *Int J Urol* 2014, 21:1106-12.

23. Petrelli F, Cortellini A, Indini A et al. Association of obesity with survival outcomes in patients with cancer: A systematic review and meta-analysis. *JAMA Netw Open* 2021, 4: e213520.

24. Caan BJ, Cespedes Feliciano EM, Kroenke CH. The importance of body composition in explaining the overweight paradox in cancer-counterpoint. *Cancer Res* 2018; 78:1906-12.

25. Sanchez A, Furberg H, Kuo F et al. Transcriptomic signatures related to the obesity paradox in patients with clear cell renal cell carcinoma: a cohort study. *Lancet Oncol* 2020, 21:283-293.

26. Hakimi AA, Furberg H, Zabor EC et al. An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. *J Natl Cancer Inst* 2013; 105:1862-70

27. Sanchez A, Kissel S, Coletta A et al. Impact of body size and body composition on bladder cancer outcomes: Risk stratification and opportunity for novel interventions. *Urol Oncol* 2020; 38:713-18.

28. Mayr R, Gierth M, Zeman F et al. Sarcopenia as a comorbidity-independent predictor of survival following radical cystectomy for bladder cancer. *J Cachexia Sarcopenia Muscle* 2018; 9:505-13

29. Mayr R, Fritsche HM, Zeman F et al. Sarcopenia predicts 90-day mortality and postoperative complications after radical cystectomy for bladder cancer. *World J Urol* 2018; 36:1201-07

30. Hansen TTD, Omland LH, von Heymann A et al. Development of sarcopenia in patients with bladder cancer: A systematic review. *Semin Oncol Nurs* 2021; 37:151108

31. Ebadi M, Martin L, Ghosh S et al. Subcutaneous adiposity is an independent predictor of mortality in cancer patients. *Br J Cancer* 2017; 117:148-55.

32. Caan BJ, Meyerhardt JA, Kroenke CH et al. Explaining the obesity paradox: The association between body composition and colorectal cancer survival (C-SCANS Study). *Cancer Epidemiol Biomarkers Prev* 2017; 26:1008-15

33. An KY, Arthuso FZ, Kang DW et al. Exercise and health-related fitness predictors of chemotherapy completion in breast cancer patients: pooled analysis of two multicenter trials. *Breast Cancer Res Treat* 2021, 188: 399-407

Table 2-1. Baseline demographic and disease characteristics of bladder cancer patients, overall and by body mass index.

Variables	Overall (n=488)	Body Mass Index (kg/m^2) Normal weight 18.5-24.9 (n=155)	Overweight 25-29.9 (n=186)	Obese ≥30 (n=147)	p value
Body Mass Index (kg/m^2), M±SD	27.7±4.8	22.6±1.6	27.3±1.4	33.4±3.3	-
Weight (kg), M±SD	81.8±17.1	65.8±9.5	81.4±9.6	99.3±13.5	-
Sex (male), n (%)	383 (78.5)	107 (69.0)	154 (82.8)[a]	122 (83.0)[a]	0.002
Age (years), M±SD	65.8±10.0	65.6±10.9	66.7±9.9	64.7±9.1	0.18
Urothelial Carcinoma, n (%)	438 (89.8)	138 (89.0)	164 (88.2)	136 (92.5)	0.41
Lymphovascular Invasion, n (%)	153 (31.4)	59 (38.1)	55 (29.6)	39 (26.5) [a]	0.08
High-grade, n (%)	432 (88.5)	143 (92.3)	159 (85.5)	130 (88.4)	0.15
Pathologic T Stage (≥T2), n (%)	347 (71.1)	124 (80.0)	130 (69.9)[a]	93 (63.3)[a]	0.005
Pathologic N Stage (N+), n (%)	104 (21.3)	41 (26.5)	37 (19.9)	26 (17.7)	0.15

[a]$p<.05$ versus normal weight

Table 2-2. Treatment and survival outcomes of bladder cancer patients, overall and by body mass index.

Variables	Overall	Body Mass Index (kg/m^2)			p value
		Normal weight 18.5-24.9	Overweight 25-29.9	Obese ≥30	
	(n=488)	(n=155)	(n=186)	(n=147)	
Neoadjuvant chemotherapy, n (%)	5 (1.0)	2 (1.3)	2 (1.1)	1 (0.7)	
Surgical Procedure, n (%)					
Anterior Exenteration (women)	105 (100)	48 (100)	32 (100)	25 (100)	
Radical Cystoprostate (men)	376 (98.2)	103 (96.3)	152 (98.7)	121 (99.2)	
Positive Surgical Margin, n (%)	60 (12.3)	18 (11.6)	23 (12.4)	19 (12.9)	0.94
Lymph Node Dissection, n (%)					
None/Limited	37 (7.6)	18 (11.6)	12 (6.5)	7 (4.8)	0.63
Standard	416 (85.2)	124 (80.0)	161 (86.6)	131 (89.1)	
Extended	35 (7.2)	13 (8.4)	13 (7.0)	9 (6.1)	
Diversion, n (%)					
Ileal Conduit	379 (77.7)	121 (78.1)	147 (79.0)	111 (75.5)	0.62
Neobladder	99 (20.3)	29 (18.7)	36 (19.4)	34 (23.1)	
Other	10 (2.0)	5 (3.2)	3 (1.6)	2 (1.4)	
Estimated Blood Loss (ml), M±SD	1.3±0.8	1.3±0.9	1.3±0.8	1.3±0.8	0.74
Hospital Stay (days), M±SD	14.7±16.8	13.7±14.5	13.2±8.4	17.5±24.9[b]	0.050
Adjuvant chemotherapy, n (%)	79 (16.2)	30 (19.4)	26 (14.0)	23 (15.6)	0.39
30-day Mortality, n (%)	15 (3.1)	7 (4.5)	1 (0.5) [a]	7 (4.8) [b]	0.039
90-day Mortality, n (%)	31 (6.4)	19 (12.3)	2 (1.1)[a]	10 (6.8) [b]	<0.001
Bladder Cancer Death, n (%)	197 (40.4)	74 (47.7)	74 (39.8)	49 (33.3) [a]	0.038
Overall Death, n (%)	363 (74.4)	117 (75.5)	138 (74.2)	108 (73.5)	0.92

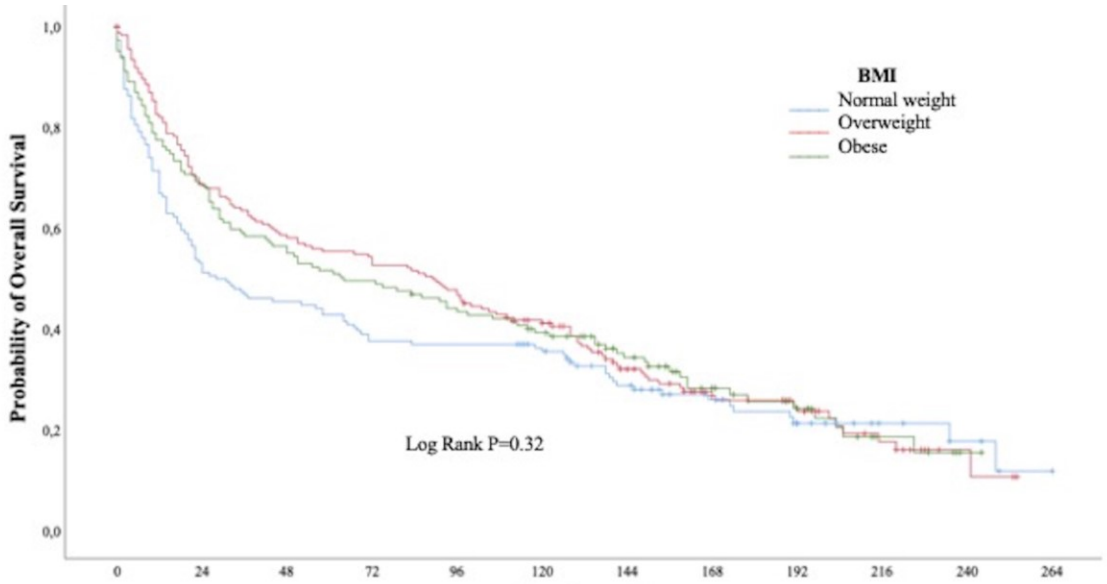
[a]p<.05 versus normal weight

[b]p<.05 versus overweight

Table 2-3. Cox Proportional HRs and 95% CIs for the association of body mass index with 90-day mortality, bladder cancer-specific mortality, and all-cause mortality.

Body Mass Index (kg/m^2)	**Overall** (n=488)		
	No. of Deaths/ No. of Person-Years	**HR (95% CI)**	**p**
90-day Mortality			
Normal weight (18.5-24.9)	19/985	Referent	
Overweight (25-29.9)	2/1,417	0.09 (0.02 to 0.38)	0.001
Obese (≥30)	10/1,071	0.63 (0.29 to 1.39)	0.25
Per 1-unit increase		0.93 (0.85 to 1.02)	0.11
Bladder cancer–specific mortality			
Normal weight (18.5-24.9)	74/985	Referent	
Overweight (25-29.9)	74/1,417	0.79 (0.57 to 1.10)	0.16
Obese (≥30)	49/1,071	0.76 (0.52 to 1.09)	0.13
Per 1-unit increase		0.98 (0.95 to 1.01)	0.21
All-cause Mortality			
Normal weight (18.5-24.9)	117/985	Referent	
Overweight (25-29.9)	138/1,417	0.84 (0.65 to 1.09)	0.18
Obese (≥30)	108/1,071	1.00 (0.77 to 1.31)	1.00
Per 1-unit increase		1.01 (0.98 to 1.03)	0.70
All-cause Mortality with time-varying covariate			0.020*
≤63 months			
Normal weight (18.5-24.9)	88/136	Referent	
Overweight (25-29.9)	82/166	0.66 (0.49 to 0.90)	0.008
Obese (≥30)	72/141	0.88 (0.64 to 1.20)	0.42
>63 months			
Normal weight (18.5-24.9)	29/841	Referent	
Overweight (25-29.9)	56/1,244	1.41 (0.89 to 2.23)	0.14
Obese (≥30)	36/920	1.38 (0.84 to 2.28)	0.21

HR: hazard ratio; CI: confidence interval. *p value for time-interaction.
Adjusted for age, sex, cancer subtype, lymphovascular invasion, tumor grade, pathologic T stage, pathologic N stage, and adjuvant chemotherapy.



No. at risk												
Normal weight	154	82	70	58	57	52	37	25	17	7	4	0
Overweight	185	127	108	100	88	20	46	32	23	11	3	0
Obese	146	101	83	73	64	55	39	25	17	6	1	0

Figure 2-1. Kaplan-Meier curves for overall survival stratified by BMI category.

Supplementary Table 2-1. Multivariate Cox Proportional HRs and 95% CIs for the association of body mass index with 90-day mortality, bladder cancer-specific mortality, and all-cause mortality

Covariates	HR (95% CI)	p value
90-day Mortality		
Body Mass Index		
Overweight vs Normal	0.09 (0.02 to 0.38)	0.001
Obese vs Normal	0.63 (0.29 to 1.39)	0.25
Age (continuous)	1.00 (0.96 to 1.04)	0.93
Sex (male vs female)	1.01 (0.44 to 2.30)	0.98
Cancer subtype (urothelial vs non-urothelial)	0.68 (0.23 to 2.03)	0.49
Lymphovascular invasion (yes vs no)	1.47 (0.68 to 3.20)	0.33
Tumor grade (high grade vs low-grade)	0.97 (0.29 to 3.30)	0.97
Pathologic T Stage (≥T2 vs <T2)	2.13 (0.76 to 5.96)	0.15
Pathologic N Stage (yes vs no)	0.55 (0.18 to 1.68)	0.30
Adjuvant chemotherapy (no vs yes)	6.24 (0.80 to 48.36)	0.08
Bladder cancer–specific mortality		
Body Mass Index		
Overweight vs Normal	0.79 (0.57 to 1.10)	0.16
Obese vs Normal	0.76 (0.52 to 1.09)	0.13
Age (continuous)	1.01 (1.00 to 1.03)	0.10
Sex (male vs female)	0.92 (0.65 to 1.28)	0.61
Cancer subtype (urothelial vs non-urothelial)	0.92 (0.57 to 1.47)	0.73
Lymphovascular invasion (yes vs no)	1.53 (1.12 to 2.08)	0.007
Tumor grade (high grade vs low-grade)	0.72 (0.46 to 1.13)	0.15
Pathologic T Stage (≥T2 vs <T2)	3.07 (1-97 to 4.08)	<0.001
Pathologic N Stage (yes vs no)	1.93 (1.36 to 2.74)	<0.001
Adjuvant chemotherapy (no vs yes)	1.42 (0.95 to 2.10)	0.08
All-cause Mortality		
Body Mass Index		
Overweight vs Normal	0.84 (0.65 to 1.09)	0.18
Obese vs Normal	1.00 (0.77 to 1.31)	1.00
Age (continuous)	1.03 (1.01 to 1.04)	<0.001
Sex (male vs female)	1.02 (0.79 to 1.32)	0.89
Cancer subtype (urothelial vs non-urothelial)	0.96 (0.67 to 1.36)	0.80
Lymphovascular invasion (yes vs no)	1.41 (1.10 to 1.79)	0.006
Tumor grade (high grade vs low-grade)	0.74 (0.54 to 1.04)	0.08
Pathologic T Stage (≥T2 vs <T2)	1.71 (1.32 to 2.23)	<0.001
Pathologic N Stage (yes vs no)	1.37 (1.03 to 1.83)	0.031
Adjuvant chemotherapy (no vs yes)	1.30 (0.95 to 1.79)	0.10

CHAPTER 3: PAPER 2

Bladder cancer and exercise training during intravesical therapy – the brave trial: a study protocol for a prospective, single-center, two-armed randomised controlled trial

A version of this paper has been published.

Arthuso, F. Z., Fairey, A. S., Boulé, N. G., & Courneya, K. S. (2021). Bladder cancer and exeRcise trAining during intraVesical thErapy-the BRAVE trial: a study protocol for a prospective, single-centre, phase II randomised controlled trial. *BMJ open*, *11*(9), e055782. https://doi.org/10.1136/bmjopen-2021-055782

3.1 Abstract

Introduction: Non-muscle invasive bladder cancer (NMIBC) accounts for about 75% of newly diagnosed bladder cancers. The treatment for NMIBC involves surgical removal of the tumor followed by six weekly instillations of immunotherapy or chemotherapy directly into the bladder (i.e., intravesical therapy). NMIBC has a high rate of recurrence (31-78%) and progression (15%). Moreover, bladder cancer and its treatment may affect patient functioning and quality of life. Exercise is a safe and effective intervention for many cancer patient groups, however, no studies have examined exercise during intravesical therapy for NMIBC. The primary objective of the Bladder cancer and exeRcise trAining during intraVesical thErapy (BRAVE) trial is to examine the safety and feasibility of an exercise intervention in bladder cancer patients undergoing intravesical therapy. The secondary objectives are to investigate the preliminary efficacy of exercise on health-related fitness and patient-reported outcomes; examine the social cognitive predictors of exercise adherence; and explore the potential effects of exercise on tumor recurrence and progression. **Methods and Analysis:** BRAVE is a phase II randomised controlled trial that aims to include 66 patients with NMIBC scheduled to receive intravesical therapy. Participants will be randomly assigned to the exercise intervention or usual care. The intervention consists of three supervised, high-intensity interval training sessions/week for 12-weeks.Feasibility will be evaluated by eligibility, recruitment, adherence, and attrition rates. Preliminary efficacy will focus on changes in cardiorespiratory fitness and patient-reported outcomes from baseline (prior to intravesical therapy) to pre-cystoscopy (3 months). Cancer outcomes will be tracked at 3 months, and one-year follow-up by cystoscopy. Analysis of covariance will compare

between-group differences at post-intervention (pre-cystoscopy) for all health-related fitness and patient-reported outcomes. **Ethics and dissemination:** The study was approved by the Health Research Ethics Board of Alberta-Cancer Committee (#20-0184). Dissemination will include publication and presentations at scientific conferences and public channels.

3.2 Introduction

Bladder cancer is the fifth most common cancer in Canada and most new cases are non-muscle invasive bladder cancer (NMIBC) [1]. The treatment for NMIBC initially involves surgical removal of the tumor through a procedure called transurethral resection of the bladder tumor (TURBT). Surgery is usually followed by six weeks of intravesical therapy, which consists of weekly instillations of immunotherapy or chemotherapy placed inside the bladder through the urethra [1, 2]. Additional intravesical therapy may be offered to the patient depending on the risk profile and initial response to treatments. NMIBC has a high rate of recurrence (31-78%) [1] and progression (15%) [3], making it one of the most distressing and expensive cancers to treat [4]. Moreover, bladder cancer and its treatments may affect patient functioning and quality of life [5], and increase the risk of cardiovascular mortality [6].

Exercise is generally safe and effective for most cancer patients and is recommended specifically for improving health-related fitness and some side effects [7]. Few exercise studies, however, have focused on bladder cancer patients [8]. Limited research has suggested that exercise in bladder cancer patients may improve health related quality of life, cardiorespiratory fitness, functional capacity, and muscle power [9-15]; however, none of these studies have focused on NMIBC patients receiving intravesical therapy [9-15]. Currently, it is unclear if exercise is safe and feasible for NMIBC patients receiving intravesical therapy or whether it has any meaningful benefits (or harms).

Here, we propose the Bladder cancer and exeRcise trAining during intraVesical thErapy (BRAVE) trial, the first phase II randomised controlled trial with the primary

objective of determining the safety and feasibility of exercise in bladder cancer patients scheduled to receive intravesical therapy. The secondary objectives are to examine the preliminary effects of exercise on health-related fitness (cardiorespiratory fitness and physical functioning), patient-reported outcomes (health-related quality of life, fear of cancer recurrence, anxiety, depression, fatigue, perceived stress, self-esteem, and sleep quality), and social cognitive predictors of exercise adherence (motivation, perceived benefits, enjoyment, support from others, self-efficacy, and barriers). An exploratory objective is to track the short-term bladder cancer recurrence and progression rates for each trial arm. The hypotheses of the BRAVE trial are: (1) exercise will be feasible and safe in this patient population, (2) exercise will significantly improve health-related fitness and patient-reported outcomes, and (3) social cognitive variables from the theory of planned behavior will predict exercise adherence.

3.3 Methods

Study design

The BRAVE Trial will be conducted as a prospective, single-center, two-armed, phase II randomised controlled trial at the University of Alberta and the Northern Alberta Urology Centre (NAUC) in Edmonton, Alberta, Canada. Participants will be randomly assigned to either the usual care or exercise training group. The proposed participant flow through the study includes 1) enrollment, 2) baseline assessment (before intravesical therapy), 3) allocation, 4) post-intravesical therapy assessment (6-week), 5) pre-cystoscopy (post-intervention) assessment (3-month) and 6) 1 year follow-up assessment (Figure 3-1). The study design is described based on the Standard Protocol Item for

Randomised Trials (SPIRIT) guideline [16] and the Consolidated Standards of Reporting Trials (CONSORT) statement for randomised pilot and feasibility trials [17].

Study Population

Eligible participants will include men and women that (1) are ≥ 18 years old, (2) have a confirmed diagnosis of NMIBC (clinical stage cis, Ta or T1), and (3) are scheduled to begin or have received only one induction intravesical therapy with chemotherapy (e.g., Gemcitabine or Mitomycin) or immunotherapy (i.e., Bacillus Calmette Guerin – BCG) agents. In the face of a slower-than-expected recruitment rate, eligibility criteria may be extended to patients in the maintenance phases of treatment for NMIBC, where patients receive three weekly instillations of intravesical therapy. Exclusion criteria for participants include: (1) not medically cleared to participate in the exercise intervention by their treating urologist and a certified exercise physiologist using the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) [18], (2) contraindications for cardiopulmonary stress and/or physical fitness tests (e.g., resting hypertension, mental impairment with limited ability to cooperate, physical disability that precludes safe and adequate testing) [7], (3) already meeting the exercise guidelines for cancer survivors [19] [20], assessed by the Godin Leisure-Time Exercise Questionnaire (GLTEQ) [21], (4) unable to read and comprehend English, and (5) not willing to be randomised to a supervised exercise training program or usual care (no exercise) for 12 weeks.

The target accrual number is 66 patients over 24 months (May 2021 to April 2023). According to Cancer Control Alberta [22], 1,040 bladder cancers were diagnosed in 2020 in Alberta of which 75% (780) were NMIBC [1]. Approximately one third of

these cases (n=260) will be in the Edmonton region. Considering approximately 520 available patients over 2 years, we anticipate a 50% eligibility rate (n=260) and a 25% recruitment rate (n=66) will achieve our target sample size.

Recruitment and screening

Recruitment will be conducted through NAUC medical records and checkup visits at the Kaye Edmonton Clinic, Alberta, Canada. Specifically, the study coordinator will verify if the patients are ≥ 18 years old and have a confirmed diagnosis of NMIBC. The study coordinator will then notify the urologist about a potential eligible participant prior to the appointment. If the patient is scheduled to begin or has received one intravesical therapy, the urologist will hand out the study brochure and ask for consent for contact by the study coordinator. The study coordinator will then contact the patient to provide further details about the study, clarify any questions, document enrollment data, and screen for current physical activity readiness and participation level. Using the GLTEQ, patients will be asked to recall their average weekly frequency and duration of light, moderate, and vigorous exercise that lasted 10 minutes or longer and was done during free time in the past month. The total minutes of exercise per week will be calculated as moderate minutes plus two times the vigorous minutes. Eligibility will be confirmed if the total minutes of exercise per week is <150 minutes. Eligible patients will be scheduled for baseline testing.

Randomization and blinding

After completing baseline assessments, patients will be randomly assigned to either the exercise training group or usual care group in a 1:1 ratio using a computer-generated program with random blocks of 4 or 6. The allocation sequence will be

generated independently by a research assistant, not otherwise involved in the trial, and concealed from the study coordinator. The results of the randomization will be reported in person to the patient immediately after the baseline assessment. Participants and investigators will not be blinded to group assignment given the nature of the intervention. Outcome assessors will be blinded to group assignment for the clinical outcomes of tumor recurrence and progression. Fitness outcome assessors will not be blinded to group assignment but will follow a detailed protocol and be trained in the importance of standardizing outcome assessments.

Intervention

Exercise Group: In addition to standard medical care, which includes offer of a smoking cessation program for current smokers, the exercise group will be asked to perform36 high-intensity interval training sessions over a 12-week period. The exercise frequency will be three times per week during the 6 weeks of intravesical therapy and the 6 weeks of recovery (total 12 weeks) prior to the 3-month surveillance cystoscopy. Figure 3-2 shows the intervention within the treatment timeline. The intervention will be performed on a treadmill and will include a warm-up and cool-down at 50-60% and 40% of the VO_{2peak} respectively, for five minutes. The HIIT protocol will be 4x4, which consists of four bouts of four minutes at a workload corresponding to vigorous intensity (75-95% of the baseline and 6-week VO_{2peak}) alternating with three minutes of recovery intervals at 40% of the VO_{2peak} (Figure 3-3). The exercise session will last 35 minutes and include 16 minutes of high intensity exercise. The exercise program will be personalized to patients: the intensity of the exercise will be modified by changing the speed and/or grade of the treadmill following a standardized equation [23] based on 75-95% of VO_{2peak}

measured at baseline and updated at post-intravesical therapy (6-week). Moreover, a gradual approach for progression will be used to enhance adherence and reduce risk of cardiovascular events and injuries (Figure 3-4) [24]. To address safety concerns, prior to the beginning of each exercise session, the participants will have resting blood pressure, resting heart rate, and overall symptoms screened. Participants will be asked to wear a heart monitor while exercising. Heart rate will be registered at the last minute of each session component (warm-up, high-intensity interval, recovery interval and cool-down). The average heart rate and the highest heart rate of the entire HIIT session will be monitored. Exercise tolerance will be assessed at the end of the session using the 0-10 Borg's ratio of perceived exertion scale [25]. After the post-intervention assessments and 3-month cystoscopy, patients will be provided with an updated exercise prescription and encouraged to continue the exercise program on their own.

Usual Care: The usual care group will receive standard medical care, which does not include any exercise program or recommendations, only a smoking cessation program for current smokers. Patients in the usual care group will be asked not to initiate an exercise program or to increase their exercise level from baseline during the 12-week study. After the post-intervention assessments and 3-month cystoscopy, patients in the usual care group will be offered a 4-week supervised exercise program.

Feasibility Measures

Feasibility will be evaluated by tracking the eligibility rate (and reasons for ineligibility), recruitment rate (and reasons for declining), exercise adherence rate (including reasons for dose modification and exercise interruption), and follow-up assessment rate (and reasons for drop out). The eligibility rate will be the number of

NMIBC patients scheduled for intravesical induction therapy divided by the number of patients deemed eligible. The recruitment rate will be the number of NMIBC patients randomised in the study divided by the number of eligible patients. Adherence to the program will be measured by the number of exercise sessions completed with and without dose modifications. Reasons for not completing the exercise session or for dose adjustments will be recorded. The follow-up assessment rate will be determined by the number of participants who complete the post-intervention or follow-up assessments for each of the outcomes.

To evaluate the safety of the program, any adverse events during the physical fitness assessments or exercise sessions will be recorded. Once the event has been evaluated, a decision will be made regarding the avoidance of future events, and whether the participant can return to the intervention. If the adverse event requires medical attention, the participant will need to be cleared by a physician before returning to the study. The research team will forward all adverse event report forms to the ethics board.

Outcome measures

There will be four assessment time-points: baseline (pre-intravesical therapy), post-intravesical therapy (6 weeks), pre-cystoscopy/post-intervention (12 weeks), and 1-year follow-up (Table 3-1). Health-related fitness will be assessed at baseline, post-intravesical therapy, and post-intervention. Patient-reported outcomes and social cognitive predictors of exercise adherence will be assessed at baseline, pre-cystoscopy (post-intervention), and 1-year follow-up. Tumor recurrence and progression will be assessed at post-intervention (3-month surveillance cystoscopy) and 1-year follow-up (1-year surveillance cystoscopy). No follow-up research visits are required. All the

information needed for the follow-up assessments will be collected via medical records and by mail or email, as preferred by the participant.

Cardiorespiratory fitness will be assessed through direct measurement of VO_{2peak} (mL/kg/min) by the modified Bruce treadmill protocol exercise test, using a metabolic measurement system (Parvo Medics TrueOne® 2400; Sandy, UT, USA) [26]. This protocol was chosen because it was originally designed for high-risk and elderly individuals, it is widely used in the clinical setting, and because of its specificity with the exercise intervention for this study, which will be on a treadmill. Overall, the test consist of stages that are three minutes long starting at 0% grade and a speed of 1.7 mph, with a gradual increase of intensity by changing first the incline, then both incline and speed. The test will terminate when the patient achieves volitional exhaustion or in the presence of any test termination criteria [23]. VO_{2peak} will be determined as the highest value obtained over a 30-second average [27]. The ventilatory threshold, defined as an increase in ventilation without a corresponding increase in VO_2, will be determined by the V-slope method [28]. Physical functioning will be assessed by the Senior Fitness Test (SFT) which is used to evaluate health-related physical fitness and functional capacity among older adults [23]. The SFT includes: 1) 30-second chair stand, 2) Arm curl, 3) Chair sit-and-reach, 4) Back Scratch, 5) 8-foot up-and-go, and 6) 6-minute walk. These tests are used to assess, respectively, lower and upper body strength, lower and upper body flexibility, agility/dynamic balance, and aerobic endurance [29]. Anthropometry and body composition measurements will include height, weight, waist, hip, and calf circumferences [7, 30].

Patient-reported outcomes will include the assessment of health-related quality of life (HRQoL) using the European Organization for Research and Treatment of Cancer (EORTC) core 30-item questionnaire (QLQ-C30) version 3.0 [31]. The EORTC QLQ-C30 is designed to cover a range of quality of life issues relevant to cancer patients, including functional scales (physical, cognitive, role, emotional, and social), symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, and diarrhea), perceived financial impact scale, and a global health status/QoL scale [31]. The assessment of HRQoL will be complemented by the EORTC QLQ NMIBC C24 [32], which evaluates urinary symptoms, intravesical treatment issues, future perspective, fever and feeling ill, abdominal bloating and flatulence, and sexual functioning [32]. Patient-reported outcome evaluation will also include fear of cancer recurrence/progression assessed by the Fear of Cancer Recurrence Inventory [33], anxiety using the 10-item State-trait anxiety inventory [34], depression using the 10-item Center for Epidemiologic Studies Depression Scale (CES-D) [35], fatigue using the Functional Assessment of Cancer Therapy–Fatigue [36], perceived stress using the14-item Perceived Stress Scale [37], self-esteem using the Rosenberg self-esteem scale [38], and sleep quality using the Insomnia Severity Index (ISI) [39]. Social cognitive predictors of exercise adherence: motivation, perceived benefits, enjoyment, support from others, self-efficacy, and barriers will be assessed using standard scales for the Theory of Planned Behavior [40]. Patient-reported outcomes and social cognitive predictors will be assessed using e-mail or mail delivery format.

Intravesical therapy adherence will be tracked by medical records of attendance and self-report drug retention time. Treatment toxicities will be abstracted from medical

records. Bladder cancer recurrence and progression will be assessed by cystoscopy. Specifically, the outcome of interest will be complete response (CR), defined as negative cytology, imaging, and cystoscopy and, when the TURBT is indicated, a negative biopsy. CR will be assessed at 3-month and one-year follow-up.

Sociodemographic information will be obtained through baseline questionnaire and will include age, sex, ethnicity, marital status, education, income, smoking status, and comorbidities. Medical information will be assessed via medical records and will include date of cystoscopy, date of the surgical resection (TURBT), tumor histology, grade, stage, and intravesical therapy protocol.

Sample size

Given the descriptive nature of the primary objectives (safety and feasibility), we selected VO_{2peak} for the sample size calculation because improvement in cardiorespiratory fitness (i.e. VO_{2peak}) is the intended immediate effect of the intervention. Moreover, VO_{2peak} may be considered a "bridge" between feasibility and efficacy because it reflects the patient's ability and willingness to do the exercise program (feasibility) and is a potential surrogate for improved patient-reported outcomes and cancer outcomes (efficacy). If we reach the accrual of 66 participants (33 per group), it provides 80% power using a two-tailed alpha <0.05 to detect a clinically meaningful difference of one metabolic equivalent (MET = 3.5 ml/kg/min) in VO_{2peak} assuming a standard deviation of 5.6 ml/kg/min, 10% missing data, and adjustment for baseline value and other prognostic covariates[41]. This power may also be sufficient for detecting differences in some patient-reported outcomes if the effects exceed standardized effect sizes of approximately $\geq$ d=0.60. This power is unlikely sufficient for detecting

differences in any of the cancer outcomes (recurrence and progression). Given that the purpose of this trial is to inform larger phase II and phase III trials, the patient-reported and clinical outcomes will be interpreted for clinical significance based on the direction and the magnitude of the numerical differences.

Data collection and management

All data will be recorded on Case Report Forms (CRFs) and stored anonymized in the Behavioral Medicine Laboratory at the University of Alberta. The investigators will provide access to the data file upon reasonable request. The investigator is ultimately responsible for the collection and timely reporting of all applicable data entered in CRFs and ensuring they are accurate, original, attributable, complete, legible, contemporaneous, and available when required.

Statistical considerations

All randomised participants will be included in the analyses using the intention-to-treat approach. If missing data is <10% we will conduct a complete case analysis. If missing data is >10%, we will employ a multiple imputation missing data strategy [42, 43]. There will be no interim analyses. Continuous variables will be described using mean (standard deviation) or median (interquartile range), while categorical variables will be described using frequencies (percentages) and confidence intervals. Descriptive analyses will be performed for participant characteristics, feasibility outcomes, and disease recurrence and progression. Analysis of covariance will be conducted for health-related fitness outcomes and patient-reported outcomes to compare the between-group differences at post-intervention (pre-cystoscopy) after adjustment for the baseline value of the outcome as well as other potential covariates. All analyses will be performed using

SPSS (SPSS Inc., Chicago, IL, USA). The level of statistical significance will be set at 0.05 and all hypotheses tests will be two-sided.

Strategies to minimize drop-outs and protocol deviations will include: 1) reducing the intensity of the exercise session, 2) reducing the number of high-intensity intervals, and/or 3) reducing the frequency of visits to the exercise facility by offering home-based unsupervised exercise sessions when necessary and feasible. All patients who drop out of the intervention will be invited to complete the follow-up assessments in order to keep a low rate of missing data for the intention to treat analysis.

Patient and public involvement

A patient and public involvement panel were not specifically conducted to inform the research question, study design, recruitment, or dissemination plan for this study.

Ethics and dissemination

The BRAVE Trial was approved by the Health Research Ethics Board of Alberta-Cancer Committee (#20-0184). All patients will provide written informed consent prior to the beginning of the study. The outcomes of the BRAVE trial will be disseminated through peer-reviewed academic journals, conferences, via the webpage www.bravestudy.ca, and monthly newsletter for stakeholders.

3.4 Discussion

Exercise is recommended to many cancer patients in different clinical settings, however, there are no studies examining the effects of exercise in NMIBC patients receiving intravesical therapy [44]. The NMIBC patient group is older and has significant comorbidities that may make exercise more unsafe or less feasible compared to other cancer patient groups. Moreover, no study to date has examined exercise during

intravesical therapy. Feasibility studies are important for understanding if further investigation should be conducted considering the sustainability and relevance of the research and findings [45]. The primary focus of the BRAVE Trial will be safety and feasibility because it is the first exercise trial in this patient population.

To date, only four randomised controlled trials have been conducted exclusively among bladder cancer patients and all four have been in the prehabilitation setting (i.e., prior to radical cystectomy) [9-15]. These studies have provided promising evidence that exercise interventions prior to radical cystectomy may be associated with improvements in specific domains of health-related quality of life, including the physical domain [12] and disease-specific symptoms [10]. In addition, these studies have reported benefits in cardiorespiratory fitness [9, 11], functional capacity [12, 13, 15], and muscle power [14]. These studies have limitations, however, because they lack important information about the exercise intervention [9, 12], do not report recruitment and eligibility rates[14], include variability in disease invasiveness [10-14], have small sample sizes (18 to 107), and have substantial loss to follow-up (8% to 44%). As noted earlier, however, the most critical issue from our perspective is that these studies were conducted in the preoperative setting and focused on preparation for radical cystectomy [8-15]. To our knowledge, no studies have examined the feasibility, safety, and efficacy of exercise during intravesical therapy for NMIBC.

HIIT was selected as the exercise intervention in the BRAVE trial for several reasons. First, HIIT seems to be safe and efficient for improving cardiovascular and metabolic function in both healthy [46] and chronic illness population [47-50], including a variety types of cancers such as lung [51], colorectal with liver metastasis [52],

testicular [53], prostate [54, 55], colorectal [56, 57], breast [58], bladder [11], and mixed cancers [59, 60]. Second, HIIT is a good option to increase the amount of time spent in vigorous intensity during an exercise session [23], resulting in comparable or greater improvements in cardiorespiratory fitness when compared to traditional moderate continuous endurance training [46, 49, 61-64]. The evidence suggests a dose-response relationship between the physical activity intensity and cancer risk reduction [65, 66] and cancer mortality [67]. Exercise intensity mediates physiological adaptations related to the aerobic energy metabolism, such as metabolic signal and mitochondrial protein synthesis rate, that are greater at higher intensities of exercise when training volumes are equal to moderate continuous training, or similar when the volume of the interval training is inferior [68]. When compared to moderate-intensity continuous training, HIIT has the ability to maximize the benefits on cardiorespiratory fitness with larger improvements in the volume of oxygen consumption [68, 69], and higher levels of cardiorespiratory fitness are strongly related with a reduced risk of cancer mortality [70]. In addition, HIIT may be perceived to be as enjoyable or more enjoyable than moderate intensity continuous training due to the changing stimulus [71, 72].

Moreover, HIIT may play a therapeutic role in tumor recurrence and progression, attenuating inflammatory processes and modifying the tumor microenvironment [73]. Changes at the tumor microenvironment level may contribute to an optimal therapeutic response [74]. Lastly, HIIT may protect against treatment-related cardiotoxicity and cardiometabolic disease [73, 75]. For instance, in animal models with urothelial carcinoma and disease-related cardiac dysfunction, HIIT induced biological processes related to cardiac regenerative ability (e.g., ATP metabolism), highlighting the exercise-

related protective effect on cardiac function and providing insights on the beneficial effects of exercise training after bladder cancer diagnosis [76].

The BRAVE trial has several limitations including the modest sample size, the short-term follow-up, and the absence of a correlative (biological) component such as gene expression alterations potentially associated with bladder cancer recurrence and progression. The study is principally aimed at establishing safety and feasibility, and is underpowered to determine the efficacy of exercise on the most important clinical outcomes of tumor progression and recurrence. Moreover, the progression rate in this clinical setting is only 5% at 1 year, and the recurrence rate is 10%-30% depending on the treatment and disease stage [77]. We have included tumor recurrence and progression as an exploratory outcome in our trial primarily to demonstrate the feasibility of collecting such data at our site. We will also determine if there is any signal in the hypothesized direction (numerically superior) although we acknowledge that the likelihood of demonstrating a statistically significant effect is very low. This information will help inform the objectives and design of larger exercise trials in this clinical setting, should they be warranted.

The BRAVE trial has several strengths including the novel patient population, the randomised controlled trial design, the supervised exercise, and the comprehensive and valid assessment of important outcomes. It will be the first randomised controlled trial to test the safety and feasibility of any exercise intervention in NMIBC patients receiving intravesical therapy. The BRAVE trial will also provide preliminary evidence on whether exercise may improve health-related fitness and patient-reported outcomes during intravesical therapy. Finally, the BRAVE trial will establish if social cognitive variables

from the theory of planned behavior predict exercise adherence during intravesical therapy, which will inform strategies to maximize adherence in future trials. The BRAVE trial may inform larger phase II and III trials designed to test the efficacy of exercise on important clinical outcomes in this setting including quality of life, symptom management, progression, recurrence, and overall survival.

3.5 References

1. National Comprehensive Cancer Network [NCCN]. NCCN Clinical Practice Guidelines on Oncology: Bladder Cancer 2019.

2. Kassouf W, Traboulsi SL, Kulkarni GS, et al. CUA guidelines on the management of non-muscle invasive bladder cancer. *Can Urol Assoc J* 2015;9(9-10):E690-704. doi: 10.5489/cuaj.3320 [published Online First: 2015/10/13]

3. Fujii Y. Prediction models for progression of non-muscle-invasive bladder cancer: A review. *Int J Urol* 2018;25(3):212-18. doi: 10.1111/iju.13509 [published Online First: 2017/12/16]

4. Avritscher EBC, Cooksley CDG, B.Sabichi, A. L.Hamblin, L.Dinney, C. P.Elting, L. S. Clinical model of lifetime cost of treating bladder cancer and associated complications *Urology* 2006;68(3):549-53. doi: https://doi.org/10.1016/j.urology.2006.03.062

5. Smith AB, Jaeger B, Pinheiro LC, et al. Impact of bladder cancer on health-related quality of life. *BJU Int* 2018;121(4):549-57. doi: 10.1111/bju.14047 [published Online First: 2017/11/01]

6. Sturgeon KM, Deng L, Bluethmann SM, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J* 2019;40(48):3889-97. doi: 10.1093/eurheartj/ehz766

7. Liguori G, Feito Y, Fountaine C, et al. ACSM's G*uidelines for Exercise Testing and Prescription* . Eleventh edition ed. Philadelphia: Wolters Kluwer 2021.

8. Rammant E, Decaestecker K, Bultijnck R, et al. A systematic review of exercise and psychosocial rehabilitation interventions to improve health-related outcomes in patients

with bladder cancer undergoing radical cystectomy. *Clin Rehabil* 2018;32(5):594-606. doi: 10.1177/0269215517746472 [published Online First: 2017/12/12]

9. Banerjee S, Manley K, Thomas L, et al. O2 Preoperative exercise protocol to aid recovery of radical cystectomy: results of a feasibility study. *Eur Urol Suppl* 2013;12(6):125. doi: https://doi.org/10.1016/S1569-9056(13)62320-9

10. Jensen BT, Jensen JB, Laustsen S, et al. Multidisciplinary rehabilitation can impact on health-related quality of life outcome in radical cystectomy: secondary reported outcome of a randomized controlled trial. *J Multidiscip Healthc* 2014;7:301-11. doi: 10.2147/JMDH.S62172 [published Online First: 2014/07/16]

11. Banerjee S, Manley K, Shaw B, et al. Vigorous intensity aerobic interval exercise in bladder cancer patients prior to radical cystectomy: a feasibility randomised controlled trial. *Support Care Cancer* 2018;26(5):1515-23. doi: 10.1007/s00520-017-3991-2 [published Online First: 2017/11/27]

12. Porserud A, Sherif A, Tollbäck A. The effects of a physical exercise programme after radical cystectomy for urinary bladder cancer. A pilot randomized controlled trial. *Clin Rehabil* 2014;28(5):451-9. doi: 10.1177/0269215513506230 [published Online First: 2013/11/18]

13. Jensen BT, Petersen AK, Jensen JB, et al. Efficacy of a multiprofessional rehabilitation programme in radical cystectomy pathways: a prospective randomized controlled trial. *Scand J Urol* 2015;49(2):133-41. doi: 10.3109/21681805.2014.967810 [published Online First: 2014/10/21]

14. Jensen BT, Laustsen S, Jensen JB, et al. Exercise-based pre-habilitation is feasible and effective in radical cystectomy pathways-secondary results from a randomized

controlled trial. *Support Care Cancer* 2016;24(8):3325-31. doi: 10.1007/s00520-016-3140-3 [published Online First: 2016/03/10]

15. Minnella EM, Awasthi R, Bousquet-Dion G, et al. Multimodal Prehabilitation to Enhance Functional Capacity Following Radical Cystectomy: A Randomized Controlled Trial. *Eur Urol Focus* 2019;7(1):132-38. doi: 10.1016/j.euf.2019.05.016 [published Online First: 2019/06/08]

16. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi: 10.1136/bmj.e7586 [published Online First: 2013/01/08]

17. Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ* 2016;355:i5239. doi: 10.1136/bmj.i5239 [published Online First: 20161024]

18. Warburton DE, Jamnik VK, Bredin SS, et al. The 2011 Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and the Electronic Physical Activity Readiness Medical Examination (ePARmed-X+): Heal Fit J Canada, 2011.

19. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin* 2012;62(4):243-74. doi: 10.3322/caac.21142 [published Online First: 2012/04/26]

20. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010;42(7):1409-26. doi: 10.1249/MSS.0b013e3181e0c112

21. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. *Can J Appl Sport Sci* 1985;10(3):141-6.

22. Surveillance & Reporting. The 2019 Report on Cancer Statistics in Alberta Edmonton: CancerControl Alberta,, Alberta Health Services; 2019 [Available from: https://public.tableau.com/profile/cancercontrol.ab#!/vizhome/The2019ReportonCancerStatisticsinAlberta/Highlights?publish=yes accessed September 7 2020.

23. Riebe D, Ehrman JK, Liguori G, et al. ACSM's G*uidelines for Exercise Testing and Prescription* . . Tenth edition ed. Philadelphia: Wolters Kluwer 2018.

24. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;43(7):1334-59. doi: 10.1249/MSS.0b013e318213fefb

25. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14(5):377-81.

26. McInnis KJ, Balady GJ. Comparison of submaximal exercise responses using the Bruce vs modified Bruce protocols. *Med Sci Sports Exerc* 1994;26(1):103-7.

27. Society AT, Physicians ACoC. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167(2):211-77. doi: 10.1164/rccm.167.2.211

28. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol (1985)* 1986;60(6):2020-7. doi: 10.1152/jappl.1986.60.6.2020

29. Jones CJ, Rikli RE. Measuring Functional: The journal on active aging; 2002 [Available from:

https://www.um.es/desarrollopsicomotor/wq/2010/wqcarrasco2010/BL22_files/Senior%20Fitness%20Test_Rikli02.pdf accessed May 17th, 2020.

30. Gonzalez MC, Mehrnezhad A, Razaviarab N, et al. Calf circumference: cutoff values from the NHANES 1999-2006. *Am J Clin Nutr* 2021;113(6):1679-87. doi: 10.1093/ajcn/nqab029

31. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365-76. doi: 10.1093/jnci/85.5.365

32. Blazeby JM, Hall E, Aaronson NK, et al. Validation and reliability testing of the EORTC QLQ-NMIBC24 questionnaire module to assess patient-reported outcomes in non-muscle-invasive bladder cancer. *Eur Urol* 2014;66(6):1148-56. doi: 10.1016/j.eururo.2014.02.034 [published Online First: 2014/02/25]

33. Simard S, Savard J. Fear of Cancer Recurrence Inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence. *Support Care Cancer* 2009;17(3):241-51. doi: 10.1007/s00520-008-0444-y [published Online First: 2008/04/15]

34. Spielberger CD. State-Trait anxiety inventory. Wiley Online Library, 2010.

35. Lewinsohn PM, Seeley JR, Roberts RE, et al. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging* 1997;12(2):277-87. doi: 10.1037//0882-7974.12.2.277

36. Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;13(2):63-74. doi: 10.1016/s0885-3924(96)00274-6

37. Cohen S, Kamarck T, Mermelstein R. Perceived stress scale. Measuring stress: a guide for health and social scientists., 1994.

38. Rosenberg M. Rosenberg self-esteem scale (RSE). Acceptance and commitment therapy Measures package . 1965.

39. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2(4):297-307. doi: 10.1016/s1389-9457(00)00065-4

40. Ajzen I. The theory of planned behavior Organ Behav Hum Decis Process 1991:179-211.

41. Borm GF, Fransen J, Lemmens WA. A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol* 2007;60(12):1234-8. doi: 10.1016/j.jclinepi.2007.02.006 [published Online First: 2007/06/06]

42. Royston P. Multiple imputation of missing values. Stata journal., 2004:227-41.

43. Armijo-Olivo S, Warren S, Magee D. Intention to treat analysis, compliance, dropouts and how to deal with missing data in clinical research: a review. *Physical Therapy Reviews* 2009;14(1):36-49.

