The Role of Lutetium-177 in the Treatment of Metastatic Gastroenteropancreatic Neuroendocrine Tumors

By Bianka Bawani Saravana-Bawan

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School of Public Health
University of Alberta

Abstract

Purpose

The incidence of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) has been increasing over recent decades. Lutetium therapy has demonstrated benefit towards quality of life (QoL) overall in patients with metastatic GEP-NETs. However, factors influencing individual response to ^{177}Lu-DOTATATE with regards to QoL, and methods for easy integration of QoL monitoring into clinical practice are not yet well understood. This work seeks to identify optimal methods for QoL assessment and prognostic factors for QoL response in patients with progressive GEP-NETs treated with ^{177}Lu-DOTATATE.

Methods

This study was conducted as part of the Phase II open label clinical trial at the Cross Cancer Institute in Edmonton. Treatment consisted of an induction phase of 5.55 GBq administered at four treatments, 10 weeks apart. QoL over ^{177}Lu-DOTATATE treatment was assessed with EORTC QLQ-C30, GI.NET-21 and ESAS-r at baseline and subsequent to each treatment. Planned analysis of change in QoL by corresponding assessment method and factors related to change in QoL was completed in all patients with GEP-NETs. Repeated measures ANOVA was performed to assess QoL change and purposeful logistic regression for identification of prognostic factors.

Results

In total 85 patients met inclusion criteria. Both EORTC and ESAS-r demonstrated maintained overall quality of life. EORTC demonstrated statistically and clinically significant improvement in insomnia, GI and endocrine symptoms. ESAS-r demonstrated statistically but no clinically significant improvement in insomnia, anxiety and emotional functioning.

In the final regression model for prognostic factors for QoL a statistically significant correlation was demonstrated between global health score at baseline and time from diagnosis to treatment initiation with ^{177}Lu-DOTATATE. The presence of metastatic disease was marginally statistically significant with regards to change in global health score after ^{177}Lu-DOTATATE induction therapy.

Conclusions

^{177}Lu-DOTATATE is not only effective in improving PFS for patients with metastatic GEP-NETs but also impacts overall quality of life. Consideration in treatment initiation in this palliative setting should include potential impact to patient QoL as the impact of ^{177}Lu-DOTATATE therapy on QoL improvement appears to decrease in correlation to delay in ^{177}Lu-DOTATATE treatment. To monitor changes in QoL during treatment all assessment tools have inherent benefits and limitations which must be considered in clinical use. ESAS-r provides a quick and easy to interpret tool; however, it is not NET specific and as such may not be as sensitive in this population. The EORTC assessment questionnaires better reflect QoL in the NET population. Modifications or use of computer integration could be considered to facilitate clinical incorporation.

Preface

This thesis is an original work by Bianka Saravana-Bawan. This study was approved by the Health Research Ethics Board at the University of Alberta and Health Canada.

Chapter 2 of this thesis is accepted for publication in the Journal of Clinical Nuclear Medicine. I was responsible for the data collection, analysis and manuscript composition. A.Bajwa and J.Paterson were also assisted with data collection and manuscript edits. T.McMullen was the supervisory author involved in research oversight and manuscript completion.

Chapter 3 of this thesis is currently undergoing revisions for publication in the International Journal of Endocrine Oncology. Chapter 4 of this thesis is currently submitted to the European Journal of Nuclear Medicine and Molecular Imaging. I was responsible for the data collection, analysis and manuscript composition. M. Wieler, S. Koumna and A. McEwan contributed to editing of the manuscript. T.McMullen was the supervisory author involved in research oversight and manuscript completion.