44. Zuniga KB, Graff RE, Feiger DB, et al. Lifestyle and Non-muscle Invasive Bladder Cancer Recurrence, Progression, and Mortality: Available Research and Future Directions. *Bladder Cancer* 2020;6:9-23. doi: 10.3233/BLC-190249

45. Bowen DJ, Kreuter M, Spring B, et al. How we design feasibility studies. *Am J Prev Med* 2009;36(5):452-7. doi: 10.1016/j.amepre.2009.02.002

46. Milanović Z, Sporiš G, Weston M. Effectiveness of High-Intensity Interval Training (HIT) and Continuous Endurance Training for VO2max Improvements: A Systematic Review and Meta-Analysis of Controlled Trials. *Sports Med* 2015;45(10):1469-81. doi: 10.1007/s40279-015-0365-0

47. Batacan RB, Duncan MJ, Dalbo VJ, et al. Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. *Br J Sports Med* 2017;51(6):494-503. doi: 10.1136/bjsports-2015-095841 [published Online First: 2016/10/20]

48. Wewege MA, Ahn D, Yu J, et al. High-Intensity Interval Training for Patients With Cardiovascular Disease-Is It Safe? A Systematic Review. *J Am Heart Assoc* 2018;7(21):e009305. doi: 10.1161/JAHA.118.009305

49. Blackwell JEM, Doleman B, Herrod PJJ, et al. Short-Term (<8 wk) High-Intensity Interval Training in Diseased Cohorts. *Med Sci Sports Exerc* 2018;50(9):1740-49. doi: 10.1249/MSS.0000000000001634

50. Wallen MP, Hennessy D, Brown S, et al. High-intensity interval training improves cardiorespiratory fitness in cancer patients and survivors: A meta-analysis. *Eur J Cancer Care (Engl)* 2020;29(4):e13267. doi: 10.1111/ecc.13267 [published Online First: 2020/05/29]

51. Licker M, Karenovics W, Diaper J, et al. Short-Term Preoperative High-Intensity Interval Training in Patients Awaiting Lung Cancer Surgery: A Randomized Controlled

Trial. *J Thorac Oncol* 2017;12(2):323-33. doi: 10.1016/j.jtho.2016.09.125 [published Online First: 2016/10/19]

52. Dunne DF, Jack S, Jones RP, et al. Randomized clinical trial of prehabilitation before planned liver resection. *Br J Surg* 2016;103(5):504-12. doi: 10.1002/bjs.10096 [published Online First: 2016/02/11]

53. Adams SC, DeLorey DS, Davenport MH, et al. Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: A phase 2 randomized controlled trial. *Cancer* 2017;123(20):4057-65. doi: 10.1002/cncr.30859 [published Online First: 2017/07/14]

54. Kang DW, Fairey AS, Boulé NG, et al. Exercise duRing Active Surveillance for prostatE cancer-the ERASE trial: a study protocol of a phase II randomised controlled trial. *BMJ Open* 2019;9(7):e026438. doi: 10.1136/bmjopen-2018-026438 [published Online First: 2019/07/04]

55. Kang DW, Fairey AS, Boulé NG, et al. Effects of Exercise on Cardiorespiratory Fitness and Biochemical Progression in Men With Localized Prostate Cancer Under Active Surveillance: The ERASE Randomized Clinical Trial. *JAMA Oncol* 2021 doi: 10.1001/jamaoncol.2021.3067 [published Online First: 20210819]

56. Devin JL, Sax AT, Hughes GI, et al. The influence of high-intensity compared with moderate-intensity exercise training on cardiorespiratory fitness and body composition in colorectal cancer survivors: a randomised controlled trial. *J Cancer Surviv* 2016;10(3):467-79. doi: 10.1007/s11764-015-0490-7 [published Online First: 2015/10/19]

57. Morielli AR, Usmani N, Boulé NG, et al. Exercise during and after neoadjuvant rectal cancer treatment (the EXERT trial): study protocol for a randomized controlled trial. *Trials* 2018;19(1):35. doi: 10.1186/s13063-017-2398-1 [published Online First: 2018/01/12]

58. Schulz SVW, Laszlo R, Otto S, et al. Feasibility and effects of a combined adjuvant high-intensity interval/strength training in breast cancer patients: a single-center pilot study. *Disabil Rehabil* 2018;40(13):1501-08. doi: 10.1080/09638288.2017.1300688 [published Online First: 2017/03/21]

59. Schmitt J, Lindner N, Reuss-Borst M, et al. A 3-week multimodal intervention involving high-intensity interval training in female cancer survivors: a randomized controlled trial. *Physiol Rep* 2016;4(3) doi: 10.14814/phy2.12693

60. Blackwell JEM, Doleman B, Boereboom CL, et al. High-intensity interval training produces a significant improvement in fitness in less than 31 days before surgery for urological cancer: a randomised control trial. *Prostate Cancer Prostatic Dis* 2020;23(4) doi: 10.1038/s41391-020-0219-1 [published Online First: 2020/03/10]

61. Ramos JS, Dalleck LC, Tjonna AE, et al. The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. *Sports Med* 2015;45(5):679-92. doi: 10.1007/s40279-015-0321-z

62. Williams CJ, Gurd BJ, Bonafiglia JT, et al. A Multi-Center Comparison of O. *Front Physiol* 2019;10:19. doi: 10.3389/fphys.2019.00019 [published Online First: 2019/02/05]

63. Wen D, Utesch T, Wu J, et al. Effects of different protocols of high intensity interval training for VO. *J Sci Med Sport* 2019;22(8):941-47. doi: 10.1016/j.jsams.2019.01.013 [published Online First: 2019/01/29]

64. Taylor JL, Holland DJ, Keating SE, et al. Short-term and Long-term Feasibility, Safety, and Efficacy of High-Intensity Interval Training in Cardiac Rehabilitation: The FITR Heart Study Randomized Clinical Trial. *JAMA Cardiol* 2020 doi: 10.1001/jamacardio.2020.3511 [published Online First: 2020/09/02]

65. Brown J, Winters-Stone K, Lee A, et al. Cancer, Physical Activity, and Exercise. 2012;2(4):2775–809. doi: 10.1002/cphy.c120005

66. Matthews CE, Moore SC, Arem H, et al. Amount and Intensity of Leisure-Time Physical Activity and Lower Cancer Risk. *J Clin Oncol* 2020;38(7):686-97. doi: 10.1200/JCO.19.02407 [published Online First: 2019/12/26]

67. Davey Smith G, Shipley MJ, Batty GD, et al. Physical activity and cause-specific mortality in the Whitehall study. *Public Health* 2000;114(5):308-15. doi: 10.1038/sj.ph.1900675

68. MacInnis MJ, Gibala MJ. Physiological adaptations to interval training and the role of exercise intensity. *J Physiol* 2017;595(9):2915-30. doi: 10.1113/JP273196 [published Online First: 2016/12/07]

69. Helgerud J, Høydal K, Wang E, et al. Aerobic high-intensity intervals improve VO2max more than moderate training. *Med Sci Sports Exerc* 2007;39(4):665-71. doi: 10.1249/mss.0b013e3180304570

70. Schmid D, Leitzmann MF. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. *Ann Oncol* 2015;26(2):272-8. doi: 10.1093/annonc/mdu250 [published Online First: 2014/07/09]

71. Olney N, Wertz T, LaPorta Z, et al. Comparison of Acute Physiological and Psychological Responses Between Moderate-Intensity Continuous Exercise and Three Regimes of High-Intensity Interval Training. *J Strength Cond Res* 2018;32(8):2130-38. doi: 10.1519/JSC.0000000000002154

72. Thum JS, Parsons G, Whittle T, et al. High-Intensity Interval Training Elicits Higher Enjoyment than Moderate Intensity Continuous Exercise. *PLoS One* 2017;12(1):e0166299. doi: 10.1371/journal.pone.0166299 [published Online First: 2017/01/11]

73. Papadopoulos E, Santa Mina D. Can we HIIT cancer if we attack inflammation? *Cancer Causes Control* 2018;29(1):7-11. doi: 10.1007/s10552-017-0983-y [published Online First: 2017/11/21]

74. Annels NE, Simpson GR, Pandha H. Modifying the Non-muscle Invasive Bladder Cancer Immune Microenvironment for Optimal Therapeutic Response. *Front Oncol* 2020;10:175. doi: 10.3389/fonc.2020.00175 [published Online First: 2020/02/18]

75. Campbell WW, Kraus WE, Powell KE, et al. High-Intensity Interval Training for Cardiometabolic Disease Prevention. *Med Sci Sports Exerc* 2019;51(6):1220-26. doi: 10.1249/MSS.0000000000001934

76. Ferreira R, Neuparth MJ, Nogueira-Ferreira R, et al. Exercise Training Impacts Cardiac Mitochondrial Proteome Remodeling in Murine Urothelial Carcinoma. *Int J Mol Sci* 2018;20(1) doi: 10.3390/ijms20010127 [published Online First: 2018/12/31]

77. Kamat AM, Sylvester RJ, Böhle A, et al. Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. *J Clin Oncol* 2016;34(16):1935-44. doi: 10.1200/JCO.2015.64.4070 [published Online First: 2016/01/25]

Table 3-1. Outcomes measures and assessment time points of the BRAVE trial

Outcome	Instrument	Pre-Intravesical Therapy (baseline)	Post-Intravesical Therapy (6-weeks)	Post-Intervention/ Pre-cystoscopy (3-months)	Follow-up (12-months)
Cardiorespiratory fitness	Cardiopulmonary Exercise Test	X	X	X	
Physical Functioning					
Lower body strength	30-second chair stand	X	X	X	
Upper body strength	Arm curl	X	X	X	
Flexibility	Chair sit-and-reach and back scratch	X	X	X	
Agility	8-foot up-and-go	X	X	X	
Aerobic endurance	6-minute walk	X	X	X	
Anthropometry and body composition	BMI and circumferences	X	X	X	
Patient reported-outcomes					
Health-related quality of Life	EORTC QLQ-C30 and EORTC NMIBC C24	X		X	X
Fear of cancer recurrence	9-item Fear of Cancer Recurrence Inventory	X		X	X
Anxiety	10-item State-trait anxiety inventory	X		X	X
Depression	10-item CES-D	X		X	X
Fatigue	FACIT - Fatigue scale	X		X	X
Stress	14-item Perceived Stress Scale	X		X	X
Self-esteem	Rosenberg Self-esteem Scale	X		X	X
Sleep quality	Insomnia Severity Index	X		X	X
Behavioural Outcomes					
Social cognitive variables	Theory of Planned Behavior constructs	X		X	X
Physical activity level	Godin Leisure-time questionnaire	X		X	X
Cancer-related outcomes					
Intravesical therapy adherence	Medical Records		X		
Intravesical therapy toxicity	Medical Records		X		
Tumour recurrence and progression	Cystoscopy			X	X
Baseline descriptive variables					
Sociodemographic details	Participant self-report	X			
Medical information	Medical Records	X			

EORTC QLQ-C 30: European Organization for Research and Treatment of Cancer core 30-item questionnaire; EORTC NMIBC C24: European Organization for Research and Treatment of Cancer for non-muscle invasive bladder cancer 24-item; CES-D: Center for Epidemiologic Studies Depression Scale; FACIT: Functional Assessment of Cancer Therapy; BMI: body mass index

Figure 3-1

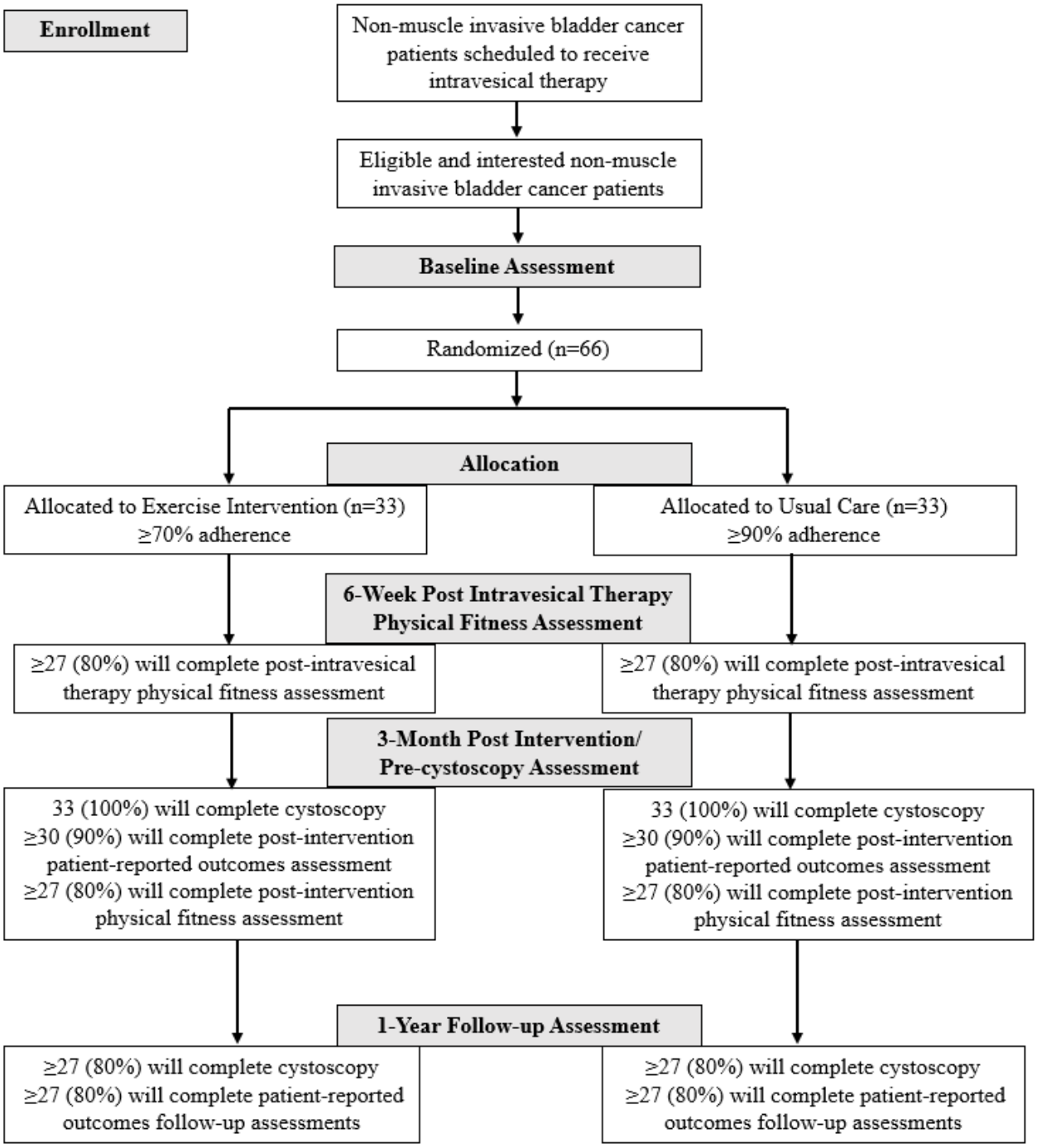

Enrollment
Non-muscle invasive bladder cancer patients scheduled to receive intravesical therapy
Eligible and interested non-muscle invasive bladder cancer patients
Baseline Assessment
Randomized (n=66)
Allocation
Allocated to Exercise Intervention (n=33)
≥70% adherence
Allocated to Usual Care (n=33)
≥90% adherence
6-Week Post Intravesical Therapy Physical Fitness Assessment
≥27 (80%) will complete post-intravesical therapy physical fitness assessment
≥27 (80%) will complete post-intravesical therapy physical fitness assessment
3-Month Post Intervention/ Pre-cystoscopy Assessment
33 (100%) will complete cystoscopy
≥30 (90%) will complete post-intervention patient-reported outcomes assessment
≥27 (80%) will complete post-intervention physical fitness assessment
33 (100%) will complete cystoscopy
≥30 (90%) will complete post-intervention patient-reported outcomes assessment
≥27 (80%) will complete post-intervention physical fitness assessment
1-Year Follow-up Assessment
≥27 (80%) will complete cystoscopy
≥27 (80%) will complete patient-reported outcomes follow-up assessments
≥27 (80%) will complete cystoscopy
≥27 (80%) will complete patient-reported outcomes follow-up assessments

Figure 3-2

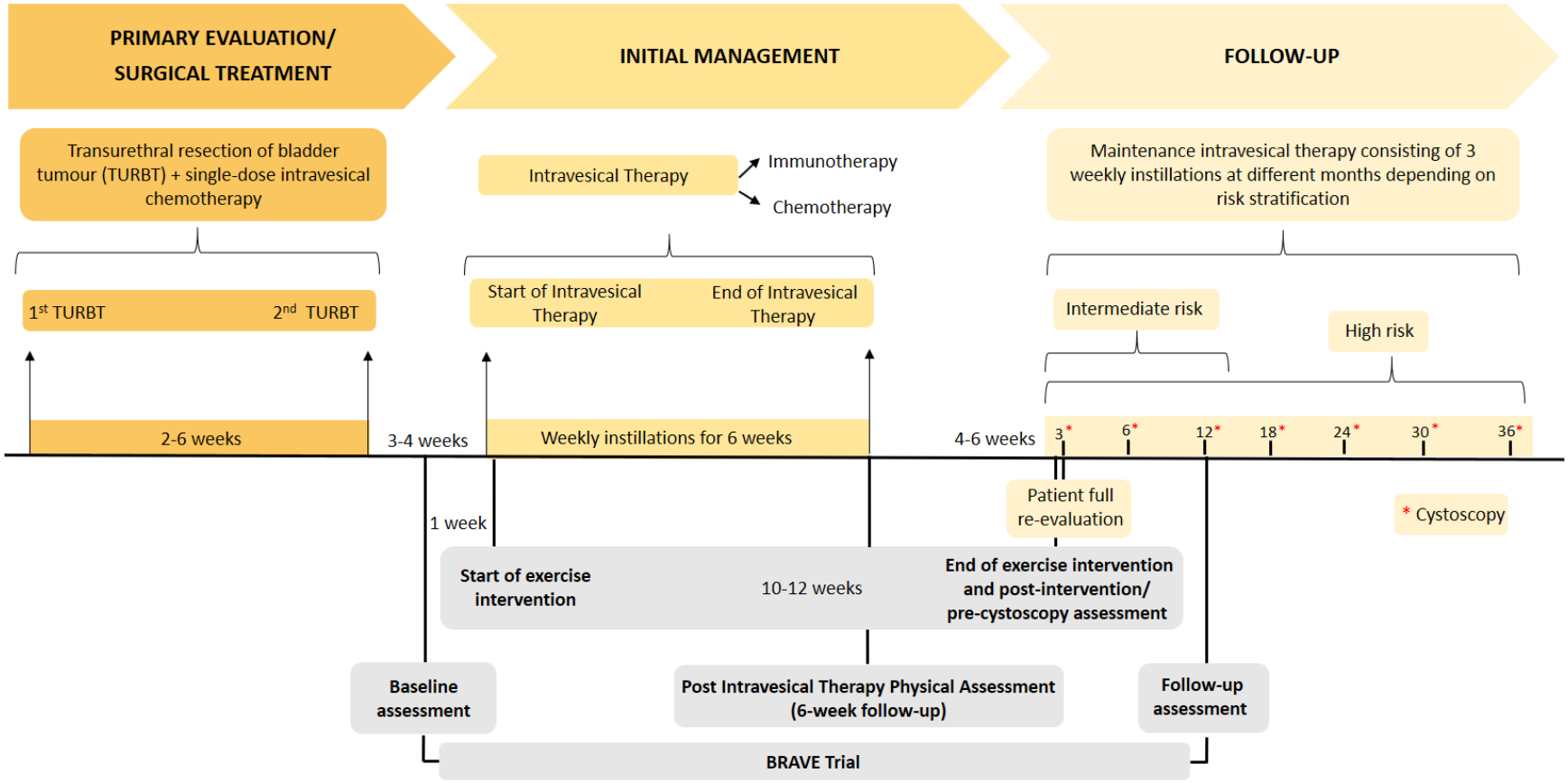

PRIMARY EVALUATION/ SURGICAL TREATMENT
INITIAL MANAGEMENT
FOLLOW-UP
Transurethral resection of bladder tumour (TURBT) + single-dose intravesical chemotherapy
Intravesical Therapy
Immunotherapy
Chemotherapy
Maintenance intravesical therapy consisting of 3 weekly instillations at different months depending on risk stratification
1st TURBT
2nd TURBT
Start of Intravesical Therapy
End of Intravesical Therapy
Intermediate risk
High risk
2-6 weeks
3-4 weeks
Weekly instillations for 6 weeks
4-6 weeks
3*
6*
12*
18*
24*
30*
36*
Patient full re-evaluation
* Cystoscopy
1 week
Start of exercise intervention
10-12 weeks
End of exercise intervention and post-intervention/ pre-cystoscopy assessment
Baseline assessment
Post Intravesical Therapy Physical Assessment (6-week follow-up)
Follow-up assessment
BRAVE Trial

Figure 3-3

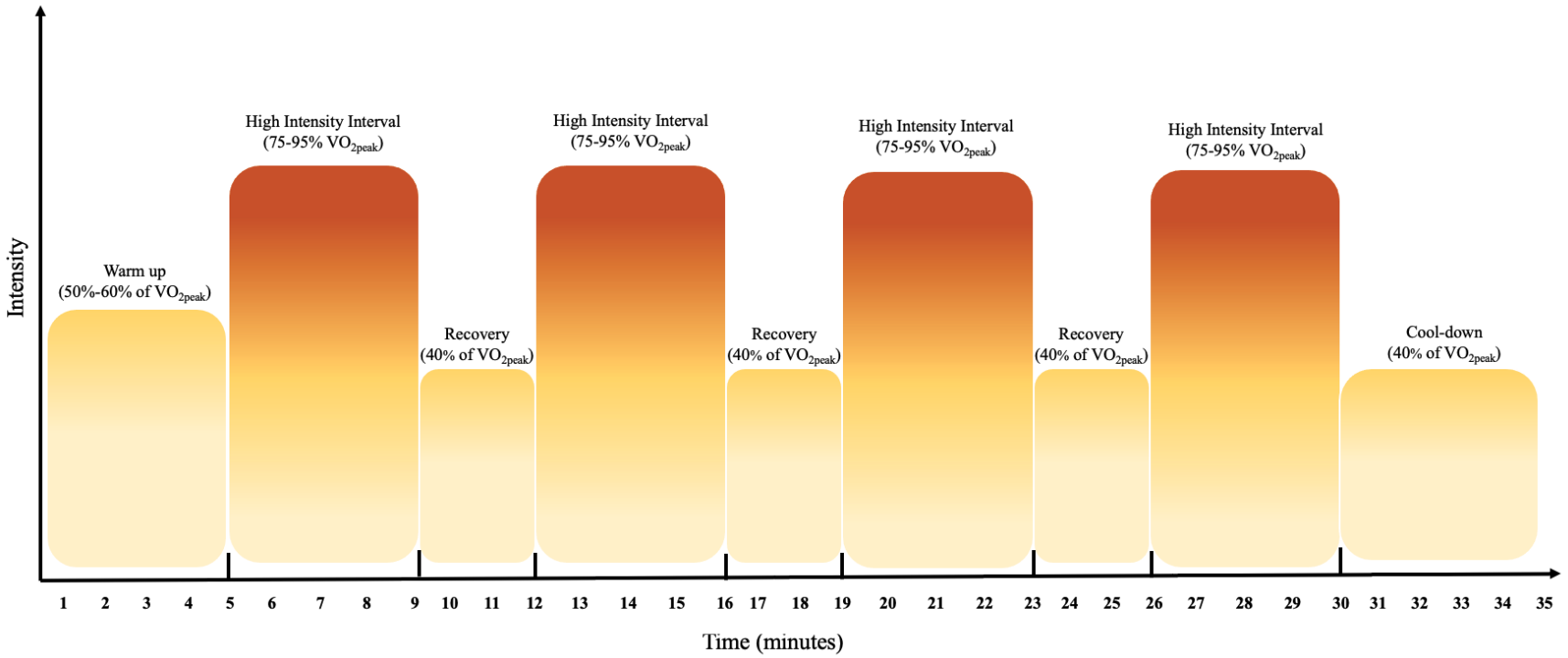
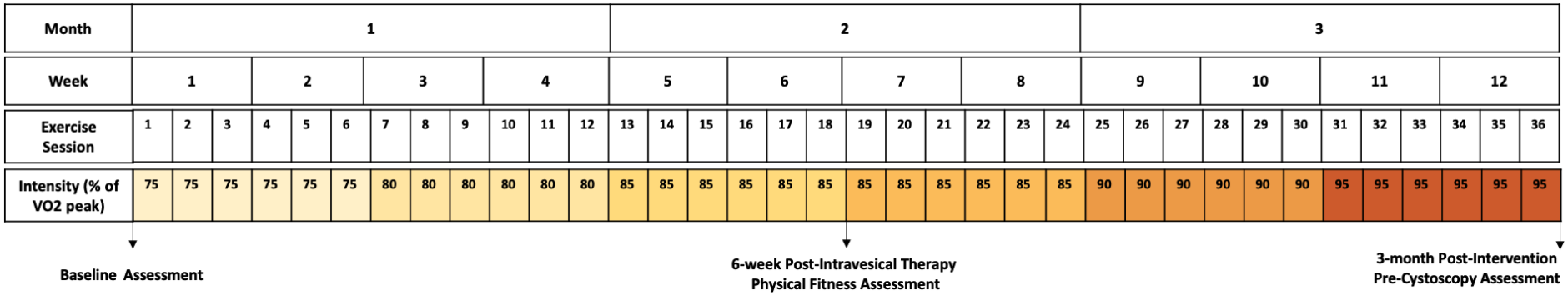

Intensity
Warm up
(50%-60% of VO_{2peak})
High Intensity Interval
(75-95% VO_{2peak})
Recovery
(40% of VO_{2peak})
High Intensity Interval
(75-95% VO_{2peak})
Recovery
(40% of VO_{2peak})
High Intensity Interval
(75-95% VO_{2peak})
Recovery
(40% of VO_{2peak})
High Intensity Interval
(75-95% VO_{2peak})
Cool-down
(40% of VO_{2peak})
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
Time (minutes)

Figure 3-4


Month
1
2
3
Week
1
2
3
4
5
6
7
8
9
10
11
12
Exercise Session
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
Intensity (% of VO2 peak)
75 75 75 75 75 75 80 80 80 80 80 80 85 85 85 85 85 85 85 85 85 85 85 85 90 90 90 90 90 90 95 95 95 95 95 95
Baseline Assessment
6-week Post-Intravesical Therapy Physical Fitness Assessment
3-month Post-Intervention Pre-Cystoscopy Assessment

CHAPTER 4: PAPER 3

Feasibility, safety, and preliminary efficacy of high-intensity interval training during or after intravesical therapy for bladder cancer patients

4.1 Abstract

Background: Standard treatment for non-muscle invasive bladder cancer (NMIBC) is tumor resection followed by 6 weeks of induction intravesical therapy and 1-3 years of maintenance intravesical therapy. NMIBC has a high rate of recurrence (15-40%) and progression (1-10%), making it one of the most distressing and expensive cancers to treat. NMIBC and its treatment affects patient functioning and quality of life. High-intensity interval training (HIIT) is beneficial for many chronic diseases including cancer, however, no studies have examined HIIT for NMIBC. The primary aim of the BRAVE trial was to evaluate the feasibility and safety of HIIT in NMIBC patients during or after intravesical therapy. A secondary aim was to assess the preliminary efficacy of HIIT on cardiorespiratory fitness and physical functioning. **Methods:** Patients scheduled to receive intravesical treatment or on surveillance after intravesical treatment for NMIBC were randomly assigned to usual care (n=8) or HIIT (n=13). The HIIT group performed thrice-weekly, supervised HIIT at 75-95% of peak cardiorespiratory fitness (VO_{2peak}) for 12 weeks. **Results:** In 24 months, 224 patients were screened, 129 (57.6%) were eligible, and 21 (16.3%) were randomized. Median exercise attendance was 100% and VO_{2peak} was achieved by 71% to 82% of the participants during assessments at different time points. VO_{2peak} increased from baseline to 12 weeks by 1.2 ml/kg/min in the HIIT group but was not significantly higher than the usual care group (adjusted between-group mean difference, 1.4 ml/kg/min; 95%CI: -1.8 to 4.7; p=0.33). Compared to the usual care group at 12 weeks, the HIIT group significantly improved six-minute walk distance (adjusted between-group mean difference, 43 meters; 95%CI: 4 to 82; p=0.034) and the timed 8-foot up-and-go (adjusted between-group mean difference, -1.1 seconds; 95%CI: -2.2 to -0.1; p=0.039). **Conclusion:** Despite limited accrual, the BRAVE trial demonstrated that HIIT during or after intravesical therapy was feasible and safe

for NMIBC patients and resulted in significant improvements in several indicators of physical functioning. Additional feasibility studies are necessary to establish the safety, applicability, and tolerability of different fitness assessment protocols in this understudied and challenging patient population and setting.

4.2 Introduction

Bladder cancer is the 9th most commonly diagnosed cancer globally [1] and the 5th in Canada [2] with the majority of patients (>75%) being diagnosed with non-muscle invasive bladder cancer (NMIBC). Transurethral resection of the bladder tumor (TURBT) followed by intravesical therapy is the standard treatment for NMIBC [3]. The TURBT is essential to determine tumor grade and stage, and to treat low-risk bladder cancer tumors, while intravesical therapy is used to prevent tumor recurrence and progression [3]. Intravesical therapy regimens usually include an induction phase, which consists of 6 weeks of immunotherapy or chemotherapy, which may be followed by a maintenance phase consisting of intermittent therapy for one to three years [3, 4].

NMIBC has a high rate of recurrence (15-40%) and progression (1-10%) [5], leading to frequent medical follow-ups and extended periods of treatment, making it one of the most distressing and expensive cancers to treat [6]. NMIBC and its treatments affect patient functioning and quality of life [7, 8]. Intravesical therapy can trigger bladder symptoms such as dysuria and hematuria, and systemic side effects including flu-like symptoms, body aches, and fatigue [9, 10]. Moreover, patients with bladder cancer are at an increased risk of death from cardiovascular diseases compared to other cancer populations [11]. Interventions aimed to reduce the burden of bladder cancer and potentially improve clinical, patient-reported, and health-related outcomes are warranted [12].

Exercise is an intervention that benefits many cancer patient groups. Cancer-specific physical activity and exercise guidelines [13-15] were created based on the evidence that exercise improves cardiorespiratory fitness, strength, fatigue, physical functioning, quality of life, and possibly survival [16]. Moreover, exercise is emerging as a possible adjuvant and

maintenance cancer therapy to treat known or suspected micrometastases [17] by promoting biological and hemodynamics adaptations associated with tumor cell growth suppression [18, 19]. The impact, however, of exercise interventions on bladder cancer patients is understudied. Research conducted to date [20-26] is limited to patients with advanced stages of bladder cancer in the pre- and/or post-operative cystectomy setting [27]. Trials providing insights into the feasibility and effects of exercise in different treatments and stages of bladder cancer are needed before incorporating it into exercise guidelines and making clinical recommendations [28]. To date, no studies have examined the safety, feasibility, and efficacy (benefits and harms) of exercise during or after intravesical therapy for NMIBC.

The primary aim of the Bladder cancer and exeRcise trAining during or after intraVesical thErapy (BRAVE) trial was to determine the feasibility and safety of exercise in NMIBC patients during or after intravesical therapy. A secondary aim was to examine the preliminary efficacy of exercise on cardiorespiratory fitness and physical functioning. We hypothesized that exercise during and/or after intravesical therapy for NMIBC would be feasible, safe, and produce meaningful improvements in health-related fitness outcomes.

4.3 Methods

Study Design

The BRAVE trial protocol has been reported elsewhere [29]. Briefly, BRAVE was planned as a phase II, prospective, two-armed, randomized controlled trial conducted at the University of Alberta, Edmonton, Canada (Clinical Trial Registration #NCT04593862). The BRAVE trial was approved by the Health Research Ethics Board of Alberta-Cancer Committee. The trial is reported in line with the Consolidated Standards of Reporting Trials (CONSORT) extension to randomized pilot and feasibility trials [30].

Participants and Procedures

Participants were recruited from the Northern Alberta Urology Centre at the Kaye Edmonton Clinic in Edmonton, Alberta, Canada between May 24, 2021, and May 31, 2023. Patients scheduled to receive intravesical treatment or on surveillance after intravesical treatment for NMIBC were pre-screened via electronic medical records. Potentially eligible participants were approached by their urologists during checkup visits to request permission for the researcher coordinator to contact them. The study coordinator approached agreeable potential participants to inquire about their interest in participating in the study, assess further eligibility criteria, and obtain consent for study enrollment. Written informed consent was obtained from all individual participants included in the study before enrollment.

Eligible participants included include men and women who (1) were ≥18 years old, (2) had a confirmed diagnosis of NMIBC (clinical stage cis, Ta or T1), (3) were scheduled for induction intravesical therapy, and (4) living in Edmonton or surrounding area within 40 kilometers of the fitness center. As a consequence of slower-than-expected accrual, eligibility criteria were expanded after 2 months of recruitment to patients in the maintenance phases and then to the surveillance phases after 10 months of recruitment. Participants were excluded if they: (1) were not medically cleared to participate in the exercise intervention, (2) had contraindications for cardiopulmonary stress and/or physical fitness tests, (3) were already meeting the exercise guidelines for cancer survivors, (4) were unable to read and comprehend English, and (5) were not willing to be randomized to a supervised exercise training program or usual care for 12 weeks.

We aimed to schedule eligible participants for baseline assessments at least one week before their intravesical instillation if on induction or maintenance phase, or within about four

months of their next scheduled follow-up cystoscopy if on surveillance. After completion of baseline testing, participants were randomized to either the exercise group or the usual care group in a 1:1 ratio. Participants were randomized in block sizes of four or six by computer-generated randomization, stratified by their current treatment protocol (TURBT + single instillation, TURBT + induction phase, TURBT + induction + maintenance phase, or surveillance). The allocation sequence was generated independently and concealed from the study coordinator who assigned participants to groups. Participants and interventionists were not blinded to group assignment. Outcome assessors were not blinded to group assignment for the feasibility, health-related fitness, and patient-reported outcome assessments; however, they were blinded for clinical outcomes assessments (i.e., cystoscopy outcomes).

Intervention

The details of the intervention have been reported elsewhere [29]. Briefly, participants allocated to the exercise group were asked to complete a 12-week individualized high-intensity interval training (HIIT) program. We chose a HIIT intervention because of its potential safety, feasibility, and efficacy for optimizing cardiovascular fitness in other cancer populations [31, 32]. The program started within a week of the baseline assessments and consisted of thrice-weekly supervised sessions of 35 minutes duration.

The exercise sessions were prescribed at a workload corresponding to a determined percentage (75%-95%) of the peak oxygen consumption (VO_{2peak}) achieved at the baseline and 6-week assessment. The criteria for achieving a valid VO_{2peak} test included at least two of the following: a respiratory exchange ratio ≥ 1.10; heart rate peak within 10 beats per minute of the predicted maximum heart rate (208-07*age) or failure of heart rate increase with increases in

workload for those with Ischemic Heart Disease; and rated perceived exertion ≥ 7 (on a 0-10 scale, with 0 indicating no exertion at all and 10 indicating maximum exertion) [33].

Each exercise session was planned to include a five-minute warm-up at a workload corresponding to 60% of the VO_{2peak}, four bouts of four minutes (4x4 minutes) at a workload corresponding to vigorous intensity (75% to 95% of the VO_{2peak}) alternating with a 3-minute of recovery intervals at a workload corresponding to 40% of the VO_{2peak}, and a five-minute cool-down at a workload corresponding to 40% of the VO_{2peak}. Progression was gradual with changes in the intensity by 5% every two weeks for the first 6 weeks (75% to 85%VO_{2peak} of the baseline assessment), and 5% every two weeks following the 6-week assessment (85% to 95%VO_{2peak} of the 6-week assessment). Participants in the HIIT group who were symptom-limited and did not reach the criteria for a valid VO_{2peak} test had the exercise prescription based on the 30-second average of the VO_2 achieved during the baseline and 6-week assessment with adjustments based on rate of perceived exertion to match the initial planned exercise prescription (somewhat strong to very strong, RPE 4-7 in 0 to 10 scale).

The missed sessions were rescheduled if the participant was willing and if the session was completed before the follow-up cystoscopy exam. Although not planned in the protocol, some participants required assessments and intervention on a cycle ergometer instead of the treadmill due to mobility and balance issues. Participants received the HIIT intervention on the same modality on which they were tested. Treadmill speed and grade, or pedal frequency and resistance of the cycle ergometer, were selected to match the targeted percentage of $\dot{V}O_{2peak}$ (or VO_2, if not a peak value) based on the baseline and the 6-week fitness levels using standardized equations [33].

Participants randomized to the usual care group were asked not to increase their current exercise levels for the duration of the intervention. After the post-intervention fitness assessments and the follow-up cystoscopy, the usual care group was offered a 4-week supervised HIIT program at our facility and/or referred to a 12-week community-based exercise program.

Outcomes Measures

Outcomes were measured at four assessment time points based on the original plan to recruit patients starting 6-week induction intravesical therapy: baseline (pre-intravesical therapy), 6-week (or post-intravesical therapy), pre-cystoscopy/post-intervention (12-week), and 1-year follow-up. Health-related fitness outcomes were assessed at baseline, post-intravesical therapy, and post-intervention. Patient-reported outcomes and social cognitive predictors of exercise adherence were assessed at baseline, post-intervention (12-week), and 1-year follow-up. Tumor recurrence and progression were assessed at post-intervention (follow-up surveillance cystoscopy) and 1-year follow-up (1-year surveillance cystoscopy).

Primary Outcome

The primary outcome of the BRAVE trial was feasibility and safety. Feasibility was evaluated by the eligibility rate (and reasons for ineligibility), recruitment rate (and reasons for declining), participation rate (combined eligibility and recruitment rate), VO_{2peak} achievement rate (and reasons for test termination without achieving VO_{2peak} criteria), adherence rate to the HIIT (including reasons for dose modification and exercise interruption), and follow-up assessment rates (and reasons for dropout) for both exercise intervention and usual care groups.

The eligibility rate was measured as the percentage of patients who were eligible out of the number who met our inclusion criteria. The recruitment rate was defined as the percentage of randomized participants out of the number of eligible patients. The participation rate was defined

as the percentage of randomized participants out of the total number of patients who met our inclusion criteria. Although not planned in the original protocol, we opted to incorporate VO_{2peak} achievement rates as a feasibility outcome. This decision was influenced by the fact that changes in VO_{2peak} is a common metric for calculating sample sizes in exercise oncology trials, including our own. The VO_{2peak} achievement rate was defined as the number of participants who completed the test and met the VO_{2peak} criteria out of the number of participants who attempted the test.

Adherence to the exercise program was measured by attendance rates (defined by the percentage of exercise sessions attended out of the total number of sessions prescribed) and exercise prescription compliance (defined by the percentage of exercise sessions completed without dose modifications out of the total number of sessions attended). Reasons for not completing the exercise session or for dose adjustments were recorded. The follow-up assessment rate was determined by the number of participants who completed the post-intervention or follow-up assessments for each of the outcomes. Criteria for the feasibility and follow-up assessment rates were established a priori and reported elsewhere [29]. Briefly, we proposed a 50% eligibility rate, a 25% recruitment rate, 12.5% participation rate, 100% VO_{2peak} achievement rate, ≥ 70% exercise adherence, ≥ 80% follow-up fitness assessment completion rates at 6 weeks and 12 weeks, ≥ 90% patient-reported outcomes completion rate at 12 weeks and one-year follow-up, and a 100% follow-up cystoscopy rate.

Safety was assessed by patient-reported and observed adverse events during the fitness assessments or exercise sessions. Participants in the HIIT group were questioned at each supervised session about any adverse event experience during and/or between sessions. Details of the adverse event were recorded by a certified exercise specialist and further investigated by the study coordinator. The adverse events were reported and graded following the National

Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v5.0) [34]. If the adverse event required medical attention, the participant would need to be cleared by a physician before returning to the study.

Secondary Outcomes

Secondary outcomes were related to efficacy and included cardiorespiratory fitness, physical functioning, and anthropometry measures. Cardiorespiratory fitness was assessed through direct measurement of VO_{2peak} (mL/kg/min) by an incremental exercise test conducted on a treadmill [35] or an electronically-braked cycle ergometer [36], using a metabolic measurement system (Parvo Medics TrueOne 2400; Sandy, Utah, USA). VO_{2peak} was calculated by averaging the highest values of oxygen uptake among every 30-second interval [37].

Physical functioning was assessed by the Senior Fitness Test (SFT) and included (1) 30-second chair stand, (2) arm curl, (3) chair sit-and-reach, (4) back scratch, (5) 8-foot up-and-go and (6) 6-minute walk [38]. Anthropometry measurements included waist circumference, waist-hip ratio, and calf circumference [39]. Additional pre-specified secondary outcomes not reported here included quality of life and exercise motivation.

Statistical analysis

Our goal was to recruit 66 participants (33 per group) over a 24-month period [29] to provide sufficient data for our feasibility outcomes. This sample size would also provide 80% power using a two-tailed alpha <0.05 to detect a clinically meaningful difference of one metabolic equivalent (MET=3.5 mL/kg/min) in VO_{2peak} assuming a SD of 5.6 mL/kg/min, 10% missing data, and adjustment for baseline value and other prognostic covariates [40]. Given that the purpose of the BRAVE trial was to inform larger phase II and phase III trials, outcomes were interpreted for clinical significance based on the direction and the magnitude of the numerical

differences of at least a small-to-medium standardized effect size d≥0.33. The effect size was calculated using Cohen's d by dividing the mean change with the pooled standard deviation at baseline.

Descriptive analyses were performed for participant characteristics, feasibility outcomes, and disease recurrence and progression. Analysis of covariance was performed for health-related fitness outcomes to determine the between-group mean differences at 6-week and 12-week post-intervention assessments after adjusting for baseline values of the outcome and current treatment status. For the cardiorespiratory fitness outcome, all participants who achieved a VO_{2peak} test at baseline and 6-week or baseline and 12-week were included in the analysis regardless of testing protocol (i.e., treadmill or cycle ergometer). For any other outcomes, all randomized participants who had baseline and follow-up data were included in the analyses. All analyses were performed using SPSS version 28 (SPSS Inc., Chicago, IL).

4.4 Results

Eligibility, Recruitment, and Participation Rates

Figure 4-1 shows the flow of participants through the BRAVE trial. Enrollment started in May 2021 and closed in May 2023. In 24 months, we screened 224 NMIBC patients who met our inclusion criteria, 129 (57.6%) were eligible, and 21 were randomized (16.3%) for an overall participation rate of 9.4%. Patients were ineligible mostly because of medical conditions (56.8%). Eligible patients declined mostly because they were not interested/declined contact (39.8%) or could not commit to the study requirements (20.4%). The 21 participants were randomized to the HIIT group (n = 13) or the usual care group (n = 8). The projected and achieved eligibility, recruitment, and participation rates are presented in Figure 4-2A.

Baseline Characteristics

Baseline sociodemographic, medical and behavioral characteristics are presented in Table 4-1. Of the 21 randomized participants, 19 (90%) were male, 18 (86%) self-identified as White, the mean age was 69.8±9.0 years, 20 (96%) had a body mass index (BMI) ≥25 kg/m^2, 15 (71%) were current or ex-smokers, and 12 (57%) had more than 3 comorbidities. Baseline bladder cancer and treatment details are presented in Table 4-2. In terms of their cancer, 12 (57%) participants had or were being treated for a recurrent malignancy, 13 (62%) were in the maintenance phase of therapy, and 3 (14%) were scheduled to initiate induction therapy. At baseline, 16 (76%) participants had a history of BCG exposure and a negative cystoscopy and cytology. The remaining 5 (23%) participants had a positive cystoscopy and/or cytology at baseline, of which, three participants were BCG-naïve (HIIT n=2; usual care n=1) and two participants were BCG-relapsing (HIIT n=1; usual care n=1). Baseline health-related fitness outcomes are presented in Table 4-3. Briefly, 15 (71%) participants achieved a VO_{2peak} test at baseline, the treadmill-determined VO_{2peak} (n=12) was 6.8 mL/kg/min higher than the VO_{2peak} determined from a cycle ergometer (n=3). Nine participants (43%, HIIT n=6 and usual care n=3) had low BMI-adjusted calf circumference (CC), of which 6 (29%, HIIT n=4 and usual care n=2) were in the severe low category (defined as BMI-adjusted CC≤32 cm in males and CC≤31cm in females) [39].

Follow-up assessment completion rates and VO_{2peak} achievement rates

Overall, 18 (86%) participants completed the 6-week fitness assessments, 17 (81%) completed the 12-week fitness assessments, 19 (90%) completed the 12-week questionnaires, and 100% completed the follow-up cystoscopy (Figure 4-2B). Reasons for missed fitness assessments included hip arthritis (n=2 participants at 6-week and 12-week), work commitments (n=1 participant at 6-week and 12-week) and COVID-19 infection (n=1 at 12-week). Among

those who attempted the VO_{2peak} test, the VO_{2peak} criteria was achieved by 15/21 (71%) at baseline, 14/18 (78%) at 6-weeks, and 14/17 (82%) at 12 weeks (Figure 4-2C). Reasons for test termination without achieving VO_{2peak} test criteria included symptom-limitation (n=7 participants at different time-points, supplementary Table 4-1) and inability to maintain the required protocol speed (n=2 participants, one at all assessment time-points and one at 6-week only).

A well-defined bladder cancer clinical outcome was obtained in 20/21 (95%) of the follow-up cystoscopies. In total, 10/13 (77%) in the HIIT group and 8/8 (100%) in the usual care group had no disease at the treated tumor site based on follow-up cystoscopy and negative urine cytology. Among the remaining three participants in the HIIT group, one participant had a change from baseline cystoscopy status and was positive for carcinoma in situ, another participant was positive for multifocal low-grade bladder cancer recurrence tumors (no change from baseline cystoscopy status), and one case was ambiguous due to negative cystoscopy but positive cytology (atypical cells in the urine). There was no statistically significant difference between the groups regarding the cystoscopy outcomes (data not shown).

Adherence to the HIIT program

Figure 4-2D shows HIIT median exercise attendance and rate of exercise prescription compliance. The total number of attended sessions was 341/450 (75.8%) and median exercise attendance was 36 (100%) with a range of 1 (3%) to 41 (114%). One participant had work commitments out of town by the end of the intervention period and completed five extra unsupervised exercise sessions while away. The participant was provided with the exercise prescription, a heart rate monitor, and the rate of perceived exertion scale to maintain compliance with the intervention protocol. The most common reasons for missed sessions were fatigue, COVID-19 infection, travel, cold weather, and death in the family. In total, four participants

discontinued the exercise intervention because of aggravation of pre-existing medical conditions (n=2), hospitalization due to COVID-19 (n=1), and work commitments (n=1).

Modifications to the exercise intervention protocol were necessary for two participants. One participant completed five sessions with lower intensity and duration due to pre-existing conditions (hip arthritis and lower limb lymphedema) limiting instrumental activities of daily living. Another participant had the duration of one session reduced due to fatigue, the participant was able to complete only the warm-up and one high-intensity interval (9/35 minutes in total).

Safety outcomes

Supplementary Table 4-1 outlines adverse events that occurred during the 12-week study period, their relation with the exercise or the fitness assessments, and their implications. In summary, there were two moderate adverse events related to aggravation of previous medical issues (arthritis and lower limb lymphedema with wound complication) potentially related to HIIT that resulted in discontinuation of the exercise program after completing one and five HIIT sessions and omission from the follow-up fitness assessments. The decision to discontinue the exercise was made by the participant in one case, and by the primary care physician in the other due to wound complications.

There were four mild adverse events reported during the study period in the HIIT group and one in the UC group. Dizziness was reported by three participants, two at the end of the VO_{2peak} test, resulting in symptom-limited assessments, and another while the participant was stretching after the completion of the HIIT session. Musculoskeletal and connective tissue disorder was reported by two participants during the exercise sessions and included calf stiffness and shin pain. Additionally, there were six mild adverse events possibly related to and/or potentially aggravated by exercise. Three of those were in the HIIT group and included fatigue

(n=2) and ankle pain (n=1). The three participants in the usual care group reported knee pain (n=2) and vertigo (n=1), all resulting in symptom-limited VO_{2peak} tests.

Efficacy outcomes

Within-group changes and between-group differences in health-related fitness outcomes are presented in Table 4-4 and Table 4-5. At 6-weeks, VO_{2peak} increased by 0.9 ml/kg/min in both the HIIT and usual care groups (adjusted between-group mean difference, -0.2ml/kg/min; 95%CI: -2.1 to 1.7; p=0.85; d=0.15). Among the physical functioning variables, the 30-second chair stand increased by 2 repetitions in the HIIT group compared to no change in the usual care group (adjusted between-group mean difference, 2.2 repetitions; 95%CI: 0.5 to 3.9; p=0.016; d=0.81). The 30-second arm curl and back scratch were meaningfully (d≥0.33) superior in the HIIT group compared with the usual care group. No statistically significant between-group differences were observed for any of the anthropometry outcomes at 6-week, however, waist-circumference and calf circumference were meaningfully (d≥0.33) lower in the HIIT group.

From baseline to 12 weeks, VO_{2peak} increased by 1.2 ml/kg/min in the HIIT compared to a decrease of 0.2 ml/kg/min in the usual care group (adjusted between-group mean difference, 1.4 ml/kg/min; 95%CI: -1.8 to 4.7; p=0.33; d=0.47). Compared with the usual care group, the HIIT group significantly improved six-minute walk distance (adjusted between-group mean difference, 43 meters; 95%CI: 4 to 82; p=0.034, d=0.58) and 8-foot up-and-go time (adjusted between-group mean difference, -1.1 seconds; 95%CI: -2.2 to -0.1; p=0.039; d=-0.54). The 30-second chair stand, the 30-second arm curl, and sit-and reach were meaningfully (d≥0.33) superior in the HIIT group compared with the usual care group at 12-weeks. The waist-hip ratio decreased by 0.03 in the HIIT group and increased by 0.01 in the usual care group (adjusted between-group mean difference, -0.04; 95%CI: -0.07 to -0.01; p=0.008; d=-0.75).

4.5 Discussion

The BRAVE trial is the first randomized controlled trial to examine the feasibility, safety, and preliminary efficacy of an exercise intervention in NMIBC patients during or after intravesical therapy. Contrary to our projections, the BRAVE trial demonstrated lower-than-expected rates for recruitment and VO_{2peak} achievement. Consistent with our projections, the BRAVE trial demonstrated acceptable rates of eligibility, follow-up assessments, exercise attendance, and exercise compliance. Moreover, although HIIT did not meaningfully improve cardiorespiratory fitness, it did result in significant improvements in several indicators of physical functioning.

Eligibility and recruitment posed significant challenges in the BRAVE trial. A notable proportion of patients were ineligible primarily because of medical conditions (56.8%), including secondary or metastatic cancer, physical or cognitive impairment, and cardiovascular diseases with contraindications to exercise (data not shown). We anticipated recruiting 66 patients on induction intravesical therapy over 24 months; however, after expanding the eligibility criteria we recruited 21 (three patients on induction therapy, 13 on maintenance therapy, and five on surveillance) out of 129 eligible patients, resulting in a recruitment rate of 16%. Notably, our recruitment rate was below the median recruitment rate of 38% observed in a systematic review of recruitment rates in exercise trials among cancer survivors [41]. The systematic review, however, was based on interventional trials targeting the most common cancer types (i.e., breast, prostate, and colorectal cancers) after they had completed primary treatment. There is no study focused exclusively on exercise for NMIBC to directly compare our findings, however, our

recruitment rate was also lower than the rates of exercise trials in muscle-invasive bladder cancer patients (20.22% - 90.21%) [21-25]. Variations in recruitment may be attributed to differences in the delivery mode of the intervention (supervised versus home-based program) [24], the duration of participant commitment to the exercise intervention (from 2 to 4 weeks versus 3 months) [22, 24], and the number of sites recruiting patients [20]. For instance, Kaye et al. had an increase in patient recruitment rate from 7 to 11.5 patients per year after expanding the study to nine additional intervention sites [20]. In the BRAVE trial, a single-center approach yielded an annual accrual rate of 10.5 NMIBC patients during and after intravesical therapy. Overall, our data indicates that multicenter trials will be required to achieve adequate accrual of NMIBC patients in a reasonable time, especially if testing supervised exercise interventions and limited to patients on induction intravesical therapy.

The reasons for non-participation were similar to the ones identified in previous exercise trials in cancer survivors, including big commitment, lack of interest, failure to return contact, and travel distance [41]. Travel distance, in particular, was mentioned by two patients as a barrier associated with the symptoms of bladder cancer. Patients with bladder cancer may experience urinary frequency and urgency [9], therefore the distance to the exercise facility and the time they would spend in traffic were reasons why these patients declined participation. Future studies may improve eligibility and recruitment by using less strenuous assessment protocols and adopting a multi-center approach. These adjustments can offer valuable insights for designing more inclusive trials and interventions tailored to patients with NMIBC during or after intravesical therapy.

The overall assessment follow-up rates for both health-related fitness and patient-reported outcomes were as projected. In fact, our follow-up assessments completion rate was similar [22]

or even higher [21, 23, 25, 42] in comparison to previous studies in bladder cancer patients in the pre- and post-operative setting. Although, the reasons for the loss of follow-up are not explicitly stated in all these studies, the higher retention rate in our study is potentially due to the better survival prognosis of NMIBC [43] compared to muscle-invasive bladder cancer patients undergoing surgery, who may experience surgical complications and are at higher risk of dying. The follow-up cystoscopy completion rates were also as expected, with 100% adherence to recommended medical care. This finding indicates the feasibility of assessing bladder cancer clinical outcomes in future exercise trials among NMIBC patients, including recurrence and progression rates.

Interestingly, among those who attempted the maximal cardiorespiratory fitness assessment, only 71% to 82% of the participants were able to achieve a VO_{2peak} test at the three different assessment time points. The test was prematurely ended because of symptom limitations. Bladder cancer is most often diagnosed in older individuals, predominantly among people aged 65-74 [43]. Moreover, bladder cancer patients often have a history of tobacco exposure, are overweight or obese, and are insufficiently active [44]. Therefore, it is possible that the combination of lifestyle factors and age-related changes [45] means that many patients with bladder cancer face multiple comorbidities that limit or even preclude maximal exercise testing. Although the cardiopulmonary exercise test remains the gold standard for the evaluation of exercise capacity, alternatives should be considered in this population. The 6MWT is a safe, easily performed, and well-tolerated test for the assessment of functional capacity of patients with cancer [46], and other chronic conditions [47, 48]. Moreover, the walking distance is correlated with VO_{2peak} and perceived function [46]. In the BRAVE trial, all the participants were able to perform the 6MWT without adverse events.

HIIT has been demonstrated as a safe and beneficial intervention for some cancer patient groups [31, 32, 49], however, it has not been tested in NMIBC patients. Moreover, caution is needed due to the general inadequacy of harm assessment and reporting in exercise trials for cancer patients [50]. Although HIIT was relatively safe in the BRAVE trial, two moderate-severe adverse events, possibly related to the exercise program, occurred during the study. One occurred in a participant with a history of hip arthritis, and the other in a participant with hip arthritis, lower limb lymphedema, and diabetes. The exercise sessions were adapted from the beginning for those participants and performed on a cycle ergometer with reduced intensity (moderate, RPE=3 on a 0-10 scale) and duration (2 to 3 moderate intervals), considering the participant's rate of perceived exertion and feedback. However, exercise can be painful and difficult to perform in patients with lower-limb arthritis [48]. Despite our precautionary measures, one participant reported significant limitations on instrumental activities of daily living and decided to withdraw from the exercise program and follow-up assessments. Another participant experienced worsening in lower limb lymphedema accompanied by wound complications. These adverse events were potentially exacerbated by a concurrent heat wave, exercise training, and difficulties in wound healing due to diabetes. The participant was not cleared by the primary care physician to return to the exercise program. Additionally, two participants in the HIIT group reported mild adverse effects related to musculoskeletal disorders (i.e., calf stiffness and shin pain). To minimize muscle soreness, discomfort, and potential injuries, changes in the speed and/or grade of the treadmill were made according to metabolic equivalent equations for the estimation of energy expenditure relative to the individual’s peak capacity [33]. This strategy was essential to maintain the desired intensity of the training session (i.e., compliance) and the attendance to the exercise sessions. Our results indicate that HIIT may be feasible for the

majority of NMIBC patients during and after intravesical therapy based on satisfactory attendance and compliance with the exercise program.

Contrary to our hypothesis, HIIT during and after the intravesical therapy did not improve VO_{2peak} at 6 weeks or 12 weeks, possibly due to the limited number of patients who completed the assessments and were included in the analyses. Note that among the three participants from the HIIT group who did not achieve a VO_{2peak} at baseline, two did not complete the follow-up assessments. The one who remained in the study achieved a VO_{2peak} at the 6-week and 12-week assessment time points, without symptom-limitation (i.e., dizziness), suggesting that the exercise prescription was adequate to result in training adaptations and improve exercise tolerance. In addition, we found a statistically significant and clinically important increase of 43 meters in walking distance at the 12-week 6MWT, surpassing the distance of 14-30.5 meters suggested as clinically meaningful across multiple patient groups [51]. Moreover, HIIT resulted in statistically significant and/or meaningful improvements in several indicators of physical functioning, including lower and upper body endurance, lower body flexibility, and agility/dynamic balance. Our results contrast a systematic review of randomized controlled trials evaluating the effects of HIIT on physical and function outcomes in cancer patients, showing significant improvements in walking distance and relative VO_{2peak} following HIIT interventions [32]. Our small sample size, the loss to follow-up, and the strenuous protocol resulting in symptom-limited fitness assessments may have impacted our ability to detect any changes in cardiorespiratory fitness through the VO_{2peak} measurement.

Our study has important strengths and limitations. Strengths of our study include the novel cancer patient population and setting, the randomized controlled trial design, the supervised and individualized exercise program, and satisfactory adherence and compliance rates

to the intervention. The major limitation of our study is the small sample size, attributed to a slower-than-anticipated accrual rate from a single center. The small sample size may have hindered our ability to accurately estimate feasibility outcomes and detect meaningful differences in some of the health-related fitness outcomes. Other limitations include post-registration changes in the protocol, including (1) the expansion of eligibility criteria; (2) the assessment and HIIT program on the cycle ergometer for some participants; and (3) the addition of VO_{2peak} achievement rates as a feasibility outcome. Worth noting, the changes in the protocol were made, respectively, to: (1) enhance study recruitment; (2) improve protocol safety and well-being of the participants; and (3) document unexpected findings that will inform future research design in this population. Consequently, the findings should be interpreted as preliminary, and further feasibility work is necessary in this patient population before definitive exercise trials are launched.

In conclusion, the BRAVE trial is the first randomized controlled trial to assess the safety and feasibility of an exercise intervention in patients with NMIBC during or after intravesical therapy. We highlighted the significant challenges with eligibility, recruitment, and protocol assessments while also demonstrating the potential safety and feasibility of HIIT. The BRAVE trial provides novel and relevant information, contributing to the knowledge base and practice in the field of exercise oncology for an understudied patient group. Given the limitations of the BRAVE trial, additional feasibility studies are necessary to establish the safety, applicability, and tolerability of different fitness assessment protocols (e.g. submaximal cardiorespiratory fitness assessments) and intervention delivery methods (e.g. home-based exercise interventions) for patients with NMIBC during or after intravesical therapy. Future trials should consider expanding the number of collaborating centers, providing different exercise intervention delivery

methods, and tailoring assessment protocols to accommodate the this predominantly elderly, comorbid population.

4.6 References

1. Sung, H., et al., *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.* CA Cancer J Clin, 2021. **71**(3): p. 209-249.
2. Brenner, D.R., et al., *Projected estimates of cancer in Canada in 2022.* CMAJ, 2022. **194**(17): p. E601-E607.
3. National Comprehensive Cancer Network [NCCN], *NCCN Clinical Practice Guidelines on Oncology: Bladder Cancer, Version 3.2023*. 2023.
4. Lamm, D.L., et al., *Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study.* J Urol, 2000. **163**(4): p. 1124-9.
5. Kamat, A.M., et al., *Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group.* J Clin Oncol, 2016. **34**(16): p. 1935-44.
6. Avritscher, E.B.C. and C.D.G. Cooksley, B.Sabichi, A. L.Hamblin, L.Dinney, C. P.Elting, L. S., *Clinical model of lifetime cost of treating bladder cancer and associated complications* Urology, 2006. **68**(3): p. 549-553.
7. Jung, A., et al., *Quality of Life in Non-Muscle-Invasive Bladder Cancer Survivors: A Systematic Review.* Cancer Nurs, 2019. **42**(3): p. E21-E33.

8. Nayak, A., J. Cresswell, and P. Mariappan, *Quality of life in patients undergoing surveillance for non-muscle invasive bladder cancer-a systematic review.* Transl Androl Urol, 2021. **10**(6): p. 2737-2749.

9. Koch, G.E., W.W. Smelser, and S.S. Chang, *Side Effects of Intravesical BCG and Chemotherapy for Bladder Cancer: What They Are and How to Manage Them.* Urology, 2021. **149**: p. 11-20.

10. Kuperus, J.M., et al., *Comparison of Side Effects and Tolerability Between Intravesical Bacillus Calmette-Guerin, Reduced-Dose BCG and Gemcitabine for Non-Muscle Invasive Bladder Cancer.* Urology, 2021. **156**: p. 191-198.

11. Sturgeon, K.M., et al., *A population-based study of cardiovascular disease mortality risk in US cancer patients.* Eur Heart J, 2019. **40**(48): p. 3889-3897.

12. van Hoogstraten, L.M.C., et al., *Global trends in the epidemiology of bladder cancer: challenges for public health and clinical practice.* Nat Rev Clin Oncol, 2023. **20**(5): p. 287-304.

13. Campbell, K.L., et al., *Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable.* Med Sci Sports Exerc, 2019. **51**(11): p. 2375-2390.

14. Ligibel, J.A., et al., *Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline.* J Clin Oncol, 2022. **40**(22): p. 2491-2507.

15. Rock, C.L., et al., *American Cancer Society nutrition and physical activity guideline for cancer survivors.* CA Cancer J Clin, 2022. **72**(3): p. 230-262.

16. Lavery, J.A., et al., *Pan-Cancer Analysis of Postdiagnosis Exercise and Mortality.* J Clin Oncol, 2023: p. JCO2300058.

17. Courneya, K.S. and C.M. Booth, *Exercise as cancer treatment: A clinical oncology framework for exercise oncology research.* Front Oncol, 2022. **12**: p. 957135.

18. Esteves, M., M.P. Monteiro, and J.A. Duarte, *The Effects of Physical Exercise on Tumor Vasculature: Systematic Review and Meta-analysis.* Int J Sports Med, 2021. **42**(14): p. 1237-1249.

19. Courneya, K.S. and C.M. Friedenreich, *Designing, analyzing, and interpreting observational studies of physical activity and cancer outcomes from a clinical oncology perspective.* Front Oncol, 2023. **13**: p. 1098278.

20. Kaye, D.R., et al., *The Feasibility and Impact of a Presurgical Exercise Intervention Program (Prehabilitation) for Patients Undergoing Cystectomy for Bladder Cancer.* Urology, 2020. **145**.

21. Taaffe, D.R., et al., *Efficacy and Feasibility of Presurgical Exercise in Bladder Cancer Patients Scheduled for Open Radical Cystectomy.* Med Sci Sports Exerc, 2023. **55**(7): p. 1123-1132.

22. Banerjee, S., et al., *Vigorous intensity aerobic interval exercise in bladder cancer patients prior to radical cystectomy: a feasibility randomised controlled trial.* Support Care Cancer, 2018. **26**(5): p. 1515-1523.

23. Porserud, A., A. Sherif, and A. Tollbäck, *The effects of a physical exercise programme after radical cystectomy for urinary bladder cancer. A pilot randomized controlled trial.* Clin Rehabil, 2014. **28**(5): p. 451-9.

24. Jensen, B.T., et al., *Exercise-based pre-habilitation is feasible and effective in radical cystectomy pathways-secondary results from a randomized controlled trial.* Support Care Cancer, 2016. **24**(8): p. 3325-31.

25. Minnella, E.M., et al., *Multimodal Prehabilitation to Enhance Functional Capacity Following Radical Cystectomy: A Randomized Controlled Trial.* Eur Urol Focus, 2019. **7**(1): p. 132-138.

26. Banerjee, S., et al., *O2 Preoperative exercise protocol to aid recovery of radical cystectomy: results of a feasibility study. Eur. Urol. Suppl* 2013. **12**(6): p. 125.

27. Rammant, E., et al., *A systematic review of exercise and psychosocial rehabilitation interventions to improve health-related outcomes in patients with bladder cancer undergoing radical cystectomy.* Clin Rehabil, 2018. **32**(5): p. 594-606.

28. Bessa, A., et al., *Is there a role for physical activity interventions in the treatment pathway of bladder cancer? A scoping review of the literature.* BMJ Open Sport Exerc Med, 2021. **7**(1): p. e000951.

29. Arthuso, F.Z., et al., *Bladder cancer and exeRcise trAining during intraVesical thErapy-the BRAVE trial: a study protocol for a prospective, single-centre, phase II randomised controlled trial.* BMJ Open, 2021. **11**(9): p. e055782.

30. Eldridge, S.M., et al., *CONSORT 2010 statement: extension to randomised pilot and feasibility trials.* BMJ, 2016. **355**: p. i5239.

31. Palma, S., et al., *High-intensity interval training in the prehabilitation of cancer patients-a systematic review and meta-analysis.* Support Care Cancer, 2021. **29**(4): p. 1781-1794.

32. Neuendorf, T., et al., *Effects of high-intensity interval training on functional performance and maximal oxygen uptake in comparison with moderate intensity continuous training in cancer patients: a systematic review and meta-analysis.* Support Care Cancer, 2023. **31**(12): p. 643.

33. Riebe, D., Ehrman, J. K., Liguori, G., & Magal, M. (Eds.). *ACSM's guidelines for exercise testing and prescription* Tenth edition ed. 2018: Wolters Kluwer.

34. National Cancer Institute [NIH]. *Cancer Therapy Evaluation Program: Common Terminoloty Criteria for Avderse Events v5.0 (CTCAE)*. 2017 March 11, 2024]; Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50.

35. McInnis, K.J. and G.J. Balady, *Comparison of submaximal exercise responses using the Bruce vs modified Bruce protocols.* Med Sci Sports Exerc, 1994. **26**(1): p. 103-7.

36. Myers, J. and D. Bellin, *Ramp exercise protocols for clinical and cardiopulmonary exercise testing.* Sports Med, 2000. **30**(1): p. 23-9.

37. Society, A.T. and A.C.o.C. Physicians, *ATS/ACCP Statement on cardiopulmonary exercise testing.* Am J Respir Crit Care Med, 2003. **167**(2): p. 211-77.

38. Jones, C.J. and R.E. Rikli. *Measuring Functional*. 2002 May 17th, 2020]; Available from: https://www.um.es/desarrollopsicomotor/wq/2010/wqcarrasco2010/BL22_files/Senior%20Fitness%20Test_Rikli02.pdf.

39. Gonzalez, M.C., et al., *Calf circumference: cutoff values from the NHANES 1999-2006.* Am J Clin Nutr, 2021. **113**(6): p. 1679-1687.

40. Borm, G.F., J. Fransen, and W.A. Lemmens, *A simple sample size formula for analysis of covariance in randomized clinical trials.* J Clin Epidemiol, 2007. **60**(12): p. 1234-8.

41. Reynolds, S.A., et al., *Recruitment rates and strategies in exercise trials in cancer survivorship: a systematic review.* J Cancer Surviv, 2023.

42. Jensen, B.T., et al., *Efficacy of a multiprofessional rehabilitation programme in radical cystectomy pathways: a prospective randomized controlled trial.* Scand J Urol, 2015. **49**(2): p. 133-41.

43. NCI, N., *Surveillance, Epidemiology, and End Results Program*, in *Cancer Stat Facts: Bladder Cancer.* 2023.

44. Catto, J.W.F., et al., *Lifestyle Factors in Patients with Bladder Cancer: A Contemporary Picture of Tobacco Smoking, Electronic Cigarette Use, Body Mass Index, and Levels of Physical Activity.* Eur Urol Focus, 2023.

45. Lund, L.H. and D.M. Mancini, *Peak VO2 in elderly patients with heart failure.* Int J Cardiol, 2008. **125**(2): p. 166-71.

46. Schmidt, K., et al., *Validity of the six-minute walk test in cancer patients.* Int J Sports Med, 2013. **34**(7): p. 631-6.

47. Singh, S.J., et al., *An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease.* Eur Respir J, 2014. **44**(6): p. 1447-78.

48. Laboratories, A.C.o.P.S.f.C.P.F., *ATS statement: guidelines for the six-minute walk test.* Am J Respir Crit Care Med, 2002. **166**(1): p. 111-7.

49. Wang, L., et al., *Effects of High-Intensity Interval Training and Combined High-Intensity Interval Training Programs on Cancer-Related Fatigue and Cancer Pain: A Systematic Review and Meta-analysis.* Med Sci Sports Exerc, 2023. **55**(9): p. 1620-1631.

50. Thomsen, S.N., et al., *Harms of exercise training in patients with cancer undergoing systemic treatment: a systematic review and meta-analysis of published and unpublished controlled trials.* EClinicalMedicine, 2023. **59**: p. 101937.

51. Bohannon, R.W. and R. Crouch, *Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review.* J Eval Clin Pract, 2017. **23**(2): p. 377-381.

Table 4-1. Baseline demographic, medical, and behavioral characteristics of participants in the BRAVE Trial.

Variable	Overall (n=21)	HIIT (n=13)	Usual care (n=8)
Sociodemographic profile			
Age, y, mean (SD)	69.8 (9.0)	69.5 (9.8)	70.1 (8.1)
Sex, male, n (%)	19 (90)	11(85)	8 (100)
Ethnicity, Caucasian, n (%)	18 (86)	11(85)	7 (88)
Married, n (%)	17 (81)	11(85)	6 (75)
Completed university or college, n (%)	11 (52)	8 (62)	3 (38)
Employed, n (%)	6 (29)	4 (31)	2 (25)
Family income ≥$100,000/year, n (%)	8 (38)	5 (38)	3 (38)
Medical Profile			
Weight, kg, mean (SD)	93.9 (22.1)	91.2 (18.9)	98.4 (27.2)
BMI kg/m^2, mean (SD)	31.0 (6.5)	30.5 (5.6)	31.8 (8.1)
Number of comorbidities, n (%)			
None	3 (14)	3 (23)	-
1-2	6 (29)	3 (23)	3 (38)
≥3	12 (57)	7 (54)	5 (63)
Most common comorbidities, n (%)			
Hypertension	11 (52)	5 (38)	6 (75)
Hyperlipidemia	10 (48)	6 (46)	4 (50)
Arthritis	8 (38)	5 (38)	3 (38)
Behavioral profile			
Smoking status, n (%)			
Current cigarette smoker	3 (14)	2 (15.4)	1 (12.5)
Former cigarette smoker	12 (57)	7 (53.8)	5 (62.5)
Exercise behavior, median (IQR)			
Vigorous aerobic exercise, min/wk	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Moderate aerobic exercise, min/wk	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Resistance exercise, min/wk	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)

HIIT: high intensity interval training; BMI: body mass Index

Table 4-2. Baseline bladder cancer and treatment characteristics of participants in the BRAVE Trial.

Variable	Overall (n=21)	HIIT (n=13)	Usual care (n=8)
Bladder cancer profile			
Clinical stage, n (%)			
Tis	3 (14)	2 (15)	1 (13)
Ta	7 (33)	4 (31)	3 (38)
T1	11 (52)	7 (54)	4 (50)
Clinical grade, n (%)			
Low grade	1 (5)	1 (8)	-
High grade	20 (95)	12 (92)	8 (100)
Concurrent CIS, n (%)	10 (48)	7 (54)	3 (38)
Tumor size, n (%)			
<1 cm	2 (10)	2 (15)	-
1-3 cm	8 (38)	4 (31)	4 (50)
≥3 cm	2 (10)	1 (8)	1 (13)
Unknown	9 (43)	6 (46)	3 (38)
Focality, n (%)			
Unifocal	8 (38)	4 (31)	4 (50)
Multifocal	12 (57)	8 (62)	4 (50)
Unknown	1 (5)	1 (8)	-
Current disease status			
Primary malignancy, n (%)	9 (43)	6 (46)	3 (38)
Recurrent malignancy, n (%)	12 (57)	7 (54)	5 (63)
Current treatment protocol			
TURBT + single instillation, n (%)	1 (5)	1 (8)	-
TURBT + induction, n (%)	3 (14)	2 (15)	1 (13)
TURBT + induction + maintenance, n (%)	13 (62)	7 (54)	6 (75)
Surveillance, n (%)	4 (19)	3 (23)	1 (13)
Number of prior instillations, median (range)	15 (0-27)	19 (0-27)	13.5 (0-27)
Time since last instillation, months, mean (SD)	9.3 (10.7)	11.2 (12.9)	6.1 (4.2)

HIIT: high intensity interval training; CIS: carcinoma in situ; TURBT: transurethral resection of bladder tumor

Table 4-3. Baseline health-related fitness of participants in the BRAVE Trial.

Variable	Overall (n=21)	HIIT (n=13)	Usual care (n=8)
Cardiorespiratory fitness			
Treadmill Protocol*			
Peak VO_2, mL/kg/min	23.2 (4.7)	23.1 (4.2)	23.3 (6.3)
Peak VO_2, L/min	2.19 (0.42)	2.05 (0.41)	2.46 (0.33)
Bike Protocol*			
Peak VO_2, mL/kg/min	16.4 (1.7)	17.2 (1.3)	14.7
Peak VO_2, L/min	1.28 (0.24)	1.35 (0.28)	1.13
Physical functioning			
Six-minute walk, m	456 (132)	450 (148)	467 (109)
30-second chair stand, n	11.7 (3.4)	11.5 (4.1)	11.9 (1.8)
30-second arm curls, n	15.6 (2.6)	15.6 (2.8)	15.6 (2.6)
Sit-and-reach, cm	-9.5 (10.6)	-8.2 (10.9)	-11.4 (10.3)
Back scratch, cm	-28.0 (17.3)	-25.1 (15.5)	-32.8 (20.1)
8-foot up-and-go, s	6.4 (2.4)	6.7 (2.6)	6.1 (2.0)
Anthropometry			
Waist circumference, cm	112.4 (15.6)	110.8 (14.4)	115.0 (18.2)
Waist-hip ratio	1.04 (0.09)	1.04 (0.11)	1.05 (0.04)
Calf circumference, cm	39.1 (4.8)	39.0 (4.7)	39.4 (5.2)
Calf circumference adjusted by BMI, cm	34.3 (3.7)	34.0 (3.5)	34.8 (4.1)

HIIT: high intensity interval training; BMI: body mass Index; VO_2: volume of oxygen consumption

*Sample sizes are peak VO_2 treadmill protocol n=12 (HIIT n=8, usual care n=4), peak VO_2 cycle ergometer n=3 (HIIT n=2, usual care n=1).

Table 4-4. Effects of 6 weeks of exercise on health-related fitness outcomes in the BRAVE Trial.

Outcome	Baseline	6-week	Baseline to 6-week			
			Mean Change	Adjusted Between-group Difference*		
	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI)	*p*	*d*
Cardiorespiratory fitness						
Peak VO_2, mL/kg/min						
HIIT (n=8)	22.3 (5.0)	23.2 (5.8)	0.9 (-0.2 to 2.1)	-0.2 (-2.1 to 1.7)	0.85	0.15
Usual care (n=4)	21.5 (7.7)	22.3 (7.8)	0.9 (-0.1 to 1.8)			
Peak VO_2, L/min						
HIIT (n=8)	1.88 (0.51)	1.96 (0.61)	0.08 (-0.02 to 0.17)	-0.05 (-0.17 to 0.07)	0.39	-0.57
Usual care (n=4)	2.23 (0.75)	2.30 (0.75)	0.07 (-0.03 to 0.18)			
Physical functioning						
Six-minute walk, m						
HIIT (n=10)	482 (113)	502 (117)	21 (-6 to 47)	3 (-23 to 29)	0.82	0.15
Usual care (n=8)	467 (109)	482 (95)	14 (-10 to 38)			
30-second chair stand, n						
HIIT (n=10)	12.9 (2.2)	14.6 (2.0)	1.7 (0.3 to 3.1)	2.2 (0.5 to 3.9)	0.016	0.81
Usual care (n=8)	11.9 (1.8)	11.8 (2.1)	-0.1 (-1.3 to 1.1)			
30-second arm curls, n						
HIIT (n=10)	15.3 (2.9)	17.8 (4.7)	2.5 (0.6 to 4.4)	0.9 (-1.5 to 3.3)	0.43	0.33
Usual care (n=8)	15.6 (2.6)	16.9 (3.1)	1.3 (-0.6 to 3.1)			
Sit-and-reach, cm						
HIIT (n=10)	-9.0 (10.0)	-10.0 (8.9)	-1 (-5.3 to 3.4)	-0.8 (-8.5 to 6.8)	0.82	0.14
Usual care (n=8)	-11.4 (10.3)	-11.5 (12.3)	-0.1 (-7.1 to 6.9)			
Back scratch, cm						
HIIT (n=10)	-23.8 (15.9)	-21.6 (15.3)	2.3 (-1.0 to 5.5)	-3.4 (-14.5 to 7.6)	0.51	0.41
Usual care (n=8)	-32.8 (20.1)	-28.7 (22.7)	4.1 (-8.3 to 6.5)			
8-foot up-and-go, s						
HIIT (n=10)	5.8 (1.6)	5.3 (1.2)	-0.5 (-1.0 to 0.1)	-0.2 (-0.7 to 0.4)	0.55	-0.17
Usual care (n=8)	6.1 (2.0)	5.7 (1.4)	-0.4 (-1.1 to 0.3)			
Anthropometry						
Body weight, kg						

HIIT (n=10)	85.1 (14.7)	85.0 (15.1)	-0.1 (-1.3 to 1.2)	0.6 (-1.1 to 2.3)	0.47	-0.57
Usual care (n=8)	98.4 (27.2)	97.8 (27.2)	-0.6 (-1.4 to 0.3)			
Waist circumference, cm						
HIIT (n=10)	105.8 (12.2)	103.9 (11.2)	-1.9 (-5.1 to 1.2)	-1.1 (-4.9 to 2.8)	0.56	-0.65
Usual care (n=8)	115.0 (18.2)	114.2 (18.6)	-0.8 (-2.2 to 0.5)			
Waist-hip ratio						
HIIT (n=10)	1.04 (0.08)	1.02 (0.07)	-0.02 (0.04 to 0.00)	-0.02 (-0.05 to 0.01)	0.16	-0.03
Usual care (n=8)	1.05 (0.04)	1.05 (0.06)	0.00 (-0.02 to 0.02)			
Calf circumference, cm						
HIIT (n=10)	37.6 (2.9)	37.9 (3.0)	0.3 (-0.3 to 0.9)	0.4 (-0.4 to 1.2)	0.26	-0.33
Usual care (n=8)	39.4 (5.2)	39.5 (5.6)	0.1 (-0.4 to 0.5)			

HIIT: high intensity interval training; VO_2: volume of oxygen consumption. *Adjusted for age, baseline value of the outcome, and current treatment status

Table 4-5. Effects of 12 weeks of exercise on health-related fitness outcomes in the BRAVE Trial.

Outcome	Baseline	12-week	Baseline to 12-week			
			Mean Change	Adjusted Between-group Difference*		
	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI)	*p*	*d*
Cardiorespiratory fitness						
Peak VO_2, mL/kg/min						
HIIT (n=8)	22.9 (4.4)	24.1 (5.1)	1.2 (-0.4 to 2.8)	1.4 (-1.8 to 4.7)	0.33	0.47
Usual care (n=4)	21.5 (7.7)	21.3 (7.7)	-0.2 (-1.9 to 1.5)			
Peak VO_2, L/min						
HIIT (n=8)	1.95 (0.43)	2.04 (0.58)	0.09 (-0.06 to 0.25)	0.05 (-0.20 to 0.30)	0.65	-0.34
Usual care (n=4)	2.23 (0.75)	2.24 (0.74)	0.01 (-0.14 to 0.16)			
Physical functioning						
Six-minute walk, m						
HIIT (n=9)	504 (95)	547 (82)	44 (22 to 66)	43 (4 to 82)	0.034	0.56
Usual care (n=8)	467 (109)	471 (105)	3 (-33 to 39)			
30-second chair stand, n						
HIIT (n=9)	12.8 (2.3)	14.9 (2.2)	2.1 (0.4 to 3.8)	4.7 (-0.4 to 9.8)	0.07	1.57
Usual care (n=8)	11.9 (1.8)	9.5 (6.4)	-2.4 (-7.3 to 2.5)			
30-second arm curls, n						
HIIT (n=9)	15.8 (2.6)	18.9 (7.2)	3.1 (-0.9 to 7.1)	0.9 (-2.1 to 4.0)	0.51	0.84
Usual care (n=8)	15.6 (2.6)	16.6 (3.5)	1.0 (-0.5 to 2.5)			
Sit-and-reach, cm						
HIIT (n=9)	-11.0 (8.2)	-7.7 (9.2)	3.3 (1.2 to 5.3)	3.9 (-0.9 to 8.8)	0.10	0.44
Usual care (n=8)	-11.4 (10.3)	-12.4 (8.7)	-1.0 (-5.7 to 3.7)			
Back scratch, cm						
HIIT (n=9)	-26.9 (13.4)	-22.3 (12.0)	4.6 (-1.6 to 10.8)	-2.4 (-12.6 to 7.8)	0.61	0.28
Usual care (n=8)	-32.8 (20.1)	-27.1 (18.4)	5.6 (-5.1 to 16.3)			
8-foot up-and-go, s						
HIIT (n=9)	5.7 (1.6)	4.7 (0.8)	-1.0 (-1.8 to -0.2)	-1.1 (-2.2 to -0.1)	0.039	-0.54
Usual care (n=8)	6.1 (2.0)	6.0 (1.6)	-0.1 (-1.3 to 1.1)			
Anthropometry						
Body weight, kg						

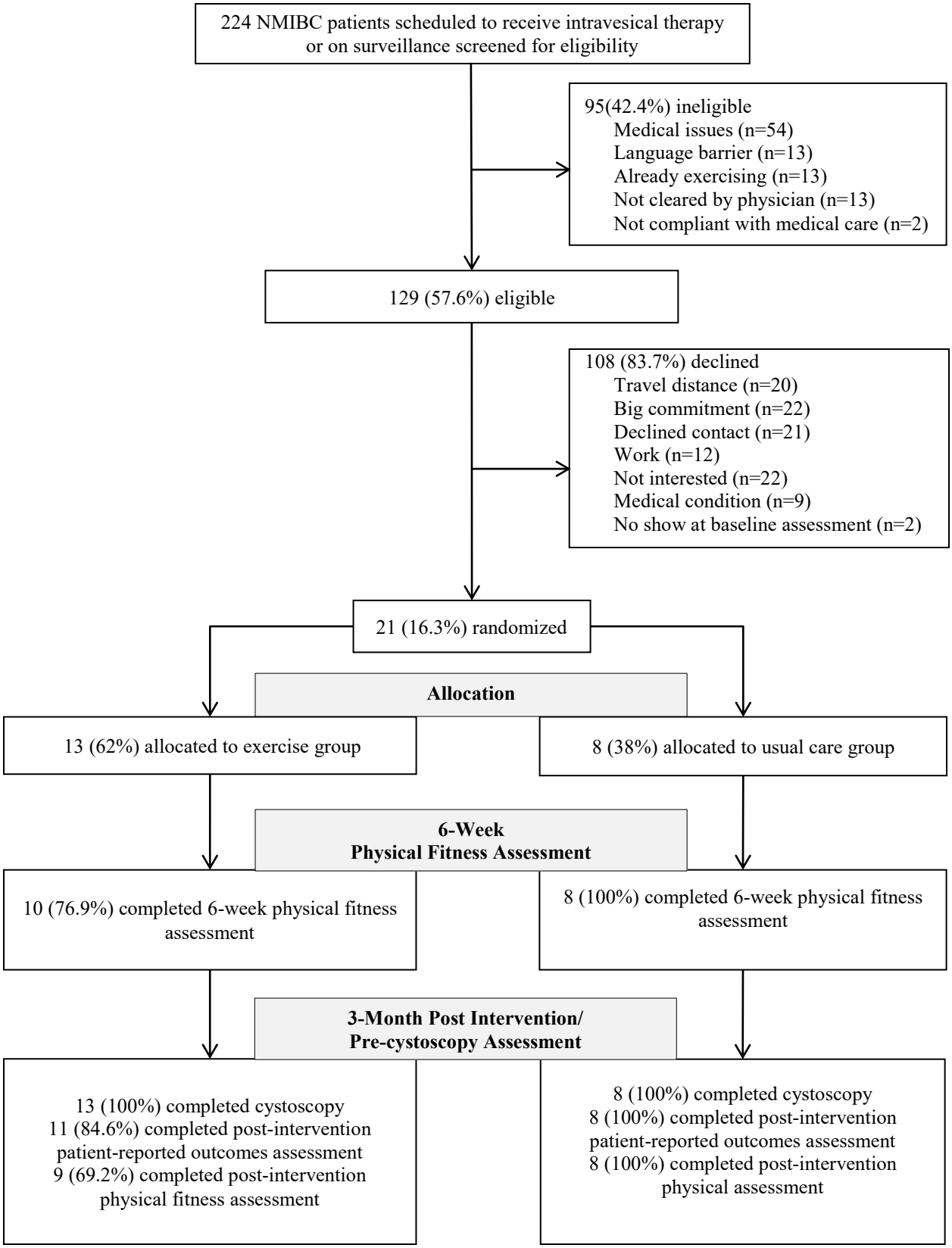
HIIT (n=9)	86.7 (14.7)	85.8 (15.3)	-0.9 (-2.6 to 0.8)	-0.7 (-4.5 to 3.0)	0.66	-0.57
Usual care (n=8)	98.4 (27.2)	98.6 (28.0)	0.3 (-2.8 to 3.3)			
Waist circumference, cm						
HIIT (n=9)	106.7 (12.6)	103.2 (11.6)	-3.6 (-7.0 to -0.2)	-4.1 (-9.5 to 1.4)	0.13	-0.75
Usual care (n=8)	115.0 (18.2)	115.2 (18.9)	0.2 (-3.4 to 3.8)			
Waist-hip ratio						
HIIT (n=9)	1.04 (0.09)	1.01 (0.06)	-0.03 (-0.06 to 0.00)	-0.04 (-0.07 to -0.01)	0.008	-0.06
Usual care (n=8)	1.05 (0.04)	1.06 (0.05)	0.01 (-0.01 to 0.02)			
Calf circumference, cm						
HIIT (n=9)	38.0 (2.8)	38.1 (3.1)	0.1 (-0.4 to 0.7)	0.0 (-0.9 to 0.8)	0.97	-0.33
Usual care (n=8)	39.4 (5.2)	39.7 (5.6)	0.3 (-0.4 to 1.0)			

HIIT: high intensity interval training; VO_2: volume of oxygen consumption. *Adjusted for age, baseline value of the outcome, and current treatment status .

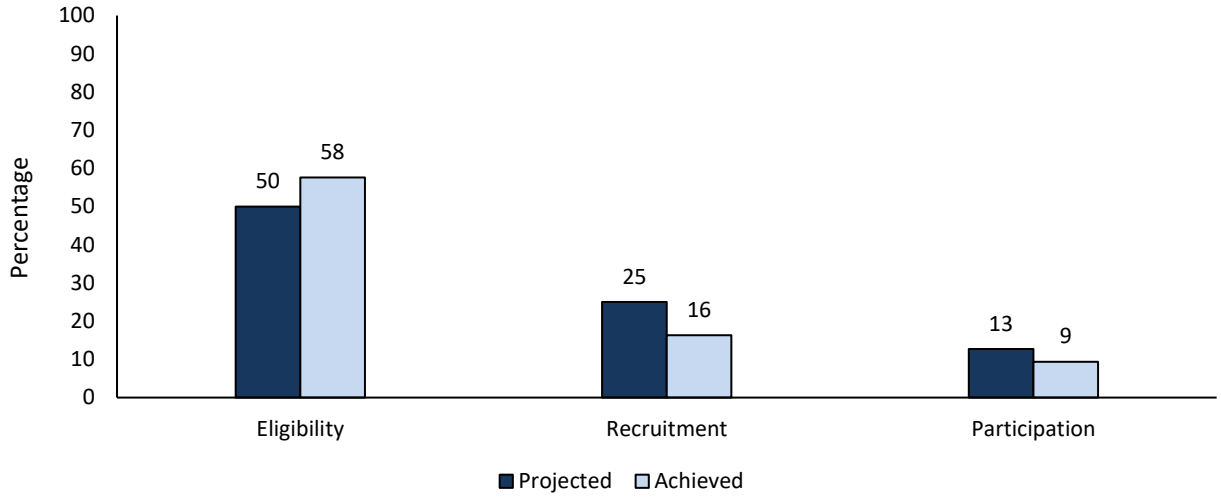
Figure Caption

Figure 4-1. CONSORT diagram showing flow of participants through the BRAVE trial.

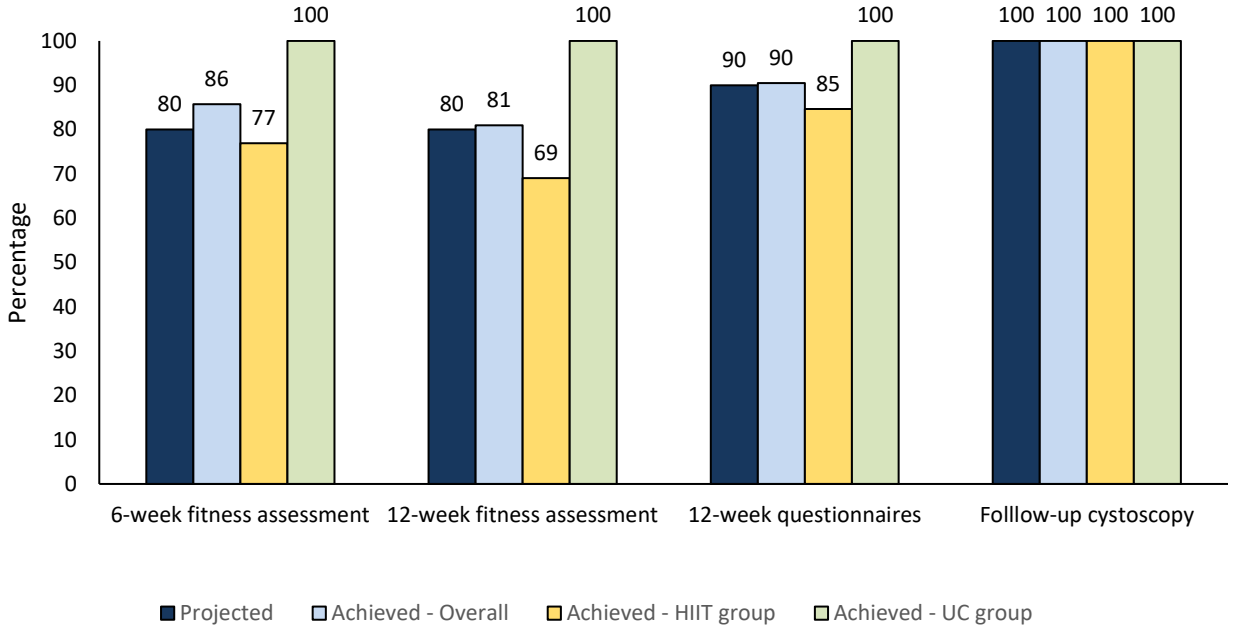
Figure 4-2. Projected and achieved feasibility outcomes in the BRAVE trial. A. Eligibility, Recruitment, and Participation Rates, B. Follow-up Assessments Completion Rates. C. VO_{2peak} Achievement Rates, D. High-Intensity Interval Training Adherence Rates. HIIT: high intensity interval training; UC: usual care; VO_{2peak}: peak volume of oxygen consumption. All the values are expressed as mean percentage except exercise attendance which is expressed as median percentage.


224 NMIBC patients scheduled to receive intravesical therapy or on surveillance screened for eligibility
95(42.4%) ineligible
Medical issues (n=54)
Language barrier (n=13)
Already exercising (n=13)
Not cleared by physician (n=13)
Not compliant with medical care (n=2)
129 (57.6%) eligible
108 (83.7%) declined
Travel distance (n=20)
Big commitment (n=22)
Declined contact (n=21)
Work (n=12)
Not interested (n=22)
Medical condition (n=9)
No show at baseline assessment (n=2)
21 (16.3%) randomized
Allocation
13 (62%) allocated to exercise group
8 (38%) allocated to usual care group
6-Week
Physical Fitness Assessment
10 (76.9%) completed 6-week physical fitness assessment
8 (100%) completed 6-week physical fitness assessment
3-Month Post Intervention/
Pre-cystoscopy Assessment
13 (100%) completed cystoscopy
11 (84.6%) completed post-intervention patient-reported outcomes assessment
9 (69.2%) completed post-intervention physical fitness assessment
8 (100%) completed cystoscopy
8 (100%) completed post-intervention patient-reported outcomes assessment
8 (100%) completed post-intervention physical assessment

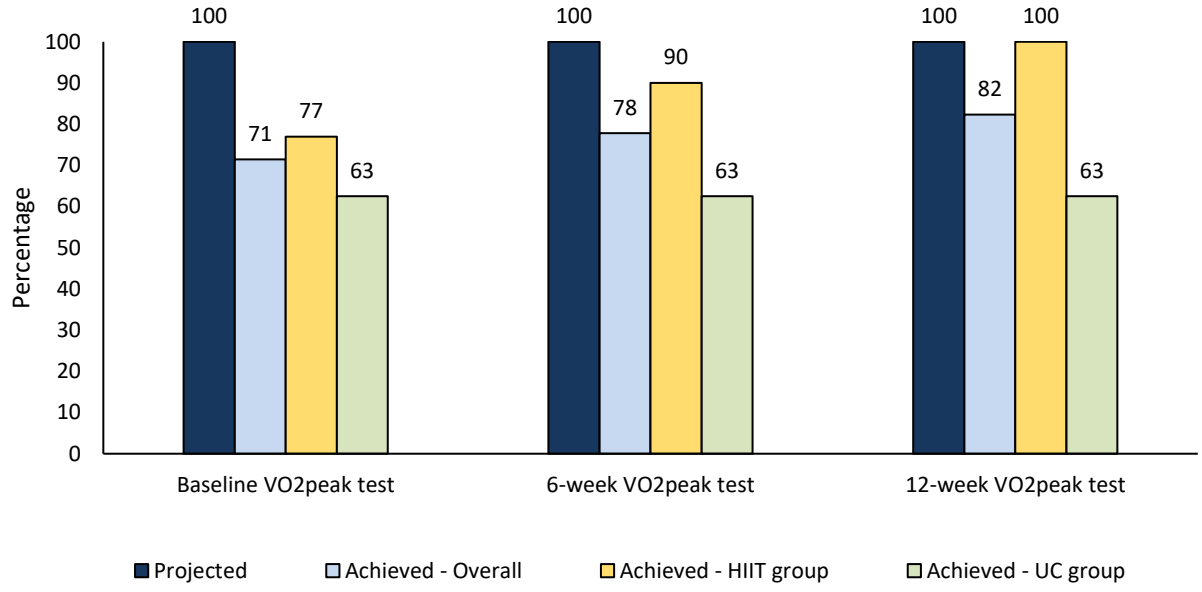
A


100
90
80
70
60
50
40
30
20
10
0
Percentage
50
58
25
16
13
9
Eligibility
Recruitment
Participation
Projected
Achieved

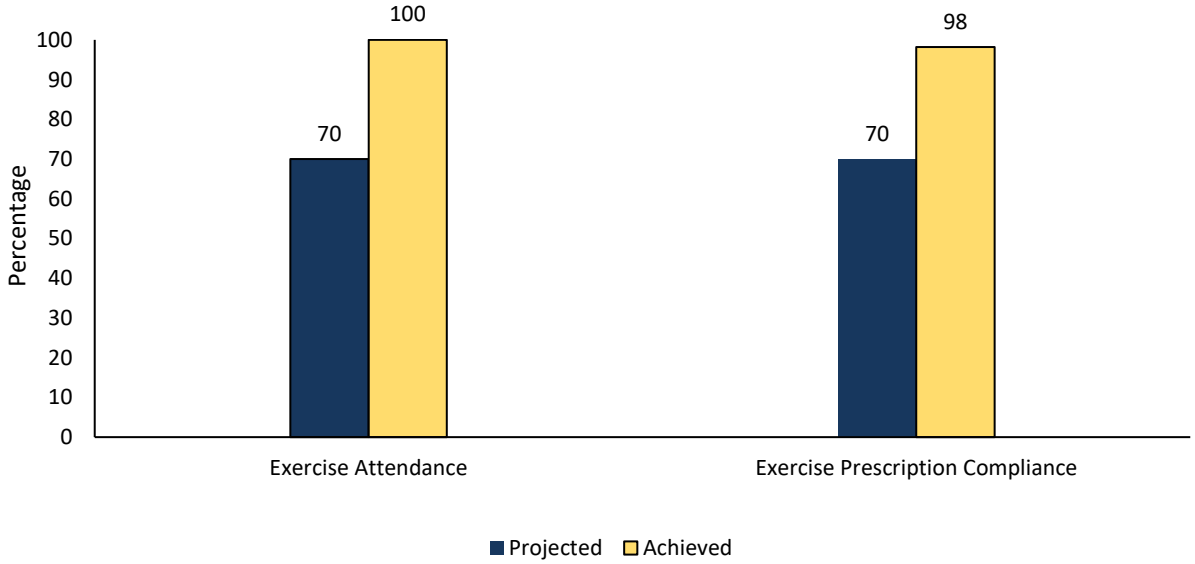
B


100
90
80
70
60
50
40
30
20
10
0
Percentage
80
86
77
100
80
81
69
100
90
90
85
100
100
100
100
100
6-week fitness assessment
12-week fitness assessment
12-week questionnaires
Folllow-up cystoscopy
Projected
Achieved - Overall
Achieved - HIIT group
Achieved - UC group

C


100
71
77
63
100
78
90
63
100
82
100
63
Percentage
100
90
80
70
60
50
40
30
20
10
0
Baseline VO2peak test
6-week VO2peak test
12-week VO2peak test
Projected
Achieved - Overall
Achieved - HIIT group
Achieved - UC group

D


70
100
70
98
Percentage
100
90
80
70
60
50
40
30
20
10
0
Exercise Attendance
Exercise Prescription Compliance
Projected
Achieved

Supplementary Table 1. Adverse events

Event #	Group	Type	Severity	Related to Exercise	Remained in the Study	# of missed or adapted sessions	Omitted from testing
Severe Adverse Event (Grade 3 CTCAE v5.0)							
1	HIIT	Infection and infestations, COVID-19 positive	Hospitalization	Unrelated	No	4	12-week
Moderate Adverse Event (Grade 2 CTCAE v5.0)							
1	HIIT	Arthritis, hip	Limiting instrumental activities of daily living	Pre-existing condition possibly aggravated by exercise.	No	1 session with reduced intensity and duration	Baseline symptom limited VO_{2peak} test, omitted from 6-week and 12-week
2	HIIT	Arthritis (hip), lower limb lymphedema, and wound complication	Local intervention indicated, limiting instrumental activities of daily living	Pre-existing conditions possibly aggravated by exercise and/or extreme heat.	No	5 sessions with reduced intensity and duration	Baseline symptom limited VO_{2peak} test, omitted from 6-week and 12-week
3	HIIT	Infection and infestations, bladder infection	Oral intervention indicated	Unrelated	Yes	0	No
4	HIIT	Infection and infestations, COVID-19 positive	Oral intervention indicated	Unrelated	Yes	3	No
Mild Adverse Event (Grade 1 CTCAE v5.0)							
1	HIIT	Dizziness	Mild unsteadiness or sensation of movement	Related	Yes	0	No
2	HIIT	Dizziness	Mild unsteadiness or sensation of movement	Related	Yes	0	Baseline symptom limited VO_{2peak} test
3	UC	Dizziness	Mild unsteadiness or sensation of movement	Related	Yes	Not applicable	Baseline symptom limited VO_{2peak} test
4	HIIT	Musculoskeletal and connective tissue disorder - Other, calf stiffness	Mild symptoms	Related	Yes	0	No
5	HIIT	Musculoskeletal and connective tissue disorder - Other, shin pain	Mild symptoms	Related	Yes	0	No
6	HIIT	Fatigue	Intervention not indicated	Possibly related, participant exercised while holding BCG	Yes	0	No

				drug in the bladder and reported increased fatigue after the session. Participant preferred not to exercise on same day as BCG therapy.			
7	HIIT	Fatigue	Intervention not indicated	Possibly aggravated by exercise.	Yes	1 session with reduced total duration	No
8	HIIT	Musculoskeletal and connective tissue disorder - Other, ankle pain	Mild symptoms	Pre-existing condition possibly aggravated by exercise.	Yes	0	No
9	UC	Musculoskeletal and connective tissue disorder - Other, knee pain	Mild symptoms	Pre-existing condition possibly aggravated by exercise.	Yes	Not applicable	Baseline, 6-week, and 12-week symptom limited VO_{2peak} test
10	UC	Musculoskeletal and connective tissue disorder - Other, knee pain	Mild symptoms	Pre-existing condition possibly aggravated by exercise.	Yes	Not applicable	12-week symptom limited VO_{2peak} test
11	UC	Vertigo	Mild symptoms	Pre-existing condition possibly aggravated by exercise.	Yes	Not applicable	12-week symptom limited VO_{2peak} test
12	HIIT	Fatigue	Intervention not indicated	Unrelated, participant reported increased fatigue following BCG inductions and canceled exercise sessions.	Yes	7	No
13	HIIT	Headache	Mild pain	Unrelated	Yes	0	No
14	HIIT	Musculoskeletal and connective tissue disorder - Other, back pain	Mild symptoms	Unrelated	Yes	0	No
15	HIIT	Ventricular arrhythmia	Asymptomatic, intervention not indicated	Unrelated	Yes	1	No
16	HIIT	Urinary frequency	Present	Unrelated	Yes	0 – multiple washroom breaks (4) during exercise session	No

17	HIIT	Urinary Tract Pain	Present	Unrelated	Yes	0	No
18	HIIT	Urinary Tract Pain	Present	Unrelated	Yes	0	No

CTCAE: common terminology criteria for adverse events; HIIT: high-intensity interval training; UC: usual care

CHAPTER 5: PAPER 4

Effects of exercise during or after intravesical therapy for bladder cancer on perceptions of exercise motivation, benefits, harms, and barriers: results from a feasibility randomized controlled trial

5.1 Abstract

Background: Understanding the motivational effects of exercise during or after intravesical therapy for non-muscle invasive bladder cancer (NMIBC) may help patients to initiate and sustain exercise behavior. We aimed to explore the motivational outcomes, perceived benefits and harms, and perceived barriers to exercise during or after intravesical therapy for NMIBC. **Methods:** NMIBC patients scheduled to receive intravesical therapy or post therapy surveillance were randomly assigned to usual care (n=8) or exercise (n=13) groups. The exercise group performed thrice-weekly, supervised high-intensity interval training (HIIT) for 12 weeks. Using the theory of planned behavior, we assessed exercise motivation, perceived benefits and harms, and perceived barriers before and/or after the intervention. **Results:** Compared to what they anticipated before the intervention, the HIIT group reported after the intervention that the exercise was meaningfully (defined as a standardized effect size d≥0.33) more enjoyable (mean change=0.6; 95%CI:-0.2 to 1.5, p=0.13, d=0.58), elicited higher confidence (mean change=0.5; 95%CI=-0.5 to 1.4, p=0.32, d=0.49), and was less difficult (mean change=-0.5; 95% CI=-1.5 to 0.4, p=0.24, d=-0.51). Compared to the usual care after the intervention, the HIIT reported meaningfully lower motivation (mean change=-0.5; 95%CI:-2.0 to 0.9, p=0.46, d=-0.58), lower confidence (mean change=-0.4; 95%CI=-1.8 to 1.0, p=0.52, d=-0.46), and higher difficulty (mean change=0.9; 95%CI=-0.1 to 2.0, p=0.080, d=0.84) to exercise on their own for the next 6 months. The most common perceived benefits of exercising during or after intravesical therapy were cardiovascular endurance (91%), physical functioning (91%), and quality of life (82%). The most common exercise barriers were being too busy/having limited time (46%) and joint pain/soreness (36%). **Conclusions:** HIIT during or after intravesical therapy for NMIBC was more motivating than anticipated with many perceived benefits and few perceived harms or

barriers, however, it appeared to reduce confidence and motivation to exercise on their own over the next 6 months.

5.2 Introduction

Non-muscle invasive bladder cancers (NMIBC) are often managed by transurethral resection of the bladder tumor (TURBT) followed by induction intravesical therapy for six weeks. Due to the high rate of bladder cancer recurrence and progression to muscle-invasive bladder cancer (MIBC), NMIBC patients often receive intermittent maintenance therapy for one to three years and repeated surveillance cystoscopy for up to five years [1]. NMIBC imposes a significant strain on both the patient and healthcare system and is ranked among the most expensive cancers to treat [2].

An NMIBC diagnosis and treatments significantly impact physical and mental health-related quality of life [3]. Adhering to recommended lifestyle behaviors, including healthy body weight, diet, and regular physical activity, is associated with better quality of life outcomes [4] and potentially decreased risk of NMIBC recurrence [5]. Patients with bladder cancer, however, do not meet the recommended guidelines for lifestyle behaviors [6]. Specifically, physical activity levels are generally low in this population [6-9], with one in three bladder cancer patients leading a sedentary lifestyle [7]. It is plausible that the negative side effects of bladder cancer and its treatment may impact patients' ability and willingness to adhere to physical activity programs [8].

Exercise, a structured and planned subset of physical activity, may ameliorate some of the functional challenges experienced by NMIBC patients. We recently completed the Bladder cancer and exeRcise trAining during or after intraVesical thErapy (BRAVE) feasibility trial, where we identified that a 12-week supervised exercise program consisting of high-intensity interval training (HITT) was feasible, safe, and positively associated with improvements in several physical functioning parameters in NMIBC patients during or after intravesical therapy compared to usual care [10]. Identifying and understanding the motivational effects of exercise during or after intravesical therapy is important in helping

NMIBC patients initiate and sustain exercise behavior to achieve potential benefits. No study to date, however, has specifically examined the effects of exercise on motivational outcomes of NMIBC patients during or after intravesical therapy.

The Theory of Planned Behavior (TPB) is a social psychological theoretical model that attempts to explain and predict human behavior [11]. The TPB has been used to study exercise motivation and behavior across a broad range of cancer patient groups, including breast [12], lung [13], lymphoma [14], rectal [15], kidney [16], prostate [17], and bladder cancers [8]. The TPB proposes that the immediate precursor of a behavior is the intention (i.e. motivation) to perform the behavior, which indicates the extent of effort a person is willing to exert. In turn, intention is derived from behavioral attitudes, subjective norms, and perceived behavioral control. Behavioral attitudes reflect perceptions of the behavior (i.e., positive or negative evaluation of the behavior) and consist of instrumental attitudes (i.e., perceived benefits and harms) and affective attitudes (i.e., perceived enjoyment and displeasure). Subjective norms represent the perceived social pressure to perform the behavior, including injunctive norms (i.e., perceived support from others) and descriptive norms (i.e., perceived engagement of others in the behavior). Perceived behavioral control refers to individuals' views of the ease or difficulty of performing the behavior and consists of self-efficacy (i.e., confidence in performing the behavior and overcoming barriers), and perceived controllability (i.e., perceived control over the behavior). According to the TPB [11], the more favorable the attitude and perceived norms, and the greater the perceived behavioral control, the stronger the individual's intention to perform the behavior.

By identifying changes in behavioral attitudes, subjective norms, and perceived behavioral control among NMIBC patients who perform the behavior of interest (i.e., exercise during or after intravesical therapy), and those who do not, we can better understand the effects of exercise on motivation and provide information for the design of future exercise

behavioral change interventions [11]. Therefore, the primary purpose of this study was to examine the effects of a supervised HIIT program during or after intravesical therapy on motivational outcomes of NMIBC patients. We also aimed to identify the perceived benefits, harms, and barriers to exercise. Based on previous research in other cancer patient groups who completed a HIIT program [17, 18], we hypothesized that participants assigned to the HIIT intervention group would perceive exercise as more enjoyable and less difficult than anticipated. We also hypothesized that the HIIT group would be more motivated than the usual care group to exercise in the future. Finally, we expected that the HIIT group would report many benefits and few harms and barriers with respect to the HIIT program.

5.3 Methods

Study Design

The BRAVE trial (Clinicaltrials.gov identifier: NCT04593862) has been described elsewhere [19]. Briefly, BRAVE was planned as a phase II, prospective, two-armed, randomized controlled trial examining the safety, feasibility, and effects of a 12-week HIIT program in bladder cancer patients managed by intravesical therapy. The trial was approved by the Health Research Ethics Board of Alberta-Cancer Committee (HREBA. CC-20-0184) and conducted at the University of Alberta, Edmonton, Canada. After completion of baseline testing, participants were randomized to either the HIIT group or the usual care group in a 1:1 ratio using a computer-generated program. Participants were randomized in block sizes of four or six and stratified by their current treatment protocol (TURBT + single instillation, TURBT + induction phase, TURBT + induction + maintenance phase, or surveillance). The allocation sequence was generated independently and concealed from the study coordinator who assigned participants to groups. The BRAVE trial is reported in line with the Consolidated Standards of Reporting Trials (CONSORT) extension to randomized pilot and feasibility trials [20].

Participants and Procedures

Participants were recruited from the Northern Alberta Urology Centre at the Kaye Edmonton Clinic in Edmonton, Alberta, Canada. All participants provided written informed consent for study participation. Eligibility criteria included men and women who (1) were ≥18 years old, (2) had a confirmed diagnosis of NMIBC (clinical stage cis, Ta, or T1), (3) were scheduled for induction intravesical therapy, maintenance intravesical therapy, or surveillance, and (4) living in Edmonton or surrounding area within 40 kilometers of the fitness center. Participants were excluded if they (1) were not medically cleared to participate in the exercise intervention, (2) had contraindications for cardiopulmonary stress and/or physical fitness tests, (3) were already meeting the exercise guidelines for cancer survivors, (4) were unable to read and comprehend English, and (5) were not willing to be randomized to a supervised exercise training program or usual care for 12 weeks.

Intervention

Participants in the exercise group were asked to complete a thrice-weekly supervised HIIT program for 12 weeks. The HIIT sessions consisted of four intervals of four minutes (4x4 minutes) at a workload corresponding to vigorous intensity (75% to 95% of the VO_{2peak}) alternating with 3-minute recovery intervals at a workload corresponding to 40% of the VO_{2peak}. All the HIIT sessions included a 5-minute warm-up at a workload corresponding to 60% of the VO_{2peak} and a 5-minute cool-down at a workload corresponding to 40% of the VO_{2peak} corresponding to 35 minutes in total. Progression was gradual with changes in the intensity by 5% every two weeks for the first 6 weeks (75% to 85%VO_{2peak} of the baseline assessment), and 5% every two weeks following the 6-week assessment (85% to 95%VO_{2peak} of the 6-week assessment). Participants in the HIIT group who were symptom-limited and did not reach the criteria for a valid VO_{2peak} test had the exercise prescription based on the 30-second average of the VO_2 achieved during the baseline and 6-week assessment with

adjustments based on rate of perceived exertion to match the initial planned exercise prescription (somewhat strong to very strong, RPE 4-7 in 0 to 10 scale).

Exercise sessions were completed either on a treadmill or a cycle ergometer based on participants' mobility and balance conditions. Treadmill speed and grade, or pedal frequency and resistance of the cycle ergometer, were selected to match the targeted percentage of $\dot{V}O_{2peak}$ based on the baseline and the 6-week fitness levels using standardized equations [21]. The usual care group was asked not to participate in any new or additional exercise above their normal activities for the duration of the study. After the post-intervention fitness assessments and the follow-up cystoscopy, the usual care group was offered a 4-week supervised HIIT program at our facility and/or referred to a 12-week community-based exercise program.

Outcomes Measures

Motivational Outcomes

Motivational outcomes were derived from key constructs of the TPB [11] and included instrumental (beneficial) and affective (enjoyable) attitudes, subjective norms (support), intention (motivation), and perceived behavioral control (difficulty, confidence, and controllability). The questions to assess each TPB construct were on a 5-point Likert scale with identical response options at all assessment time points (i.e., 1=not at all, 2=a little bit, 3=somewhat, 4=quite a bit, and 5=very much). Participants were assessed at baseline and 12 weeks (post-intervention). At baseline (prior randomization), all participants were asked to anticipate how beneficial, enjoyable, supported, motivated, difficult, confident, and controllable it would be for them to exercise for the next 12 weeks during or after their intravesical therapy. At post-intervention, participants in the HIIT group were asked to complete a retrospective evaluation of their actual motivation experienced in the past 12 weeks of exercise during or after their intravesical therapy (e.g., how beneficial was it, how

enjoyable was it). At the same assessment time point (post-intervention), participants in both groups were asked to anticipate how beneficial, enjoyable, supported, motivated, difficult, confident, and controllable it would be for them to exercise on their own over the next 6 months, with an additional item about their exercise plan (i.e., “Do you have a specific plan for where, when, and how you are going to do exercise over the next six months?”).

Perceived benefits/harms and barriers

Perceived benefits and harms of the exercise program were assessed in the exercise group after completing the supervised HIIT using a 20-item questionnaire that listed the main health-related fitness and patient-reported outcomes assessed in the study, including questions relevant to NMIBC patients (e.g., fear of bladder cancer recurrence and progression, urinary symptoms, and intravesical treatment completion). Participants were asked, “What effect, if any, did the exercise program have on each of the following for you?”. Responses were assessed using a 7-point scale ranging from 1-3 (very much – somewhat – slightly worse) to 4 (no change) to 5-7 (slightly – somewhat – very much better). Perceived barriers to exercise in the exercise group were also measured post-intervention. A 17-item questionnaire listing expected side effects from intravesical therapy (e.g., urinary incontinence, feeling unwell) and common barriers to exercise in cancer survivors (e.g., medical appointments, fatigue) was used at the 12-week assessment time point. Participants were asked, “How much of a barrier was each of the following factors for you in trying to do the exercise program?". Responses were assessed using a 7-point scale ranging from 1 (not at all) to 3 (somewhat) to 5 (a fair bit) to 7 (very much) with higher scores indicating a greater perceived barrier.

Statistical analysis

Descriptive statistics were used to report baseline motivational outcomes, perceived benefits and harms, and perceived barriers to exercise during or after intravesical therapy.

Paired t-test was used to assess changes in anticipated versus experienced motivational outcomes before and after the intervention within the HIIT group. Between-group mean differences in motivational outcomes for exercising over the next 6 months were analyzed using analyses of covariance with adjustment for age, baseline value of the motivational outcome, and current treatment protocol. Given that this was a small feasibility study, results were interpreted for their meaningful differences of at least a small-to-medium standardized effect size of $d \geq 0.33$ [22]. Perceived benefits were presented as the percentage of patients who reported an outcome improved (score of 5-7) whereas perceived harms were reported as the percentage of patients who reported an outcome had worsened (score of 1-3). Perceived barriers were presented as the percentage of patients who reported each barrier (i.e., Not at all=score 1, Somewhat=score 2-4, and Very much=score 5-7). All randomized participants who had baseline and follow-up data were included in the analyses. The analyses were performed using SPSS version 28 (SPSS Inc., Chicago, IL).

5.4 Results

Flow of participants through the BRAVE trial and the baseline characteristics of the sample are reported elsewhere. Briefly, 21 of 129 (16.3%) eligible patients were randomized to the HIIT (n=13) or usual care (n=8) over a 24-month recruitment period. The main reason for ineligibility was significant medical contraindications to exercise (58.8%). Common reasons for refusal included lack of interest/declined contact (39.8%). Participants had a mean age of 69.8±9.0 years and were predominantly male (90%), Caucasian (86%), married (81%), overweight or obese (96%), ex-smokers (57%), and had more than three comorbidities (57%). In terms of bladder cancer profile, 52% had T1 NMIBC, 95% had high-grade NMIBC, and 48% had a concurrent carcinoma in situ. Regarding treatment status, 57% were being treated for a recurrence, 62% were on maintenance intravesical therapy, and 14% were initiating induction intravesical therapy. Motivational outcome data were obtained from

11/13 (84.6%) participants in the HIIT group and 8/8 (100%) participants in the usual care group. Two participants from the HIIT group who withdrew from the intervention due to medical conditions (i.e., COVID-19 and hip pain) did not returned the 12-week follow-up questionnaires. The total number of attended sessions was 341/450 (75.8%), and the median exercise attendance was 100% with 98% compliance with the exercise protocol.

Motivational outcomes

Table 5-1 describes the baseline motivation of NMIBC patients to exercise during or after their intravesical therapy. The groups were balanced on baseline motivation. Overall, participants expected that exercise during or after intravesical therapy would be quite beneficial (4.3±0.8), somewhat/quite enjoyable (3.5±1.1), somewhat difficult (2.6±1.1), and somewhat/quite controllable (3.7±0.9). Participants were also quite motivated (4.0±0.9), somewhat/quite confident (3.9±0.9), and felt they would be quite supported by family/friends (4.2±1.1).

Table 5-2 reports the changes in exercise motivation among participants assigned to the 12-week HIIT intervention during or after their intravesical therapy. There were no statistically significant differences in the anticipated versus experienced outcomes. There were, however, meaningful increases in enjoyment (mean change=0.6; 95%CI:-0.2 to 1.5, p=0.13, d=0.58), support (mean change=0.4; 95%CI=-0.5 to 1.2, p=0.37, d=0.33), confidence (mean change=0.5; 95%CI=-0.5 to 1.4, p=0.32, d=0.49), and a meaningful decrease in difficulty (mean change=-0.5; 95% CI=-1.5 to 0.4, p=0.24, d=-0.51).

The effects of the supervised HIIT program on motivation for exercising over the next six months after the BRAVE trial is reported in Table 5-3 and illustrate in Figure 5-1. There were no statistically significant differences in the HIIT group versus usual care, however, the HIIT group anticipated that exercising over the next six months would be meaningfully less enjoyable (mean change=-0.4; 95%CI:1.7 to 0.9, p=0.55, d=-0.35), they would be less

motivated (mean change=-0.5; 95%CI:-2.0 to 0.9, p=0.46, d=-0.58) and less confident (mean change=-0.4; 95%CI=-1.8 to 1.0, p=0.52, d=-0.46), and it would be more difficult (mean change=0.9; 95%CI=-0.1 to 2.0, p=0.080, d=0.84) compared to the usual care group. The HIIT group also reported meaningfully higher controllability (mean change=0.4; 95%CI=-0.4 to 1.3, p=0.33, d=0.45) and a more detailed plan (mean change=0.2; 95% CI=-1.2 to 1.6, p=0.77, d=0.46) compared to the usual care group. The patterns of change in motivational outcomes across the intervention are illustrated in Figure 5-2.

Perceived Benefits/Harms and Barriers

Table 5-4 lists the perceived benefits and harms of HIIT during or after intravesical therapy for patients with NMIBC. The most common reported benefits following the supervised HIIT were for cardiovascular endurance (91%), physical functioning (91%), quality of life (82%), fatigue (73%), and preparation for additional treatments (73%). There were three outcomes with reported harms: fear/worry of cancer recurrence or progression (9%), treatment efficacy (10%), and sense of control over bladder cancer (9%).

Table 5-5 lists the perceived barriers to do HIIT during or after intravesical therapy for patients with NMIBC. When combining the percentage of patients who reported "somewhat" and "very much" as a barrier, the most common reported barriers for the supervised HIIT during or after intravesical therapy were too busy/limited time (46%), joint pain or soreness (36%), followed by fatigue, lack of motivation, muscle pain, and feeling unwell (27% each).

5.5 Discussion

The primary aim of this study was to examine the effects of a supervised HIIT program on motivational outcomes in patients with NMIBC during or after intravesical therapy. Although not statistically significant, the HIIT group experienced meaningful positive changes in enjoyment, support, and confidence following the 12-week supervised

exercise program. Contrary to our hypothesis, the HIIT group reported less motivation and confidence in their ability to exercise in the future compared to the usual care group. The HIIT group also anticipated that exercising on their own would be meaningfully less enjoyable and more difficult despite higher control and a more specific plan than the usual care group.

Overall, NMIBC patients were quite motivated to exercise during or after their intravesical therapy. Instrumental attitude (i.e., benefit) was the strongest construct at baseline, followed by subjective norms (i.e. support) and intention (i.e., motivation). High baseline levels of benefits, support, and motivation are commonly seen in clinical exercise trials among cancer patients [13, 15-18]. These findings are potentially due to recruitment bias of participants who are more interested and aware of the general benefits of exercise and have more support from family [15, 18]. Previous studies in cancer patients have identified spouse and physicians' approval as important normative beliefs correlated with subjective norm and exercise behavior [23, 24]. In the BRAVE trial, 81% of the participants were married and possibly received support from their spouses to join the study, moreover, all of the participants were referred by their treating oncologists to the study. Finally, the characteristics of the study intervention, which included a supervised exercise program in a research-based facility, potentially contributed to high levels of anticipated support. Future studies are needed to identify the salient beliefs towards exercise and comprehend why NMIBC patients held certain attitudes, subjective norms, and perception of control concerning exercising during and following intravesical therapy.

To the best of our knowledge, the BRAVE study is pioneering in its investigation of how supervised HIIT intervention impacts the motivational outcomes of NMIBC patients during or after intravesical therapy. Nonetheless, the effects of a supervised HIIT program on exercise motivation of other cancer patient groups have been assessed in two previous

studies: 1) the ERASE trial, which included prostate cancer patients on surveillance [17] and 2) the EXERT trial in rectal cancer patients on chemoradiation therapy [18]. Both studies used the TPB to assess prospective (i.e., anticipated) and retrospective (i.e., experienced) motivational constructs. Additionally, in both studies, the exercise program consisted of bouts of 2-minute high-intensity intervals (85%-95% of $VO_{2\ peak}$) followed by 2-minute active recovery intervals, with gradual progression of the number of high-intense intervals and/or intensity. In the ERASE trial, the HIIT intervention was experienced as significantly more enjoyable, and elicited higher motivation, control, and confidence and was meaningfully less difficult than anticipated [17]. In the EXERT trial, with rectal cancer patients during chemoradiation therapy, the results were non-statistically significant but suggested meaningful positive changes in enjoyment, control, and confidence, and lower difficulty [18]. Although the BRAVE study adopted a different HIIT protocol (i.e., 4 high-intensity bouts of 4 minutes interspersed by a 3-minute recovery), the intervention was also perceived as meaningful more enjoyable and less difficult and elicited higher confidence than anticipated.

Commonly, in all three studies (ERASE, EXERT, and BRAVE trials) the exercise program was prescribed based on each participant's baseline cardiopulmonary fitness assessment with gradual increments, and conducted in an exercise oncology research-based facility [17, 18]. In the BRAVE trial specifically, participants had the option to perform the fitness assessments and exercise program on a treadmill or a cycle ergometer considering their mobility and balance issues. Additionally, adjustments to the treadmill speed and grade, or pedal frequency and resistance of the cycle ergometer, were made according to metabolic equivalent equations for the estimation of energy expenditure relative to the individual's tests results [25].This strategy was essential to maintain the desired intensity of the training session considering participant's needs and preferences, contributing to satisfactory levels of

adherence (78.5%) and high compliance (98%). The TPB postulates that performance of a behavior results in information about the actual (as opposed to anticipated) outcome experiences [11]. Therefore, taking part in a tailored exercise program with gradual progress in intensity potentially contributed to changes in individuals' views of the difficulty of a HIIT program and increased their confidence in performing the exercise. Additionally, positive changes in enjoyment can potentially be attributed to the inherent characteristics of the HIIT program (i.e., the interval changes in stimuli within the session) [26, 27], and to the peer interactions including the exercise specialists supervising the sessions and other cancer patients exercising at the same facility.

Conversely, in the BRAVE trial the HIIT group elicited small-to-medium effects on support at post-intervention, while no changes were observed in the two other HIIT studies among cancer patients [17, 18]. As previously mentioned, subjective norm was measured as the overall perceived social support to perform the HIIT intervention. In the BRAVE study, two out of 13 participants in the HIIT group requested to bring their spouse to some of the supervised sessions for logistical (the spouse would drive them) and personal (companionship) reasons and may have contributed to our meaningful findings. Second, worthy of note, the BRAVE study started after lifting the social restrictions of the COVID-19 pandemic, in a post-isolation era, contributing to increased access to support networks (i.e., exercising among peers). Finally, previous studies had slightly higher levels of anticipated support at baseline, leading to ceiling effects on these outcomes, when compared to the BRAVE trial [17, 18].

At the 12-week follow-up assessment, all participants were asked about their motivation to exercise on their own over the next six months. We found that the HIIT group, compared to the usual care group, reported meaningful lower exercise intention, affective attitudes, and some constructs of perceived behavioral control. This means that at the end of

the study, those in the HIIT group felt lower motivation and confidence to exercise in the future, and that the exercise would be less enjoyable and more difficulty. This finding is concerning as intention and perceived behavioral control are independent predictors of exercise behavior among bladder cancer survivors [8]. A decrease in motivation following a supervised exercise intervention has been observed among non-small cell lung cancer survivors [13]. As suggested by Peddle McIntyre, the transition from a highly supervised exercise program to a self-directed program may impact motivation [13]. It is plausible that the anticipated absence of a an exercise specialist providing a tailored exercise prescription and encouraging them through the sessions, potentially contributed to decreased levels of perceived behavioral control (i.e., lower confidence and higher difficulty) which in turn may moderate the effect of intention on behavior as postulated by the TPB [11].

Interestingly, and similar to the ERASE trial, participants from the HIIT group reported meaningfully higher controllability and a detailed plan to exercise in the future, compared to the usual care group. The TPB explains that the degree of an individual's control over the behavior depends on their ability to overcome barriers and on the presence of facilitating factors, such as previous experience [28]. We speculate that the structured supervise program possibly provided the participants with some experience and guidance on how to perform an interval training program, how to monitor exercise intensity, and how to manage their chronic conditions to overcome barriers and perform the behavior. The majority of the participants from the BRAVE trial were able to successfully navigate through potential NMIBC-related constrains including treatment medical appointments, fatigue, urinary symptoms, and additional comorbidities, potentially influencing control beliefs regarding exercise during or after intravesical therapy. Planning has been added to the TPB as an attempt to overcome the intention-behavior gap [29]. For bladder cancer survivors specifically, planning was found to be another independent predictor of exercise, therefore

having a more specific plan to carry out the behavior can assist in translating intentions into actions [8]. Although the HIIT group reported a meaningful higher plan, it was the lowest construct observed, meaning that NMIBC patients need education on how to develop a specific plan for where, when, and how to exercise on their own.

Our study also aimed to explore benefits, harms, and barriers to exercise during or after intravesical therapy for NMIBC patients. Health-related fitness outcomes were the most common benefits reported following the exercise intervention, including cardiovascular endurance and physical functioning. This finding is aligned with our objective measurements showing significant improvements in several physical functioning parameters [10], and with previous studies [17, 18]. Furthermore, other common reported benefits included quality of life, fatigue, and preparation for additional treatment. These findings are particularly important for NMIBC patients due to the prolonged period of time on maintenance therapy and the frequent intravesical treatment and cystoscopies [1], negatively impacting their quality of life and symptoms like fatigue [3, 30, 31]. Overall, exercise has been recommended during and after cancer treatment in many cancer patient groups because of its efficacy in ameliorating treatment-related side effects and improving quality of life [32, 33]. Future analysis of the BRAVE trial will explore the effects of the HIIT on important patient-reported outcomes, including fatigue and quality of life.

Exercise harms were uncommon (≤10%), but one participant reported increased fear/worry of cancer recurrence or progression, and another reported slightly worse treatment efficacy and sense of control over bladder cancer. Patients on intravesical therapy for NMIBC are required to hold the drug inside the bladder for one or two hours after treatment instillation [34]. If patients are experiencing bladder cancer-related urinary symptoms such as urgency, frequency, or bladder spasms, the ability to keep the medication in the bladder for the required period of time is impaired. It is currently unknown either aerobic exercise plays

any influence on bladder cancer symptoms or treatment efficacy. Previous studies have investigated the effects of pelvic floor muscle training on bladder function (e.g., urinary incontinence) of cancer patients, including gynecological cancers [33] and prostate cancer [34], the level of evidence differed among cancer group. Future studies should address this important issue for patients with NMIBC on intravesical treatment and investigate either exercise helps NMIBC patients to hold the drug for the necessary time, as well as the effects of exercise on bladder cancer symptoms and treatment efficacy.

With respect to the barriers of exercise during or after intravesical therapy, participants in the HIIT group reported too busy/limited time as the most common limiting factor followed by joint pain or soreness. Lack of time is a prominent barrier to exercise for survivors of varied types of cancer [35]. Although HIIT has been suggested as a more time-efficient exercise option [35], time commitment should include the time to perform the exercise, the time required for travel to and from the exercise facility, and time spent for hygiene following the activity [36]. In order to address this barrier and contribute to a sustained behavior, education on effective time management strategies may be necessary, including prioritizing, scheduling, as well as alternate locations and home-based exercise programs. Our finding of joint pain or soreness as another common reported barrier to the HIIT was somewhat consistent with the findings from the ERASE trial. Common to both studies, sample characteristics included predominantly elderly comorbid population with pre-existing joint or age-related musculoskeletal issues that were potentially exacerbated by the exercise program. In the BRAVE study, 5 out of the 13 (38%) participants allocated to the exercise group had arthritis, therefore, some level of join pain or soreness is unsurprising. However, two participants with hip arthritis experienced considerable aggravation of their baseline condition leading to discontinuation of the exercise program and fitness assessments. Details of the adverse events have been reported elsewhere [10]. Interestingly, NMIBC-

specific barriers, such as tumor resection recovery, having intravesical therapy and urinary incontinence, were not commonly reported as significant barriers to the HIIT (9-11%), indicating that having NMIBC or going through intravesical therapy are not limiting factors to perform a HIIT program. Alternative exercise modalities and intensities should be tested in the future.

Several strengths and limitations of this study should be acknowledged. Strengths of our study include (1) the first to explore the motivational outcomes of exercise in NMIBC patients during or after intravesical therapy, (2) the unique and understudied patient population, (3) the use of a validated theoretical model to assess constructs of motivation, (4) the assessment of anticipated and experienced motivational outcomes, (5) the assessment of perceived benefits, harms, and barriers to exercise during or after intravesical therapy, and (6) the randomized controlled design allowing to explore prospective motivation to exercise based on group allocation (usual care and exercise groups). Limitations of the study include (1) the small sample size with limited statistical power, (2) the inability to distinguish motivational outcomes, benefits and harms, and barriers based on treatment timeline (during versus after intravesical therapy), (3) the single item assessments of motivational constructs, and (4) the potential selection bias toward participants who are more motivated to exercise.

In conclusion, the BRAVE study provides important hypothesis-generating data that highlights potential effects of exercise on motivational outcomes of NMIBC patients during or after intravesical therapy. Based on our preliminary findings, NMIBC patients are quite motivated to initiate a supervised exercise program. Moreover, the HIIT elicited general positive motivational outcomes and perceived benefits with minimal perceived harms or barriers. The transition, however, to a self-directed program may be motivationally challenging to these patients. More investigation is necessary to validate our findings, however, future interventions among NMIBC patients should consider applying evidence-

based and theory-informed interventions targeting affective attitudes, confidence, and planning in an attempt to prevent or overcome decreases in motivation and promote a sustained behavior. Moreover, future research is needed to understand specific motives and barriers to exercise at different phases (i.e. induction therapy, maintenance therapy, surveillance) along the treatment continuum of NMIBC.

5.6 References

1. National Comprehensive Cancer Network [NCCN], *NCCN Clinical Practice Guidelines on Oncology: Bladder Cancer, Version 3.2023*. 2023.
2. Avritscher, E.B.C. and C.D.G. Cooksley, B.Sabichi, A. L.Hamblin, L.Dinney, C. P.Elting, L. S., *Clinical model of lifetime cost of treating bladder cancer and associated complications* Urology, 2006. **68**(3): p. 549-553.
3. Jung, A., et al., *Quality of Life in Non-Muscle-Invasive Bladder Cancer Survivors: A Systematic Review.* Cancer Nurs, 2019. **42**(3): p. E21-E33.
4. Vidra, N., et al., *Longitudinal associations of adherence to lifestyle recommendations and health-related quality of life in patients with non-muscle invasive bladder cancer.* Int J Cancer, 2023. **152**(10): p. 2032-2042.
5. van Zutphen, M., et al., *Adherence to lifestyle recommendations after non-muscle invasive bladder cancer diagnosis and risk of recurrence.* Am J Clin Nutr, 2023. **117**(4): p. 681-690.
6. Chung, J., et al., *Modifiable lifestyle behaviours impact the health-related quality of life of bladder cancer survivors.* BJU Int, 2020. **125**(6): p. 836-842.
7. Koelker, M., et al., *Impact of exercise on physical health status in bladder cancer patients.* Can Urol Assoc J, 2023. **17**(1): p. E8-E14.
8. Karvinen, K.H., et al., *A prospective study of the determinants of exercise in bladder cancer survivors using the Theory of Planned Behavior.* Support Care Cancer, 2009. **17**(2): p. 171-9.
9. Wang , E.Y., et al., *Diet, Physical Activity, and Smoking in Patients Living with Non-Muscle Invasive Bladder Cancer*. 2023: *Annals of Urologic Oncology*. p. 28-34.

10. Arthuso, F.Z., et al., *Feasibility, safety, and preliminary efficacy of high-intensity interval training during or after intravesical therapy for bladder cancer patients*. 2024: Manuscript in preparation.

11. Ajzen, I., *The theory of planned behavior* 1991, Organ Behav Hum Decis Process p. 179-211.

12. Courneya, K.S., et al., *Motivation for Different Types and Doses of Exercise During Breast Cancer Chemotherapy: a Randomized Controlled Trial.* Ann Behav Med, 2016. **50**(4): p. 554-63.

13. Peddle-McIntyre, C.J., et al., *Changes in motivational outcomes after a supervised resistance exercise training intervention in lung cancer survivors.* Cancer Nurs, 2013. **36**(1): p. E27-35.

14. Courneya, K.S., et al., *Effects of supervised exercise on motivational outcomes and longer-term behavior.* Med Sci Sports Exerc, 2012. **44**(3): p. 542-9.

15. Morielli, A.R., et al., *Exercise motivation in rectal cancer patients during and after neoadjuvant chemoradiotherapy.* Support Care Cancer, 2016. **24**(7): p. 2919-26.

16. Trinh, L., et al., *Changes in motivational outcomes following a supervised physical activity program with behavioral counseling in kidney cancer survivors: a pilot study.* Psychooncology, 2015. **24**(9): p. 1204-7.

17. Kang, D.W., et al., *Effects of supervised high-intensity interval training on motivational outcomes in men with prostate cancer undergoing active surveillance: results from a randomized controlled trial.* Int J Behav Nutr Phys Act, 2022. **19**(1): p. 126.

18. Arthuso, F.Z., et al., *Effects of Exercise on Motivational Outcomes in Rectal Cancer Patients During and After Neoadjuvant Chemoradiation: A Phase II Randomized Controlled Trial.* Semin Oncol Nurs, 2023. **39**(4): p. 151419.

19. Arthuso, F.Z., et al., *Bladder cancer and exeRcise trAining during intraVesical thErapy-the BRAVE trial: a study protocol for a prospective, single-centre, phase II randomised controlled trial.* BMJ Open, 2021. **11**(9): p. e055782.

20. Eldridge, S.M., et al., *CONSORT 2010 statement: extension to randomised pilot and feasibility trials.* BMJ, 2016. **355**: p. i5239.

21. Liguori, G., et al., *ACSM's Guidelines for Exercise Testing and Prescription* . Eleventh edition ed. 2021, Philadelphia: Wolters Kluwer.

22. Brucker, P.S., et al., *General population and cancer patient norms for the Functional Assessment of Cancer Therapy-General (FACT-G).* Eval Health Prof, 2005. **28**(2): p. 192-211.

23. Courneya, K.S. and C.M. Friedenreich, *Utility of the theory of planned behavior for understanding exercise during breast cancer treatment.* Psychooncology, 1999. **8**(2): p. 112-22.

24. Courneya, K.S., et al., *Understanding exercise motivation in colorectal cancer patients: A prospective study using the theory of planned behavior.* 1999: *Rehabilitation Psychology*. p. 68-84.

25. Riebe, D., Ehrman, J. K., Liguori, G., & Magal, M. (Eds.). *ACSM's guidelines for exercise testing and prescription* Tenth edition ed. 2018: Wolters Kluwer.

26. Thum, J.S., et al., *High-Intensity Interval Training Elicits Higher Enjoyment than Moderate Intensity Continuous Exercise.* PLoS One, 2017. **12**(1): p. e0166299.

27. Schlüter, K., et al., *Feasibility of Two High-Intensity Interval Training Protocols in Cancer Survivors.* Med Sci Sports Exerc, 2019. **51**(12): p. 2443-2450.

28. Ajzen, I., *The theory of planned behavior: Frequently asked questions.* 2020: *Hum Behav & Emerg Tech* . . p. 314-324.

29. Norman, P. and M. Conner, *The Theory of Planned Behavior and Exercise: Evidence for the Mediating and Moderating Roles of Planning on Intention-Behavior Relationships*. 2005: Journal of Sport & Exercise Psychology p. 488-504.

30. Nayak, A., J. Cresswell, and P. Mariappan, *Quality of life in patients undergoing surveillance for non-muscle invasive bladder cancer-a systematic review.* Transl Androl Urol, 2021. **10**(6): p. 2737-2749.

31. Koch, G.E., W.W. Smelser, and S.S. Chang, *Side Effects of Intravesical BCG and Chemotherapy for Bladder Cancer: What They Are and How to Manage Them.* Urology, 2021. **149**: p. 11-20.

32. Ligibel, J.A., et al., *Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline.* J Clin Oncol, 2022. **40**(22): p. 2491-2507.

33. Campbell, K.L., et al., *Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable.* Med Sci Sports Exerc, 2019. **51**(11): p. 2375-2390.

34. Bhindi, B., et al., *Canadian Urological Association guideline on the management of non-muscle-invasive bladder cancer - Full-text.* Can Urol Assoc J, 2021. **15**(8): p. E424-E460.

35. Clifford, B.K., et al., *Barriers and facilitators of exercise experienced by cancer survivors: a mixed methods systematic review.* Support Care Cancer, 2018. **26**(3): p. 685-700.

36. Chao, D., C.G. Foy, and D. Farmer, *Exercise adherence among older adults: challenges and strategies.* Control Clin Trials, 2000. **21**(5 Suppl): p. 212S-7S.

Table 5-1. Motivation of bladder cancer patients prior to randomization to perform the 12-week supervised high intensity interval training program during or after intravesical therapy.

Motivation Variables	**Overall (N=21)** Mean (SD)	**HIIT (N=13)** Mean (SD)	**UC (N=8)** Mean (SD)
Beneficial	4.3 (0.8)	4.3 (0.8)	4.3 (0.9)
Enjoyable	3.5 (1.1)	3.6 (1.3)	3.4 (0.7)
Supported	4.2 (1.1)	4.4 (0.9)	4.0 (1.4)
Motivated	4.0 (0.9)	4.0 (1.0)	4.1 (0.6)
Difficult	2.6 (1.1)	2.8 (1.1)	2.1 (1.0)
Controllable	3.7 (0.9)	3.5 (0.9)	4.0 (0.9)
Confident	3.9 (0.9)	3.8 (0.9)	3.9 (1.0)

Motivational variables assessed on a 5-point scale from 1 (not at all) to 5 (very much). HIIT, high intensity interval training; UC, usual care

Table 5-2. Changes in motivation for the 12-week supervised high intensity interval training program in bladder cancer patients assigned to the exercise intervention during or after intravesical therapy (n=11).

Variables	Baseline (Anticipated)	Postintervention (Experienced)	Mean change		
	Mean (SD)	Mean (SD)	Mean (95% CI)	*p*	*d*
Beneficial	4.2 (0.8)	4.1 (1.2)	-0.1 (-1.2 to 1.0)	0.85	-0.11
Enjoyable	3.5 (1.3)	4.1 (1.3)	0.6 (-0.2 to 1.5)	0.13	0.58
Supported	4.3 (0.9)	4.6 (0.7)	0.4 (-0.5 to 1.2)	0.37	0.33
Motivated	3.8 (1.0)	3.8 (1.3)	0.0 (-1.2 to 1.2)	1.00	0.00
Difficult	2.9 (1.2)	2.4 (0.9)	-0.5 (-1.5 to 0.4)	0.24	-0.51
Controllable	3.4 (0.9)	3.5 (1.2)	0.2 (-0.9 to 1.3)	0.72	0.21
Confident	3.6 (0.8)	4.1 (1.2)	0.5 (-0.5 to 1.4)	0.32	0.49

Motivational variables assessed on a 5-point scale from 1 (not at all) to 5 (very much).

Table 5-3. Effects of the 12-week high intensity interval training program on motivation for exercising over the next 6 months in bladder cancer patients during or after intravesical therapy.

Variables	Mean (SE)	Adjusted between-group difference[1]		
		Mean (95% CI)	*p*	*d*
Beneficial				
HIIT (n=11)	4.2 (0.3)	0.0 (-1.0 to 0.9)	0.92	-0.06
Usual Care (n=8)	4.3 (0.3)			
Enjoyable				
HIIT (n=11)	3.4 (0.4)	-0.4 (-1.7 to 0.9)	0.55	-0.35
Usual Care (n=8)	3.8 (0.5)			
Supported				
HIIT (n=11)	4.4 (0.2)	0.2 (-0.4 to 0.9)	0.44	0.23
Usual Care (n=8)	4.2 (0.2)			
Motivated				
HIIT (n=11)	3.5 (0.4)	-0.5 (-2.0 to 0.9)	0.46	-0.58
Usual Care (n=8)	4.0 (0.5)			
Difficult				
HIIT (n=11)	2.9 (0.3)	0.9 (-0.1 to 2.0)	0.080	0.84
Usual Care (n=8)	2.0 (0.4)			
Controllable				
HIIT (n=11)	4.3 (0.2)	0.4 (-0.4 to 1.3)	0.33	0.45
Usual Care (n=8)	3.9 (0.3)			
Confident				
HIIT (n=11)	3.5 (0.4)	-0.4 (-1.8 to 1.0)	0.52	-0.46
Usual Care (n=8)	3.9 (0.5)			
Specific Plan				
HIIT (n=11)	3.0 (0.4)	0.2 (-1.2 to 1.6)	0.77	0.46
Usual Care (n=8)	2.8 (0.5)			

Motivational variables assessed on a 5-point scale from 1 (not at all) to 5 (very much). HIIT, high intensity interval training.
[1] Adjusted for age, baseline value of the outcome, and current treatment status

Table 5-4. Perceived benefits and harms of the 12-week high intensity interval training program during or after intravesical therapy in bladder cancer patients assigned to the exercise intervention.

Variables	Mean (SD)	Percentage distribution		
		Improved[a]	No change[b]	Worsened[c]
Cardiovascular endurance	6.3 (1.0)	90.9%	9.1%	0%
Physical functioning	6.0 (1.0)	90.9%	9.1%	0%
Quality of life	5.8 (1.2)	81.8%	18.2%	0%
Fatigue	5.5 (1.2)	72.7%	27.3%	0%
Preparation for additional treatments	5.4 (1.1)	72.7%	27.3%	0%
Ability to recover from TURBT (n=10)	5.2 (1.2)	60.0%	40.0%	0%
Self-esteem	5.2 (1.3)	54.5%	45.5%	0%
Treatment efficacy (n=10)	5.1 (1.3)	60.0%	30.0%	10.0%
Stress	5.1 (1.3)	45.5%	54.5%	0%
Body weight/shape	5.0 (1.1)	54.5%	45.5%	0%
Stop thinking about bladder cancer	5.0 (1.3)	45.5%	54.5%	0%
Depressed feelings	4.9 (1.4)	36.4%	63.6%	0%
Sense of control over bladder cancer	4.8 (1.3)	45.5%	45.5%	9.1%
Fear/worry of cancer recurrence/progression	4.8 (1.5)	45.5%	45.5%	9.1%
Sleep quality	4.8 (1.3)	36.4%	63.6%	0%
Anxious feelings	4.7 (1.1)	36.4%	63.6%	0%
Ability to complete intravesical therapy (n=9)	4.7 (1.1)	33.3%	66.7%	0%
Urinary burning	4.6 (1.2)	27.3%	72.7%	0%
Urinary leakage	4.6 (1.2)	18.2%	81.8%	0%
Urinary frequency	4.5 (1.0)	18.2%	81.8%	0%

Self-reported benefits and harms assessed on a 7-point scale from 1 (very much worse) to 4 (no change) 7 (very much improved). HIIT, high intensity interval training; TURBT, transurethral resection of the bladder tumor.
[a] Improved =5-7; [b] No change = 4; [c] Worsened =1-3.

Table 5-5. Perceived barriers to the 12-week high intensity interval training program during or after intravesical therapy in bladder cancer patients assigned to the exercise intervention.

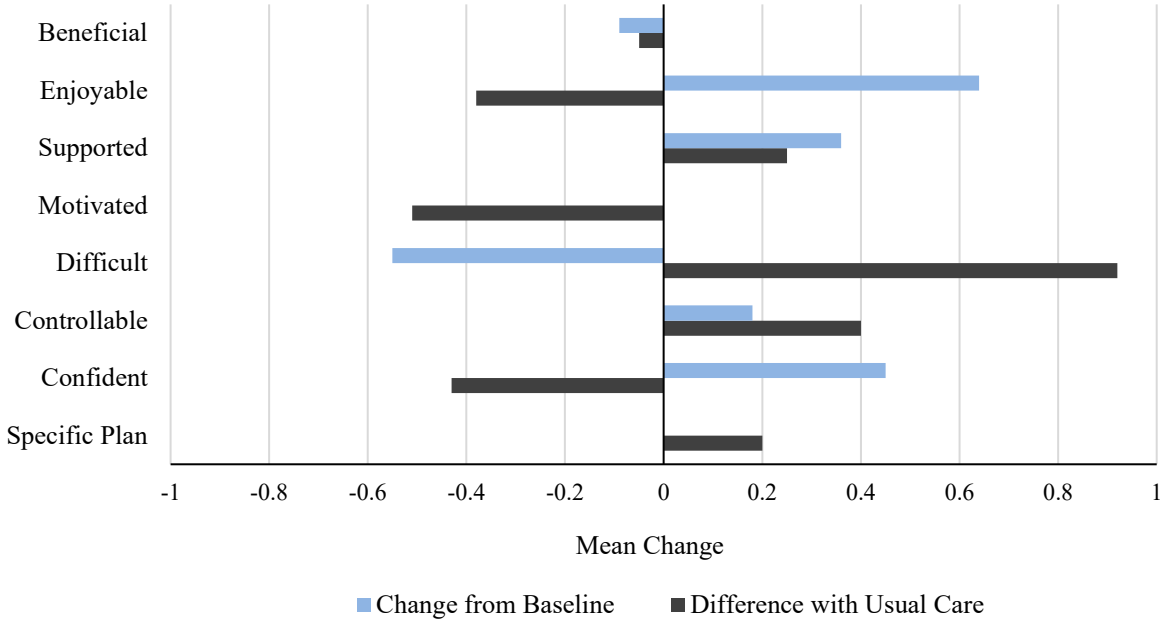
Variables	Mean (SD)	Percentage distribution		
		Not at all[a]	Somewhat[b]	Very much[c]
Too busy/limited time	2.1(1.8)	54.5%	36.4%	9.1%
Joint pain or soreness	1.8 (1.2)	63.6%	36.4%	0%
Recovering from TURBT (n=9)	1.7 (1.7)	77.8%	11.1%	11.1%
Feeling tired/fatigued	1.6 (1.3)	72.7%	18.2%	9.1%
Muscle pain or soreness	1.6 (1.1)	72.7%	27.3%	0%
Feeling sick/not well	1.5 (0.8)	72.7%	27.3%	0%
Lack of motivation	1.5 (0.9)	72.7%	27.3%	0%
Fear of a cancer progression or recurrence	1.4 (1.2)	90.9%	0%	9.1%
Having bladder cancer	1.1 (0.3)	90.9%	9.1%	0%
Urinary incontinence	1.1 (0.3)	90.9%	9.1%	0%
Bowel problems	1.1 (0.3)	90.9%	9.1%	0%
Travelling to fitness centre	1.1 (0.3)	90.9%	9.1%	0%
Exercise program too difficult	1.1 (0.3)	90.9%	9.1%	0%
Having intravesical therapy (n=10)	1.1 (0.3)	90%	10%	0%
Bad weather	1.0 (0.0)	100%	0%	0%
Medical appointment	1.0 (0.0)	100%	0%	0%
Lack of family support	1.0 (0.0)	100%	0%	0%

Self-reported barriers assessed on a 7-point scale from 1 (not at all) to 7 (very much). HIIT, high intensity interval training; TURBT, transurethral resection of the bladder tumor. [a] Not at all = 1; [b] Somewhat = 2-4; [c] Very much = 5-7

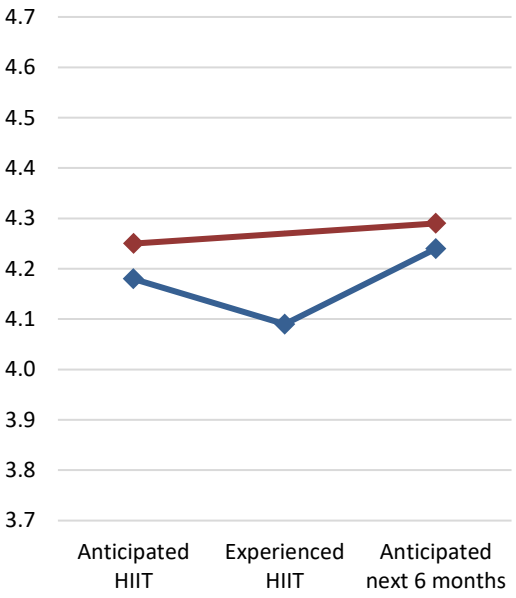
Figure Caption

Figure 5-1. Changes in exercise motivation for the 12-week high-intensity interval training program within the exercise group and comparison of exercise motivation for the next 6 months between the exercise and usual care groups in the BRAVE trial.

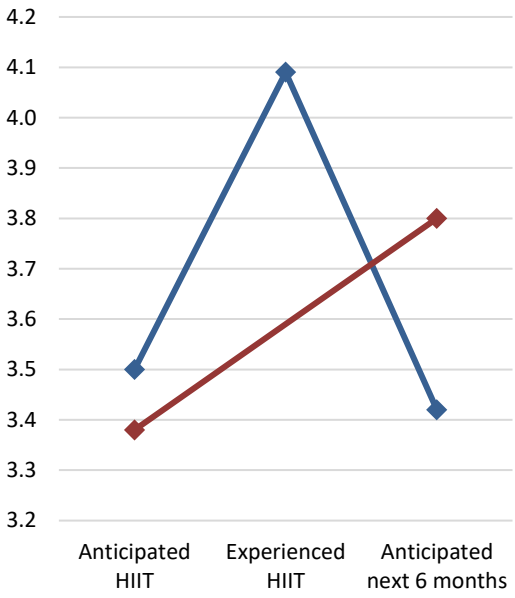
Figure 5-2. Effects of the 12-week high-intensity interval training program on (a) benefits, (b) enjoyment, (c) support, (d) motivation, (e) difficulty, (f) control, and (g) confidence. Experienced HIIT and anticipated next 6 months means are adjusted for age, baseline value of the outcome, and current treatment status.


Beneficial
Enjoyable
Supported
Motivated
Difficult
Controllable
Confident
Specific Plan
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1
Mean Change
Change from Baseline
Difference with Usual Care

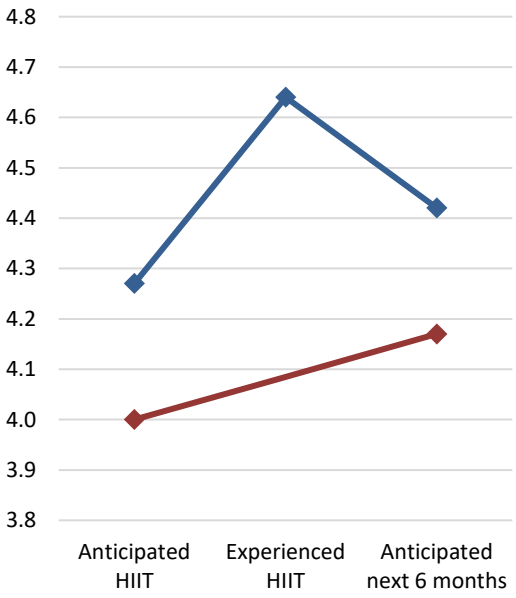
A. Benefits



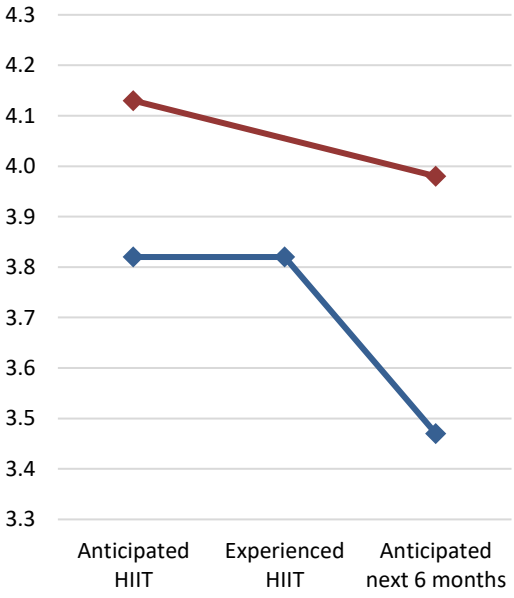
B. Enjoyment



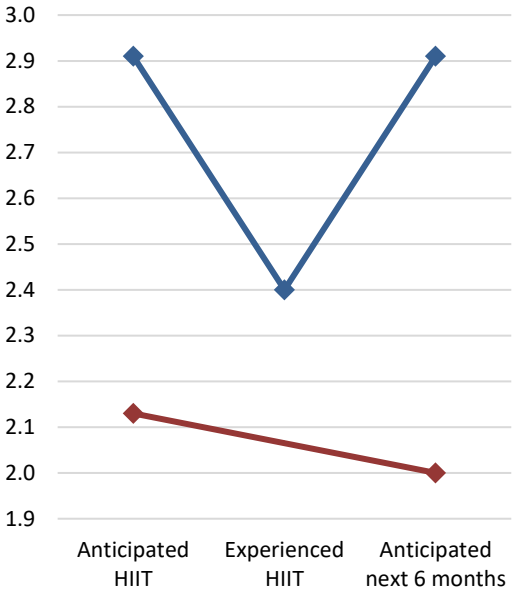
C. Support



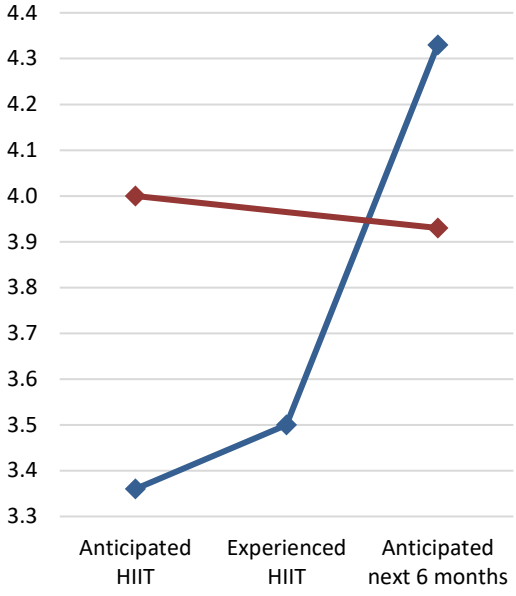
D. Motivation



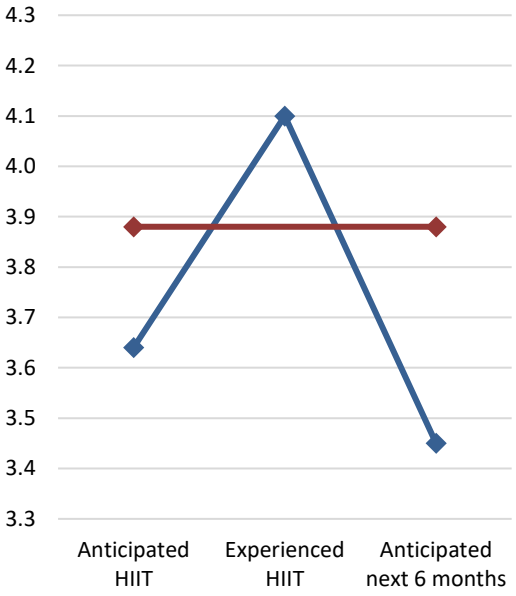
E. Difficulty

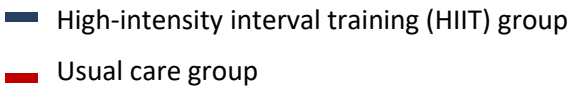


F. Control



G. Confidence





CHAPTER 6: PAPER 5

Physical activity in patients with kidney cancer: A scoping review

A version of this chapter has been published.

Arthuso, F. Z., & Courneya, K. S. (2022). Physical Activity in Patients With Kidney Cancer: A Scoping Review. *Clinical genitourinary cancer*, *20*(5), e369–e379. https://doi.org/10.1016/j.clgc.2022.04.003

6.1 Abstract

Introduction: Physical activity (PA) helps many cancer patients improve health-related fitness, treatment-related side effects, quality of life, and possibly survival; however, limited research has been conducted in patients with kidney cancer (KC). The aim of this scoping review focused on PA in patients with KC was to summarize current findings, delineate strengths and limitations, and provide key recommendations for future research. **Materials and Methods:** A scoping review was conducted and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews guidelines. The electronic databases of PubMed and Cochrane Library were screened for studies on October 14th, 2021, and the search was updated on October 31st, 2021. The data were abstracted and synthesized by study design. **Results:** 17 articles from nine independent studies were identified including one cross-sectional study (n=8 articles), one randomized controlled trial (n=2 articles) and seven cohort studies (n=7 articles). The cross-sectional study and randomized controlled trial reported on PA participation rates, preferences, social-cognitive correlates, and quality of life in patients with KC. The seven cohort studies mostly reported on the risk of KC mortality in general population samples. Overall, no conclusions can be drawn from current research on the safety, feasibility, and efficacy (benefits and harms) of PA in patients with KC. **Conclusions:** Future research is urgently needed on PA in patients with KC, taking into account their unique disease- and treatment-related factors. This research is necessary to inform clinical exercise guidelines in this understudied cancer patient group.

Keywords: Kidney neoplasm, exercise, physical activity, cancer, scoping review, renal cell carcinoma

6.2 Introduction

Kidney cancer (KC) is the ninth most common cancer in Canada and the fifteenth most common worldwide [1, 2]. Globally, an estimated 431,288 people will be diagnosed with KC in 2020 and 179,368 will die of the disease [2]. KC affects men twice as often as women and the median age at diagnosis is 64 years [3]. In Canada, the incidence has been rising on average 0.3% each year, while deaths rates have been decreasing on average 1.5% each year [1]. Overall, the 5-year survival rate for KC in Canada is 73% [1], however, the range is 13.9% to 92.7% depending on tumor (i.e., stage, grade, local extension, and evidence of metastasis) and patient (i.e., age, comorbidities, frailty) characteristics at the time of diagnosis [3]. Approximately 65.4% of KCs are localized at the time of diagnosis whereas 16% have spread to regional lymph nodes and 16% have metastasized [3].

Surgery is the first-line treatment for patients with non-metastatic KC, independent of the stage [4]. Surgery options include partial or radical nephrectomy, which consists of the partial or total removal of the organ [4]. Alternatively, if clinically indicated, patients may be treated with tumor ablation techniques (i.e., extreme heat or cold on the tumor and surrounding tissue) or undergo active surveillance (i.e., close monitoring through frequent medical examinations) [4]. Adjuvant therapies for KC have failed to demonstrate a survival advantage, however, novel drugs are being investigated [5, 6]. Treatment options for metastatic KC include cytoreductive surgery, targeted therapy, or immunotherapy [4].

KC and its treatment impose a significant burden on the patient, with psychosocial and physical challenges that may affect their quality of life and survival [7-9]. Patients undergoing surgical treatment for KC may experience anxiety, depressive symptoms, and fatigue, as well as limited ability to engage in physical activity (PA) following surgery [8]. Moreover, kidney removal predisposes patients to increased risks of chronic renal insufficiency [10] and cardiovascular morbidity and mortality [11]. Even after surgery, about

20% to 30% of patients with localized tumors experience a relapse in a median time of 1 to 2 years [4, 12]. Patients with KC have unmet supportive care needs for psychological and physical health[8] that decrease quality of life and have been associated with an 11%-21% increased risk of death [9]. Strategies to help patients with KC manage treatment-related side effects, improve quality of life, and extend survival are needed.

PA, defined as any movement produced by the contraction of skeletal muscles that requires more energy than resting [13], has been linked to positive outcomes such as quality of life, physical function, and fatigue in many cancer patient groups [14, 15]. In addition, recent randomized controlled trials have suggested that the adoption a PA program after a cancer diagnosis can potentially help patients complete their treatment [16], alter the course of the disease [17, 18] and possibly extent survival [19]. Most of the evidence, however, has come from studies in breast and prostate cancers [14, 15]. Although KC is a common cancer and the most lethal urological malignancy [1], it remains an understudied cancer in the field of exercise oncology. KC and its treatments may alter the safety, feasibility, and efficacy of PA and, therefore, it is critical to research PA specifically in patients with KC before making clinical recommendations.

Identifying what information is currently available in the literature is an initial step to inform where progress has been made, and identify research priorities for future investigations. For this reason, scoping reviews are indicated to detect and report the volume, variety, and characteristics of the available evidence on a given topic [20]. To date, no attempt has been made to collate and understand the currently available literature on PA in patients with KC. Here, we report the first scoping review on PA in patients with KC focused on the extent (amount), range (variety), and nature (characteristics) of the available evidence. This review aims to summarize current findings, identify strengths and limitations in the

existing literature, highlight important research gaps, and provide key recommendations for future research in this understudied cancer population.

6.3 Methods

Search strategy

The protocol for the current scoping review was not published a priori. The scoping review was conducted and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) guidelines [21]. To identify potentially relevant documents, the electronic databases of PubMed and Cochrane Library were screened for studies published in English up to October 2021. The literature search was conducted on October 14th, 2021, and updated on October 31st, 2021. The search strategy included the identification of Medical Subject Headings (MeSH) for the key concepts of the current scoping review (Supplementary Table 6-1). The use of MeSH terms allows the inclusion of all topic-related subheadings, resulting in a more efficient and precise search [22]. No additional free text searching was used during the search process. The Boolean operators "AND", "OR", and "NOT" were applied to combine or exclude search terms. Filters were used to narrow the search by language (English) and article type (reviews, comments, and editorials were excluded). No search limits were set for geographical location, race, or sex/gender.

Eligibility criteria

The eligibility criteria followed the Participant, Intervention or exposure, Comparator, Outcome, and Study design (PICOS) approach [23]. Participants included anyone diagnosed with KC regardless of type of KC, stage of disease, or phase of the cancer continuum. Studies with mixed cancer groups were included if they reported separate results for patients with KC. Intervention or exposure included any measure or intervention involving exercise, PA,

sedentary behavior or physical fitness prior to or after a KC diagnosis. Comparator was not specified as an inclusion variable. Outcomes were not specified other than the outcome had to occur after a KC diagnosis. Study Designs included observational and experimental studies in humans. Letters, editorials, commentaries, systematic reviews, meta-analyses, and preclinical studies were not eligible.

Data extraction and data synthesis

Two authors independently screened the titles and abstracts of the documents. The data charting process was conducted by FZA and reviewed by KSC. Any disagreements were resolved through discussion between the two reviewers. The studies were grouped by design (i.e., cross-sectional design, randomized controlled trial, and cohort study) and summarized in tables. The data abstraction and synthesis included the following information: first author's name, year of publication, the country where the data was collected, study design, sample information (e.g., sample size, sex, age, tumor- and treatment-related information), primary and secondary aims (if applicable), data collection and measurements, and overall findings. The methodological quality of the studies was not assessed because scoping reviews are not intended to critically appraise the risk of bias of the evidence [21].

6.4 Results

Selection of sources of evidence

The search on PubMed and Cochrane Library databases returned 62 records. After the removal of duplicates, 57 papers had the title and abstract screened, and 15 full texts were assessed for eligibility. In addition, four papers were identified from the reference list of the full articles assessed. Two articles were excluded because they included mixed cancer groups and did not report separate results for patients with KC. As shown in the PRISMA flow

diagram (Figure 6-1), 17 articles met the inclusion criteria and were incorporated in the current scoping review.

Characteristics of sources of evidence and study participants

The 17 articles included in this scoping review were published between 2007 and 2021. Of the 17 articles, 8 were from one cross sectional population-based study conducted in Alberta, Canada [24-31], 2 were from one randomized controlled trial [32, 33], and 7 were from 7 cohort studies [34-40], representing 9 independent studies. In terms of geography, 88% (n=15) of the articles were from studies conducted in North America [24-37, 40], 6% (n=1) in Japan [38], and 6% (n=1) in Germany [39].

Table 6-1 shows the characteristics of the cross-sectional study and randomized controlled trial. Overall, the sample sizes of the cross-sectional study articles ranged from 432 to 703 patients with KC [24-33]. The mean time since diagnosis was more than five years, but the wide standard deviation indicates that patients in the early survivorship phase were also included, some of which were still undergoing treatment [24-30]. The randomized controlled trial included 32 participants (50% male) posttreatment, with a mean age of 61.8 years, diagnosed with localized disease (93.8%), and treated with surgery (96.9%) [32, 33].

Table 6-2 shows the study and sample characteristics of the 7 cohort studies. The study by Wunderle et al.[39] was the only prospective study examining pre-surgical physical function as a predictor of postoperative complications. The study by Schmid et al.[34] was the only study to investigate postdiagnosis PA and KC mortality. The other 5 cohort studies assessed PA in a general population sample who were then followed for KC deaths. The follow-up duration for KC mortality ranged from 2 to 16.4 years and the number of observed events ranged from 31 to 367 deaths from KC [35, 36, 38, 40]. One article only provided the

mortality rates expressed as cases per 100,000 based on the U.S. population [37]. Most of the cohort studies lacked disease (n=6) [35-40] and treatment information (n=5) [35-38, 40].

PA measurements and outcomes of interest

The summary of aims, measurements, and results of the 17 articles are presented in Tables 6-3 and 6-4. The cross sectional study (n=8 articles) had several aims including assessing correlates of meeting PA guidelines [26, 27, 31]; estimating the prevalence of meeting the PA guidelines [24, 28]; examining the association of PA and/or sedentary behavior with quality of life [24, 25, 30]; and identifying PA preferences [29]. The measurements of PA and sedentary behavior in the cross-sectional study were self-reported and occurred after the diagnosis of KC [24-31].

The randomized controlled trial aimed to evaluate the feasibility of adding behavioral counseling to supervised PA [32] and its effects on motivational outcomes [33]. The study used self-reported measurement of PA and direct measurement of cardiorespiratory fitness and physical function [32].

The cohort studies aimed to investigate the associations of PA, sedentary behavior, or physical fitness with post-operative complications [39] or KC mortality [34-38, 40]. Specifically, Wunderle et al.[39] used geriatric assessment tools, including direct measurements of physical functioning (i.e., time up and go, handgrip strength, and full tandem stand), as predictors of post-operative complications in patients with KC scheduled for partial nephrectomy [39]. Schmid et al. examined the associations of self-reported postdiagnosis PA and/or sedentary behavior with KC-specific and all-cause mortality [34]. The other 5 cohort studies examined the associations of pre-diagnosis PA [35-38] or fitness level [40] with KC mortality in general populations.

Overall Findings

The cross-sectional study identified that higher PA was associated with better quality of life in many domains [24]. Moreover, 81.1% of patients with KC felt they would, or might, be able to participate in an exercise program at some point after their diagnosis [29], however, more than 65% were not meeting PA guidelines [28]. The most recent publication identified that 7.2% of the variance in meeting the PA guidelines was accounted for by demographic variables, 16.5% by medical variables, and 20.5% by social-cognitive variables (e.g., planning and intention) [27].

The randomized controlled trial evaluating the feasibility of adding behavioral counseling to supervised PA in KC patients identified that the intervention was feasible and the supervised PA plus motivationally enhanced behavioral counseling group increased PA by a non-significant 34 minutes more than the comparison group [32]. Adding behavioral counseling to supervised PA had significant effects on the motivational outcomes of planning, control, and behavioral beliefs [33], but there were no meaningful changes in parameters of quality of life [32].

The study by Wunderle et al. reported that low handgrip strength and full tandem stand <10s were significant predictors of major post-operative complications (OR=4.76, p=0.021 and OR=4.25, p=0.047, respectively) [39]. Additionally, low handgrip strength (OR=0.28, p=.037), full-tandem-stand <10s (OR=0.18, p=.010), and time up and go (OR=0.11, p=.011) were associated with trifecta failure (i.e., surrogate of surgical quality defined by negative surgical margin, ischemia time <25 min, and no major complications) [39]. The authors` suggested that assessment of frailty and physical performance should be included before surgery to inform the treatment plan and alternative therapies for those KC patients at high preoperative risk [39].

Regarding the associations of PA and KC mortality, the literature has reported contrasting findings. Three studies found no significant associations between PA or sedentary

behavior and KC deaths [34, 38, 40], while one study identified that those who reported any PA were about 50% less likely to die of KC than those reporting no PA (HR=0.50, 95% CI = 0.27-0.93, p=0.0028) [35]. Another study found that physical inactivity correlated with increased renal cell carcinoma mortality rates among males (p=0.002) and females (p=0.03) [37]. Finally, one study reported an unexpected increased risk of KC mortality with higher moderate to vigorous intensity leisure time PA (HR for ≥7 hrs/wk of PA 1.42, 95% CI = 0.98–2.03; p-trend = 0.016) [36]. The only study that measured PA in patients with KC reported that increased moderate to vigorous PA was significantly associated with reduced all-cause mortality (HR for ≥7 hrs/wk of PA = 0.60, 95% CI = 0.38–0.96; p-trend =0.03), but there were no significant associations between PA or sedentary behavior with KC mortality [34].

6.5 Discussion

This scoping review is the first to focus on PA in patients with KC and to examine the extent, range, and nature of available evidence. The information presented here was obtained from 17 articles reporting nine independent studies that diverge in terms of design, exposure assessment tools, primary outcomes, and findings.

Summary of evidence

In summary, the preliminary findings suggest that patients with KC have low PA participation rates and their PA behavior is strongly correlated with social cognitive (motivational) variables [24, 26-29, 31]. Behavioral interventions may be feasible in this population and potentially beneficial given that higher doses of PA might be associated with improvements in many domains of quality of life [32, 33]. The association of PA with KC survival, however, remains unclear [34-38, 40].

The studies included in this scoping review must be interpreted with respect to their strengths and limitations. Overall, the cross-sectional study was derived from a large population-based survey from a Canadian Provincial Registry, which to our knowledge, is the first and only survey on PA in patients with KC. The survey provided a comprehensive assessment of PA patterns, preferences, and prevalence rates, as well as demographic, medical, environmental, and social-cognitive correlates of PA. The comprehensive approach adopted in the cross-sectional study is considered a strength because the findings can be used to guide future PA interventions in patients with KC. The main limitation of the cross-sectional study is that causality cannot be determined because exposures and outcomes are assessed at the same time. Additionally, the use of self-reported measurements of PA and medical information can lead to inaccuracy of the information provided. Finally, there is the risk of many chance findings as result of the numerous statistical analyses reported across the eight articles that derived from this single population-based survey.

The only randomized controlled trial in this setting included balanced groups and was the first to implement behavioral counseling in a supervised PA program in any cancer group [32, 33]. Some of the limitations were the small sample size, the short intervention time, the limited follow-up, and the absence of a true control group that may have restricted the ability to detect any differences in anthropometric measures, cardiorespiratory fitness, and quality of life parameters. Additionally, the study included highly motivated participants that previously reported an interest in joining an exercise study; therefore, the results may not be generalizable to those patients with KC most in need of PA behavior change interventions.

The 7 cohort studies had a relatively well-defined and long follow-up time that allows observation of the event of interest (e.g., KC specific mortality). The majority of the cohort studies, however, were limited in design and methodology, including heterogeneous populations, a low number of events, insufficient statistical power, and absence of objective

PA measurements, resulting in inaccurate and inconsistent findings. The main limitation, however, is that 6 of the 7 cohort studies measured PA in a general population that were followed for KC mortality. Consequently, it is unclear what role, if any, postdiagnosis PA played in influencing the survival outcomes. Moreover, most of the studies lacked information on KC, including treatment and disease variables (e.g., treatment type and status, disease grade and stage), which could potentially confound their findings.

Future research

This scoping review has highlighted that research into PA in patients with KC is preliminary in nature and no conclusions can be drawn. The most important research questions for this patient group relate to the effects of PA on cancer outcomes such as treatment tolerance, treatment response, cancer progression and recurrence, and cancer-specific and overall survival. Additional important research questions concern the effects of PA on patient-reported outcomes such as symptoms and side effects, quality of life, and psychosocial outcomes. Finally, research on health-related fitness outcomes is needed to determine the role of physical fitness in improving these important outcomes. Given the very limited existing research, phase I and phase II clinical trials are initially needed to examine the safety, feasibility, and preliminary efficacy (benefits and harms) of PA in KC patients. Ultimately, large scale phase III trials will be needed to provide definitive answers to these important questions and to inform clinical exercise guidelines for this understudied cancer patient group. Here, we propose future research directions on PA in KC patients organized along four distinct post-diagnosis cancer-related time periods: pretreatment, treatment, survivorship, and end-of life [41].

Pretreatment is defined as the time between the cancer diagnosis and the beginning of treatment [41]. For instance, patients with small renal masses on active surveillance are deferring treatment until symptoms appear or tumor conditions change. A tumor growth rate

of 5 mm/year is one of the triggers for surgical intervention when on active surveillance [42]. PA interventions during active surveillance could potentially contribute to a decrease in tumor progression rate and prevent or delay the need for radical treatment. Proof of principle for this concept has been demonstrated in a randomized controlled trial in prostate cancer patients on active surveillance where biochemical progression was slowed by a high intensity interval training program for 12-weeks [17]. Moreover, it is plausible that PA interventions may have a positive effect on other aspects of patient functioning that are considered on the treatment pathway decision, including quality of life, renal function, frailty, and performance status. Taking the potential benefits together, PA interventions in the pretreatment phase may help avoid or delay treatments, prepare for treatments (prehabilitation), decrease the risk of complications following surgery, and reduce the use of medical resources in patients with KC [43]. The links between PA interventions, KC outcomes, and patient outcomes in the active surveillance setting are only hypotheses, however, and research is clearly warranted.

The treatment time period is defined as the time that includes the main cancer treatments, such as surgery or systemic therapy [41]. Previous studies examining the effects of PA during cancer treatment have demonstrated improved side effects and quality of life [44, 45], a higher treatment completion rate [16, 46] and/or improved treatment response (e.g., pathologic complete response) [18, 46] in patients with breast, lymphoma, and rectal cancer. According to these studies, PA interventions may influence treatment tolerance and response rate by improving lean body mass, managing treatment-related side effects, direct influences on the tumor microenvironment, and improved efficacy of drug delivery or radiation effects [16, 18, 46]. The evidence of PA on cancer treatment efficacy is limited to a few pre-clinical and clinical studies, none of them in KC [47].

Future studies in the treatment setting for KC should also assess the role of PA interventions on renal function since kidney removal predisposes patients to increased risk of

chronic kidney disease [10]. Renal function can be assessed via estimated glomerular filtration rate (eGFR) and albuminuria. Glomerular filtration rate is the best overall index of kidney function in health and disease, while albuminuria is a marker of kidney damage [48]. The prognosis of chronic kidney disease includes a combination of these markers, where GFR < 60 mL/min per 1.73 m^2 and an albuminuria-albumin-to-creatinine ratio (ACR) > 30mg/g put the patient at a moderate, high risk, or very high risk of chronic kidney disease [48]. Pre-operative renal function is a determinant of renal function following surgical management of KC [49], and about 45% of patients are able to return to their baseline glomerular filtration rate. A considerable proportion of patients (55%), however, have not recovered baseline renal function two years after surgery [50]. A previous study suggested that higher levels and intensity of PA were associated with a lower risk of kidney function decline in 4011 participants aged 65 or older [51]. Whether a PA program before or shortly after surgery for KC is safe, feasible, and has any short- and/or long-term effects on renal function is unknown and an important topic for future research.

The survivorship phase refers to the time between the end of primary treatment until the development of cancer recurrence or death [41], therefore, the most critical issues in this phase are supportive care outcomes (e.g., physical and psychosocial adverse effects of cancer and its treatments) and disease outcomes (e.g., disease-free survival and overall survival). To date, however, there are no high quality cohort studies designed and powered to examine the association of PA with recurrence and survival in patients treated for KC. The Alberta Moving Beyond Breast Cancer (AMBER) study is an example of a prospective cohort study designed specifically to investigate the role of PA and health-related fitness in breast cancer survivorship [52]. Specifically, the AMBER study will inform whether PA and health-related fitness have any effects on treatment completion rates, treatment side effects, quality of life, cancer recurrence, and survival in patients with breast cancer [52]. Similar to the AMBER

study, future research in KC survivorship may include self-report and objective measures of PA and sedentary behavior, a comprehensive assessment of key patient-reported outcomes (e.g., fatigue, anxiety, depression, and quality of life), health-related fitness (i.e., cardiorespiratory fitness, body composition, physical functioning), and clinical outcomes (i.e., disease and treatment related outcomes).

Finally, the end of life phase refers to the metastatic setting, when the disease is incurable and progressive [41]. Patients with metastatic KC could potentially benefit from PA in terms of quality of life, physical function, and alleviating treatment-related side effects as demonstrated by systematic reviews and meta-analysis in patients with advanced-stage cancer [53, 54]. It is also possible that PA interventions may slow disease progression and improve survival in patients with metastatic KC. Studies assessing the safety, feasibility, and efficacy of PA interventions in the metastatic KC setting are needed.

The strengths of this scoping review include the novelty of examining PA in patients with KC, the comprehensive overview of the available literature, the future research directions across the cancer continuum, the methodological quality, and following the PRISMA extension guidelines for scoping reviews. The current review is limited by including articles only published in English, including articles with PA assessed before KC diagnosis, the number of sources searched, and the number of reviewers included in the process.

6.6 Conclusion

This paper reports the first scoping review to provide a synthesis of the current literature on PA in patients with KC. Overall, research on the effects of PA in patients with KC is profoundly limited and preliminary in nature. Our review highlights that only one experimental study has been conducted to date, and it focused on behavior change rather than efficacy outcomes. Currently, there are no randomized controlled trials demonstrating that

PA can improve cancer outcomes, treatment-related side effects, quality of life, or health-related fitness in the pretreatment, treatment, survivorship, or end of life settings for patients with KC. Systematic research is warranted to assess the safety, feasibility, and efficacy (benefits and harms) of PA interventions in patients with KC across the cancer continuum.

6.7 References

1. Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, Statistics Canada and the Public Health Agency of Canada. Canadian Cancer Statistics 2021. Accessed November 29, 2021, cancer.ca/Canadian-Cancer-Statistics-2021-EN

2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 05 2021;71(3):209-249. doi:10.3322/caac.21660

3. Institute NC. Cancer Stat Facts: Kidney and Renal Pelvis Cancer. Accessed November 26, 2021, https://seer.cancer.gov/statfacts/html/kidrp.html

4. Network NCC. Kidney Cancer (Version 3.2022). https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1440

5. Motzer RJ, Haas NB, Donskov F, et al. Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma. *J Clin Oncol*. Dec 10 2017;35(35):3916-3923. doi:10.1200/JCO.2017.73.5324

6. Pal SK, Haas NB. Adjuvant therapy for renal cell carcinoma: past, present, and future. *Oncologist*. Aug 2014;19(8):851-9. doi:10.1634/theoncologist.2014-0105

7. Ames SC, Parker AS, Crook JE, et al. Quality of life of patients undergoing surgical treatment for newly-diagnosed, clinically localized renal cell carcinoma. *J Psychosoc Oncol*. 2011;29(6):593-605. doi:10.1080/07347332.2011.616574

8. O'Dea A, Gedye C, Jago B, Paterson C. Identifying the unmet supportive care needs of people affected by kidney cancer: a systematic review. *J Cancer Surviv*. Oct 01 2021;doi:10.1007/s11764-021-01113-8

9. Bhandari NR, Kamel MH, Kent EE, et al. Association of Health-Related Quality of Life with Overall Survival in Older Americans with Kidney Cancer: A Population-Based Cohort Study. *Healthcare (Basel)*. Oct 10 2021;9(10)doi:10.3390/healthcare9101344

10. McKiernan J, Simmons R, Katz J, Russo P. Natural history of chronic renal insufficiency after partial and radical nephrectomy. *Urology*. Jun 2002;59(6):816-20. doi:10.1016/s0090-4295(02)01501-7

11. Huang WC, Levey AS, Serio AM, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol*. Sep 2006;7(9):735-40. doi:10.1016/S1470-2045(06)70803-8

12. Eggener SE, Yossepowitch O, Pettus JA, Snyder ME, Motzer RJ, Russo P. Renal cell carcinoma recurrence after nephrectomy for localized disease: predicting survival from time of recurrence. *J Clin Oncol*. Jul 01 2006;24(19):3101-6. doi:10.1200/JCO.2005.04.8280

13. Liguori G, Feito Y, Fountaine C, Roy BA, Medicine ACoS. *ACSM's Guidelines for Exercise Testing and Prescription* . Eleventh edition ed. Wolters Kluwer; 2021.

14. Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc*. 11 2019;51(11):2375-2390. doi:10.1249/MSS.0000000000002116

15. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012 Jul-Aug 2012;62(4):243-74. doi:10.3322/caac.21142

16. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter

randomized controlled trial. *J Clin Oncol*. Oct 01 2007;25(28):4396-404. doi:10.1200/JCO.2006.08.2024

17. Kang DW, Fairey AS, Boulé NG, Field CJ, Wharton SA, Courneya KS. Effects of Exercise on Cardiorespiratory Fitness and Biochemical Progression in Men With Localized Prostate Cancer Under Active Surveillance: The ERASE Randomized Clinical Trial. *JAMA Oncol*. Aug 19 2021;doi:10.1001/jamaoncol.2021.3067

18. Morielli AR, Usmani N, Boulé NG, et al. Feasibility, Safety, and Preliminary Efficacy of Exercise During and After Neoadjuvant Rectal Cancer Treatment: A Phase II Randomized Controlled Trial. *Clin Colorectal Cancer*. May 26 2021;doi:10.1016/j.clcc.2021.05.004

19. Courneya KS, Segal RJ, McKenzie DC, et al. Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. *Med Sci Sports Exerc*. Sep 2014;46(9):1744-51. doi:10.1249/MSS.0000000000000297

20. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol*. 11 19 2018;18(1):143. doi:10.1186/s12874-018-0611-x

21. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. 10 02 2018;169(7):467-473. doi:10.7326/M18-0850

22. Baumann N. How to use the medical subject headings (MeSH). *Int J Clin Pract*. Feb 2016;70(2):171-4. doi:10.1111/ijcp.12767

23. Brown P, Brunnhuber K, Chalkidou K, et al. How to formulate research recommendations. *BMJ*. Oct 14 2006;333(7572):804-6. doi:10.1136/bmj.38987.492014.94

24. Trinh L, Plotnikoff RC, Rhodes RE, North S, Courneya KS. Associations between physical activity and quality of life in a population-based sample of kidney cancer survivors. *Cancer Epidemiol Biomarkers Prev*. May 2011;20(5):859-68. doi:10.1158/1055-9965.EPI-10-1319

25. Trinh L, Plotnikoff RC, North S, Rhodes R, Courneya KS. Associations between sitting time and quality of life in a population-based sample of kidney cancer survivors. Mental Health and Physical Activity; 2013. p. 16-23.

26. Trinh L, Plotnikoff RC, Rhodes RE, North S, Courneya KS. Correlates of physical activity in a population-based sample of kidney cancer survivors: an application of the theory of planned behavior. *Int J Behav Nutr Phys Act*. Aug 06 2012;9:96. doi:10.1186/1479-5868-9-96

27. Tabaczynski A, Strom DA, Wong JN, et al. Demographic, medical, social-cognitive, and environmental correlates of meeting independent and combined physical activity guidelines in kidney cancer survivors. *Support Care Cancer*. Jan 2020;28(1):43-54. doi:10.1007/s00520-019-04752-x

28. Trinh L, Strom DA, Wong JN, Courneya KS. Modality-specific exercise guidelines and quality of life in kidney cancer survivors: A cross-sectional study. *Psychooncology*. 10 2018;27(10):2419-2426. doi:10.1002/pon.4844

29. Trinh L, Plotnikoff RC, Rhodes RE, North S, Courneya KS. Physical activity preferences in a population-based sample of kidney cancer survivors. *Support Care Cancer*. Aug 2012;20(8):1709-17. doi:10.1007/s00520-011-1264-z

30. Tabaczynski A, Courneya KS, Trinh L. Replacing sedentary time with physical activity and sleep: associations with quality of life in kidney cancer survivors. *Cancer Causes Control*. Jul 2020;31(7):669-681. doi:10.1007/s10552-020-01308-x

31. Trinh L, Larsen K, Faulkner GE, et al. Social-ecological correlates of physical activity in kidney cancer survivors. *J Cancer Surviv*. Feb 2016;10(1):164-75. doi:10.1007/s11764-015-0462-y

32. Trinh L, Plotnikoff RC, Rhodes RE, North S, Courneya KS. Feasibility and preliminary efficacy of adding behavioral counseling to supervised physical activity in kidney cancer survivors: a randomized controlled trial. *Cancer Nurs*. 2014 Sep-Oct 2014;37(5):E8-22. doi:10.1097/NCC.0b013e3182a40fb6

33. Trinh L, Plotnikoff RC, Rhodes RE, North S, Courneya KS. Changes in motivational outcomes following a supervised physical activity program with behavioral counseling in kidney cancer survivors: a pilot study. *Psychooncology*. Sep 2015;24(9):1204-7. doi:10.1002/pon.3754

34. Schmid D, Matthews CE, Leitzmann MF. Physical activity and sedentary behavior in relation to mortality among renal cell cancer survivors. *PLoS One*. 2018;13(6):e0198995. doi:10.1371/journal.pone.0198995

35. Liss M, Natarajan L, Hasan A, Noguchi JL, White M, Parsons JK. Physical Activity Decreases Kidney Cancer Mortality. *Curr Urol*. Nov 2017;10(4):193-198. doi:10.1159/000447180

36. Arem H, Moore SC, Park Y, et al. Physical activity and cancer-specific mortality in the NIH-AARP Diet and Health Study cohort. *Int J Cancer*. Jul 15 2014;135(2):423-31. doi:10.1002/ijc.28659

37. Colli JL, Busby JE, Amling CL. Renal cell carcinoma rates compared with health status and behavior in the United States. *Urology*. Feb 2009;73(2):431-6. doi:10.1016/j.urology.2008.06.044

38. Washio M, Mori M, Khan M, et al. Diabetes mellitus and kidney cancer risk: the results of Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study). *Int J Urol*. May 2007;14(5):393-7. doi:10.1111/j.1442-2042.2007.01744.x

39. Wunderle MF, Härtel N, Wagener N, et al. Prospective geriatric assessment for perioperative risk stratification in partial nephrectomy. *Eur J Surg Oncol*. 04 2021;47(4):913-919. doi:10.1016/j.ejso.2020.11.001

40. Thompson AM, Church TS, Janssen I, Katzmarzyk PT, Earnest CP, Blair SN. Cardiorespiratory fitness as a predictor of cancer mortality among men with pre-diabetes and diabetes. *Diabetes Care*. Apr 2008;31(4):764-9. doi:10.2337/dc07-1648

41. Courneya KS, Friedenreich CM. Physical activity and cancer control. *Semin Oncol Nurs*. Nov 2007;23(4):242-52. doi:10.1016/j.soncn.2007.08.002

42. Sanchez A, Feldman AS, Hakimi AA. Current Management of Small Renal Masses, Including Patient Selection, Renal Tumor Biopsy, Active Surveillance, and Thermal Ablation. *J Clin Oncol*. 12 20 2018;36(36):3591-3600. doi:10.1200/JCO.2018.79.2341

43. Tan HJ, Shirk JD, Chamie K, Litwin MS, Hu JC. Patient Function and the Value of Surgical Care for Kidney Cancer. *J Urol*. 05 2017;197(5):1200-1207. doi:10.1016/j.juro.2016.12.012

44. Buffart LM, Kalter J, Sweegers MG, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. *Cancer Treat Rev*. Jan 2017;52:91-104. doi:10.1016/j.ctrv.2016.11.010

45. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during

active treatment. *Cochrane Database Syst Rev*. Aug 15 2012;(8):CD008465. doi:10.1002/14651858.CD008465.pub2

46. Courneya KS, Sellar CM, Stevinson C, et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *J Clin Oncol*. Sep 20 2009;27(27):4605-12. doi:10.1200/JCO.2008.20.0634

47. Yang L, Morielli AR, Heer E, et al. Effects of Exercise on Cancer Treatment Efficacy: A Systematic Review of Preclinical and Clinical Studies. *Cancer Res*. 10 01 2021;81(19):4889-4895. doi:10.1158/0008-5472.CAN-21-1258

48. Levey AS, Coresh J. Chronic kidney disease. *Lancet*. Jan 14 2012;379(9811):165-80. doi:10.1016/S0140-6736(11)60178-5

49. Mason R, Kapoor A, Liu Z, et al. The natural history of renal function after surgical management of renal cell carcinoma: Results from the Canadian Kidney Cancer Information System. Urol Oncol. 11 2016;34(11):486.e1-486.e7. doi:10.1016/j.urolonc.2016.05.025

50. Zabor EC, Furberg H, Lee B, et al. Long-Term Renal Function Recovery following Radical Nephrectomy for Kidney Cancer: Results from a Multicenter Confirmatory Study. *J Urol*. 04 2018;199(4):921-926. doi:10.1016/j.juro.2017.10.027

51. Robinson-Cohen C, Katz R, Mozaffarian D, et al. Physical activity and rapid decline in kidney function among older adults. *Arch Intern Med*. Dec 14 2009;169(22):2116-23. doi:10.1001/archinternmed.2009.438

52. Courneya KS, Vallance JK, Culos-Reed SN, et al. The Alberta moving beyond breast cancer (AMBER) cohort study: a prospective study of physical activity and health-related fitness in breast cancer survivors. *BMC Cancer*. Nov 16 2012;12:525. doi:10.1186/1471-2407-12-525

53. Nadler MB, Desnoyers A, Langelier DM, Amir E. The Effect of Exercise on Quality of Life, Fatigue, Physical Function, and Safety in Advanced Solid Tumor Cancers: A Meta-analysis of Randomized Control Trials. *J Pain Symptom Manage*. 11 2019;58(5):899-908.e7. doi:10.1016/j.jpainsymman.2019.07.005

54. Chen YJ, Li XX, Ma HK, et al. Exercise Training for Improving Patient-Reported Outcomes in Patients With Advanced-Stage Cancer: A Systematic Review and Meta-Analysis. *J Pain Symptom Manage*. 03 2020;59(3):734-749.e10. doi:10.1016/j.jpainsymman.2019.09.010

Table 6-1. Study and sample characteristics of the cross-sectional study and randomized controlled trial of physical activity in patients with kidney cancer included in the scoping review.

Author and year of publication	Country	Sample size	Male (%)	Age M ± SD (years)	Time since diagnosis M±SD	Treatment Status	Localized disease (%)	Surgery (%)
Cross-Sectional Design								
Tabaczynski et al. (2020)[27] and Trinh et al. (2012)[26]	Canada	651	62.4	64.4 ± 11.0	68.6 ± 56.5	91.5% off treatment	83.3	97.5
Tabaczynski et al. (2020)[30]	Canada	463	63.9	62.7 ± 10.4	66.7 ± 55.7	90.3% off treatment	84.2	98.1
Trinh et al. (2018)[28], Trinh et al. (2012)[29], and Trinh et al. (2011)[24]	Canada	703	62.9	65.0 ± 11.1	69.0 ± 55.5	91.3% off treatment	81.7	97.3
Trinh et al. (2016)[31]	Canada	432	63.2	64.4 ± 11.1	72.3 ± 60.8	Not reported	82.2	97.5
Trinh et al. (2013)[25]	Canada	540	63.5	63.3 ± 10.7	66.7 ± 55.2	90.7% off treatment	83.3	97.6
Randomized controlled trial								
Trinh et al. (2015)[33] and Trinh et al. (2014)[32]	Canada	32	50	61.8 ± 9.8	74.0 ± 38.9	100 % off treatment	93.8	96.9

Table 6-2. Study and sample characteristics of the cohort studies of physical activity and kidney cancer outcomes included in the scoping review.

Author and year of publication	Country	Sample size	Male (%)	Age, median and/or range (years)	Localized disease (%)	Surgery (%)	Follow-up duration (mean or range)	Number of events
Wunderle et al. (2021)[39]	Germany	150	97	67 (33-93)	Not reported	100	30 days	23 post-surgery complications
Schmid et al. (2018)[34]	United States	667	73	50-71	81.5	42	7.1 years	57 kidney cancer deaths
Liss et al. (2017)[35]	United States	222,163	48	45 (43 - 45)	Not reported	Not reported	2 - 8 years	71 kidney cancer deaths
Arem et al. (2014)[36]	United States	293,511	58	50-71	Not reported	Not reported	12.1 years	367 kidney cancer deaths
Colli et al. (2009)[37]*	United States	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Thompson et al. (2008)[40]	United States	21,637	100	20-88	Not reported	Not reported	16.4 years	31 kidney cancer deaths
Washio et al. (2007)[38]	Japan	110,788	42	40-79	Not reported	Not reported	Males: 12.8 years Females: 13.3 years	66 kidney cancer deaths

*The authors provided only the mortality rates expressed as cases/100 000 based on the U.S. population

Table 6-3. Summary of aims, measurements, and findings of the cross-sectional and randomized controlled studies of physical activity in patients with kidney cancer included in the scoping review.

Author (year)	Primary and Secondary aim(s)	Data collection and measurements	Overall findings
Cross-Sectional Studies			
Tabaczynski et al. (2020)[27]	To examine the demographic, medical, social-cognitive, and environmental correlates of meeting independent and combined PA guidelines compared with meeting neither guideline. To examine the demographic, medical, social-cognitive, and environmental correlates of meeting independent, combined, and neither PA guidelines compared with one another.	- Canadian provincial registry, self-administered mailed survey (May - September 2010) - Self-reported demographic and medical information - Modified GLTEQ - Modified version of the TPB - NEWS - IPAPSESM - Built Environment characteristics through geographic information system-based	PA participation correlates vary based on modality of interest. Compared with meeting neither guideline, meeting aerobic-only guideline was associated with higher intentions, planning, and access to workout attire (all p<.01), and proximity to retail (p=.02); meeting strength training-only guideline was associated with higher intentions (p=.02), planning (p<.01), and lower perceived behavior control (p=.03), healthy weight (p=.01) and older age (p<.01); meeting combined guidelines was associated with higher intentions (p<.01), planning (p=.02), higher instrumental attitudes (p<.01), higher education (p=.04), better heatlh (p<.01), and localized cancer (p=.05). 7.2% of the variance in meeting the PA guidelines was accounted by demographic variables. Medical variables explained 16.5% of the variance. Social-Cognitive variables accounted for 20.5% for the variance in meeting the PA guidelines.
Tabaczynski et al. (2020)[30]	To examine the association of reallocating sedentary time to sleep, light PA, or moderate-to-vigorous PA on quality of life in patients with KC. To identify the threshold of sedentary time substitution at	- Canadian provincial registry, self-administered mailed survey (May - September 2010) - Self-reported demographic and medical information - Modified GLTEQ - Domain-Specific Sitting Time Questionnaire	Reallocating sedentary time to sleep, light PA, or moderate-to-vigorous PA was statistically significant associated with different subscales of quality of life. 65 minutes a day of sedentary time reallocated to light PA would be necessary for clinically meaningful improvements in fatigue. 83 minutes of sedentary time reallocated to moderate-to vigorous PA might be necessary for clinically meaningful improvements in overall quality of life, fatigue, physical and functional well-being.

	which the associations are significant.	- FACT-General - FACT-Fatigue -TOI-F	200 minutes a day of sedentary time reallocated to sleep would be needed for associations to be clinically meaningful.
Trinh et al. (2018)[28]	To estimate the prevalence of meeting the combined and independent aerobic and strength PA guidelines in patients with KC. To determine any associations of meeting the combined and independent aerobic and strength PA guidelines with quality of life in patients with KC.	- Canadian provincial registry, self-administered mailed survey (May - September 2010) - Modified GLTEQ - FACT-General - FACT-Fatigue - FACT-Kidney Symptom Index - TOI-F - Self-reported demographic and medical information	15.9% of patients with KC reported meeting aerobic-only PA guidelines, 8.8% meeting strength training-only PA guidelines, 10.1% meeting combined guidelines, and 65.1% meeting neither guidelines. Univariate correlates of the various exercise guidelines were age, education, employment, drinking status, drug treatment, current disease status, and BMI. Meeting the combined guidelines was superior to meeting neither guideline (p<.001), strength training-only guideline (p=.021), and aerobic only guideline (p=.051) for TOI-F. Meeting either guideline independently was superior to meeting neither PA guideline (p<.001 for aerobic and p=.045 for strength), but not different from each other for TOI-F.
Trinh et al. (2016)[31]	To examine the associations between demographic, medical, social-cognitive, and environmental correlates of PA in patients with KC using several aspects of the social-ecological model.	- Canadian provincial registry, self-administered mailed survey (May - September 2010) - Self-reported demographic and medical information - Modified GLTEQ - Modified version of the TPB - NEWS - IPAPSESM - Built Environment characteristics through geographic information system-based	Social-Cognitive variables accounted for 44.0% for the variance in meeting the PA guidelines. Perceived and objective built environment characteristics contributed to 1.7% and 2.4% of the variance explained in meeting PA guidelines. In the social-ecological model, meeting PA guidelines in patients with KC was associated with disease stage (p=.005), having drug therapy (p=.009), higher levels of instrumental attitudes (p=.053), higher levels of intention (p=.002), and the perceived presence of retail shops in the neighborhood (p=.032).

Trinh et al. (2013)[25]	To estimate the prevalence of sitting time and to determine any associations of quality of life in patients with KC. To explore if medical or demographic variables moderate the associations between sitting time and quality of life	- Canadian provincial registry, self-administered mailed survey (May - September 2010) - Modified version of the domain-specific sitting time questionnaire -Modified GLTEQ - FACT-General - FACT-Fatigue - FACT-Kidney Symptom Index - TOI-F - Self-reported demographic and medical information	The mean sitting time hours on a work day was 8.0 ±4.7h and 6.5 ± 3.8h on a non-work day. There were no significant associations between sitting time and quality of life for non-word day and work day, except for appositive association between sitting time on a work day and emotional well-being (p=.019). Age was the only variable to moderate the association between sitting time and quality of life. PA categories did not moderate association between sitting time and quality of life, and sitting time did not differ across PA categories for both work day and non-work day.
Trinh et al. (2012)[26]	To test the utility of the modified TPB in patients with KC and to determine the most important social cognitive correlates of PA intentions and behavior. To determine if the TPB operates equivalently across demographic and medical variables. To identify the most common behavioral, control, and normative beliefs in patients with KC.	- Canadian provincial registry, self-administered mailed survey (May - September 2010) - Modified GLTEQ - Modified version of the TPB - Self-reported demographic and medical information	The theory of planned behavior accounted for 69%, 63%, and 42% of the variance in intention, planning, and PA levels, respectively, supporting its utility. PA behavior was strongly associated with planning, intention (both p<.01). Intention was associated with perceived behavioral control (p<.01), instrumental attitude (p=.03), and descriptive norm (p=.01). Planning was strongly associated with intention (p<.01).
Trinh et al. (2012)[29]	To identify the PA preferences of patients with KC.	- Canadian provincial registry, self-administered mailed survey (May - September 2010)	PA preferences include: receive PA information from a fitness expert at a cancer center, receive information via print material, start a PA program after treatment, exercise with a spouse, exercise at home, do moderate-intensity PA, and walk in both the summer and winter.

	To explore the associations between medical/demographic variables and PA preferences	- Questionnaire on PA preferences with open and closed-ended questions drawn from previous studies in cancer survivors - Self-reported demographic and medical information	Preferences were associated with age, sex, and current PA.
Trinh et al. (2011)[24]	To estimate the prevalence of PA in patients with KC and determine any associations with quality of life. To explore if medical or demographic variables moderate the association between PA and quality of life	- Canadian provincial registry, self-administered mailed survey (May - September 2010) - Modified GLTEQ - FACT-General - FACT-Fatigue - FACT-Kidney Symptom Index - TOI-F - Self-reported demographic and medical information	56.3% of patients with KC were completely sedentary, 17.6% were insufficiently active, 11.9% were within the guidelines, 14.1% were above guidelines. Dose-response association between PA and many domains of quality of life of patients with KC (p for trend <.001), from completely sedentary to within the guidelines, with no further increases for exceeding guidelines. Education, age, and comorbidities moderated the association between PA and TOI-F.
Randomized controlled trial			
Trinh et al. (2015)[33]	To investigate the impact of a supervised PA plus exercise counseling versus supervised PA plus behavioral counseling on motivation levels among patients with KC.	- Self-reported demographic and medical information - Modified version of the TPB	Adding behavioral counseling to supervised PA had positive effects on planning (p=.017), and different behavioral and control beliefs.

Trinh et al. (2014)[32]	Feasibility of a supervised PA plus exercise counseling versus supervised PA plus motivationally enhanced behavioral counseling in patients with KC. To examine the preliminary effects of the intervention on PA, quality of life, body composition, cardiorespiratory fitness and physical function.	- Feasibility was determined by recruitment rate, measurement completion rate, loss to follow-up, adherence to the intervention, adverse events, and program evaluation items assessing burden and satisfaction. - Modified GLTEQ - FACT-General - FACT-Fatigue - FACT-Kidney Symptom Index - TOI-F - SF-36 - Submaximal aerobic test (modified Balke protocol) - Senior's fitness test - Anthropometric measures (height, weight, and waist circumferences) - Self-reported demographic and medical information	35.2 % recruitment rate 88% and 94% measurement completion rates for fitness test and questionnaires, respectively 94% adherence rate to the 4-week intervention program. The supervised PA plus motivationally enhanced behavioral counseling group significantly improved the 6-minute walk scores (p=.046) and increased PA by 34 minutes more than the comparison group (non-significant, p=.47). No meaningful changes in the anthropometric measures or quality of life parameters.

Abbreviations: BMI: body mass index; FACT: Functional Assessment of Cancer Therapy; GLTEQ: Godin Leisure Time Exercise Questionnaire; IPAPSESM: International Physical Activity Prevalence Study Environmental Survey Module; KC: kidney cancer; NEWS: Neighborhood Environment Walkability Scale; PA: physical activity; TOI-F: Trial Outcome Index Fatigue; TPB: Theory of Planned Behavior

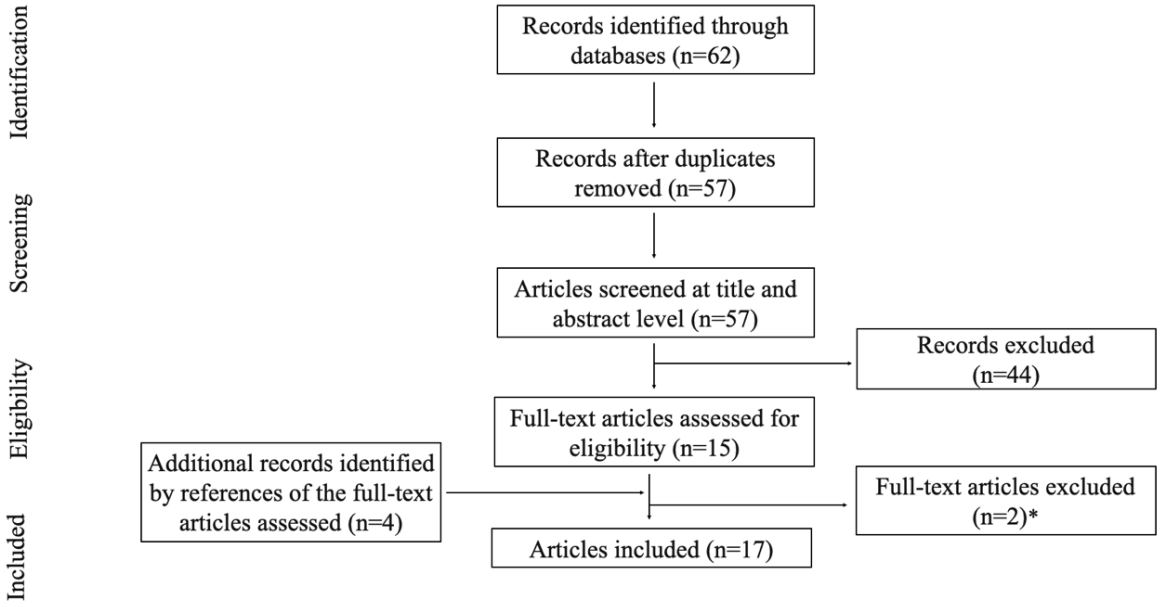
Table 6-4. Summary of aims, measurements, and findings of the cohort studies of physical activity and kidney cancer outcomes included in the scoping review.

Author (year)	Primary and Secondary aim(s)	Data collection and measurements	Overall findings
Wunderle et al. (2021)[39]	To examine geriatric assessment tools, including physical functioning, in post-operative complications in kidney cancer patients undergoing partial nephrectomy.	- Time up and go - Handgrip strength measurement – - Full-Tandem Stand - Postoperative complications grade - Failure of trifecta (surrogate of surgical quality - negative surgical margin, ischemia time <25 min, and no major complications) – 30-day readmissions rate	23 post-surgery complications within 30-days. Low handgrip (OR=4.76, p=.021), full-tandem-stand <10s (OR=4.25, p=.047) were significant predictors of major post-operative complications. Low handgrip (OR=0.28, p=.037), full-tandem-stand <10s (OR=0.18, p=.010), and time up and go tests (OR=0.11, p=.011) were significantly associated with trifecta failure.
Schmid et al. (2018)[34]	To examine the relations of PA and sedentary behavior with all-cause and cancer-specific mortality among individuals diagnosed with kidney cancer.	- National Institutes of Health - AARP Diet and Health Study cohort - Self-report questionnaire of PA (weekly time spent doing moderate to vigorous PA over the prior 12 months) - Self-report questionnaire of TV viewing, and total sitting time - Participants reported categorical duration of activities (never, rarely, <1hr week, 1-3hr week, 4-7hr week, and >7hr week) - Renal cell cancer incidence and mortality was assessed via National Cancer Registry	57 deaths of kidney cancer in 7.1 years of follow-up. There were no significant associations between PA or sedentary behavior with cancer-specific mortality among renal cell cancer patients. HRs for <1 hr/wk (reference), 1 to 3 hrs/wk, ≥3 to <7 hrs/wk, and ≥7 hrs/wk = 1.0, 0.92 (95% CI = 0.44-1.91), 1.04 (95% CI = 0.45-2.37), and 0.57 (95% CI = 0.24–1.33; p-trend = 0.30). Increasing levels of moderate to vigorous PA was significantly inverse associated to all-cause mortality HRs for <1 hr/wk (reference), 1 to 3 hrs/wk, ≥3 to <7 hrs/wk, and ≥7 hrs/wk = 1.0, 1.16 (95% CI = 0.78-1.72), 0.94 (95% CI = 0.60-1.49), and 0.60 (95% CI = 0.38–0.96; p-trend = 0.03). Being physically active (4h per week of more) before and after diagnosed was associated with a significant reduced risk of all-cause-mortality (HR=0.56, 95% CI = 0.32-0.96)

Liss et al. (2017)[35]	To investigate the association of Kidney cancer mortality with obesity, PA, and smoking.	- National Health Information survey data - Self-report PA (average minutes of vigorous or moderate exercise per week); in-person interview	71 deaths of kidney cancer Individuals who reported any physical activity were about 50% less likely to die of kidney cancer than non-exercises (HR=0.50, 95% CI = 0.27-0.93, p=.0028) Obese individuals were about 3 times more likely to die of kidney cancer (HR=2.84, 95% CI = 1.30-6.23 p=0.009) Former smokers were twice as likely to die of kidney cancer (HR=2.00, 95% CI = 1.05-3.80 p=0.034)
Arem et al. (2014)[36]	To examine the associations of pre-diagnosis physical activity and cancer-specific mortality.	National Institutes of Health - AARP Diet and Health Study cohort - Non-validated PA questionnaire assessing leisure time activity performed in the last 10 years. - Participants reported categorical duration of activities (never, rarely, <1hr week, 1-3hr week, 4-7hr week, and >7hr week). - Mortality was assessed via National Registry	367 deaths of kidney cancer in 12.1 years of follow-up. Significant positive trend between moderate to vigorous intensity leisure time physical activity and kidney cancer mortality. HRs for never/rare (reference), <1 hr/wk, 1 to 3 hrs/wk, ≥3 to <7 hrs/wk, and ≥7 hrs/wk = 1.0, 1.10 (0.71-1.70), 1.14(95% CI = 0.80-1.64), 1.47 (95% CI = 1.03-2.09), and 1.42 (95% CI = 0.98–2.03; p-trend = 0.016).
Colli et al. (2009)[37]*	To explore the relationship between renal cell carcinoma rates with heath behaviors.	The renal cell carcinoma mortality rates were obtained from the National Center of Health Statistics - Self-reported physical inactivity (no PA or exercise in the past month), telephone interviews	Smoking, obesity, and physical inactivity correlated with renal cell carcinoma mortality rates among males (p=0.002) and females (p=0.03).
Thompson et al. (2008)[40]	To examine the risk of cancer mortality across levels of fitness.	- Submaximal aerobic test (modified Balke protocol)	31 deaths of kidney cancer in 16.4 years of follow-up. Relative risk of cancer mortality for kidney cancer-only was 0.91(95% CI: 0.45-2.68).

Washio et al. (2007)[38]	To evaluate the association between diabetes mellitus and kidney cancer mortality among the Japanese population.	- Self-reported leisure time per week - Self-reported occupational PA	46 males and 20 females died of kidney cancer in 12.8 and 13.3 years of follow-up, respectively. There was no association between leisure time PA, and occupational PA and kidney cancer death. In the multivariate analysis, diabetes mellitus was not associated with kidney cancer death.

Figure 6-1. PRISMA flow diagram of the search results of studies of physical activity in patients with kidney cancer.



*Reasons for exclusion: two articles included mixed cancer groups and did not report separate results for kidney cancer

Supplementary Table 6-1. Search strategy for studies of physical activity in patients with kidney cancer.

PubMed	
#1	"Resistance Training" [Mesh] OR Exercise[Mesh] OR "Physical Fitness" [Mesh] OR "Leisure activities" [Mesh]
#2	"Kidney Neoplasms"[Mesh]
#3	Humans[Mesh]
#4	English[Language]
#5	(review[Publication Type]) NOT (comment[Publication Type])) NOT (editorial[Publication Type])
#6	#1 AND #2 AND #3 AND #4 NOT #5
Cochrane Library	
#1	MeSH descriptor: [Resistance Training] explode all trees
#2	MeSH descriptor: [Exercise] explode all trees
#3	MeSH descriptor: [Physical Fitness] explode all trees
#4	MeSH descriptor: [Leisure Activities] explode all trees
#5	#1 OR #2 OR #3 OR #4
#6	MeSH descriptor: [Kidney Neoplasms] explode all trees
#7	#5 AND #6

CHAPTER 7. DISCUSSION

7.1 Overview

The overall purpose of this paper-based dissertation was to generate new knowledge in the field oncology in two common, yet understudied, cancer groups - bladder and kidney cancer. Among the objectives of this dissertation, I aimed to (1) investigate the association between body mass index and bladder cancer outcomes in MIBC patients treated by radical cystectomy (Chapter 2, Paper 1); (2) examine the safety, feasibility, and preliminary efficacy of HIIT in NMIBC patients during or after intravesical therapy (Chapter 3 and Chapter 4, Paper 2 and Paper 3); (3) examine the motivational outcomes, perceived benefits and harms, and perceived barriers to exercise during or after intravesical therapy in patients with NMIBC (Chapter 5, Paper 4); and (4) conduct a scoping review of physical activity and kidney cancer, report current findings, delineate strengths and limitations, and provide key recommendations for future research (Chapter 6, Paper 5).

7.2 Summary of Findings

To summarize, **Chapter 2 (Paper 1)**, through a retrospective analysis of a previously established database, reported that patients with a BMI higher than 25 kg/m^2 had a lower 90-day mortality rate and a better overall survival within the first five years of radical cystectomy, when most deaths are due to surgical complications or bladder cancer. After five years, however, when most deaths are due to other causes, patients with a BMI higher than 25 kg/m^2 had an increased risk of all-cause mortality, resulting in no difference in longer-term overall survival. These data suggest that the obesity paradox in bladder cancer patients treated with radical cystectomy may be short-lived.

The BRAVE trial rationale, design, and detailed study protocol have been described in **Chapter 3 (Paper 2)**. The major findings of the BRAVE trial have been discussed in Chapters 4 and 5. Briefly, **Chapter 4 (Paper 3)** reported the primary findings of the BRAVE trial, where despite limited accrual, the BRAVE trial demonstrated that HIIT was feasible and safe and resulted in significant improvements in several indicators of physical functioning of NMIBC patients during or after intravesical therapy, but not on peak oxygen consumption. **Chapter 5 (Paper 4)** reported that HIIT during or after intravesical therapy for NMIBC was more motivating than anticipated with many perceived benefits (e.g., cardiovascular endurance, physical functioning, and quality of life) and few barriers or harms (e.g., busy/having limited time and joint pain/soreness). However, after the intervention, the HIIT group reported lower motivation and confidence, and higher difficulty in exercising on their own for the next 6 months when compared to the usual care group.

Finally, **Chapter 6 (Paper 5)** reported a scoping review of physical activity in kidney cancer patients. This chapter highlighted the limited and preliminary nature of the available evidence on physical activity and kidney cancer. A comprehensive search identified 17 articles from nine independent studies, including one cross-sectional study (n=8 articles), one randomized controlled trial (n=2 articles) and seven cohort studies (n=7 articles). Due to the limited and preliminary nature of the evidence, no conclusions could be drawn from current research on the safety, feasibility, and efficacy (benefits and harms) of physical activity in patients with kidney cancer. Our findings highlight the urgent need for further research to inform clinical exercise guidelines in this understudied cancer patient group.

7.3 Strengths and Limitations

In this section, I will further expand on the key strengths and limitations of each study. The study reported in **Chapter 2 (Paper 1)** has several strengths, including adequate sample size, a relatively clinically homogeneous cohort with the majority of patients scheduled to receive the same first line of treatment (i.e., radical cystectomy), the long follow-up time allowing observation of the event of interest, and the rigorous analysis, including the verification of the proportional hazard assumption. However, limitations should be acknowledged. First, although BMI has been widely used as a surrogate of adiposity to identify risk factors associated with excess body weight, it does not distinguish between adipose, skeletal, and muscle tissues, therefore there are significant variation in body composition within levels of BMI which may yield paradoxical findings [1]. Further limitations include the exploratory nature of the analysis and the retrospective design of the study [2]. Since the data was not collected in a pre-designed and prospective manner, important data that have the potential to impact the outcome were missing, including behavioral measurements (i.e., smoking status and physical activity levels), and medical conditions (i.e., comorbidities). Finally, the observational nature of this study provides associative, not causal, evidence between risk factors and outcomes [2].

The BRAVE trial reported in **Chapters 3, 4, and 5 (Papers 2, 3, and 4)** was the focus of this dissertation due to its novelty and study design. The primary strength of the BRAVE trial is being the first randomized controlled trial examining the safety, feasibility, and preliminary efficacy of HIIT in patients with NMIBC during or after their intravesical therapy. Patients with NMIBC are an understudied cancer population with a

unique treatment protocol (i.e., intravesical therapy) not previously investigated in exercise oncology trials, therefore the BRAVE trial provides important considerations for exercise safety, feasibility, and potential benefit in this clinical setting. Second, BRAVE is the first exercise oncology trial to assess the feasibility of collecting bladder cancer clinical outcomes. Clinical outcomes are extremely important considering the high rate of cancer recurrence and progression in this patient group, potentially leading to additional therapy or radical treatment [3]. The BRAVE trial demonstrated the feasibility of collecting bladder cancer clinical outcomes, providing relevant information that will guide future research designed to examine the role of exercise as an adjuvant cancer treatment [4]. Third, the BRAVE trial is the first to explore the motivational basis of a HIIT program in NMIBC patients during or after intravesical therapy. Moreover, motivational outcomes were assessed using a validated theoretical model both prospectively and retrospectively.

The outcomes of the BRAVE trial will inform the design of theoretical-based exercise interventions and may contribute to improved recruitment and adherence. Another major strength of the BRAVE is the quality of adverse events reporting, utilizing the Common Terminology Criteria for Adverse Events (CTCAE), a recognized and standardized classification of adverse events used in cancer therapy [5]. The BRAVE trial encoded the grade of the adverse event based on the CTCAE system, classified the adverse event in relation to the exercise sessions or assessments, and provided the consequence of the adverse event (e.g., study discontinuation). Previous research has highlighted the poor quality of adverse events reporting in exercise trials among cancer patients [6]. The approach adopted in the BRAVE trial provides a comprehensive

understanding of the adverse event and may serve as an example for future exercise oncology studies. Other important strengths of the BRAVE trial include the comprehensive and validated measurements of health-related fitness outcomes and patients-reported outcomes.

Despite the strengths of the BRAVE Trial, several limitations should be considered for the interpretation of the findings and planning future research. First, the BRAVE Trial did not reach the targeted sample size due to a slower-than-anticipated accrual. Additionally, the slower-than-anticipated accrual led to changes in the eligibility criteria. Eligibility criteria were expanded first from induction to patients in the maintenance phases and then to those on surveillance, resulting in greater heterogeneity of clinical oncology scenarios. The clinical oncology scenarios were proposed by Courneya and Booth [4] in the Exercise as Cancer Treatment (EXACT) framework. The EXACT framework consists of a systematic and clinically informed approach that considers tumor status (i.e., surgically removed, not surgically removed, or metastatic disease) and treatment status (i.e., treatment naïve, actively treated, or previously treated). It is important to distinguish the scenarios in exercise oncology trials because the feasibility and the potential benefit of exercise may differ [4]. For instance, patients on induction intravesical therapy fall within the "actively treated micrometastases" clinical oncology scenario. In this scenario, complete surgical resection (i.e., TURBT) is followed by regional adjuvant therapy (i.e., induction intravesical therapy) with the main goal of treating known or suspected micrometastases. Exercise feasibility might be lower in this scenario because of possible concurrent treatment side effects in comparison to patients on surveillance (i.e., previously treated micrometastases oncology scenario) who had

completed their therapy. In terms of the benefit of exercise on bladder cancer outcomes, the potential benefit is probably higher in the scenario where patients were recently diagnosed are being actively treated given the high likelihood of recurrence within the first two years of diagnosis [3, 7], compared to those on surveillance and many years after diagnosis. Although the BRAVE trial is not powered for bladder cancer outcomes, these limitations should be considered when interpreting the findings and planning future research. Finally, another important limitation of the BRAVE trial is the low generalizability of our findings due to selection bias of motivated participants to initiate an exercise program and a higher proportion of men compared to women.

Chapter 6 (Paper 5), the final study of the dissertation, also has important strengths and limitations. A major strength of the scoping review reported in Chapter 7 is the originality of examining physical activity in kidney cancer patients. This is the first study to collate, summarize, and provide a comprehensive overview of the currently available literature on physical activity in kidney cancer. A second strength is the study design, which was conducted and reported following the PRISMA guidelines extension for scoping review [8], resulting in methodological transparency and high-quality reporting. Third, scoping reviews guide future research and inform whether a systematic review of the literature is warranted [9]. The extent (amount), range (variety), and nature (characteristics) of the available evidence in physical activity and kidney cancer are still limited and preliminary, therefore more research should be conducted before proceeding to systematic reviews and meta-analysis. Another strength of the scoping review is the important research directions provided across the four phases of the cancer continuum (i.e., pretreatment, treatment, survivorship and end-of life).

The limitations should also be acknowledged, most of which were related to the nature of the included studies and the inherent limitations of scoping reviews. First, no conclusions could be drawn regarding the safety, feasibility, and efficacy of physical activity interventions in kidney cancer patients. The review was designed to identify the extent, range, and nature of the evidence on physical activity and kidney cancer, focusing on stimulating future research. A second limitation is the lack of quality assessment. Scoping reviews are not intended to critically appraise the risk of bias of the evidence [8], leading to the inclusion of studies regardless of their methodological quality. Third, the search strategy was limited by language and number of databases searched, which may have impacted the number of studies included.

7.4 Future Research Directions

The limitations discussed above hinder our ability to translate exercise into the standard of care for bladder and kidney cancer patients. Further phase I and phase II feasibility studies are urgent needed among these patient groups to confirm the safety, applicability, tolerability, and preliminary efficacy of physical activity and exercise interventions across the cancer continuum, including pretreatment, treatment, survivorship, and end-of-life phases. The key research questions for both patient groups that future investigations should address relate to: 1) the effects of physical activity and exercise interventions on cancer outcomes (e.g., treatment tolerance, treatment response, cancer recurrence, cancer progression); 2) the effects of physical activity and exercise interventions on patient-reported outcomes (e.g., symptoms and side effects, quality of life); and 3) the role of physical fitness and body composition in improving these important outcomes.

An important challenge to consider when conducting research on bladder and kidney cancer patients is the risk of low patient accrual. Low patient accrual is the main factor associated with trial termination in genitourinary cancers [10], and may result in inappropriate interpretations of the findings, researcher and patient disappointment, and negative financial impact. Moreover, recruitment rates in exercise trials in cancer are often suboptimal and lower than cancer clinical trials [11]. Strategies to overcome low accrual should be planned and included in the trial protocol. For instance, collaboration with other institutions including those located in low- and middle-income countries. Research has found that multicenter trials were associated with higher completion rates among prostate, bladder, and kidney cancers [10]. Additionally, genitourinary cancer trials conducted in lower- and middle-income countries had higher completion rates in contrast to those in high-income countries [10]. Potential reasons for that may include the discrepancy in the number of trials available (small number of trials conducted in low- and middle-income countries) [10], but also the access to a larger patient pool since low- and middle-income countries often have larger populations.

Another strategy that future studies should consider to address low accrual relates to changes in the study protocol, such as expanded eligibility criteria or modifications in the study intervention. For instance, one of the common reasons to decline participation in the BRAVE trial was that patients could not commit to the study requirements (20.4%). The BRAVE trial consisted of three supervised exercise sessions per week on a treadmill or a cycle ergometer for 12 weeks (if allocated to the exercise group), plus fitness assessments at three time points (baseline, 6-week, and 12-week), and completion of questionnaires at three time points (baseline, 12-week, and 12-month). Future studies

should reconsider the number of assessment time points and investigate if a reduced number of supervised exercise sessions would result in higher recruitment rates and still elicit benefits on parameters of physical functioning and motivation. Importantly, the findings from the BRAVE trial suggest that NMIBC patients do not have a well established plan and may have lower motivation and confidence in self-directed exercise programs. Therefore, unsupervised exercise could be challenging and may require distance-based behavioral support. Additional research is warranted to establish long-term exercise benefits and adherence among NMIBC patients during or after intravesical therapy. The BRAVE trial will provide important information on the long-term effects of the HIIT intervention on patient-reported outcomes, exercise behavior, and cystoscopy outcomes. This data is being collected and will be reported in future papers.

Several other insights for future research directions in bladder and kidney cancer patients were identified and discussed in the respective studies comprising the main body of this dissertation. However, the final point I would like to emphasize is that for exercise to be part of the standard of care of bladder and kidney cancer patients, future exercise oncology research should be systematically designed and analyzed to demonstrate compelling connections between exercise and cancer variables in the distinct scenarios of clinical oncology practice [4, 12]. This approach is important to establish exercise feasibility and efficacy within a specific clinical oncology scenario, given the diversity of cancer types, the range and sequencing of treatment, and the timing of exercise in relation to these treatments [4].

7.5 Practical Implications

The findings from this dissertation provide valuable information on the design, reporting, and direction of future exercise oncology trials in bladder and kidney cancer patient groups. The most notable practical implications are 1) the highlighted need for further research to understand the underlying mechanisms of the obesity paradox in bladder cancer patients treated with radical cystectomy; 2) the identification of challenges related to recruitment and assessment protocols in a typically elder and comorbid cancer population; 3) the demonstrated feasibility of assessing bladder cancer clinical outcomes; 4) the identification of potential barriers, benefits, harms, and motivational outcomes of HIIT in NMIBC patients during or after intravesical therapy; and 5) the insightful guidance of research in physical activity and kidney cancer across the treatment continuum. In summary, this dissertation provides novel findings and important directions toward the development of further research examining how exercise could benefit patients with bladder and kidney cancer and be incorporated into the standard clinical care.

7.6 Conclusion

The overarching goal of this paper-based dissertation was to investigate and provide advancements to the field of exercise oncology in two common, yet understudied, cancer groups - bladder and kidney cancer. This thesis highlight the need of further research to understand the underlying mechanisms of the obesity paradox in bladder cancer patients treated with radical cystectomy. This thesis supports the safety and feasibility of a 12-week HIIT exercise program for people with NMIBC during or after intravesical therapy based on satisfactory adherence and high protocol compliance. Moreover, the HIIT program resulted in significant improvements in several parameters

of physical functioning, and was experienced as more enjoyable and less difficulty than anticipated, however, appeared to reduce NMIBC patients' confidence and motivation to exercise on their own. Finally, this thesis highlighted that physical activity research in kidney cancer patients is preliminary in nature, therefore no conclusions can be drawn regarding the safety, feasibility, and efficacy of physical activity in patients with kidney cancer.

7.7 References

1. Prado, C.M., M.C. Gonzalez, and S.B. Heymsfield, *Body composition phenotypes and obesity paradox.* Curr Opin Clin Nutr Metab Care, 2015. **18**(6): p. 535-51.
2. Talari, K. and M. Goyal, *Retrospective studies - utility and caveats.* J R Coll Physicians Edinb, 2020. **50**(4): p. 398-402.
3. Kamat, A.M., et al., *Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group.* J Clin Oncol, 2016. **34**(16): p. 1935-44.
4. Courneya, K.S. and C.M. Booth, *Exercise as cancer treatment: A clinical oncology framework for exercise oncology research.* Front Oncol, 2022. **12**: p. 957135.
5. National Cancer Institute [NIH]. *Cancer Therapy Evaluation Program: Common Terminoloty Criteria for Avderse Events v5.0 (CTCAE)*. 2017 March 11, 2024]; Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50.
6. Thomsen, S.N., et al., *Harms of exercise training in patients with cancer undergoing systemic treatment: a systematic review and meta-analysis of published and unpublished controlled trials.* EClinicalMedicine, 2023. **59**: p. 101937.
7. Chamie, K., et al., *Recurrence of high-risk bladder cancer: a population-based analysis.* Cancer, 2013. **119**(17): p. 3219-27.

8. Tricco, A.C., et al., *PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation.* Ann Intern Med, 2018. **169**(7): p. 467-473.

9. Munn, Z., et al., *Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach.* BMC Med Res Methodol, 2018. **18**(1): p. 143.

10. Alhajahjeh, A., et al., *Understanding the Termination of Urologic Cancer Clinical Trials: Insights and Challenges.* JCO Glob Oncol, 2024. **10**: p. e2300349.

11. Reynolds, S.A., et al., *Recruitment rates and strategies in exercise trials in cancer survivorship: a systematic review.* J Cancer Surviv, 2023.

12. Courneya, K.S. and C.M. Friedenreich, *Designing, analyzing, and interpreting observational studies of physical activity and cancer outcomes from a clinical oncology perspective.* Front Oncol, 2023. **13**: p. 1098278.

BIBLOGRAPHY

1. Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., . . . de Haes, J. C. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*, *85*(5), 365-376. https://doi.org/10.1093/jnci/85.5.365

2. Adams, S. C., DeLorey, D. S., Davenport, M. H., Stickland, M. K., Fairey, A. S., North, S., . . . Courneya, K. S. (2017). Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: A phase 2 randomized controlled trial. *Cancer*, *123*(20), 4057-4065. https://doi.org/10.1002/cncr.30859

3. Ajzen, I. (1991). The theory of planned behavior In (pp. 179-211): Organ Behav Hum Decis Process

4. Ajzen, I. (2020). The theory of planned behavior: Frequently asked questions. In (pp. 314-324). *Hum Behav & Emerg Tech* . .

5. Alhajahjeh, A., Hmeidan, M., Elatrsh, M., Al-Abbadi, F., Kakish, D., Sukerji, R., . . . Shahait, M. (2024). Understanding the Termination of Urologic Cancer Clinical Trials: Insights and Challenges. *JCO Glob Oncol*, *10*, e2300349. https://doi.org/10.1200/GO.23.00349

6. Ames, S. C., Parker, A. S., Crook, J. E., Diehl, N. N., Tan, W. W., Williams, C. R., & Ames, G. E. (2011). Quality of life of patients undergoing surgical treatment for newly-diagnosed, clinically localized renal cell carcinoma. *J Psychosoc Oncol*, *29*(6), 593-605. https://doi.org/10.1080/07347332.2011.616574

7. An, K. Y., Arthuso, F. Z., Kang, D. W., Morielli, A. R., Ntoukas, S. M., Friedenreich, C. M., . . . Courneya, K. S. (2021). Exercise and health-related fitness predictors of chemotherapy completion in breast cancer patients: pooled analysis of two multicenter trials. *Breast Cancer Res Treat*. https://doi.org/10.1007/s10549-021-06205-8

8. Annels, N. E., Simpson, G. R., & Pandha, H. (2020). Modifying the Non-muscle Invasive Bladder Cancer Immune Microenvironment for Optimal Therapeutic Response. *Front Oncol*, *10*, 175. https://doi.org/10.3389/fonc.2020.00175

9. Antoni, S., Ferlay, J., Soerjomataram, I., Znaor, A., Jemal, A., & Bray, F. (2017). Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. *Eur Urol*, *71*(1), 96-108. https://doi.org/10.1016/j.eururo.2016.06.010

10. Arem, H., Moore, S. C., Park, Y., Ballard-Barbash, R., Hollenbeck, A., Leitzmann, M., & Matthews, C. E. (2014). Physical activity and cancer-specific mortality in the NIH-AARP Diet and Health Study cohort. *Int J Cancer*, *135*(2), 423-431. https://doi.org/10.1002/ijc.28659

11. Armijo-Olivo, S., Warren, S., & Magee, D. (2009). Intention to treat analysis, compliance, dropouts and how to deal with missing data in clinical research: a review. *Physical Therapy Reviews*, *14*(1), 36-49. https://doi.org/10.1179/174328809X405928

12. Arthuso, F. Z., Fairey, A. S., Boulé, N. G., & Courneya, K. S. (2021). Bladder cancer and exeRcise trAining during intraVesical thErapy-the BRAVE trial: a study protocol for a prospective, single-centre, phase II randomised controlled trial. *BMJ Open*, *11*(9), e055782. https://doi.org/10.1136/bmjopen-2021-055782

13. Arthuso, F. Z., Morielli, A. R., Usmani, N., Joseph, K., Nijjar, T., Tankel, K., . . . Courneya, K. S. (2023). Effects of Exercise on Motivational Outcomes in Rectal Cancer Patients During and After Neoadjuvant Chemoradiation: A Phase II Randomized Controlled Trial. *Semin Oncol Nurs*, *39*(4), 151419. https://doi.org/10.1016/j.soncn.2023.151419

14. Avgerinos, K. I., Spyrou, N., Mantzoros, C. S., & Dalamaga, M. (2019). Obesity and cancer risk: Emerging biological mechanisms and perspectives. *Metabolism*, *92*, 121-135. https://doi.org/10.1016/j.metabol.2018.11.001

15. Avritscher, E. B., Cooksley, C. D., Grossman, H. B., Sabichi, A. L., Hamblin, L., Dinney, C. P., & Elting, L. S. (2006). Clinical model of lifetime cost of treating bladder cancer and associated complications. *Urology*, *68*(3), 549-553. https://doi.org/10.1016/j.urology.2006.03.062

16. Avritscher, E. B. C., & Cooksley, C. D. G., B.Sabichi, A. L.Hamblin, L.Dinney, C. P.Elting, L. S. (2006). Clinical model of lifetime cost of treating bladder cancer and associated complications *Urology*, *68*(3), 549-553. https://doi.org/https://doi.org/10.1016/j.urology.2006.03.062

17. Bachir, B. G., Aprikian, A. G., Izawa, J. I., Chin, J. L., Fradet, Y., Fairey, A., . . . Kassouf, W. (2014). Effect of body mass index on the outcomes of patients with upper and lower urinary tract cancers treated by radical surgery: results from a Canadian

multicenter collaboration. *Urol Oncol*, *32*(4), 441-448. https://doi.org/10.1016/j.urolonc.2013.10.016

18. Banerjee, S., Manley, K., Shaw, B., Lewis, L., Cucato, G., Mills, R., . . . Saxton, J. M. (2018). Vigorous intensity aerobic interval exercise in bladder cancer patients prior to radical cystectomy: a feasibility randomised controlled trial. *Support Care Cancer*, *26*(5), 1515-1523. https://doi.org/10.1007/s00520-017-3991-2

19. Banerjee, S., Manley, K., Thomas, L., Shaw, B., Saxton, J., Mills, R., & Rochester, M. (2013). O2 Preoperative exercise protocol to aid recovery of radical cystectomy: results of a feasibility study. *Eur. Urol. Suppl* *12*(6), 125. https://doi.org/https://doi.org/10.1016/S1569-9056(13)62320-9

20. Bastien, C. H., Vallières, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*, *2*(4), 297-307. https://doi.org/10.1016/s1389-9457(00)00065-4

21. Batacan, R. B., Duncan, M. J., Dalbo, V. J., Tucker, P. S., & Fenning, A. S. (2017). Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. *Br J Sports Med*, *51*(6), 494-503. https://doi.org/10.1136/bjsports-2015-095841

22. Baumann, N. (2016). How to use the medical subject headings (MeSH). *Int J Clin Pract*, *70*(2), 171-174. https://doi.org/10.1111/ijcp.12767

23. Beaver, W. L., Wasserman, K., & Whipp, B. J. (1986). A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol (1985)*, *60*(6), 2020-2027. https://doi.org/10.1152/jappl.1986.60.6.2020

24. Bessa, A., Bosco, C., Mehrotra, S., Rowland, M., Zhang, H., Russell, B., . . . Van Hemelrijck, M. (2021). Is there a role for physical activity interventions in the treatment pathway of bladder cancer? A scoping review of the literature. *BMJ Open Sport Exerc Med*, *7*(1), e000951. https://doi.org/10.1136/bmjsem-2020-000951

25. Bhandari, N. R., Kamel, M. H., Kent, E. E., McAdam-Marx, C., Ounpraseuth, S. T., Tilford, J. M., & Payakachat, N. (2021). Association of Health-Related Quality of Life with Overall Survival in Older Americans with Kidney Cancer: A Population-Based Cohort Study. *Healthcare (Basel)*, *9*(10). https://doi.org/10.3390/healthcare9101344

26. Bhindi, B., Kool, R., Kulkarni, G. S., Siemens, D. R., Aprikian, A. G., Breau, R. H., . . . Kassouf, W. (2021). Canadian Urological Association guideline on the management of non-muscle-invasive bladder cancer - Full-text. *Can Urol Assoc J*, *15*(8), E424-E460. https://doi.org/10.5489/cuaj.7367

27. Bi, H., Huang, Y., Wang, G., Ma, L., & Lu, M. (2020). Impact of Body Mass Index and Pretreatment Hemoglobin Level on Prognosis Following Radical Cystectomy for Bladder Cancer in Males and Females. *Urol Int*, *104*(1-2), 28-35. https://doi.org/10.1159/000500561

28. Blackwell, J. E. M., Doleman, B., Boereboom, C. L., Morton, A., Williams, S., Atherton, P., . . . Lund, J. N. (2020). High-intensity interval training produces a significant improvement in fitness in less than 31 days before surgery for urological cancer: a randomised control trial. *Prostate Cancer Prostatic Dis*, *23*(4). https://doi.org/10.1038/s41391-020-0219-1

29. Blackwell, J. E. M., Doleman, B., Herrod, P. J. J., Ricketts, S., Phillips, B. E., Lund, J. N., & Williams, J. P. (2018). Short-Term (<8 wk) High-Intensity Interval Training in Diseased Cohorts. *Med Sci Sports Exerc*, *50*(9), 1740-1749. https://doi.org/10.1249/MSS.0000000000001634

30. Blazeby, J. M., Hall, E., Aaronson, N. K., Lloyd, L., Waters, R., Kelly, J. D., & Fayers, P. (2014). Validation and reliability testing of the EORTC QLQ-NMIBC24 questionnaire module to assess patient-reported outcomes in non-muscle-invasive bladder cancer. *Eur Urol*, *66*(6), 1148-1156. https://doi.org/10.1016/j.eururo.2014.02.034

31. Bohannon, R. W., & Crouch, R. (2017). Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract*, *23*(2), 377-381. https://doi.org/10.1111/jep.12629

32. Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*, *14*(5), 377-381.

33. Borm, G. F., Fransen, J., & Lemmens, W. A. (2007). A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol*, *60*(12), 1234-1238. https://doi.org/10.1016/j.jclinepi.2007.02.006

34. Bowen, D. J., Kreuter, M., Spring, B., Cofta-Woerpel, L., Linnan, L., Weiner, D., . . . Fernandez, M. (2009). How we design feasibility studies. *Am J Prev Med*, *36*(5), 452-457. https://doi.org/10.1016/j.amepre.2009.02.002

35. Brenner, D. R., Poirier, A., Woods, R. R., Ellison, L. F., Billette, J. M., Demers, A. A., . . . Committee, C. C. S. A. (2022). Projected estimates of cancer in Canada in 2022. *CMAJ*, *194*(17), E601-E607. https://doi.org/10.1503/cmaj.212097

36. Brenner, D. R., Weir, H. K., Demers, A. A., Ellison, L. F., Louzado, C., Shaw, A., . . . Committee, C. C. S. A. (2020). Projected estimates of cancer in Canada in 2020. *CMAJ*, *192*(9), E199-E205. https://doi.org/10.1503/cmaj.191292

37. Briggs, L. G., Reitblat, C., Bain, P. A., Parke, S., Lam, N. Y., Wright, J., . . . Psutka, S. P. (2022). Prehabilitation Exercise Before Urologic Cancer Surgery: A Systematic and Interdisciplinary Review. *Eur Urol*, *81*(2), 157-167. https://doi.org/10.1016/j.eururo.2021.05.015

38. Brown, J., Winters-Stone, K., Lee, A., & Schmitz, K. (2012). Cancer, Physical Activity, and Exercise. *2*(4), 2775–2809. https://doi.org/10.1002/cphy.c120005

39. Brown, P., Brunnhuber, K., Chalkidou, K., Chalmers, I., Clarke, M., Fenton, M., . . . Young, P. (2006). How to formulate research recommendations. *BMJ*, *333*(7572), 804-806. https://doi.org/10.1136/bmj.38987.492014.94

40. Brucker, P. S., Yost, K., Cashy, J., Webster, K., & Cella, D. (2005). General population and cancer patient norms for the Functional Assessment of Cancer Therapy-General (FACT-G). *Eval Health Prof*, *28*(2), 192-211. https://doi.org/10.1177/0163278705275341

41. Buffart, L. M., Kalter, J., Sweegers, M. G., Courneya, K. S., Newton, R. U., Aaronson, N. K., . . . Brug, J. (2017). Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. *Cancer Treat Rev*, *52*, 91-104. https://doi.org/10.1016/j.ctrv.2016.11.010

42. Burg, M. L., Clifford, T. G., Bazargani, S. T., Lin-Brande, M., Miranda, G., Cai, J., . . . Daneshmand, S. (2019). Frailty as a predictor of complications after radical cystectomy: A prospective study of various preoperative assessments. *Urol Oncol*, *37*(1), 40-47. https://doi.org/10.1016/j.urolonc.2018.10.002

43. Caan, B. J., Cespedes Feliciano, E. M., & Kroenke, C. H. (2018). The Importance of Body Composition in Explaining the Overweight Paradox in Cancer-Counterpoint. *Cancer Res*, *78*(8), 1906-1912. https://doi.org/10.1158/0008-5472.CAN-17-3287

44. Caan, B. J., Meyerhardt, J. A., Kroenke, C. H., Alexeeff, S., Xiao, J., Weltzien, E., . . . Prado, C. M. (2017). Explaining the Obesity Paradox: The Association between Body Composition and Colorectal Cancer Survival (C-SCANS Study). *Cancer Epidemiol Biomarkers Prev*, *26*(7), 1008-1015. https://doi.org/10.1158/1055-9965.EPI-17-0200

45. Campbell, K. L., Winters-Stone, K. M., Wiskemann, J., May, A. M., Schwartz, A. L., Courneya, K. S., . . . Schmitz, K. H. (2019). Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc*, *51*(11), 2375-2390. https://doi.org/10.1249/MSS.0000000000002116

46. Campbell, W. W., Kraus, W. E., Powell, K. E., Haskell, W. L., Janz, K. F., Jakicic, J. M., . . . COMMITTEE*, P. A. G. A. (2019). High-Intensity Interval Training for Cardiometabolic Disease Prevention. *Med Sci Sports Exerc*, *51*(6), 1220-1226. https://doi.org/10.1249/MSS.0000000000001934

47. Canadian Cancer Statistics Advisory Committee, in, collaboration with the Canadian Cancer Society, Statistics, & Canada and the Public Health Agency of Canada. (2023). *Canadian Cancer Statistics 2023.* (0835-2976). Toronto, ON: Canadian Cancer Society Retrieved from cancer.ca/Canadian-Cancer-Statistics-2023-EN

48. Catto, J. W. F., Rogers, Z., Downing, A., Mason, S. J., Jubber, I., Bottomley, S., . . . Glaser, A. (2023). Lifestyle Factors in Patients with Bladder Cancer: A Contemporary Picture of Tobacco Smoking, Electronic Cigarette Use, Body Mass Index, and Levels of Physical Activity. *Eur Urol Focus*. https://doi.org/10.1016/j.euf.2023.04.003

49. Chan, A. W., Tetzlaff, J. M., Gøtzsche, P. C., Altman, D. G., Mann, H., Berlin, J. A., . . . Moher, D. (2013). SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*, *346*, e7586. https://doi.org/10.1136/bmj.e7586

50. Chao, D., Foy, C. G., & Farmer, D. (2000). Exercise adherence among older adults: challenges and strategies. *Control Clin Trials*, *21*(5 Suppl), 212S-217S. https://doi.org/10.1016/s0197-2456(00)00081-7

51. Chen, Y. J., Li, X. X., Ma, H. K., Zhang, X., Wang, B. W., Guo, T. T., . . . Han, X. M. (2020). Exercise Training for Improving Patient-Reported Outcomes in Patients

With Advanced-Stage Cancer: A Systematic Review and Meta-Analysis. *J Pain Symptom Manage*, *59*(3), 734-749.e710. https://doi.org/10.1016/j.jpainsymman.2019.09.010

52. Choksi, A. U., Hayden, C. S., Rahman, S. N., Lokeshwar, S. D., & Kim, I. Y. (2023). The disparities in clinical trials addressing urologic conditions among lower-income countries. In (Vol. 2). Front. Urol.

53. Chromecki, T. F., Cha, E. K., Fajkovic, H., Rink, M., Ehdaie, B., Svatek, R. S., . . . Shariat, S. F. (2013). Obesity is associated with worse oncological outcomes in patients treated with radical cystectomy. *BJU Int*, *111*(2), 249-255. https://doi.org/10.1111/j.1464-410X.2012.11322.x

54. Clements, M. B., Atkinson, T. M., Dalbagni, G. M., Li, Y., Vickers, A. J., Herr, H. W., . . . Bochner, B. H. (2022). Health-related Quality of Life for Patients Undergoing Radical Cystectomy: Results of a Large Prospective Cohort. *Eur Urol*, *81*(3), 294-304. https://doi.org/10.1016/j.eururo.2021.09.018

55. Clifford, B. K., Mizrahi, D., Sandler, C. X., Barry, B. K., Simar, D., Wakefield, C. E., & Goldstein, D. (2018). Barriers and facilitators of exercise experienced by cancer survivors: a mixed methods systematic review. *Support Care Cancer*, *26*(3), 685-700. https://doi.org/10.1007/s00520-017-3964-5

56. Cohen, S., Kamarck, T., & Mermelstein, R. (1994). Perceived stress scale. Measuring stress: a guide for health and social scientists. In.

57. Colli, J. L., Busby, J. E., & Amling, C. L. (2009). Renal cell carcinoma rates compared with health status and behavior in the United States. *Urology*, *73*(2), 431-436. https://doi.org/10.1016/j.urology.2008.06.044

58. Courneya, K. S., & Booth, C. M. (2022). Exercise as cancer treatment: A clinical oncology framework for exercise oncology research. *Front Oncol*, *12*, 957135. https://doi.org/10.3389/fonc.2022.957135

59. Courneya, K. S., & Friedenreich, C. M. (1999). Utility of the theory of planned behavior for understanding exercise during breast cancer treatment. *Psychooncology*, *8*(2), 112-122. https://doi.org/10.1002/(SICI)1099-1611(199903/04)8:2<112::AID-PON341>3.0.CO;2-L

60. Courneya, K. S., & Friedenreich, C. M. (2007). Physical activity and cancer control. *Semin Oncol Nurs*, *23*(4), 242-252. https://doi.org/10.1016/j.soncn.2007.08.002

61. Courneya, K. S., & Friedenreich, C. M. (2023). Designing, analyzing, and interpreting observational studies of physical activity and cancer outcomes from a clinical oncology perspective. *Front Oncol*, *13*, 1098278. https://doi.org/10.3389/fonc.2023.1098278

62. Courneya, K. S., Friedenreich, C. M., Arthur, K., & Bobick, T. M. (1999). Understanding exercise motivation in colorectal cancer patients: A prospective study using the theory of planned behavior. In (Vol. 44, pp. 68-84). *Rehabilitation Psychology*.

63. Courneya, K. S., Segal, R. J., Mackey, J. R., Gelmon, K., Reid, R. D., Friedenreich, C. M., . . . McKenzie, D. C. (2007). Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol*, *25*(28), 4396-4404. https://doi.org/10.1200/JCO.2006.08.2024

64. Courneya, K. S., Segal, R. J., McKenzie, D. C., Dong, H., Gelmon, K., Friedenreich, C. M., . . . Mackey, J. R. (2014). Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. *Med Sci Sports Exerc*, *46*(9), 1744-1751. https://doi.org/10.1249/MSS.0000000000000297

65. Courneya, K. S., Segal, R. J., Vallerand, J. R., Forbes, C. C., Crawford, J. J., Dolan, L. B., . . . McKenzie, D. C. (2016). Motivation for Different Types and Doses of Exercise During Breast Cancer Chemotherapy: a Randomized Controlled Trial. *Ann Behav Med*, *50*(4), 554-563. https://doi.org/10.1007/s12160-016-9782-z

66. Courneya, K. S., Sellar, C. M., Stevinson, C., McNeely, M. L., Peddle, C. J., Friedenreich, C. M., . . . Reiman, T. (2009). Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *J Clin Oncol*, *27*(27), 4605-4612. https://doi.org/10.1200/JCO.2008.20.0634

67. Courneya, K. S., Stevinson, C., McNeely, M. L., Sellar, C. M., Friedenreich, C. M., Peddle-McIntyre, C. J., . . . Reiman, T. (2012). Effects of supervised exercise on motivational outcomes and longer-term behavior. *Med Sci Sports Exerc*, *44*(3), 542-549. https://doi.org/10.1249/MSS.0b013e3182301e06

68. Courneya, K. S., Vallance, J. K., Culos-Reed, S. N., McNeely, M. L., Bell, G. J., Mackey, J. R., . . . Friedenreich, C. M. (2012). The Alberta moving beyond breast cancer (AMBER) cohort study: a prospective study of physical activity and health-related fitness

in breast cancer survivors. *BMC Cancer*, *12*, 525. https://doi.org/10.1186/1471-2407-12-525

69. Dabi, Y., Rouscoff, Y., Anract, J., Delongchamps, N. B., Sibony, M., Saighi, D., . . . Xylinas, E. (2017). Impact of body mass index on the oncological outcomes of patients treated with radical cystectomy for muscle-invasive bladder cancer. *World J Urol*, *35*(2), 229-235. https://doi.org/10.1007/s00345-016-1852-0

70. Davey Smith, G., Shipley, M. J., Batty, G. D., Morris, J. N., & Marmot, M. (2000). Physical activity and cause-specific mortality in the Whitehall study. *Public Health*, *114*(5), 308-315. https://doi.org/10.1038/sj.ph.1900675

71. Devin, J. L., Sax, A. T., Hughes, G. I., Jenkins, D. G., Aitken, J. F., Chambers, S. K., . . . Skinner, T. L. (2016). The influence of high-intensity compared with moderate-intensity exercise training on cardiorespiratory fitness and body composition in colorectal cancer survivors: a randomised controlled trial. *J Cancer Surviv*, *10*(3), 467-479. https://doi.org/10.1007/s11764-015-0490-7

72. Dunne, D. F., Jack, S., Jones, R. P., Jones, L., Lythgoe, D. T., Malik, H. Z., . . . Fenwick, S. W. (2016). Randomized clinical trial of prehabilitation before planned liver resection. *Br J Surg*, *103*(5), 504-512. https://doi.org/10.1002/bjs.10096

73. Ebadi, M., Martin, L., Ghosh, S., Field, C. J., Lehner, R., Baracos, V. E., & Mazurak, V. C. (2017). Subcutaneous adiposity is an independent predictor of mortality in cancer patients. *Br J Cancer*, *117*(1), 148-155. https://doi.org/10.1038/bjc.2017.149

74. Eggener, S. E., Yossepowitch, O., Pettus, J. A., Snyder, M. E., Motzer, R. J., & Russo, P. (2006). Renal cell carcinoma recurrence after nephrectomy for localized disease: predicting survival from time of recurrence. *J Clin Oncol*, *24*(19), 3101-3106. https://doi.org/10.1200/JCO.2005.04.8280

75. Eldridge, S. M., Chan, C. L., Campbell, M. J., Bond, C. M., Hopewell, S., Thabane, L., . . . group, P. c. (2016). CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ*, *355*, i5239. https://doi.org/10.1136/bmj.i5239

76. Esteves, M., Monteiro, M. P., & Duarte, J. A. (2021). The Effects of Physical Exercise on Tumor Vasculature: Systematic Review and Meta-analysis. *Int J Sports Med*, *42*(14), 1237-1249. https://doi.org/10.1055/a-1533-1876

77. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, . . . F, B. (2024). *Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer.* Retrieved March 4, 2024 from https://gco.iarc.who.int/today

78. Ferreira, R., Neuparth, M. J., Nogueira-Ferreira, R., Magalhães, S., Aroso, M., Bovolini, J. A., . . . Moreira-Gonçalves, D. (2018). Exercise Training Impacts Cardiac Mitochondrial Proteome Remodeling in Murine Urothelial Carcinoma. *Int J Mol Sci*, *20*(1). https://doi.org/10.3390/ijms20010127

79. Fujii, Y. (2018). Prediction models for progression of non-muscle-invasive bladder cancer: A review. *Int J Urol*, *25*(3), 212-218. https://doi.org/10.1111/iju.13509

80. Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I. M., . . . Medicine, A. C. o. S. (2011). American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*, *43*(7), 1334-1359. https://doi.org/10.1249/MSS.0b013e318213fefb

81. Gierth, M., Zeman, F., Denzinger, S., Vetterlein, M. W., Fisch, M., Bastian, P. J., . . . Mayr, R. (2018). Influence of Body Mass Index on Clinical Outcome Parameters, Complication Rate and Survival after Radical Cystectomy: Evidence from a Prospective European Multicentre Study. *Urol Int*, *101*(1), 16-24. https://doi.org/10.1159/000488466

82. Godin, G., & Shephard, R. J. (1985). A simple method to assess exercise behavior in the community. *Can J Appl Sport Sci*, *10*(3), 141-146.

83. Gonzalez, M. C., Mehrnezhad, A., Razaviarab, N., Barbosa-Silva, T. G., & Heymsfield, S. B. (2021). Calf circumference: cutoff values from the NHANES 1999-2006. *Am J Clin Nutr*, *113*(6), 1679-1687. https://doi.org/10.1093/ajcn/nqab029

84. Gopalakrishna, A., Longo, T. A., Fantony, J. J., Harrison, M. R., & Inman, B. A. (2017). Physical activity patterns and associations with health-related quality of life in bladder cancer survivors. *Urol Oncol*, *35*(9), 540.e541-540.e546. https://doi.org/10.1016/j.urolonc.2017.04.016

85. Hafron, J., Mitra, N., Dalbagni, G., Bochner, B., Herr, H., & Donat, S. M. (2005). Does body mass index affect survival of patients undergoing radical or partial cystectomy

for bladder cancer? *J Urol*, *173*(5), 1513-1517. https://doi.org/10.1097/01.ju.0000154352.54965.14

86. Hakimi, A. A., Furberg, H., Zabor, E. C., Jacobsen, A., Schultz, N., Ciriello, G., . . . Russo, P. (2013). An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. *J Natl Cancer Inst*, *105*(24), 1862-1870. https://doi.org/10.1093/jnci/djt310

87. Hansen, T. T. D., Omland, L. H., von Heymann, A., Johansen, C., Clausen, M. B., Suetta, C., . . . Rafn, B. S. (2021). Development of Sarcopenia in Patients With Bladder Cancer: A Systematic Review. *Semin Oncol Nurs*, *37*(1), 151108. https://doi.org/10.1016/j.soncn.2020.151108

88. Hayes, S. C., Newton, R. U., Spence, R. R., & Galvão, D. A. (2019). The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management. *J Sci Med Sport*, *22*(11), 1175-1199. https://doi.org/10.1016/j.jsams.2019.05.003

89. Helgerud, J., Høydal, K., Wang, E., Karlsen, T., Berg, P., Bjerkaas, M., . . . Hoff, J. (2007). Aerobic high-intensity intervals improve VO2max more than moderate training. *Med Sci Sports Exerc*, *39*(4), 665-671. https://doi.org/10.1249/mss.0b013e3180304570

90. Huang, W. C., Levey, A. S., Serio, A. M., Snyder, M., Vickers, A. J., Raj, G. V., . . . Russo, P. (2006). Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol*, *7*(9), 735-740. https://doi.org/10.1016/S1470-2045(06)70803-8

91. Jensen, B. T., Jensen, J. B., Laustsen, S., Petersen, A. K., Søndergaard, I., & Borre, M. (2014). Multidisciplinary rehabilitation can impact on health-related quality of life outcome in radical cystectomy: secondary reported outcome of a randomized controlled trial. *J Multidiscip Healthc*, *7*, 301-311. https://doi.org/10.2147/JMDH.S62172

92. Jensen, B. T., Laustsen, S., Jensen, J. B., Borre, M., & Petersen, A. K. (2016). Exercise-based pre-habilitation is feasible and effective in radical cystectomy pathways-secondary results from a randomized controlled trial. *Support Care Cancer*, *24*(8), 3325-3331. https://doi.org/10.1007/s00520-016-3140-3

93. Jensen, B. T., Petersen, A. K., Jensen, J. B., Laustsen, S., & Borre, M. (2015). Efficacy of a multiprofessional rehabilitation programme in radical cystectomy pathways: a prospective randomized controlled trial. *Scand J Urol*, *49*(2), 133-141. https://doi.org/10.3109/21681805.2014.967810

94. Jones, C. J., & Rikli, R. E. (2002). *Measuring Functional*. The journal on active aging. Retrieved May 17th, 2020 from https://www.um.es/desarrollopsicomotor/wq/2010/wqcarrasco2010/BL22_files/Senior%20Fitness%20Test_Rikli02.pdf

95. Jones, L. W., & Alfano, C. M. (2013). Exercise-oncology research: past, present, and future. *Acta Oncol*, *52*(2), 195-215. https://doi.org/10.3109/0284186X.2012.742564

96. Jung, A., Nielsen, M. E., Crandell, J. L., Palmer, M. H., Bryant, A. L., Smith, S. K., & Mayer, D. K. (2019). Quality of Life in Non-Muscle-Invasive Bladder Cancer Survivors: A Systematic Review. *Cancer Nurs*, *42*(3), E21-E33. https://doi.org/10.1097/NCC.0000000000000606

97. Kamat, A. M., Sylvester, R. J., Böhle, A., Palou, J., Lamm, D. L., Brausi, M., . . . Witjes, J. A. (2016). Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. *J Clin Oncol*, *34*(16), 1935-1944. https://doi.org/10.1200/JCO.2015.64.4070

98. Kang, D. W., Boulé, N. G., Field, C. J., Fairey, A. S., & Courneya, K. S. (2022). Effects of supervised high-intensity interval training on motivational outcomes in men with prostate cancer undergoing active surveillance: results from a randomized controlled trial. *Int J Behav Nutr Phys Act*, *19*(1), 126. https://doi.org/10.1186/s12966-022-01365-2

99. Kang, D. W., Fairey, A. S., Boulé, N. G., Field, C. J., & Courneya, K. S. (2019). Exercise duRing Active Surveillance for prostatE cancer-the ERASE trial: a study protocol of a phase II randomised controlled trial. *BMJ Open*, *9*(7), e026438. https://doi.org/10.1136/bmjopen-2018-026438

100. Kang, D. W., Fairey, A. S., Boulé, N. G., Field, C. J., Wharton, S. A., & Courneya, K. S. (2021). Effects of Exercise on Cardiorespiratory Fitness and Biochemical Progression in Men With Localized Prostate Cancer Under Active Surveillance: The ERASE Randomized Clinical Trial. *JAMA Oncol*. https://doi.org/10.1001/jamaoncol.2021.3067

101. Karvinen, K. H., Courneya, K. S., North, S., & Venner, P. (2007). Associations between exercise and quality of life in bladder cancer survivors: a population-based study. *Cancer Epidemiol Biomarkers Prev*, *16*(5), 984-990. https://doi.org/10.1158/1055-9965.EPI-06-0680

102. Karvinen, K. H., Courneya, K. S., Plotnikoff, R. C., Spence, J. C., Venner, P. M., & North, S. (2009). A prospective study of the determinants of exercise in bladder cancer survivors using the Theory of Planned Behavior. *Support Care Cancer*, *17*(2), 171-179. https://doi.org/10.1007/s00520-008-0471-8

103. Kassouf, W., Traboulsi, S. L., Kulkarni, G. S., Breau, R. H., Zlotta, A., Fairey, A., . . . Black, P. (2015). CUA guidelines on the management of non-muscle invasive bladder cancer. *Can Urol Assoc J*, *9*(9-10), E690-704. https://doi.org/10.5489/cuaj.3320

104. Kaye, D. R., Schafer, C., Thelen-Perry, S., Parker, C., Iglay-Reger, H., Daignault-Newton, S., . . . Montgomery, J. S. (2020). The Feasibility and Impact of a Presurgical Exercise Intervention Program (Prehabilitation) for Patients Undergoing Cystectomy for Bladder Cancer. *Urology*, *145*. https://doi.org/10.1016/j.urology.2020.05.104

105. Koch, G. E., Smelser, W. W., & Chang, S. S. (2021). Side Effects of Intravesical BCG and Chemotherapy for Bladder Cancer: What They Are and How to Manage Them. *Urology*, *149*, 11-20. https://doi.org/10.1016/j.urology.2020.10.039

106. Koelker, M., Alkhatib, K., Briggs, L., Labban, M., Meyer, C. P., Dieli-Conwright, C. M., . . . Mossanen, M. (2023). Impact of exercise on physical health status in bladder cancer patients. *Can Urol Assoc J*, *17*(1), E8-E14. https://doi.org/10.5489/cuaj.8008

107. Kuperus, J. M., Busman, R. D., Kuipers, S. K., Broekhuizen, H. T., Noyes, S. L., Brede, C. M., . . . Lane, B. R. (2021). Comparison of Side Effects and Tolerability Between Intravesical Bacillus Calmette-Guerin, Reduced-Dose BCG and Gemcitabine for Non-Muscle Invasive Bladder Cancer. *Urology*, *156*, 191-198. https://doi.org/10.1016/j.urology.2021.04.062

108. Kwon, T., Jeong, I. G., You, D., Han, K. S., Hong, S., Hong, B., . . . Kim, C. S. (2014). Obesity and prognosis in muscle-invasive bladder cancer: the continuing controversy. *Int J Urol*, *21*(11), 1106-1112. https://doi.org/10.1111/iju.12530

109. Laboratories, A. C. o. P. S. f. C. P. F. (2002). ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*, *166*(1), 111-117. https://doi.org/10.1164/ajrccm.166.1.at1102

110. Lamm, D. L., Blumenstein, B. A., Crissman, J. D., Montie, J. E., Gottesman, J. E., Lowe, B. A., . . . Crawford, E. D. (2000). Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol*, *163*(4), 1124-1129.

111. Lavery, J. A., Boutros, P. C., Scott, J. M., Tammela, T., Moskowitz, C. S., & Jones, L. W. (2023). Pan-Cancer Analysis of Postdiagnosis Exercise and Mortality. *J Clin Oncol*, JCO2300058. https://doi.org/10.1200/JCO.23.00058

112. Lee, L., & Shih, J. H. (2018). An Introduction to Survival Analysis. In *Principles and Practice of Clinical Research* (pp. 373-381). https://doi.org/10.1016/B978-0-12-849905-4.00026-5

113. Levey, A. S., & Coresh, J. (2012). Chronic kidney disease. *Lancet*, *379*(9811), 165-180. https://doi.org/10.1016/S0140-6736(11)60178-5

114. Lewinsohn, P. M., Seeley, J. R., Roberts, R. E., & Allen, N. B. (1997). Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging*, *12*(2), 277-287. https://doi.org/10.1037//0882-7974.12.2.277

115. Licker, M., Karenovics, W., Diaper, J., Frésard, I., Triponez, F., Ellenberger, C., . . . Bridevaux, P. O. (2017). Short-Term Preoperative High-Intensity Interval Training in Patients Awaiting Lung Cancer Surgery: A Randomized Controlled Trial. *J Thorac Oncol*, *12*(2), 323-333. https://doi.org/10.1016/j.jtho.2016.09.125

116. Ligibel, J. A., Bohlke, K., May, A. M., Clinton, S. K., Demark-Wahnefried, W., Gilchrist, S. C., . . . Alfano, C. M. (2022). Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline. *J Clin Oncol*, *40*(22), 2491-2507. https://doi.org/10.1200/JCO.22.00687

117. Liguori, G., Feito, Y., Fountaine, C., Roy, B. A., & Medicine, A. C. o. S. (2021). *ACSM's Guidelines for Exercise Testing and Prescription* . (Eleventh edition ed.). Wolters Kluwer.

118. Liss, M., Natarajan, L., Hasan, A., Noguchi, J. L., White, M., & Parsons, J. K. (2017). Physical Activity Decreases Kidney Cancer Mortality. *Curr Urol*, *10*(4), 193-198. https://doi.org/10.1159/000447180

119. Lund, L. H., & Mancini, D. M. (2008). Peak VO2 in elderly patients with heart failure. *Int J Cardiol*, *125*(2), 166-171. https://doi.org/10.1016/j.ijcard.2007.10.004

120. MacInnis, M. J., & Gibala, M. J. (2017). Physiological adaptations to interval training and the role of exercise intensity. *J Physiol*, *595*(9), 2915-2930. https://doi.org/10.1113/JP273196

121. Maibom, S. L., Joensen, U. N., Poulsen, A. M., Kehlet, H., Brasso, K., & Røder, M. A. (2021). Short-term morbidity and mortality following radical cystectomy: a systematic review. *BMJ Open*, *11*(4), e043266. https://doi.org/10.1136/bmjopen-2020-043266

122. Mason, R., Kapoor, A., Liu, Z., Saarela, O., Tanguay, S., Jewett, M., . . . Rendon, R. A. (2016). The natural history of renal function after surgical management of renal cell carcinoma: Results from the Canadian Kidney Cancer Information System. *Urol Oncol*, *34*(11), 486.e481-486.e487. https://doi.org/10.1016/j.urolonc.2016.05.025

123. Matthews, C. E., Moore, S. C., Arem, H., Cook, M. B., Trabert, B., Håkansson, N., . . . Lee, I. M. (2020). Amount and Intensity of Leisure-Time Physical Activity and Lower Cancer Risk. *J Clin Oncol*, *38*(7), 686-697. https://doi.org/10.1200/JCO.19.02407

124. Mayr, R., Fritsche, H. M., Zeman, F., Reiffen, M., Siebertz, L., Niessen, C., . . . Gierth, M. (2018). Sarcopenia predicts 90-day mortality and postoperative complications after radical cystectomy for bladder cancer. *World J Urol*, *36*(8), 1201-1207. https://doi.org/10.1007/s00345-018-2259-x

125. Mayr, R., Gierth, M., Zeman, F., Reiffen, M., Seeger, P., Wezel, F., . . . Martini, T. (2018). Sarcopenia as a comorbidity-independent predictor of survival following radical cystectomy for bladder cancer. *J Cachexia Sarcopenia Muscle*, *9*(3), 505-513. https://doi.org/10.1002/jcsm.12279

126. McInnis, K. J., & Balady, G. J. (1994). Comparison of submaximal exercise responses using the Bruce vs modified Bruce protocols. *Med Sci Sports Exerc*, *26*(1), 103-107.

127. McKiernan, J., Simmons, R., Katz, J., & Russo, P. (2002). Natural history of chronic renal insufficiency after partial and radical nephrectomy. *Urology*, *59*(6), 816-820. https://doi.org/10.1016/s0090-4295(02)01501-7

128. Milanović, Z., Sporiš, G., & Weston, M. (2015). Effectiveness of High-Intensity Interval Training (HIT) and Continuous Endurance Training for VO2max Improvements: A Systematic Review and Meta-Analysis of Controlled Trials. *Sports Med*, *45*(10), 1469-1481. https://doi.org/10.1007/s40279-015-0365-0

129. Minnella, E. M., Awasthi, R., Bousquet-Dion, G., Ferreira, V., Austin, B., Audi, C., . . . Kassouf, W. (2019). Multimodal Prehabilitation to Enhance Functional Capacity Following Radical Cystectomy: A Randomized Controlled Trial. *Eur Urol Focus*, *7*(1), 132-138. https://doi.org/10.1016/j.euf.2019.05.016

130. Mishra, S. I., Scherer, R. W., Snyder, C., Geigle, P. M., Berlanstein, D. R., & Topaloglu, O. (2012). Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev*(8), CD008465. https://doi.org/10.1002/14651858.CD008465.pub2

131. Morielli, A. R., Usmani, N., Boulé, N. G., Severin, D., Tankel, K., Nijjar, T., . . . Courneya, K. S. (2016). Exercise motivation in rectal cancer patients during and after neoadjuvant chemoradiotherapy. *Support Care Cancer*, *24*(7), 2919-2926. https://doi.org/10.1007/s00520-016-3110-9

132. Morielli, A. R., Usmani, N., Boulé, N. G., Severin, D., Tankel, K., Nijjar, T., . . . Courneya, K. S. (2018). Exercise during and after neoadjuvant rectal cancer treatment (the EXERT trial): study protocol for a randomized controlled trial. *Trials*, *19*(1), 35. https://doi.org/10.1186/s13063-017-2398-1

133. Motzer, R. J., Haas, N. B., Donskov, F., Gross-Goupil, M., Varlamov, S., Kopyltsov, E., . . . investigators, P. (2017). Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma. *J Clin Oncol*, *35*(35), 3916-3923. https://doi.org/10.1200/JCO.2017.73.5324

134. Munn, Z., Peters, M. D. J., Stern, C., Tufanaru, C., McArthur, A., & Aromataris, E. (2018). Systematic review or scoping review? Guidance for authors when choosing

between a systematic or scoping review approach. *BMC Med Res Methodol*, *18*(1), 143. https://doi.org/10.1186/s12874-018-0611-x

135. Myers, J., & Bellin, D. (2000). Ramp exercise protocols for clinical and cardiopulmonary exercise testing. *Sports Med*, *30*(1), 23-29. https://doi.org/10.2165/00007256-200030010-00003

136. Nadler, M. B., Desnoyers, A., Langelier, D. M., & Amir, E. (2019). The Effect of Exercise on Quality of Life, Fatigue, Physical Function, and Safety in Advanced Solid Tumor Cancers: A Meta-analysis of Randomized Control Trials. *J Pain Symptom Manage*, *58*(5), 899-908.e897. https://doi.org/10.1016/j.jpainsymman.2019.07.005

137. National Comprehensive Cancer Network [NCCN]. (2024). NCCN Clinical Practice Guidelines on Oncology: Bladder Cancer, Version 1.2024. In.

138. National Comprehensive Cancer Network [NCCN]. (2024). NCCN Clinical Practice Guidelines on Oncology: Kidney Cancer, Version 2.2024. In.

139. National Institute of Health, & National Cancer Institute. (2023). *Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Bladder Cancer*. Retrieved March 4, 2024 from https://seer.cancer.gov/statfacts/html/urinb.html

140. Nayak, A., Cresswell, J., & Mariappan, P. (2021). Quality of life in patients undergoing surveillance for non-muscle invasive bladder cancer-a systematic review. *Transl Androl Urol*, *10*(6), 2737-2749. https://doi.org/10.21037/tau-20-1333

141. Neuendorf, T., Haase, R., Schroeder, S., Schumann, M., & Nitzsche, N. (2023). Effects of high-intensity interval training on functional performance and maximal oxygen uptake in comparison with moderate intensity continuous training in cancer patients: a systematic review and meta-analysis. *Support Care Cancer*, *31*(12), 643. https://doi.org/10.1007/s00520-023-08103-9

142. Norman, P., & Conner, M. (2005). The Theory of Planned Behavior and Exercise: Evidence for the Mediating and Moderating Roles of Planning on Intention-Behavior Relationships. In (Vol. 27, pp. 488-504). Journal of Sport & Exercise Psychology

143. O'Dea, A., Gedye, C., Jago, B., & Paterson, C. (2021). Identifying the unmet supportive care needs of people affected by kidney cancer: a systematic review. *J Cancer Surviv*. https://doi.org/10.1007/s11764-021-01113-8

144. Olney, N., Wertz, T., LaPorta, Z., Mora, A., Serbas, J., & Astorino, T. A. (2018). Comparison of Acute Physiological and Psychological Responses Between Moderate-Intensity Continuous Exercise and Three Regimes of High-Intensity Interval Training. *J Strength Cond Res*, *32*(8), 2130-2138. https://doi.org/10.1519/JSC.0000000000002154

145. Ornaghi, P. I., Afferi, L., Antonelli, A., Cerruto, M. A., Odorizzi, K., Gozzo, A., . . . Moschini, M. (2020). The impact of preoperative nutritional status on post-surgical complication and mortality rates in patients undergoing radical cystectomy for bladder cancer: a systematic review of the literature. *World J Urol*, *39*(4), 1045-1081. https://doi.org/10.1007/s00345-020-03291-z

146. Pal, S. K., & Haas, N. B. (2014). Adjuvant therapy for renal cell carcinoma: past, present, and future. *Oncologist*, *19*(8), 851-859. https://doi.org/10.1634/theoncologist.2014-0105

147. Palma, S., Hasenoehrl, T., Jordakieva, G., Ramazanova, D., & Crevenna, R. (2021). High-intensity interval training in the prehabilitation of cancer patients-a systematic review and meta-analysis. *Support Care Cancer*, *29*(4), 1781-1794. https://doi.org/10.1007/s00520-020-05834-x

148. Papadopoulos, E., & Santa Mina, D. (2018). Can we HIIT cancer if we attack inflammation? *Cancer Causes Control*, *29*(1), 7-11. https://doi.org/10.1007/s10552-017-0983-y

149. Peddle-McIntyre, C. J., Bell, G., Fenton, D., McCargar, L., & Courneya, K. S. (2013). Changes in motivational outcomes after a supervised resistance exercise training intervention in lung cancer survivors. *Cancer Nurs*, *36*(1), E27-35. https://doi.org/10.1097/NCC.0b013e31824a78e4

150. Petrelli, F., Cortellini, A., Indini, A., Tomasello, G., Ghidini, M., Nigro, O., . . . Zaniboni, A. (2021). Association of Obesity With Survival Outcomes in Patients With Cancer: A Systematic Review and Meta-analysis. *JAMA Netw Open*, *4*(3), e213520. https://doi.org/10.1001/jamanetworkopen.2021.3520

151. Porserud, A., Sherif, A., & Tollbäck, A. (2014). The effects of a physical exercise programme after radical cystectomy for urinary bladder cancer. A pilot randomized controlled trial. *Clin Rehabil*, *28*(5), 451-459. https://doi.org/10.1177/0269215513506230

152. Prado, C. M., Gonzalez, M. C., & Heymsfield, S. B. (2015). Body composition phenotypes and obesity paradox. *Curr Opin Clin Nutr Metab Care*, *18*(6), 535-551. https://doi.org/10.1097/MCO.0000000000000216

153. Psutka, S. P., Boorjian, S. A., Moynagh, M. R., Schmit, G. D., Frank, I., Carrasco, A., . . . Tollefson, M. K. (2015). Mortality after radical cystectomy: impact of obesity versus adiposity after adjusting for skeletal muscle wasting. *J Urol*, *193*(5), 1507-1513. https://doi.org/10.1016/j.juro.2014.11.088

154. Qin, F., & Wu, J. (2024). Impact of sarcopenia on outcomes of bladder cancer undergoing radical cystectomy: A systematic review and meta-analysis. *Scott Med J*, 369330241234690. https://doi.org/10.1177/00369330241234690

155. Rammant, E., Decaestecker, K., Bultijnck, R., Sundahl, N., Ost, P., Pauwels, N. S., . . . Fonteyne, V. (2018). A systematic review of exercise and psychosocial rehabilitation interventions to improve health-related outcomes in patients with bladder cancer undergoing radical cystectomy. *Clin Rehabil*, *32*(5), 594-606. https://doi.org/10.1177/0269215517746472

156. Ramos, J. S., Dalleck, L. C., Tjonna, A. E., Beetham, K. S., & Coombes, J. S. (2015). The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. *Sports Med*, *45*(5), 679-692. https://doi.org/10.1007/s40279-015-0321-z

157. Reynolds, S. A., O'Connor, L., McGee, A., Kilcoyne, A. Q., Connolly, A., Mockler, D., . . . O'Neill, L. (2023). Recruitment rates and strategies in exercise trials in cancer survivorship: a systematic review. *J Cancer Surviv*. https://doi.org/10.1007/s11764-023-01363-8

158. Riebe, D., Ehrman, J. K., Liguori, G., & Magal, M. (Eds.). (2018). *ACSM's guidelines for exercise testing and prescription* (Tenth edition ed.). Wolters Kluwer.

159. Robinson-Cohen, C., Katz, R., Mozaffarian, D., Dalrymple, L. S., de Boer, I., Sarnak, M., . . . Kestenbaum, B. (2009). Physical activity and rapid decline in kidney function among older adults. *Arch Intern Med*, *169*(22), 2116-2123. https://doi.org/10.1001/archinternmed.2009.438

160. Rock, C. L., Doyle, C., Demark-Wahnefried, W., Meyerhardt, J., Courneya, K. S., Schwartz, A. L., . . . Gansler, T. (2012). Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*, *62*(4), 243-274. https://doi.org/10.3322/caac.21142

161. Rock, C. L., Thomson, C. A., Sullivan, K. R., Howe, C. L., Kushi, L. H., Caan, B. J., . . . McCullough, M. L. (2022). American Cancer Society nutrition and physical activity guideline for cancer survivors. *CA Cancer J Clin*, *72*(3), 230-262. https://doi.org/10.3322/caac.21719

162. Rosenberg, M. (1965). Rosenberg self-esteem scale (RSE). Acceptance and commitment therapy Measures package . In (Vol. 61:52).

163. Royston, P. (2004). Multiple imputation of missing values. In (Vol. 4, pp. 227-241). Stata journal.

164. Sanchez, A., Feldman, A. S., & Hakimi, A. A. (2018). Current Management of Small Renal Masses, Including Patient Selection, Renal Tumor Biopsy, Active Surveillance, and Thermal Ablation. *J Clin Oncol*, *36*(36), 3591-3600. https://doi.org/10.1200/JCO.2018.79.2341

165. Sanchez, A., Furberg, H., Kuo, F., Vuong, L., Ged, Y., Patil, S., . . . Hakimi, A. A. (2020). Transcriptomic signatures related to the obesity paradox in patients with clear cell renal cell carcinoma: a cohort study. *Lancet Oncol*, *21*(2), 283-293. https://doi.org/10.1016/S1470-2045(19)30797-1

166. Sanchez, A., Kissel, S., Coletta, A., Scott, J., & Furberg, H. (2020). Impact of body size and body composition on bladder cancer outcomes: Risk stratification and opportunity for novel interventions. *Urol Oncol*, *38*(9), 713-718. https://doi.org/10.1016/j.urolonc.2020.03.017

167. Schemper, M. (1992). Cox analysis of survival data with non-proportional hazard functions. *41*(4), 455-465. https://doi.org/https://doi.org/10.2307/2349009

168. Schlüter, K., Schneider, J., Sprave, T., Wiskemann, J., & Rosenberger, F. (2019). Feasibility of Two High-Intensity Interval Training Protocols in Cancer Survivors. *Med Sci Sports Exerc*, *51*(12), 2443-2450. https://doi.org/10.1249/MSS.0000000000002081

169. Schmid, D., & Leitzmann, M. F. (2015). Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. *Ann Oncol*, *26*(2), 272-278. https://doi.org/10.1093/annonc/mdu250

170. Schmid, D., Matthews, C. E., & Leitzmann, M. F. (2018). Physical activity and sedentary behavior in relation to mortality among renal cell cancer survivors. *PLoS One*, *13*(6), e0198995. https://doi.org/10.1371/journal.pone.0198995

171. Schmidt, K., Vogt, L., Thiel, C., Jäger, E., & Banzer, W. (2013). Validity of the six-minute walk test in cancer patients. *Int J Sports Med*, *34*(7), 631-636. https://doi.org/10.1055/s-0032-1323746

172. Schmitt, J., Lindner, N., Reuss-Borst, M., Holmberg, H. C., & Sperlich, B. (2016). A 3-week multimodal intervention involving high-intensity interval training in female cancer survivors: a randomized controlled trial. *Physiol Rep*, *4*(3). https://doi.org/10.14814/phy2.12693

173. Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvão, D. A., Pinto, B. M., . . . Medicine, A. C. o. S. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*, *42*(7), 1409-1426. https://doi.org/10.1249/MSS.0b013e3181e0c112

174. Schulz, S. V. W., Laszlo, R., Otto, S., Prokopchuk, D., Schumann, U., Ebner, F., . . . Steinacker, J. M. (2018). Feasibility and effects of a combined adjuvant high-intensity interval/strength training in breast cancer patients: a single-center pilot study. *Disabil Rehabil*, *40*(13), 1501-1508. https://doi.org/10.1080/09638288.2017.1300688

175. Simard, S., & Savard, J. (2009). Fear of Cancer Recurrence Inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence. *Support Care Cancer*, *17*(3), 241-251. https://doi.org/10.1007/s00520-008-0444-y

176. Singh, S. J., Puhan, M. A., Andrianopoulos, V., Hernandes, N. A., Mitchell, K. E., Hill, C. J., . . . Holland, A. E. (2014). An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *Eur Respir J*, *44*(6), 1447-1478. https://doi.org/10.1183/09031936.00150414

177. Smith, A. B., Jaeger, B., Pinheiro, L. C., Edwards, L. J., Tan, H. J., Nielsen, M. E., & Reeve, B. B. (2018). Impact of bladder cancer on health-related quality of life. *BJU Int*, *121*(4), 549-557. https://doi.org/10.1111/bju.14047

178. Society, A. T., & Physicians, A. C. o. C. (2003). ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*, *167*(2), 211-277. https://doi.org/10.1164/rccm.167.2.211

179. Spielberger, C. D. (2010). State-Trait anxiety inventory. In. Wiley Online Library.

180. Sturgeon, K. M., Deng, L., Bluethmann, S. M., Zhou, S., Trifiletti, D. M., Jiang, C., . . . Zaorsky, N. G. (2019). A population-based study of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J*, *40*(48), 3889-3897. https://doi.org/10.1093/eurheartj/ehz766

181. Sun, J. W., Zhao, L. G., Yang, Y., Ma, X., Wang, Y. Y., & Xiang, Y. B. (2015). Obesity and risk of bladder cancer: a dose-response meta-analysis of 15 cohort studies. *PLoS One*, *10*(3), e0119313. https://doi.org/10.1371/journal.pone.0119313

182. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*, *71*(3), 209-249. https://doi.org/10.3322/caac.21660

183. Surveillance & Reporting. (2019). *The 2019 Report on Cancer Statistics in Alberta*. CancerControl Alberta,, Alberta Health Services. Retrieved September 7 from https://public.tableau.com/profile/cancercontrol.ab#!/vizhome/The2019ReportonCancerStatisticsinAlberta/Highlights?publish=yes

184. Swartz, M. K. (2011). The PRISMA statement: a guideline for systematic reviews and meta-analyses. *J Pediatr Health Care*, *25*(1), 1-2. https://doi.org/10.1016/j.pedhc.2010.09.006

185. Taaffe, D. R., McCombie, S. P., Galvão, D. A., Newton, R. U., LA Bianca, S., Chambers, S. K., . . . Hayne, D. (2023). Efficacy and Feasibility of Presurgical Exercise in Bladder Cancer Patients Scheduled for Open Radical Cystectomy. *Med Sci Sports Exerc*, *55*(7), 1123-1132. https://doi.org/10.1249/MSS.0000000000003137

186. Tabaczynski, A., Courneya, K. S., & Trinh, L. (2020). Replacing sedentary time with physical activity and sleep: associations with quality of life in kidney cancer survivors. *Cancer Causes Control*, *31*(7), 669-681. https://doi.org/10.1007/s10552-020-01308-x

187. Tabaczynski, A., Strom, D. A., Wong, J. N., McAuley, E., Larsen, K., Faulkner, G. E., . . . Trinh, L. (2020). Demographic, medical, social-cognitive, and environmental correlates of meeting independent and combined physical activity guidelines in kidney cancer survivors. *Support Care Cancer*, *28*(1), 43-54. https://doi.org/10.1007/s00520-019-04752-x

188. Talari, K., & Goyal, M. (2020). Retrospective studies - utility and caveats. *J R Coll Physicians Edinb*, *50*(4), 398-402. https://doi.org/10.4997/JRCPE.2020.409

189. Tan, H. J., Shirk, J. D., Chamie, K., Litwin, M. S., & Hu, J. C. (2017). Patient Function and the Value of Surgical Care for Kidney Cancer. *J Urol*, *197*(5), 1200-1207. https://doi.org/10.1016/j.juro.2016.12.012

190. Taylor, J. L., Holland, D. J., Keating, S. E., Leveritt, M. D., Gomersall, S. R., Rowlands, A. V., . . . Coombes, J. S. (2020). Short-term and Long-term Feasibility, Safety, and Efficacy of High-Intensity Interval Training in Cardiac Rehabilitation: The FITR Heart Study Randomized Clinical Trial. *JAMA Cardiol*. https://doi.org/10.1001/jamacardio.2020.3511

191. Thompson, A. M., Church, T. S., Janssen, I., Katzmarzyk, P. T., Earnest, C. P., & Blair, S. N. (2008). Cardiorespiratory fitness as a predictor of cancer mortality among men with pre-diabetes and diabetes. *Diabetes Care*, *31*(4), 764-769. https://doi.org/10.2337/dc07-1648

192. Thomsen, S. N., Lahart, I. M., Thomsen, L. M., Fridh, M. K., Larsen, A., Mau-Sørensen, M., . . . Simonsen, C. (2023). Harms of exercise training in patients with cancer undergoing systemic treatment: a systematic review and meta-analysis of published and unpublished controlled trials. *EClinicalMedicine*, *59*, 101937. https://doi.org/10.1016/j.eclinm.2023.101937

193. Thum, J. S., Parsons, G., Whittle, T., & Astorino, T. A. (2017). High-Intensity Interval Training Elicits Higher Enjoyment than Moderate Intensity Continuous Exercise. *PLoS One*, *12*(1), e0166299. https://doi.org/10.1371/journal.pone.0166299

194. Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., . . . Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*, *169*(7), 467-473. https://doi.org/10.7326/M18-0850

195. Trinh, L., Larsen, K., Faulkner, G. E., Plotnikoff, R. C., Rhodes, R. E., North, S., & Courneya, K. S. (2016). Social-ecological correlates of physical activity in kidney cancer survivors. *J Cancer Surviv*, *10*(1), 164-175. https://doi.org/10.1007/s11764-015-0462-y

196. Trinh, L., Plotnikoff, R. C., North, S., Rhodes, R., & Courneya, K. S. (2013). Associations between sitting time and quality of life in a population-based sample of kidney cancer survivors. In (Vol. 6, pp. 16-23): Mental Health and Physical Activity.

197. Trinh, L., Plotnikoff, R. C., Rhodes, R. E., North, S., & Courneya, K. S. (2011). Associations between physical activity and quality of life in a population-based sample of kidney cancer survivors. *Cancer Epidemiol Biomarkers Prev*, *20*(5), 859-868. https://doi.org/10.1158/1055-9965.EPI-10-1319

198. Trinh, L., Plotnikoff, R. C., Rhodes, R. E., North, S., & Courneya, K. S. (2012a). Correlates of physical activity in a population-based sample of kidney cancer survivors: an application of the theory of planned behavior. *Int J Behav Nutr Phys Act*, *9*, 96. https://doi.org/10.1186/1479-5868-9-96

199. Trinh, L., Plotnikoff, R. C., Rhodes, R. E., North, S., & Courneya, K. S. (2012b). Physical activity preferences in a population-based sample of kidney cancer survivors. *Support Care Cancer*, *20*(8), 1709-1717. https://doi.org/10.1007/s00520-011-1264-z

200. Trinh, L., Plotnikoff, R. C., Rhodes, R. E., North, S., & Courneya, K. S. (2014). Feasibility and preliminary efficacy of adding behavioral counseling to supervised physical activity in kidney cancer survivors: a randomized controlled trial. *Cancer Nurs*, *37*(5), E8-22. https://doi.org/10.1097/NCC.0b013e3182a40fb6

201. Trinh, L., Plotnikoff, R. C., Rhodes, R. E., North, S., & Courneya, K. S. (2015). Changes in motivational outcomes following a supervised physical activity program with behavioral counseling in kidney cancer survivors: a pilot study. *Psychooncology*, *24*(9), 1204-1207. https://doi.org/10.1002/pon.3754

202. Trinh, L., Strom, D. A., Wong, J. N., & Courneya, K. S. (2018). Modality-specific exercise guidelines and quality of life in kidney cancer survivors: A cross-sectional study. *Psychooncology*, *27*(10), 2419-2426. https://doi.org/10.1002/pon.4844

203. van Hoogstraten, L. M. C., Vrieling, A., van der Heijden, A. G., Kogevinas, M., Richters, A., & Kiemeney, L. A. (2023). Global trends in the epidemiology of bladder

cancer: challenges for public health and clinical practice. *Nat Rev Clin Oncol*, *20*(5), 287-304. https://doi.org/10.1038/s41571-023-00744-3

204. van Zutphen, M., Hof, J. P., Aben, K. K., Kampman, E., Witjes, J. A., Kiemeney, L. A., & Vrieling, A. (2023). Adherence to lifestyle recommendations after non-muscle invasive bladder cancer diagnosis and risk of recurrence. *Am J Clin Nutr*, *117*(4), 681-690. https://doi.org/10.1016/j.ajcnut.2022.12.022

205. Vidra, N., Beeren, I., van Zutphen, M., Aben, K. K., Kampman, E., Witjes, J. A., . . . Vrieling, A. (2023). Longitudinal associations of adherence to lifestyle recommendations and health-related quality of life in patients with non-muscle invasive bladder cancer. *Int J Cancer*, *152*(10), 2032-2042. https://doi.org/10.1002/ijc.34418

206. Wallen, M. P., Hennessy, D., Brown, S., Evans, L., Rawstorn, J. C., Wong Shee, A., & Hall, A. (2020). High-intensity interval training improves cardiorespiratory fitness in cancer patients and survivors: A meta-analysis. *Eur J Cancer Care (Engl)*, *29*(4), e13267. https://doi.org/10.1111/ecc.13267

207. Wang , E. Y., Armas-Phan , M., Meng , M. V., Porten , S. P., & Kenfield, S. A. (2023). Diet, Physical Activity, and Smoking in Patients Living with Non-Muscle Invasive Bladder Cancer. In (Vol. 6, pp. 28-34). *Annals of Urologic Oncology*.

208. Wang, L., Quan, M., Nieman, D. C., Li, F., Shi, H., Bai, X., . . . Shi, Y. (2023). Effects of High-Intensity Interval Training and Combined High-Intensity Interval Training Programs on Cancer-Related Fatigue and Cancer Pain: A Systematic Review and Meta-analysis. *Med Sci Sports Exerc*, *55*(9), 1620-1631. https://doi.org/10.1249/MSS.0000000000003191

209. Warburton, D. E., Jamnik, V. K., Bredin, S. S., & Gledhill, N. (2011). The 2011 Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and the Electronic Physical Activity Readiness Medical Examination (ePARmed-X+). In (Vol. 4): Heal Fit J Canada.

210. Washio, M., Mori, M., Khan, M., Sakauchi, F., Watanabe, Y., Ozasa, K., . . . Group, J. S. (2007). Diabetes mellitus and kidney cancer risk: the results of Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study). *Int J Urol*, *14*(5), 393-397. https://doi.org/10.1111/j.1442-2042.2007.01744.x

211. Wen, D., Utesch, T., Wu, J., Robertson, S., Liu, J., Hu, G., & Chen, H. (2019). Effects of different protocols of high intensity interval training for VO. *J Sci Med Sport*, *22*(8), 941-947. https://doi.org/10.1016/j.jsams.2019.01.013

212. Wewege, M. A., Ahn, D., Yu, J., Liou, K., & Keech, A. (2018). High-Intensity Interval Training for Patients With Cardiovascular Disease-Is It Safe? A Systematic Review. *J Am Heart Assoc*, *7*(21), e009305. https://doi.org/10.1161/JAHA.118.009305

213. Williams, C. J., Gurd, B. J., Bonafiglia, J. T., Voisin, S., Li, Z., Harvey, N., . . . Coombes, J. S. (2019). A Multi-Center Comparison of O. *Front Physiol*, *10*, 19. https://doi.org/10.3389/fphys.2019.00019

214. Wunderle, M. F., Härtel, N., Wagener, N., Kowalewski, K. F., Nuhn, P., Walach, M. T., & Kriegmair, M. C. (2021). Prospective geriatric assessment for perioperative risk stratification in partial nephrectomy. *Eur J Surg Oncol*, *47*(4), 913-919. https://doi.org/10.1016/j.ejso.2020.11.001

215. Yafi, F. A., Aprikian, A. G., Chin, J. L., Fradet, Y., Izawa, J., Estey, E., . . . Kassouf, W. (2011). Contemporary outcomes of 2287 patients with bladder cancer who were treated with radical cystectomy: a Canadian multicentre experience. *BJU Int*, *108*(4), 539-545. https://doi.org/10.1111/j.1464-410X.2010.09912.x

216. Yang, L., Morielli, A. R., Heer, E., Kirkham, A. A., Cheung, W. Y., Usmani, N., . . . Courneya, K. S. (2021). Effects of Exercise on Cancer Treatment Efficacy: A Systematic Review of Preclinical and Clinical Studies. *Cancer Res*, *81*(19), 4889-4895. https://doi.org/10.1158/0008-5472.CAN-21-1258

217. Yang, Z., Bai, Y., Hu, X., Wang, X., & Han, P. (2020). The Prognostic Value of Body Mass Index in Patients With Urothelial Carcinoma After Surgery: A Systematic Review and Meta-Analysis. *Dose Response*, *18*(4), 1559325820979247. https://doi.org/10.1177/1559325820979247

218. Yellen, S. B., Cella, D. F., Webster, K., Blendowski, C., & Kaplan, E. (1997). Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*, *13*(2), 63-74. https://doi.org/10.1016/s0885-3924(96)00274-6

219. Zabor, E. C., Furberg, H., Lee, B., Campbell, S., Lane, B. R., Thompson, R. H., . . . Russo, P. (2018). Long-Term Renal Function Recovery following Radical Nephrectomy

for Kidney Cancer: Results from a Multicenter Confirmatory Study. *J Urol*, *199*(4), 921-926. https://doi.org/10.1016/j.juro.2017.10.027

220. Zakaria, A. S., Santos, F., Dragomir, A., Tanguay, S., Kassouf, W., & Aprikian, A. G. (2014). Postoperative mortality and complications after radical cystectomy for bladder cancer in Quebec: A population-based analysis during the years 2000-2009. *Can Urol Assoc J*, *8*(7-8), 259-267. https://doi.org/10.5489/cuaj.1997

221. Zhang, Z., Reinikainen, J., Adeleke, K. A., Pieterse, M. E., & Groothuis-Oudshoorn, C. G. M. (2018). Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med*, *6*(7), 121. https://doi.org/10.21037/atm.2018.02.12

222. Zuniga, K. B., Graff, R. E., Feiger, D. B., Meng, M. V., Porten, S. P., & Kenfield, S. A. (2020). Lifestyle and Non-muscle Invasive Bladder Cancer Recurrence, Progression, and Mortality: Available Research and Future Directions. *Bladder Cancer*, *6*, 9-23. https://doi.org/10.3233/BLC-190249

APPENDICES

APPENDIX A: BLADDER CANCER OVERVIEW

Bladder cancer overview

The bladder is a hollow muscular organ of the urinary system, located in the lower pelvis, with the function of storing urine [1, 2]. The bladder wall consists of three main layers: the urothelium or transitional epithelium, which is the inner layer; a thin layer of connective tissue called lamina propria or submucosa; and the outer layer called muscularis propria or smooth muscle, which is followed by perivesical fat [1-3]. The bladder cells located in any of the three layers might undergo a mutation, changing the pattern of cell growth and multiplication to an uncontrolled fashion, leading to the development of cancer [1, 2].

The most common histology type of bladder cancer is urothelial carcinoma (or transitional cell carcinoma), which develops in the lining tissue inside of the bladder called the urothelium [3-5]. Urothelial carcinoma accounts for more than 90% of bladder cancers [4, 5]. The remaining 10% of cases are non-urothelial bladder carcinoma which includes adenocarcinoma, squamous cell, small cell carcinoma, urachal carcinoma, and primary bladder sarcoma [4].

Microscopic or gross hematuria (blood in the urine) is the most common sign of bladder cancer [4, 6]. Other signs and symptoms include changes in bladder habits or irritative symptoms such as dysuria (painful urination), nocturia (urinating several times during the night), frequency, and urge incontinence; obstructive symptoms, including a decreased force of stream and the feeling of incomplete voiding; and, in the case of metastases or advanced disease, abdominal or pelvic pain, lower extremity edema, renal failure, and suprapubic palpable mass [2, 6].

In the presence of hematuria or symptoms related to bladder cancer, further investigation is required. The National Comprehensive Cancer Network guidelines for

bladder cancer [4] states that the initial evaluation of a suspected bladder cancer relies on cystoscopy, a medical examination in which a hollow tube is inserted through the urethra into the bladder to determine if a lesion is present. Urine cytology for microscopic examination of the cells is also recommended. Moreover, abdominal/pelvic computed tomography or magnetic resonance imaging and imaging of upper tract collecting system is indicated. The next step following the initial evaluation is the transurethral resection of the bladder tumor (TURBT), which is an examination performed under anesthesia to resect the tumor and determine the extent of disease in terms of stage and grade [4].

Bladder cancer stage is defined based on the TNM system, where T refers to the size and location of the tumor, N to the number of lymph nodes affected by the tumor, and M to the presence or absence of metastases [3]. Bladder cancer is also described as invasive or non-muscle invasive disease, based on the tumor penetration into the bladder wall [3, 4].

Non-muscle invasive bladder cancer [NMIBC] stages are classified as Ta, when the tumor is only at the epithelium and grows toward the hollow center of the bladder (papillary carcinoma); Tis (or CIS – carcinoma in situ), a flat carcinoma located at the epithelium; and T1, papillary carcinoma where the tumor cells are present in two layers, the epithelium and lamina propria (Figure A-1) [3, 4]. Muscle-invasive bladder cancer [MIBC] varies according to the extent of the tumor into the bladder wall and surrounding organs and ranges from T2 to T4 (Figure A-2). The T2 classification refers to tumor invasion into the layer muscularis propria; T3 includes perivesical tissue; and T4, more aggressive, refers to metastases [3, 4]. All the stages of the muscle invasive disease are

subclassified as "a" or "b", respectively, to signify a smaller and greater tumor progression towards the outer layer of the bladder and surrounding organs [3].

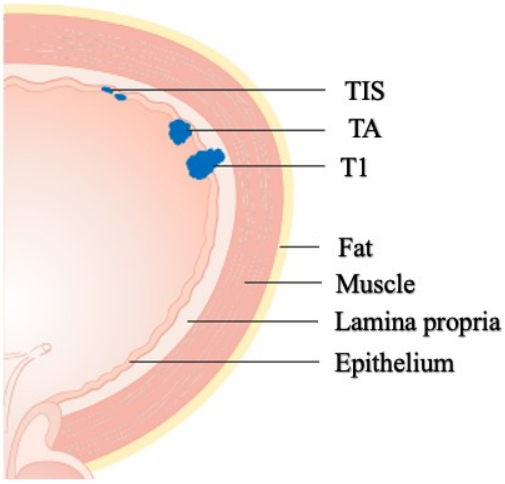


Figure A-1. Stages of non-muscle invasive bladder cancer into the different layers of the bladder wall. Adapted from Cancer Research UK (2018).

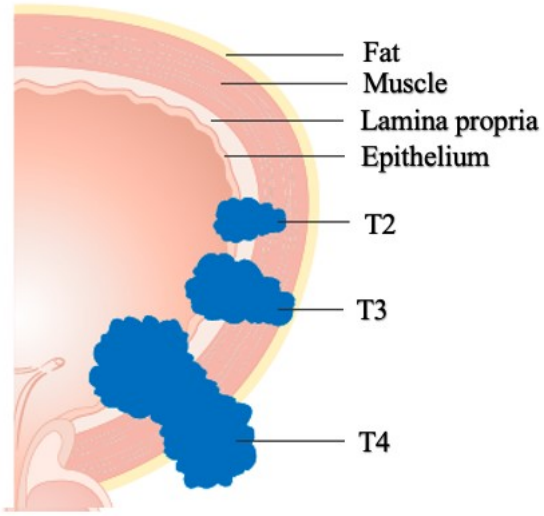


Figure A-2. Stages of muscle invasive bladder cancer into the different layers of the bladder wall. Adapted from Cancer Research UK (2018).

The grading system is used to compare tumor cells with normal cells, to verify how fast the tumor cells will grow and how likely they are to spread. The grade of the tumor is reported as "Low grade" or "High grade" depending on the aggressiveness of the disease [1, 7]. In general, high-grade cancers are muscle-invasive with cells that grow rapidly and have more probability of spreading [1]. The staging and grading system provide information on the biological aggressiveness of the disease that can be used to determine the probability of recurrence or progression of non-muscle invasive bladder cancer to muscle-invasive bladder cancer. Depending on the NMIBC risk category and treatment plan, the estimated recurrence and progression rates, respectively, range from 15% to 40% and from 1% to 10% within 24 months from diagnosis [8].

Bladder cancer epidemiology and risk factors

An estimated 13,400 new cases of bladder cancer will be diagnosed in 2023, making it the fifth most common cancer in Canada [9], and the nineth most common cancer worldwide [10]. The lifetime probability of developing bladder cancer in Canada is one in 34, with a likelihood of 4.5% for males (one in 22) and 1.4% for females (one in 70) [9]. Bladder cancer is more prevalent among individuals between 65 and 79 years old [9, 11]. Although research indicates that bladder cancer mortality has been slightly decreasing in North American populations [12], bladder cancer has the nineth highest cancer mortality rate in Canada [9]. Overall, it is estimated there will be 2,600 deaths (1,850 men and 720 women) from bladder cancer in 2023, with a lifetime probability of dying from bladder cancer higher for males (1.1%) than females (0.4%) [9]. Predicted five and 10-year survival rates for bladder cancer in Canada are 77% and 66%, respectively [9].

Risk factors for the development of bladder cancer include inherited genetic predispositions and/or exposures to carcinogens [12, 13]. The majority of bladder cancer tumors are associated with carcinogen exposures with the most important risk factor being tobacco smoking, responsible for half of the cases [1, 2, 13]. Tobacco smoke has aromatic amines that are eliminated in the urine, exposing the entire urinary system to carcinogenic substances [13]. Established risk factors for developing bladder cancer also include male sex, white race, environmental pollution (e.g., arsenic in drinking water), occupational exposure to chemicals, pelvic radiation, certain medical conditions including chronic bladder irritation, diabetes, and personal or family history of bladder cancer [1, 6, 13].

The association between other lifestyle factors, such as obesity and physical activity levels, with the risk of bladder cancer differ among the studies [14-18]. The investigation conducted by Koebnick et al. [17] indicate that, when compared with normal weight, overweight and obesity were respectively associated with 15% and 28% increase in the risk of bladder cancer, while Holick et al. [26] found no association between body mass index with bladder cancer risk. The International Agency for Research on Cancer (IARC) reunited a working group of 21 independent experts to review the scientific evidence on the association between excess body fatness and cancer risk [14]. Some of the evidence for bladder cancer was retrieved from four case-control studies, three meta-analyses, and 23 prospective cohort studies investigating the association between body mass index (BMI) and bladder cancer incidence or bladder cancer-related mortality. According to the IARC group of experts, there are inconsistent findings leading to an inadequate evidence of the relationships between BMI and bladder

cancer risk [14, 19]. Regarding physical activity, Koebnick et al. [17], Holick et al. [18], and Noguchi [15], found no association between physical activity and the risk of bladder cancer. In contrast, Keimling et al. [16] suggest 15% decreased risk of bladder cancer in those with higher levels of physical activity compared to lower levels.

Bladder cancer treatments and side effects

Bladder cancer treatments and their side effects depend on whether or not the tumor has invaded the muscularis propria layer, referred to as muscle-invasive bladder cancer and non-muscle invasive bladder cancer, respectively [4].

Non-muscle invasive bladder cancer

The standard treatment for NMIBC is the transurethral resection of the bladder tumor (TURBT), followed by a single dose of intravesical chemotherapy (e.g., gemcitabine or mitomycin) within 24 hours of surgery [4]. The transurethral resection is a procedure performed under anesthesia by inserting a cystoscope through the urethra into the bladder to confirm the diagnosis and to remove abnormal tissues or tumors inside the bladder [2, 20]. Intravesical single instillations, when the drug is placed directly in the bladder, is a crucial procedure in the management of bladder cancer to treat residual tumors by impeding the installation of any remaining cancer cells into the bladder wall and the subsequent development of cancer [5, 21]. The immediate postoperative intravesical chemotherapy is recommended for all patients with NMIBC due to its association with a significant decrease in the 5-year recurrence rate [5, 6].

A secondary TURBT within 6 weeks of the first procedure is recommended if the resection was initially incomplete or in the absence of muscle in the original specimen (for Ta high-grade tumors), or based on the clinical stage of the tumor (for T1 tumors) [4]. The repeat TURBT is associated with improved recurrence-free survival,

progression-free survival, and treatment outcomes [20, 22]. Patients diagnosed with T1 high-grade tumors should be considered for bladder removal (cystectomy) instead of repeat TURBT [4].

Adjuvant intravesical therapy is the next treatment considered for NMIBC, indicated based on the probability of recurrence and progression to muscle-invasive bladder cancer, considering size, number, and tumor grade [4]. The most common therapy agents are bacillus calmette-guerin (BCG), which is immunotherapy, and mitomycin or gemcitabine, which are chemotherapies [4]. Adjuvant intravesical therapy consists of weekly instillations initiated 3-4 weeks after the TURBT given for approximately six weeks and a possible maintenance phase depending on tumor grade [4, 5]. The role of maintenance therapy with a chemotherapy agent is controversial, while maintenance with BCG is better established and administered with the aim of preventing or delaying recurrence [4, 5]. The BCG maintenance phase consists of three weekly instillations at three, six and 12-months for intermediate-risk tumors or, in case of high-risk bladder cancer tumors, maintenance continues for another two years with instillations every 6-months [1, 4, 5].

Follow-up treatment for NMIBC differs among patients based on tumor grade, but overall it might include cystoscopy, upper tract and abdominal/pelvic imaging, blood tests (for those who underwent bladder removal), and urine tests [4]. Although more investigation is necessary to determine the optimal duration of the follow-up, it currently might last more than 10 years [4]. The long NMIBC treatment and follow-up procedures are necessary because of the high rates of recurrence and progression, making it the most expensive cancer to treat [4, 5, 7, 23].

If the follow-up cystoscopy exam is positive or indicates suspicion of recurrent or persistent NMIBC, another TURBT is required to re-stage the tumor, which is followed by a single dose of intravesical chemotherapy [4]. Sequentially, the preferred treatment for T1 high grade as well as for those patients with incomplete response to treatment is bladder removal. For Ta and Tis tumors, changes in the adjuvant intravesical agent are recommended, however, no more than two consecutive adjuvant intravesical courses should be given [4]. If the follow-up cystoscopy exam is negative, but cytology is positive, a deep evaluation based on multiple biopsies, a transurethral biopsy of the prostate, cytology of the upper tract and possible ureteroscopy are indicated to check for urothelial carcinoma of the prostate and upper tract tumors [4]. Follow-up for recurrent or persistent NMIBC will be defined based on sites of disease, tumor biology, and length under treatment, but usually is done at three months and then at longer intervals [4].

Overall, the main side effects of NMIBC treatment might include pain when urinating, irritation, burning feeling and bleeding, especially after the TURBT and intravesical chemotherapy [2]. In addition, patients treated with BCG might experience BCG associated toxicity, caused by the triggering of an immunostimulatory response that leads to the release of proinflammatory cytokines [4]. Some of the manifestations of BCG toxicity include flu-like symptoms, fever that may last 48 to 72 hours, local discomfort due to irritation of the lower urinary tract, and allergic reactions [4, 5].

Muscle-invasive bladder cancer

The primary treatment for MIBC includes cisplatin-based neoadjuvant chemotherapy [NAC] followed by cystectomy (bladder removal) [1, 5]. In addition to bladder removal, bilateral pelvic lymphadenectomy is performed and tested for cancer

spread [1, 5, 17]. Cisplatin-based NAC is a systemic treatment, usually given intravenously every three or four weeks for three or four cycles [2, 5, 17]. Despite the significant survival benefit of cisplatin-based treatment, not all patients are eligible and, in this case, the recommendation is to move forward to the radical local treatment called cystectomy [5, 17, 18].

Radical cystectomy [RC] is part of the treatment approach for those diagnosed with large tumors, metastasis or recurrent high grade cancer. It is a surgery for bladder removal, usually conducted within four to six weeks after NAC or within six weeks of the TURBT in absence of the systemic treatment [2, 5, 17]. Cystectomy varies by sex, and includes a prostatectomy in males (the removal of the prostate, seminal vesicles, proximal vas deferens, and proximal urethra) and a hysterectomy in females (removal of uterus, ovaries, fallopian tubes, urethra and part of the vagina) [2, 5, 17]. Alternatively, a partial cystectomy is a bladder preservation option [2], however, this approach is discouraged and conducted in less than 5% of the cases when a solitary small lesion extends to the muscle layer [2, 5, 17].

After the RC, a reconstructive surgery called urinary diversion is required to collect and eliminate the urine. One type of urinary diversion is an ileal conduit, also called incontinent diversion, which is a procedure where a segment of the intestine is connected to the urethra and to an opening in the abdomen, creating a path to a removable bag called a urostomy pouch that collects the urine [1, 2, 5, 7]. Another urinary diversion option is the continent diversion, which might include an Indiana Pouch, where the urine can be stored in a pouch created from a piece of the large intestine and the ileum to be posterior drained by an opening in the abdomen. Alternatively, an

Orthotopic Neobladder, or “new” bladder is created using a longer segment of the small intestine that is connected to the urethra, maintaining the normally way to urinate as before [2, 5, 7]. The decision on the type of urinary diversion depends on several factors including health conditions such as renal and hepatic function, comorbidities, life expectancy, performance status, patient preference, and tumor location [2, 17].

An additional treatment approach for MIBC includes radiotherapy as a single therapy for patients that are not eligible for radical cystectomy or chemotherapy [17]. However, whenever possible, radiotherapy should be offered as a trimodal therapy [TMT] that combines TURBT, radiotherapy and chemotherapy [17]. The TMT is a treatment approach that preserves the bladder of those selected healthy patients, diagnosed with stage II or IIIA, who wish to preserve the bladder [5, 17].

In suspected metastasis, further investigation to evaluate the extent of the disease is required and should include bone scan, chest computed tomography, central nervous system imaging, biopsy if feasible, and estimation of glomerular filtration rate to assess renal function and determine eligibility for cisplatin-based treatment [5]. The management of metastatic disease, as well as locally advanced recurrence, is generally done with systemic therapy. The specific regimen depends on overall patient clinical condition, comorbidities and performance status [1, 2, 5]. Regardless of the therapy agent used, all patients with metastatic disease are reassessed after two or three cycles. Depending on the results, the treatment might be continued up to 6 cycles or, if no treatment response is observed, therapy modifications are recommended [5]. In addition to systemic treatment, metastasectomy, the surgical removal of metastases, might be recommended for selected patients who have a positive response to treatment, single site

of metastatic lesions, and long or lymph node sites of disease [5]. Radiotherapy might also be used in addition to systemic therapy as an alternative if surgery cannot be done or to control symptoms, such as pain and bleeding [2].

Follow-up management for MIBC should include quality of life and patient reported outcomes measurements, as well as routine medical exams [5, 17]. Follow-up for patients treated with RC includes imaging and urine tests every three to six months in the first two years after cystectomy [5]. The imaging should be done annually after the two-year period while urine tests should be performed as clinically indicated. In addition, blood tests are also required every three to six months in the first year, and annually thereafter. In addition to these investigations, patients treated with bladder preservation should also undergo long-term cystoscopy exams [17].

Treatment of MIBC is associated with side effects that vary in type and intensity depending on the procedure. Some of the most common chemotherapy side effects include nausea and vomiting, loss of appetite, hair loss, mouth and throat sores, diarrhea, constipation, increased risk of infections and peripheral neuropathy fatigue [1, 2]. The most notable side effects of radiotherapy include skin changes, fatigue, diarrhea, urinary incontinence, bleeding from the rectum, and increased urinary frequency [1, 2]. The RC may cause pain, urinary tract infection, obstruction and sexual problems [2]. The urinary diversion reconstructive surgery might encompass skin irritation, infections, incontinence, restricted flow, and body image issues [7]. In addition, bladder cancer patients might experience a significant decrease in physical, mental and social health-related quality of life [19].

References

1. Canadian Cancer Society [CCS]. *Bladder Cancer*. 2020 [cited 2020 May 17th]; Available from: https://www.cancer.ca/en/cancer-information/cancer-type/bladder/bladder-cancer/?region=on.
2. American Cancer Society [ACS]. *Bladder Cancer*. 2020 [cited 2020 May 17th]; Available from: https://www.cancer.org/cancer/bladder-cancer.html.
3. Edge, S.B. and C.C. Compton, *The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM.* Ann Surg Oncol, 2010. **17**(6): p. 1471-4.
4. National Comprehensive Cancer Network [NCCN], *NCCN Clinical Practice Guidelines on Oncology: Bladder Cancer, Version 1.2024*. 2024.
5. Kassouf, W., et al., *CUA guidelines on the management of non-muscle invasive bladder cancer.* Can Urol Assoc J, 2015. **9**(9-10): p. E690-704.
6. DeGeorge, K.C., H.R. Holt, and S.C. Hodges, *Bladder Cancer: Diagnosis and Treatment.* Am Fam Physician, 2017. **96**(8): p. 507-514.
7. Bladder Cancer Canada [BCC]. *Staging and Grading*. 2020 [cited 2020 May 17th]; Available from: https://bladdercancercanada.org/en/staging-and-grading/.
8. Kamat, A.M., et al., *Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group.* J Clin Oncol, 2016. **34**(16): p. 1935-44.
9. Canadian Cancer Statistics Advisory Committee, et al., *Canadian Cancer Statistics 2023.* 2023, Canadian Cancer Society: Toronto, ON.

10. Ferlay J, et al. *Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer.* 2024 March 4, 2024]; Available from: https://gco.iarc.who.int/today.

11. GLOBOCAN. *Estimated number of new cases in 2018, worldwide, both sexes, all ages* 2018 May 17th, 2020].

12. Antoni, S., et al., *Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends.* Eur Urol, 2017. **71**(1): p. 96-108.

13. Burger, M., et al., *Epidemiology and risk factors of urothelial bladder cancer.* Eur Urol, 2013. **63**(2): p. 234-41.

14. IARC Working Group on the Evaluation of Cancer-Preventive Interventions, *Absence of excess body fatness*. 2016.

15. Noguchi, J.L., M.A. Liss, and J.K. Parsons, *Obesity, Physical Activity and Bladder Cancer.* Curr Urol Rep, 2015. **16**(10): p. 74.

16. Keimling, M., et al., *The association between physical activity and bladder cancer: systematic review and meta-analysis.* Br J Cancer, 2014. **110**(7): p. 1862-70.

17. Koebnick, C., et al., *Body Mass Index, Physical Activity, and Bladder Cancer in a Large Prospective Study*. 2008, Cancer Epidemiol Biomarkers Prev. p. 1214-1221.

18. Holick, C.N., et al., *Prospective study of body mass index, height, physical activity and incidence of bladder cancer in US men and women.* Int J Cancer, 2007. **120**(1): p. 140-6.

19. Lauby-Secretan, B., et al., *Body Fatness and Cancer--Viewpoint of the IARC Working Group.* N Engl J Med, 2016. **375**(8): p. 794-8.

APPENDIX B: EXERCISE IN BLADDER CANCER

Observational studies

Koelker et al. [1] examined, in a cross-sectional design, the association of exercise on self-reported physical health status and prevalence of sedentary behavior of bladder cancer patients. The study included 935 participants self-diagnosed with bladder cancer (invasiveness not provided) from the national health-related survey Behavioral Risk Factor Surveillance System in the United States. The authors identified a high prevalence of sedentary behavior (1 in 3 bladder cancer patients). Moreover, patients who exercised were less likely to report poor physical status (OR: 0.37, 95% CI: 0.25–0.56, $p<0.001$)[1].

Gopalakrishna et al. [2] conducted a cross-sectional study in North Carolina, United States, aiming to investigate physical activity patterns and associations with health-related quality of life of 472 NMIBC (84%) and MIBC (16%) survivors. Gopalakrishna et al. [2] found that those who reported increased levels of physical activity had a significantly higher global health-related quality of life. Additionally, the authors identified that 76% of the sample reported medium and high physical activity levels, as well as higher scores of social, functional and overall well-being when compared with the general American population [2].

A population-based study conducted in Alberta, Canada by Karvinen et al. [3] included 525 NMIBC (65%) and MIBC (35%) survivors and sought to investigate the association between exercise and quality of life. Similarly to the previous study [2], Karvinen et al. [3] found a linear association between levels of physical activity and several domains of health-related quality of life of bladder cancer survivors, with better scores presented by those who reported higher physical activity levels. However, 78% of

bladder cancer survivors do not meet the public health exercise guidelines and 68% are inactive [3].

Another Canadian, cross-sectional study by Chung et al. [4] included 586 bladder cancer patients and survivors diagnosed with NMIBC (n= 324), MIBC (n=137) and unknown cancer invasiveness (n=113), aiming to describe health behaviors, including physical activity. The authors also compared health behaviors between survivors with NMIBC vs MIBC at different cancer journeys (newly diagnosed, follow-up surveillance, or metastasis/recurrence), and its relationship with health-related quality of life. Relevant findings indicate that NMIBC and MIBC do not differ in physical activity behavior. The majority of the participants (77.3%) did not meet the guidelines recommendation of 150 minutes/week of moderate/strenuous exercise. Moreover, 60.9% were classified as overweight (n=221) or obese (n=136). Participants who met the physical activity recommendations had a healthy diet and were non-smoking, presented better scores for health-related quality of life. This was the first study to compare health behavior between NMIBC vs MIBC patients and survivors and the findings highlight the need for health behavior interventions across the bladder cancer journey [4].

Karvinen et al. [5] sought to examine the determinants of exercise intention and behavior in bladder cancer through a prospective study that included 387 NMIBC (65%) and MIBC (35%) survivors. Using the Theory of Planned Behavior, the authors found that significantly lower exercise participation was associated with treatment type (adjuvant therapy), cancer invasiveness (MIBC) and older age. The variability in exercise intention was explained by perceived benefits (instrumental attitude), enjoyment of exercise (affective attitude), the perception that important others exercise (descriptive

norm), and confidence in your own ability to exercise and perceived control over-exercising (perceived behavioral control). Additionally, perceived behavioral control was the strongest independent predictor of exercise behavior for bladder cancer survivors with 65 years or older [5].

Rammant et al. [6] also investigated the determinants of physical activity but in a qualitative study with 30 bladder cancer patients that have undergone radical cystectomy. Data interpretation was based on the five dimensions of adherence proposed by the World Health Organization and shows that determinants of physical activity in patients undergoing radical cystectomy are multifactorial, including condition-related, therapy-, patient-, social/economic- and health system-related factors [6].

Karvinen et al. [7] conducted a population-based survey aiming to identify exercise programming and counselling preferences of 397 bladder cancer survivors in Alberta, Canada. They reported that NMIBC (65%) and MIBC (35%) survivors are interested in receiving face-to-face counselling with an exercise specialist from a cancer center. Moreover, 84.3% of survivors felt they would, or might be able to, participate in an exercise program. Regarding their program preferences, bladder cancer survivors were more likely to prefer home-based, unsupervised, moderate intensity, and solitary exercise walking programs following treatment [7].

In summary, observational studies have reported a positive linear association between physical activity levels and health-related quality of life [2-4] and a protective effect of exercise on physical health status in bladder cancer [1]. Overall, limitations of observational studies include a possible misclassification of physical activity level and weight and height for BMI, due to the use of self-reported methods, the absence of a

control group, the unavailability to identify if exercise improves the quality of life or if participants with higher levels of quality of life are more likely to exercise, and the different criteria to define the level of physical activity.

A systematic search of randomized controlled trials investigating physical activity and exercise interventions in bladder cancer patients was conducted to identify and summarize current evidence and inform research gaps. Electronic databases of PubMed, Web of Science and Google Scholar were searched and only articles published in English were included. The search strategy combined the terms *bladder cancer* AND *physical activity* OR *physical exercise* OR *exercise intervention*. Additional references were found in the reference list of the selected bibliographies. The articles were screened by title and abstract and those that included the main criteria (randomized controlled trial) were included. Eleven articles were found [8-18], two of them had a pre-experimental design [15, 16] and were excluded for the purpose of this review, two other articles were study protocol [17, 18] and were not included. Among the seven included articles [8-14], the study by Jensen et al has been reported in three separate publications [9, 12, 13] and the study by Banerjee et al is described in a conference abstract and another paper [8, 10].

To date, only four randomized, controlled, exercise trials were conducted exclusively among bladder cancer patients and survivors. Two of the four studies involved the preoperative setting [8, 10, 14], one was conducted during the postoperative phase [11], and one included exercise interventions in both scenarios [9, 12, 13]. The sample sizes ranged from 18 to 107 participants, with 74-88% males, and included participants diagnosed with MIBC [14] or MIBC and NMIBC [9, 11-13]. Two investigations did not report the cancer invasiveness [8, 10], but were conducted prior to

radical cystectomy indicating a more aggressive cancer. Moreover, the intervention varied across studies in terms of the type of exercise. Three studies were characterized as multimodal programs [9, 11-14] and included strength and endurance exercise [9, 11-13], another study also included balance, mobility and stretching training [11], and another combined aerobic training with nutritional care and relaxation techniques [14]. One study investigated vigorous aerobic interval exercise on a cycle ergometer [8, 10]. The studies differed in terms of exercise frequency (two to five days per week, once or twice a day) and duration of the intervention (two to12 weeks).

Regarding the purpose of the investigations, feasibility was the aim of two studies [8, 10, 13]. Patient-related outcomes were investigated by the four studies and included health-related quality of life [9, 11, 14], patient satisfaction [9], length of hospitalization [12], and surgical complications or recovery outcomes [8, 10, 12]. Health-related fitness was also included as the primary outcome of the four studies [8, 10, 11, 13, 14].

Both studies investigating the feasibility of exercise programs for bladder cancer patients were conducted in the preoperative setting, including both MIBC and NMIBC patients [8, 10, 13]. A supervised short-term vigorous aerobic exercise program had a recruitment rate of 53.5% and median attendance of 8 (range 1-10) exercise sessions [10]. While in a short-term home-based exercise program 66% of the participants attended more than 75%, however, there was no report of the eligibility rate [13]. Overall, promising evidence suggests that exercise interventions in bladder cancer patients might be associated with improvements in specific domains of health-related quality of life, such as the physical domain [11] and disease-specific scales [9]. In addition, studies reported benefits in cardiorespiratory fitness [8, 10], functional capacity [11, 12, 14], and

muscle power [13]. Surprisingly, improvement in mobility persisted in the exercise intervention group even one year after surgery, while it decreased in the control group [11]. However, these studies have limitations including the lack of information about the exercise intervention [8, 11], the failure to report recruitment and eligibility rates [13], the variability in disease invasiveness since studies included both NMIBC and MIBC [9-13], small sample sizes, and high loss to follow-up [8-14].

References

1. Koelker, M., et al., *Impact of exercise on physical health status in bladder cancer patients.* Can Urol Assoc J, 2023. **17**(1): p. E8-E14.
2. Gopalakrishna, A., et al., *Physical activity patterns and associations with health-related quality of life in bladder cancer survivors.* Urol Oncol, 2017. **35**(9): p. 540.e1-540.e6.
3. Karvinen, K.H., et al., *Associations between exercise and quality of life in bladder cancer survivors: a population-based study.* Cancer Epidemiol Biomarkers Prev, 2007. **16**(5): p. 984-90.
4. Chung, J., et al., *Modifiable lifestyle behaviours impact the health-related quality of life of bladder cancer survivors.* BJU Int, 2020. **125**(6): p. 836-842.
5. Karvinen, K.H., et al., *A prospective study of the determinants of exercise in bladder cancer survivors using the Theory of Planned Behavior.* Support Care Cancer, 2009. **17**(2): p. 171-9.
6. Rammant, E., et al., *Understanding physical activity behavior in patients with bladder cancer before and after radical cystectomy: a qualitative interview study.* Clin Rehabil, 2019. **33**(4): p. 750-761.
7. Karvinen, K.H., et al., *Exercise programming and counseling preferences in bladder cancer survivors: a population-based study.* J Cancer Surviv, 2007. **1**(1): p. 27-34.
8. Banerjee, S., et al., *O2 Preoperative exercise protocol to aid recovery of radical cystectomy: results of a feasibility study. Eur. Urol. Suppl* 2013. **12**(6): p. 125.

9. Jensen, B.T., et al., *Multidisciplinary rehabilitation can impact on health-related quality of life outcome in radical cystectomy: secondary reported outcome of a randomized controlled trial.* J Multidiscip Healthc, 2014. **7**: p. 301-11.

10. Banerjee, S., et al., *Vigorous intensity aerobic interval exercise in bladder cancer patients prior to radical cystectomy: a feasibility randomised controlled trial.* Support Care Cancer, 2018. **26**(5): p. 1515-1523.

11. Porserud, A., A. Sherif, and A. Tollbäck, *The effects of a physical exercise programme after radical cystectomy for urinary bladder cancer. A pilot randomized controlled trial.* Clin Rehabil, 2014. **28**(5): p. 451-9.

12. Jensen, B.T., et al., *Efficacy of a multiprofessional rehabilitation programme in radical cystectomy pathways: a prospective randomized controlled trial.* Scand J Urol, 2015. **49**(2): p. 133-41.

13. Jensen, B.T., et al., *Exercise-based pre-habilitation is feasible and effective in radical cystectomy pathways-secondary results from a randomized controlled trial.* Support Care Cancer, 2016. **24**(8): p. 3325-31.

14. Minnella, E.M., et al., *Multimodal Prehabilitation to Enhance Functional Capacity Following Radical Cystectomy: A Randomized Controlled Trial.* Eur Urol Focus, 2019. **7**(1): p. 132-138.

15. Kaye, D.R., et al., *The Feasibility and Impact of a Presurgical Exercise Intervention Program (Prehabilitation) for Patients Undergoing Cystectomy for Bladder Cancer.* Urology, 2020. **145**.

16. Chestnut, C., et al., *Glycemic impact of a diet and lifestyle intervention on diabetics and prediabetics during treatment for non-muscle invasive bladder cancer.* Nutr Cancer, 2019. **72**(7): p. 1-6.

17. Porserud, A., et al., *The CanMoRe trial - evaluating the effects of an exercise intervention after robotic-assisted radical cystectomy for urinary bladder cancer: the study protocol of a randomised controlled trial.* BMC Cancer, 2020. **20**(1): p. 805.

18. Rammant, E., et al., *Development of a pre- and postoperative physical activity promotion program integrated in the electronic health system of patients with bladder cancer (The POPEYE study): An intervention mapping approach.* Eur J Cancer Care (Engl), 2020. **30**(2): p. e13363.

APPENDIX C: OBESITY AND BLADDER CANCER

Obesity in bladder cancer patients

High prevalence of sedentary behavior, overweight and obesity is observed among bladder cancer patients [1-3]. The increased risk of obesity on cardiovascular diseases, type 2 diabetes, and all-cause mortality is widely known [4]. A systematic review and meta-analysis investigated the association of obesity with survival outcomes in patients with cancer [5]. The systematic review included 170 studies for the association of obesity with overall survival and 109 studies for the association with cancer-specific survival, the median follow-up time ranged from 6.5 months to more than 10 years [5]. The findings suggested that cancer patients with obesity have worse survival outcomes, with increased overall and cancer-specific mortality, especially patients with breast, colon, and uterine cancer [5]. The effects, however, of overweight and obesity on bladder cancer survival outcomes is unclear. This systematic review and meta-analysis included only two retrospective studies that investigated the association of obesity with oncological outcomes in bladder cancer patients, moreover the studies varied in type of bladder cancer diagnosis and treatment [5].

Some studies in bladder cancer patients have reported worse prognosis among overweight and obese patients, including increased risk for recurrence, progression, and death [6-10]. The hypothesis behind this association is that the anatomical structure of obese patients is a limitation for high-quality tumor resection [7]. Moreover, the fat mass is related to inflammatory processes that contributes to tumor cells growth and proliferation [7, 8] which, associated with lower levels of anti-inflammatory adipokine, creates a cancer-stimulating microenvironment [8].

Other studies, however, have reported no association between obesity and bladder cancer outcomes [11, 12], or even better survival among those bladder cancer patients

with higher BMI [13-15], a phenomenon known as the obesity paradox. The obesity paradox has also been observed in other cancer populations such as renal cell, colorectal, lung, and metastatic melanoma patients [5, 16, 17]. Overall, the factors that are potentially associated with improved survival rates among patients with higher BMI include methodological biases (i.e., sample selection bias, residual confounding, reverse causality, collider bias) [18], clinical and biological differences including tumor expression [19], and/or body composition features and limitations of BMI to distinguish body compartments [18, 20].

References

1. Chung, J., et al., *Modifiable lifestyle behaviours impact the health-related quality of life of bladder cancer survivors.* BJU Int, 2020. **125**(6): p. 836-842.
2. Karvinen, K.H., et al., *Associations between exercise and quality of life in bladder cancer survivors: a population-based study.* Cancer Epidemiol Biomarkers Prev, 2007. **16**(5): p. 984-90.
3. Koelker, M., et al., *Impact of exercise on physical health status in bladder cancer patients.* Can Urol Assoc J, 2023. **17**(1): p. E8-E14.
4. Aune, D., et al., *BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants.* BMJ, 2016. **353**: p. i2156.
5. Petrelli, F., et al., *Association of Obesity With Survival Outcomes in Patients With Cancer: A Systematic Review and Meta-analysis.* JAMA Netw Open, 2021. **4**(3): p. e213520.
6. Noguchi, J.L., M.A. Liss, and J.K. Parsons, *Obesity, Physical Activity and Bladder Cancer.* Curr Urol Rep, 2015. **16**(10): p. 74.
7. Kluth, L.A., et al., *Obesity is associated with worse outcomes in patients with T1 high grade urothelial carcinoma of the bladder.* J Urol, 2013. **190**(2): p. 480-6.
8. Ferro, M., et al., *An increased body mass index is associated with a worse prognosis in patients administered BCG immunotherapy for T1 bladder cancer.* World J Urol, 2019. **37**(3): p. 507-514.
9. Chromecki, T.F., et al., *Obesity is associated with worse oncological outcomes in patients treated with radical cystectomy.* BJU Int, 2013. **111**(2): p. 249-55.

10. Dabi, Y., et al., *Impact of body mass index on the oncological outcomes of patients treated with radical cystectomy for muscle-invasive bladder cancer.* World J Urol, 2017. **35**(2): p. 229-235.

11. Hafron, J., et al., *Does body mass index affect survival of patients undergoing radical or partial cystectomy for bladder cancer?* J Urol, 2005. **173**(5): p. 1513-7.

12. Bachir, B.G., et al., *Effect of body mass index on the outcomes of patients with upper and lower urinary tract cancers treated by radical surgery: results from a Canadian multicenter collaboration.* Urol Oncol, 2014. **32**(4): p. 441-8.

13. Gierth, M., et al., *Influence of Body Mass Index on Clinical Outcome Parameters, Complication Rate and Survival after Radical Cystectomy: Evidence from a Prospective European Multicentre Study.* Urol Int, 2018. **101**(1): p. 16-24.

14. Bi, H., et al., *Impact of Body Mass Index and Pretreatment Hemoglobin Level on Prognosis Following Radical Cystectomy for Bladder Cancer in Males and Females.* Urol Int, 2020. **104**(1-2): p. 28-35.

15. Psutka, S.P., et al., *Mortality after radical cystectomy: impact of obesity versus adiposity after adjusting for skeletal muscle wasting.* J Urol, 2015. **193**(5): p. 1507-13.

16. Caan, B.J., et al., *Explaining the Obesity Paradox: The Association between Body Composition and Colorectal Cancer Survival (C-SCANS Study).* Cancer Epidemiol Biomarkers Prev, 2017. **26**(7): p. 1008-1015.

17. Hakimi, A.A., et al., *An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma.* J Natl Cancer Inst, 2013. **105**(24): p. 1862-70.

18. Caan, B.J., E.M. Cespedes Feliciano, and C.H. Kroenke, *The Importance of Body Composition in Explaining the Overweight Paradox in Cancer-Counterpoint.* Cancer Res, 2018. **78**(8): p. 1906-1912.

19. Sanchez, A., et al., *Transcriptomic signatures related to the obesity paradox in patients with clear cell renal cell carcinoma: a cohort study.* Lancet Oncol, 2020. **21**(2): p. 283-293.

20. Sanchez, A., et al., *Impact of body size and body composition on bladder cancer outcomes: Risk stratification and opportunity for novel interventions.* Urol Oncol, 2020. **38**(9).

APPENDIX D: BRAVE TRIAL CONSENT FORM

Informed Consent for Participation in a Research Study

Feasibility and Preliminary Efficacy of High-Intensity Interval Training in Bladder Cancer Patients During or After Intravesical Therapy: A Randomized Controlled Trial

(A study to examine the feasibility and the effects of exercise in bladder cancer patients during or after intravesical treatment)

Protocol ID: *NA*

Principal Investigator: *Kerry S. Courneya, PhD*
Faculty of Kinesiology, Sport and Recreation
University of Alberta
780-492-1031
Co-Investigator: *Adrian Fairey, MD*
Northern Alberta Urology Centre
Kaye Edmonton Clinic
780-407-5771
Co-Investigator: *Normand Boulé, PhD*
Faculty of Kinesiology, Sport and Recreation
University of Alberta
780-492-4695
Co-Investigator: *Fernanda Arthuso*
Faculty of Kinesiology, Sport and Recreation
University of Alberta
587-590-8769

Sponsor/Funder(s): *Canada Research Chairs Program, University of Alberta*

Emergency Contact Number (24 hours / 7 days a week): Health Link, *811*

Non-Emergency contact numbers are noted at the end of this document under the section heading "WHO DO I CONTACT FOR QUESTIONS?".

For assistance with terminology within this consent form, please refer to the Canadian Cancer Society Glossary of Terms at http://info.cancer.ca/e/glossary/glossary.html.

You are being invited to participate in a research study because you have been scheduled to receive or have completed at least one intravesical treatment for non-muscle invasive bladder cancer. This consent form provides detailed information about the study to assist you with making an informed decision. Please read this document carefully and ask any questions you may

have. All questions should be answered to your satisfaction before you decide whether to participate.

The study staff will tell you about timelines for making your decision. You may find it helpful to discuss the study with family and friends so that you can make the best possible decision within the given timelines.

Taking part in this study is voluntary. You may choose not to take part or, if you choose to participate, you may leave the study at any time without giving a reason. Deciding not to take part or deciding to leave the study will not result in any penalty or any loss of medical or health-related benefits to which you are entitled.

The study doctor, who is one of the researchers, will discuss this study with you and will answer any questions you may have. If you do consent to participate in this study, you will need to sign and date this consent form. You will receive a copy of the signed form.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

Bladder cancer is the fifth most common cancer in Canada and has the eighth highest cancer mortality rate. The treatment for the most frequent type of bladder cancer is surgically removing the tumour and placing a drug in the bladder at the same time. This procedure is often followed by six weeks of medication placed within the bladder and a possible intravesical therapy maintenance phase. There are physical and psychosocial challenges from bladder cancer and its treatment that may affect how patients feel and function, and consequently their quality of life. Moreover, bladder cancer patients are at a high risk of their bladder cancer coming back and getting worse. Exercise is a low-cost intervention that although not proven, it may lower the chances of bladder cancer coming back or getting worse, manage side effects related to cancer treatment, help patients feel better, and improve quality of life.

To date, however, no study has examined if it is safe or even possible for bladder cancer patients to exercise when they are receiving drugs placed into their bladder. The Bladder cancer and exeRcise trAining during intraVesical thErapy (BRAVE) Trial will be the first study to test the feasibility and safety of exercise in bladder cancer patients during and after this drug therapy. Feasibility will be evaluated by tracking the number of bladder cancer patients scheduled for intravesical therapy deemed eligible for the study, the number of bladder cancer patients that enrolled and adhered to the exercise sessions and assessments. To evaluate the safety of the program, any adverse events during the physical assessments (baseline, 6-week, and post-intervention) and during the exercise sessions will be recorded. We will ask some patients to do a supervised exercise program during their drug treatment while other patients will be asked not to exercise more than their usual. We will compare the exercise ability of the two groups through fitness testing and how they fare with their bladder cancer treatment through questionnaires. This study will provide information on whether exercise may help patients feel better, function better, and possibly even lower their chances of the disease coming back or getting worse.

The Health Research Ethics Board of Alberta – Cancer Committee (HREBA-CC), which oversees the ethical acceptability of research involving humans, has reviewed and granted ethics approval for this study.

WHY IS THIS STUDY BEING DONE?

The purpose of this feasibility study is to help understand if it is possible to do the study with a small number of participants before a larger study is started. Because there will only be a small number of participants, it is not expected to give complete answers to the research questions and will not prove safety or effectiveness. The results may be used as a guide for larger studies, although there is no guarantee that those will be conducted. Participation in a feasibility study does not mean that you will be eligible to participate in a future larger study.

WHAT ARE OTHER OPTIONS IF I DECIDE NOT TO PARTICIPATE IN THIS STUDY?

You do not have to take part in this study, in order to receive continued medical care. Other alternatives in addition to standard care may include:

- starting an exercise program on your own
- consulting with an exercise specialist
- joining a community-based exercise program

Please talk to the study team or your care doctor about the known benefits and risks of these other options before you decide to take part in this study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 66 people will take part in this study. We plan to enroll about 33 people at the Behavioural Medicine Fitness Centre (BMFC) for the exercise intervention group and 33 in the control group (no exercise intervention).

WHAT WILL HAPPEN DURING THIS STUDY?

This study should take 12 months to complete and the results should be known in about *24 months.*

ASSIGNMENT TO A GROUP

If you decide to participate then you will be "randomized" into either the exercise intervention group or the control group. Randomization means that you are put into a group by chance. We will ask some patients to do a supervised exercise program during their drug treatment while other patients will be asked not to exercise more than their usual. We will compare the 2 groups on how they fare with their bladder cancer

treatment. There is no way to predict which group you will be assigned to. You will have an equal chance of being placed in either group. Neither you, the research staff, nor the researcher can choose what group you will be in.

STUDY INTERVENTION

Group 1 (Experimental intervention): high-intensity aerobic interval exercise.
Patients randomized to the exercise group will be asked to complete a 12-week, supervised high intensity interval training program, which consists of short periods of high-intensity aerobic exercise interspersed with light-intensity exercise for recovery. The exercise will be performed on a treadmill or cycle ergometer and the intensity will be modified by changing speed and/or grade or load. Exercise frequency will be three times per week and each session will last approximately 40 minutes.

Group 2 (Non-experimental intervention): control group.
Patients randomized to the control group will be asked not to initiate any exercise program or to increase their exercise level from baseline during the 12-week study. After the post-intervention assessments, patients in the control group will be offered a 4-week supervised exercise program at the Behavioural Medicine Fitness Centre (BMFC).

STUDY PROCEDURES

Both groups will be assessed at the beginning (baseline), during the study (at 6 weeks or post-intravesical therapy), and at the end of the study (postintervention) through a cardiopulmonary fitness test, physical function test, anthropometric measurements, questionnaires, and medical chart review. In addition, questionnaire and medical chart review will also be done at 3- and 12-month follow-up.

Established Procedures

The following established procedures will be done as part of this study. Some of these procedures may be done as part of your standard care, in which case the results may be used. Some may be done more frequently than if you were not taking part in this study. Some of these procedures may be done solely for the purpose of the study. If the results show that you are not able to continue participating in the study, the study team will let you know.

- Aerobic exercise test – to determine your cardiopulmonary fitness. This test will consist of walking or jogging on a treadmill with a gradual workload. The researchers will monitor your blood pressure, heart rate, oxygen saturation, and how hard you feel you are working at regular intervals throughout the test. The aerobic exercise test can also be conducted in a cycle ergometer when a treadmill is not feasible (e.g. balance issues).

- Functional fitness tests - to determine your physical function, including strength, flexibility, and agility. Your functional fitness will be assessed through a series of small tests, including chair stands, arm curls, sit-and-reach and back scratch flexibility tests, walking around an 8-foot course, and walking for 6 minutes. We are trying to determine if the exercise program is effective at improving physical function.

- Anthropometric measurements: to estimate general health risk. Anthropometric measurements will include height, weight, and circumferences. Height will be measured using a stadiometer and weight will be measured using a balance beam scale. Height and weight will be used to calculate body mass index (BMI) [weight per height squared (kg/m²)]. Circumferences measurements will be taken of waist, hips, and calf using a flexible yet inelastic tape measure, which will be placed on the skin surface without compressing the tissue.

Questionnaires

You will be provided with questionnaires at the following four timepoints: (1) before starting this
study (baseline); (2) at 3 months (post-intervention); (3) at 12 months (follow-up). The purpose of the questionnaires are to collect information on your demographics, and health behaviours, which will help understand how exercise affects your mental health, quality of life, fatigue, symptoms. Each questionnaire will take about 30-45 minutes to complete.

The information you provide is for research purposes only and will remain strictly confidential.
Some of the questions are personal; you may choose not to answer them. Even though you
may have provided information on a questionnaire, these responses will not be reviewed by
individuals not involved in this study, e.g., your health care practitioner/team. If you would like
them to know this information, please bring to their attention.

	Baseline	*Post-Intravesical Therapy (6-week)*	*Post-Intervention (3-month)*	*Follow-up (12-month)*
Aerobic fitness test	*x*	*x*	*x*	
Functional fitness test	*x*	*x*	*x*	
Questionnaires	*x*		*x*	*x*
Medical record review	*x*		*x*	*x*

WHAT ARE THE POTENTIAL SIDE EFFECTS FROM PARTICIPATING IN THIS STUDY?

You may experience side effects from participating in this study. There are no known risks other than potentially injuring yourself during exercise. Some side effects are known and are listed below, but there may be side effects that are not expected. You should discuss these with the study team.

The study team will watch you closely to see if you have side effects.

Risks and side effects related to the *high-intensity aerobic interval training* includes:

Very likely (greater than 21% or more than 20 people in 100):

- *It is possible that some people will experience muscle soreness and fatigue following the fitness testing and high-intensity aerobic interval training sessions. This type of response is normal, will go away after approximately 72 hours, and generally poses no threat to health. If the soreness persists more than five days or might be associated with a muscle or joint injury, participants should contact the study team.*

Rarely (1 – 4% or less than 5 in 100 people):

- *During and immediately after the aerobic fitness test, it is possible to experience symptoms such as abnormal blood pressure, fainting, light-headedness, muscle cramps or strain, nausea, and in very rare cases (1 per 20,000 in testing facilities) heart rhythm disturbances or heart attack. While serious risk is highly unlikely, such risks must be acknowledged, and participants must willingly to assume the risks associated with exercise.*

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

Participation in this study may or may not be of personal benefit to you. However, based on the results of this study, it is hoped that in the long-term, patient care can be improved.

WHAT ARE MY RESPONSIBILITIES AS A STUDY PARTICIPANT?

If you choose to participate in this study, you will be expected to:

- Tell the study team about your current medical conditions;
- Tell the study team about all prescription and non-prescription medications and supplements, including vitamins and herbals, that you may be taking and check with the study doctor before starting, stopping or changing any of these. This is for your safety as these may interact with the intervention you receive on this study;
- Tell the study team if you are thinking about participating on another research study;
- Attend all scheduled study visits and undergo all of the procedures described above;
- Return any questionnaires taken home to complete;
- Agree to attend 3 exercise sessions per week for 12 weeks during and after your intravesical therapy at the Behavioural Medicine Fitness Centre (BMFC) if randomized to the exercise intervention group OR agree not to increase your current physical activity levels if randomized to the usual care group;

HOW LONG WILL I BE PARTICIPATING IN THIS STUDY?

The study intervention will last for about 12 weeks and you will also be asked to complete
questionnaires at 3 months and 1 year follow-up.
You will be asked to come to our testing location (University of Alberta) for fitness and functioning tests before starting this study and then be asked to come
back to one of our testing locations to complete assessments after 6 and 12 weeks.
Questionnaires will be mailed to you at 3 months and 1 year follow-up

WILL THERE BE ANY LONG-TERM FOLLOW-UP INVOLVED WITH THIS STUDY?

No matter which group you are randomized to, and even if you stop receiving the study intervention early, we would like to keep track of your health for up to one year to look at the
long-term effects of your participation in the study. We would do this by accessing your medical
records and asking you to complete questionnaires.

CAN I CHOOSE TO LEAVE THIS STUDY EARLY?

You can choose to end your participation in this research (called early withdrawal) at any time without having to provide a reason. If you choose to withdraw early from the study without finishing the intervention, procedure or follow-up, you are encouraged to contact the study team or study staff.

If you decide to leave the study, you can ask that the information that was collected about you not be used for the study. Let the study team know if you choose this.

CAN MY PARTICIPATION IN THIS STUDY END EARLY?

The study team may stop your participation in the study early, and without your consent, for reasons such as:

- They believe it is in your best interest to do so;
- You are unable to complete all required study procedures;
- You do not follow the study rules;
- The sponsor decides to stop the study;
- A regulatory authority (for example, Health Canada) or the research ethics board withdraws permission for the study to continue;

If this happens, it may mean that you would not receive the study intervention for the full period described in this consent form.

If you are removed from the study, the study doctor will discuss the reasons with you and plans will be made for your continued care outside of the study.

HOW WILL MY PERSONAL INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the study doctor and study staff will only collect the information they need for this study.

Records identifying you, including information collect from your medical files/records, such as your Electronic Medical Records (EMR), Netcare, charts, etc., will be kept

confidential to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

Authorized representatives of the following organizations may look at your identifiable medical/clinical study records at the site where these records are held for quality assurance purposes and/or to verify that the information collected for the study is correct and follows proper laws and guidelines:

- University of Alberta;
- Alberta Health Services;
- The Health Research Ethics Board of Alberta – Cancer Committee, which oversees the ethical conduct of this study;

Authorized representatives of the above organizations may **receive** information related to the study from your medical/clinical study records that will be kept confidential in a secure location and may be used in current or future relevant health research. Your name or other information that may identify you will not be provided (i.e., the information will be de-identified). The records received by these organizations will be coded with a number. The key that indicates what number you have been assigned will be kept secure by the researchers directly involved with your study and will not be released.

Any disclosure of your identifiable health information will be done in accordance with federal and provincial laws including the Alberta Health Information Act (HIA). The organizations listed above are required to have organizational policies and procedures to protect the information they see or receive about you, except where disclosure may be required by law. The study doctor will ensure that any personal health information collected for this study is kept in a secure and confidential location (Behavioural Medicine Laboratory, University of Alberta) as also required by law.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during the study will be used in analyses and will be published/presented to the scientific community at meetings and in journals.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated. Every effort will be made to keep your identifiable information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information.

Studies involving humans sometimes collect information on race and ethnicity as well as other characteristics of individuals because these characteristics may influence how people respond to different interventions. Providing information on your race or ethnic origin is voluntary.

A copy of the consent form that you sign to enter the study will be included in your health record/hospital chart.

WILL MY HEALTHCARE PROVIDER(S) BE INFORMED OF MY PARTICIPATION IN THIS STUDY?

Your family doctor/health care provider may be informed that you are taking part in a study so that you can be provided with appropriate medical care. If you do not want your family doctor/health care provider to be informed, please discuss with your study team to find out your options.

WILL THERE BE ANY COSTS INVOLVED WITH PARTICIPATING IN THIS STUDY?

Participation in this study will not involve any additional costs to you or your private health care insurance. The study team will cover all study-related costs including fitness testing, exercise supervision, and parking for study-related visits.

WILL I BE COMPENSATED FOR PARTICIPATING IN THIS STUDY?

You will not be paid for taking part in this study.

If you decide to participate in this study, you will be reimbursed for study-related expenses such as *parking, or public transportation.*

WHAT ARE MY RIGHTS AS A PARTICIPANT IN THIS STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of these results, please contact the study doctor.

The results of this study will be available on a clinical registry; refer to the section titled "Where can I find online information about this study?".

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the hospital, investigators, sponsor, involved institutions for compensation or their agents, nor does this form relieve these parties from their legal and professional responsibilities.

IS THERE CONFLICT OF INTEREST RELATED TO THIS STUDY?

There are no conflicts of interest declared between the study doctor and sponsor of this study.

WHERE CAN I FIND ONLINE INFORMATION ABOUT THIS STUDY?

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

The study registration number to use this website is: NCT04593862

WHO DO I CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, or if you suffer a research-related injury, you should talk to the study doctor or co-investigators. These person(s) are:

Kerry Courneya (Principal Investigator)	780-492-1031
Name	Telephone
Adrian Fairey (Co-Investigator)	780-407-5771
Name	Telephone
Fernanda Arthuso (Co-Investigator)	*587-590-8769*
Name	Telephone

A wallet card will be provided to you with information about how to contact the study staff when required.

If you have questions about your rights as a participant or about ethical issues related to this study and you would like to talk to someone who is not involved in the conduct of the study, please contact the Office of the Health Research Ethics Board of Alberta – Cancer Committee at:

Telephone: 780-423-5727 Toll Free: 1-877-423-5727

SIGNATURES

Part 1 - to be completed by the potential participant.

	Yes	No
Do you understand that you have been asked to take part in a research study?	☐	☐
Do you understand why this study is being done?	☐	☐
Do you understand the potential benefits of taking part in this study?	☐	☐
Do you understand the risks of taking part in this study and the risks of becoming pregnant or fathering a child during this study?	☐	☐
Do you understand what you will be asked to do should you decide to take part in this study?	☐	☐
Do you understand the alternatives to participating in this study?	☐	☐
Do you understand that you are free to leave the study at any time, without out having to give reason and without affecting your future health care?	☐	☐
Do you understand who will see your records, including health information that identifies you?	☐	☐
Do you understand that by signing this consent form you are giving us permission to access your health information and specimens if applicable?	☐	☐
Do you understand that by signing this consent form that you do not give up any of your legal rights?	☐	☐
Do you understand that your family doctor/health care provider will/may be informed of your participation in this study?	☐	☐
Have you had enough opportunity to ask questions and discuss this study?	☐	☐

By signing this form I agree to participate in this study.

Signature of Participant	PRINTED NAME	Date

Part 2 - to be completed by the study doctor or designee who conducted the informed consent discussion. Only compete this section if the potential participant has **agreed** to participate.

I believe that the person signing this form understands what is involved in the study and has freely decided to participate.

Signature of Person Conducting the Consent Discussion	PRINTED NAME	Date

Part 3 - to be completed only if the participant is unable to read or requires assistance of an oral translator/interpreter.

- The informed consent form was accurately explained to, and apparently understood by the participant
- Informed consent was freely given by the participant.

Signature of Impartial Witness/Interpreter	PRINTED NAME	Date

You will be given a copy of this signed and dated consent form prior to participating in this study.

APPENDIX E: BRAVE TRIAL BASELINE QUESTIONNAIRE

Date: Identification #:

Bladder cancer and exeRcise trAining during or after intraVesical thErapy: The BRAVE Trial

Fernanda Z. Arthuso, MSc; Normand Boulé, PhD; Adrian S. Fairey, MD; Kerry S. Courneya, PhD

BASELINE QUESTIONNAIRE

Instructions

Thank you for agreeing to participate in this study. In this questionnaire, we are going to ask you a series of questions about yourself. Many of the questions ask you about your physical and mental health, and some may be viewed as personal. It is important to answer as many of these questions as possible, however, if you feel uncomfortable answering certain questions please leave them blank. All responses are completely confidential and will never be used in any way that could link them to you. Many of the questions may seem similar but it is important to treat each question separately and provide an answer for each. There are no right or wrong answers and all we ask is that you provide responses that are as honest and accurate as possible. The questionnaire should take about 30-40 minutes of your time to complete. If you have any questions about completing the questionnaire, please do not hesitate to contact Fernanda Arthuso (Study Coordinator) at: (780) 492-2829 or arthuso@ualberta.ca

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

		Not at all	A little	Quite a bit	Very much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?.....	1	2	3	4
2.	Do you have any trouble taking a long walk?.....	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?.....	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?....	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?.....	1	2	3	4

During the PAST WEEK:	**Not at all**	**A little**	**Quite a bit**	**Very much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?.....	1	2	3	4
8. Were you short of breath?.....	1	2	3	4
9. Have you had pain?.....	1	2	3	4
10. Did you need to rest?.....	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?.....	1	2	3	4
13. Have you lacked appetite?.....	1	2	3	4

14. Have you felt nauseated?.....	1	2	3	4
15. Have you vomited?.....	1	2	3	4
16. Have you been constipated?.....	1	2	3	4
During the <u>PAST WEEK:</u>	**Not at all**	**A little**	**Quite a bit**	**Very much**
17. Have you had diarrhea?.....	1	2	3	4
18. Were you tired?.....	1	2	3	4
19. Did pain interfere with your daily activities?.....	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?.....	1	2	3	4
21. Did you feel tense?.....	1	2	3	4
22. Did you worry?.....	1	2	3	4
23. Did you feel irritable?.....	1	2	3	4
24. Did you feel depressed?.....	1	2	3	4
25. Have you had difficulty remembering things?.....	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?.....	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?.....	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?.....	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the <u>PAST WEEK</u>	**Not at all**	**A little**	**Quite a bit**	**Very much**
1. Have you had to urinate frequently **during the day**?	1	2	3	4
2. Have you had to urinate frequently **at night**?	1	2	3	4
3. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
4. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
5. Have you had difficulty going out of the house, because you needed to be close to a toilet?	1	2	3	4
6. Have you had any unintentional release (leakage) of urine?	1	2	3	4
7. Have you had pain or a burning feeling when urinating?	1	2	3	4
8. Did you have a fever?	1	2	3	4
9. Did you feel ill or unwell?	1	2	3	4
10. Did you have trouble arranging your life around the repeated bladder treatment appointments (cystoscopies or instillations)?	1	2	3	4
11. Did you worry about having repeated bladder treatments (cystoscopies or instillations)?	1	2	3	4
12. Were you worried about your health in the future?	1	2	3	4
13. Did you worry about the results of examinations and tests?	1	2	3	4
14. Did you worry about possible future treatments?	1	2	3	4
15. Did you have a bloated feeling in your abdomen?	1	2	3	4
16. Have you had flatulence or gas?	1	2	3	4

Most people who have been diagnosed with bladder cancer are worried, to varying degrees, that there might be a recurrence of the cancer. **By recurrence, we mean the possibility that the cancer could return or progress in the same place or in another part of the body.** This questionnaire aims to better understand the experience of worries about cancer recurrence. Please read each statement and indicate to what degree it applied to you **DURING THE PAST MONTH** by circling the appropriate number.

0	**1**	**2**	**3**	**4**
Never	Rarely	Sometimes	Most of the time	All the time

The following situations make me think about the possibility of cancer recurrence:

1. Television shows or newspaper articles about cancer or illness……..	0	1	2	3	4
2. An appointment with my doctor or other health professional……..	0	1	2	3	4
3. Medical examinations (e.g. annual check-up, blood tests, X-rays)…..	0	1	2	3	4
4. Conversations about cancer or illness in general…….	0	1	2	3	4
5. Seeing or hearing about someone who is ill…….	0	1	2	3	4
6. Going to a funeral or reading the obituary section of the paper……...	0	1	2	3	4
7. When I feel unwell physically or when I am sick……	0	1	2	3	4
8. Generally, I avoid situations or things that make me think about the possibility of cancer recurrence……	0	1	2	3	4

0	**1**	**2**	**3**	**4**
Not at all	A little	Somewhat	A lot	A great deal

9. I am worried or anxious about the possibility of cancer recurrence.....	0	1	2	3	4
10. I am afraid of cancer recurrence……...……...	0	1	2	3	4
11. I believe it is normal to be worried or anxious about the possibility of cancer recurrence……...	0	1	2	3	4
12. When I think about the possibility of cancer recurrence, this triggers other unpleasant thoughts or images (such as death, suffering, the consequences for my family)…….	0	1	2	3	4
13. I believe that I will be cured and that the cancer will not come back..	0	1	2	3	4

14. In your opinion, are you at risk of having a cancer recurrence?

0	**1**	**2**	**3**	**4**
Not at all at risk	A little at risk	Somewhat at risk	A lot at risk	A great deal at risk

15. How often do you think about the possibility of cancer recurrence?

0	**1**	**2**	**3**	**4**
Never	A few times a month	A few times a week	A few times a day	Several times a day

16. How much time **per day** do you spend thinking about the possibility of cancer recurrence?

0	**1**	**2**	**3**	**4**
I don't think about it	A few seconds	A few minutes	A few hours	Several hours

17. How long have you been thinking about the possibility of cancer recurrence?

0	**1**	**2**	**3**	**4**
I don't think about it	A few weeks	A few months	A few years	Several years

0	**1**	**2**	**3**	**4**
Not at all	A little	Somewhat	A lot	A great deal

When I think about the possibility of cancer recurrence, I feel:

18. Worry, fear or anxiety	0	1	2	3	4
19. Sadness, discouragement or disappointment……..	0	1	2	3	4
20. Frustration, anger or outrage	0	1	2	3	4
21. Helplessness or resignation……...…….	0	1	2	3	4

My thoughts or fears about the possibility of cancer recurrence disrupt:

22. My social or leisure activities (e.g. outings, sports, travel)…..……..	0	1	2	3	4
23. My work or everyday activities……..	0	1	2	3	4
24. My relationships with my partner, my family, or those close to me..	0	1	2	3	4
25. My ability to make future plans or set life goals...…….	0	1	2	3	4
26. My state of mind or my mood……...…….	0	1	2	3	4
27. My quality of life in general……...	0	1	2	3	4
28. I feel that I worry excessively about the possibility of cancer recurrence…….	0	1	2	3	4
29. Other people think that I worry excessively about the possibility of cancer recurrence……..	0	1	2	3	4
30. I think that I worry more about the possibility of cancer recurrence than other people who have been diagnosed with cancer…….	0	1	2	3	4

0	1	2	3	4
Never	Rarely	Sometimes	Most of the time	All the time

When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:

31. I call my doctor or other health professional ……..….. 0 1 2 3 4

32. I go to the hospital or clinic for an examination 0 1 2 3 4

33. I examine myself to see if I have any physical signs of cancer…….. 0 1 2 3 4

34. I try to distract myself (e.g. do various activities, watch television, read, work)…… 0 1 2 3 4

35. I try not to think about it, to get the idea out of my mind.……. 0 1 2 3 4

36. I pray, meditate or do relaxation ……... 0 1 2 3 4

37. I try to convince myself that everything will be fine or I think positively……...…… 0 1 2 3 4

38. I talk to someone about it ……... 0 1 2 3 4

39. I try to understand what is happening and deal with it 0 1 2 3 4

40. I try to find a solution……. 0 1 2 3 4

41. I try to replace this thought with a more pleasant one…… 0 1 2 3 4

42. I tell myself "stop it" 0 1 2 3 4

43. Do you feel reassured when you use these strategies?..... 0 1 2 3 4

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number that best indicates how you have felt **during <u>the past week</u>.** There are no right or wrong answers. Do not spend too much time on any one statement but give the answer that best describes how you feel.

During the <u>PAST WEEK</u>	**Not at all**	**Some-what**	**Moderately so**	**Very much so**
1. I felt calm.....	1	2	3	4
2. I was tense.....	1	2	3	4
3. I felt at ease.....	1	2	3	4
4. I worried over possible misfortunes.. …..	1	2	3	4
5. I felt frightened.....	1	2	3	4
6. I felt self-confident.....	1	2	3	4
7. I was jittery.....	1	2	3	4
8. I was relaxed.....	1	2	3	4
9. I was worried.....	1	2	3	4
10. I felt steady.....	1	2	3	4

Below is a list of statements concerning how you might have felt or behaved in the **past week**. Please use the following scale to indicate **how often** have you felt or behaved in these ways in the **past week**.

During the PAST WEEK	**Rarely or none (<1 day)**	**Some of the time (1-2 days)**	**Much of the time (3-4 days)**	**Most or all of the time (5-7 days)**
1. I felt depressed.....	0	1	2	3
2. I felt that everything I did was an effort……	0	1	2	3
3. My sleep was restless.....	0	1	2	3
4. I was happy.....	0	1	2	3
5. I felt lonely.....	0	1	2	3
6. People were unfriendly.....	0	1	2	3
7. I enjoyed life.....	0	1	2	3
8. I felt sad.....	0	1	2	3
9. I felt that people disliked me….....	0	1	2	3
10. I could not get "going"……....	0	1	2	3

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past week</u>.**

During the <u>PAST WEEK</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
1. I feel fatigued.....	0	1	2	3	4
2. I feel weak all over…….	0	1	2	3	4
3. I feel listless ("washed out")…..	0	1	2	3	4
4. I feel tired.....	0	1	2	3	4
5. I have trouble <u>starting</u> things because I am tired……...	0	1	2	3	4
6. I have trouble <u>finishing</u> things because I am tired……...	0	1	2	3	4
7. I have energy.....	0	1	2	3	4
8. I am able to do my usual activities…….	0	1	2	3	4
9. I need to sleep during the day…	0	1	2	3	4
10. I am too tired to eat……	0	1	2	3	4
11. I need help doing my usual activities……	0	1	2	3	4
12. I am frustrated by being too tired to do the things I want to do……..……..	0	1	2	3	4
13. I have to limit my social activity because I am tired…….……	0	1	2	3	4

The next questions ask you about your feelings and thoughts during the last month. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each one fairly quickly. For each question, please choose from the following alternatives:

In the <u>last month</u>, how often have you…	**Never**	**Almost never**	**Some-times**	**Fairly often**	**Very often**
1. been upset because of something that happened unexpectedly…….	0	1	2	3	4
2. felt that you were unable to control the important things in your life…….…...	0	1	2	3	4
3. felt nervous and stressed.....	0	1	2	3	4
4. dealt successfully with irritating life hassles…….	0	1	2	3	4
5. felt that you were effectively coping with important changes that were occurring in your life…….…….	0	1	2	3	4
6. felt confident about your ability to handle your personal problems…….	0	1	2	3	4
7. felt that things were going your way……...…...	0	1	2	3	4
8. found that you could not cope with all the things that you had to do……	0	1	2	3	4
9. been able to control irritations in your life……..…….	0	1	2	3	4
10. felt that you were on top of things……	0	1	2	3	4
11. been angered because of things that happened that were outside of your control……	0	1	2	3	4
12. found yourself thinking about things that you have to accomplish……	0	1	2	3	4
13. been able to control the way you spend your time……...…	0	1	2	3	4
14. felt difficulties were piling up so high that you could not overcome them…….…...	0	1	2	3	4

The next questions concern the general perceptions that you currently have about yourself. Please circle the number that best reflects your current view of yourself using the following scale as a guide for your responses.

	Strongly Disagree	**Disagree**	**Agree**	**Strongly Agree**
1. On the whole I am satisfied with myself..	1	2	3	4
2. At times I think that I am no good at all…	1	2	3	4
3. I feel that I have a number of good qualities…….	1	2	3	4
4. I am able to do things as well as most other people……...	1	2	3	4
5. I feel I do not have much to be proud of..	1	2	3	4
6. I certainly feel useless at times……..	1	2	3	4
7. I feel that I am a person of worth, at least on an equal plane with others……	1	2	3	4
8. I wish I could have more respect for myself……..…….	1	2	3	4
9. All in all, I am inclined to feel that I am a failure……	1	2	3	4
10 . I take a positive attitude toward myself……	1	2	3	4

For each question, please **CIRCLE** the number that best describes your answer.

Please rate the **CURRENT (i.e. LAST 2 WEEKS) SEVERITY** of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep……	0	1	2	3	4
2. Difficulty staying asleep……	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How **SATISFIED/DISSATISFIED** are you with your **CURRENT** sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How **NOTICEABLE** to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How **WORRIED/DISTRESSED** are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) **CURRENTLY**?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

For this next question, we would like you to recall the amount of exercise you have done **during the past month.**

When answering these questions please:

- Only count exercise sessions that lasted 10 minutes or longer in duration.
- Only count exercise that was done during free time (i.e., not occupation or housework).
- Note that the main difference between the first three categories is the intensity of the endurance (aerobic) exercise and the fourth category is for strength (resistance) exercise.
- Write the average frequency on the first line and the average duration on the second.
- Write in "0" if you did not do any exercise in one of the categories.

Considering a typical week (7 days) over the **PAST MONTH**, how many times on the average did you do the following kinds of exercise?

AEROBIC EXERCISE	Times Per Week	Average Duration
a. VIGOROUS/STRENUOUS EXERCISE = *HEART BEATS RAPIDLY, SWEATING* (e.g., running, aerobics classes, cross country skiing, vigorous swimming, vigorous bicycling)	_____ times/week	_____ minutes/time
b. MODERATE EXERCISE = *NOT EXHAUSTING, LIGHT PERSPIRATION* (e.g., fast walking, tennis, easy bicycling, easy swimming, popular or folk dancing)	_____ times/week	_____ minutes/time
c. LIGHT/MILD EXERCISE = *MINIMAL EFFORT, NO PERSPIRATION* (e.g., easy walking, yoga, bowling, shuffleboard)	_____ times/week	_____ minutes/time
RESISTANCE/STRENGTH EXERCISE (e.g., weight lifting, push-ups, sit-ups, resistance band)	_____ times/week	_____ minutes/time

The following questions ask you to rate how you feel about exercising **for the next 12 weeks during and after your intravesical therapy**. Please pay careful attention to the words and descriptions for each scale and circle the number that best represents how you feel.

1. How beneficial do you think it will be for you to exercise for the next 12 weeks during and after your intravesical therapy?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

2. How enjoyable do you think it will be for you to exercise for the next 12 weeks during and after your intravesical therapy?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

3. How supportive do you think family/friends will be of you exercising for the next 12 weeks during and after your intravesical therapy?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

4. How motivated are you to exercise for the next 12 weeks during and after your intravesical therapy?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

5. How difficult do you think it will be for you to exercise for the next 12 weeks during and after your intravesical therapy?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

6. How much control do you think you will have over exercising for the next 12 weeks during and after your intravesical therapy?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

7. How confident are you that you will be able to exercise for the next 12 weeks during and after your intravesical therapy?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

This part of the questionnaire is needed to help understand the characteristics of the people participating in the study. For this reason, it is very important information. All information is held in strict confidence and its presentation to the public will be group data only.

DEMOGRAPHIC

1. Age: _____

2. Sex: Female ☐ Male ☐

3. Current Marital Status:

Never Married ☐ Married ☐ Common Law ☐

Separated ☐ Widowed ☐ Divorced ☐

4. Education (Please check highest level attained):

Some High School ☐ Completed High School ☐

Some University/College ☐ Completed University/College ☐

Some Graduate School ☐ Completed Graduate School ☐

5. Annual Family Income:

< $20,000 ☐ $20,000 – 39,999 ☐

$40,000 – 59,999 ☐ $60,000 – 79,999 ☐

$80,000 – 99,999 ☐ > $100,000 ☐

6. Current Employment Status:

Full Time ☐ Part Time ☐ Sick Leave ☐ Temporarily off work

Retired ☐ Homemaker ☐ Disability ☐ because of COVID-19 ☐

7. What is your primary ethnic origin or race?

White ☐ Black ☐ Hispanic ☐

Asian ☐ Indigenous ☐ Other_____

8. Which of the following best describes your current cigarette smoking status?

Never Smoked ☐ Ex-Smoker ☐ Current Smoker ☐

9. Which of the following best describes your current alcohol consumption?

Never Drink ☐ Social Drinker ☐ Regular Drinker (drink every day) ☐

10. How would you rate your general health?

Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor ☐

MEDICAL

11. Has a doctor or nurse ever told you that you have any of the following conditions? (check all that apply, or leave blank if not applicable):

Heart Disease or CVD	☐	Stroke	☐
Angina (chest pains)	☐	Arthritis, Osteoporosis, or Back Problems	☐
High Blood Pressure	☐	Emphysema	☐
High Cholesterol	☐	Chronic bronchitis	☐
Diabetes	☐	Asthma or COPD	☐
Spinal Cord Injury	☐	Other Cancer: _____	

Any other long term health condition?_ _____

12. In the past month, was your ability to exercise limited by a health condition, injury, or disability?

1	2	3	4	5
Not at all	A little	Somewhat	Quite a lot	Completely

13. Are you currently taking any medications or health supplements for health problems? (e.g., blood pressure, anxiety, depression, pain, insomnia, etc).

What is the medication? (e.g., beta-blocker, Synthroid)	What is it for? (e.g., high blood pressure, hypothyroidism)
1.	
2.	
3.	
4.	
5.	
6.	

14. Have you been fully vaccinated against COVID-19?
Yes ☐ No ☐

Please feel free to make any additional comments concerning your bladder cancer, your treatments, the questionnaire, the exercise intervention, or anything else you think may be helpful to us.

Thank you very much for your participation in this research project. Please place the completed questionnaire in the envelope provided and bring it to your scheduled fitness test.

APPENDIX F: BRAVE TRIAL ADVERTISEMENT

UNIVERSITY OF ALBERTA

Alberta Health Services

ARE YOU STARTING INTRAVESICAL THERAPY FOR BLADDER CANCER?

Would you like to participate in a study about exercise during intravesical therapy for bladder cancer?

BRAVE STUDY

You are eligible if you are:

- starting intravesical therapy for bladder cancer
- not currently exercising

Participants will be asked to either:

- exercise for 12-weeks at the University of Alberta OR
- not to start to exercise for 12-weeks (If you are in this group, an exercise program will be offered after the study)

* All costs of study participation are covered including fitness testing, access to facilities, exercise supervision, and parking.

Your participation will help answer important questions that many bladder cancer patients have about exercising during intravesical therapy

www.bravestudy.ca

FOR MORE INFORMATION, PLEASE CONTACT

Fernanda - Study Coordinator: (780) 492-2829 OR arthuso@ualberta.ca

BRAVE STUDY

Bladder cancer and exeRcise trAining during intraVesical thErapy

BRAVE will be the first study to test the safety and feasibility of exercise in bladder cancer patients during their drug therapy.

We will ask some patients to do a supervised exercise program during their drug treatment while other patients will be asked not to exercise.

We will compare the 2 groups on how they fare with their bladder cancer treatment.

You are eligible if you are:

- starting intravesical therapy for bladder cancer
- not currently exercising

Participants will be asked to either:

- exercise for 12-weeks at the University of Alberta OR
- not to start to exercise for 12-weeks (If you are in this group, an exercise program will be offered after the study)

* All costs of study participation are covered including fitness testing, access to facilities, exercise supervision, and parking.

STUDY OVERVIEW

DECIDE TO PARTICIPATE

↓

SIGN CONSENT FORMS
COMPLETE QUESTIONNAIRES

↓

BASELINE TEST
Aerobic fitness test on treadmill and physical function tests at the University of Alberta

↓

GROUP ASSIGNMENT
Either exercise or usual care

↓

START OF THE EXERCISE PROGRAM
If in the exercise group

↓

6-WEEK FOLLOW-UP FITNESS TEST
Same as described above for baseline tests, both the exercise and usual care groups

↓

12-WEEK FOLLOW-UP FITNESS TEST AND QUESTIONNAIRE
Same as described above for baseline tests plus questionnaires, both groups

↓

ONE YEAR FOLLOW-UP QUESTIONNAIRE
Questionnaire sent to all participants, completed, and returned by mail or email

STUDY LOCATION

University of Alberta - Behavioural Medicine Fitness Centre

Research Transition Facility

#1001, 8308-114 Street
Edmonton, Alberta
T6G2H9

BRAVE STUDY

Your participation will help answer important questions that many bladder cancer patients have about exercising during intravesical therapy

FOR MORE INFORMATION, PLEASE CONTACT

Fernanda - Study Coordinator:
(780) 492-2829 or
arthuso@ualberta.ca

UNIVERSITY OF ALBERTA | Alberta Health Services

ARE YOU STARTING INTRAVESICAL THERAPY FOR BLADDER CANCER?

Would you like to participate in a study about exercise during intravesical therapy for bladder cancer?

BRAVE STUDY