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List of Abbreviations

AJCC: American Joint Committee on Cancer

CCI: Cross Cancer Institute

ENETS: European Neuroendocrine Tumor Society

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire core module 30

ESAS-r: Edmonton Symptom Assessment System Revised

GEP: Gastroenteropancreatic Neuroendocrine Tumor

HPF: High Powered Field

MCID: Minimally Clinically Important Difference

NEC: Neuroendocrine Carcinoma

NETs: Neuroendocrine Tumors

OS: Overall Survival

PNET: Pancreatic Neuroendocrine Tumor

PFS: Progression Free Survival

PRRT: Peptide Receptor Radiotargeted Therapy

RECIST: Response Evaluation Criteria in Solid Tumors

REDCap: Research Electronic Data Capture

RCT: Randomized Controlled Trial

SEER: Surveillance, Epidemiology, and End Results program

SWOG: Southwest Oncology Group

TTP: Time to Progression

WHO: World Health Organization

YSR: Year Survival

I. Chapter One: Introduction

I.1 Epidemiology

Neuroendocrine tumors (NETs) are tumors which can originate throughout the body with the majority arising from the bronchopulmonary and gastroenteropancreatic (GEP) system.[1] GEP NETs represent 60% of all NETs and the most common site of origin within the GEP system is the small bowel, accounting as the primary site for 20% of all NETs.[2–4] These tumors have an equal distribution amongst males and females and are most commonly diagnosed in the fifth to sixth decade of life in sporadic cases.[2,5]

At diagnosis NETs have variable presentation with 50% being localized, 25% having regional spread and 25% having distant metastasis.[6,7] The incidence of metastases at presentation does vary according to primary tumor site, histological grade and degree of differentiation. Over 50% of poorly differentiated NETs have metastases in comparison to 31 to 46% of all well differentiated NETs at diagnosis.[3,7,8] The majority of NETs are well differentiated with less than 10% being poorly differentiated or high grade.[3]

Although relatively rare the incidence of NETs has been increasing.[9] The age adjusted annual incidence has increased with a 3.65 fold increase in the United from 1972 to 2007, with an incidence of 6.98 per 100 000 based on Surveillance, Epidemiology, and End Results program (SEER) data.[8–10] This increase in incidence may not all however reflect a true increase in incidence but may be in part due to an increased rate of diagnosis due to increased use of medical imaging, improved diagnostic methods, and increased awareness and clinical suspicion.[6]

Due to their relatively indolent nature NETs have a high prevalence rate.[9] In the United States NETs are the most prevalent small bowel tumor and represent the second most prevalent gastrointestinal tumor with a prevalence of up to 35 per 100 000.[6,11,12]

I.2 Classification

NETs can be divided based upon hormonal functionality, site of origin or histologic characteristics.[1] The most common method of classification, as outlined in table 1 is based on histologic differentiation with NETs divided into well differentiated and poorly differentiated tumors with poorly differentiated NETs also referred to as neuroendocrine carcinomas (NEC).[1]

Table 1. Histologic grading of gastroenteropancreatic neuroendocrine neoplasms ENETS (2007) and WHO (2010)

Grade of GEP-NET		Mitotic Index	Ki-67 index
Grade 1 (G1) Low grade	Well-differentiated	<2/10 HPF	≤2%
Grade 2 (G2) Intermediate grade		2-20/10 HPF	3-20%
Grade 3 (G3) High grade	Poorly differentiated NEC	>20/ 10 HPF	≥20%
high power field (HPF)			

The two main staging systems utilized for NETs are from the ENETS and the American Joint Committee on Cancer (AJCC). The ENETS and AJCC TNM staging systems have significant overlap and are equivocal with regards to NETs of the small bowel and rectum but differ in their classification of NETs of the pancreas and appendix. The prognostic value of these TNM staging systems however is somewhat limited with considerable variability in patient survival within disease stages.[13] The literature does demonstrate a slight prognostic superiority with the ENETS

staging system.[14] Improvements in the staging of GEP-NETS with incorporation of tumor grade are necessary to improve prognostic utility.

I.3 Prognosis

Prognosis is impacted my many factors including tumor grade, disease stage and primary tumor location. Tumor grade is the most important prognostic factor and strongly correlates with overall survival.[15] Well differentiated NETs are considered indolent and have an over 80% 5 year survival in comparison to poorly differentiated NETs which are not considered indolent and have a less than 10% 5 year survival rate.[7,8] With regards to stage, survival for patients with loco-regional well differentiated disease is 63.3% at 5 years with a median of 149 months and 38 months for those with poorly differentiated disease.[5,8] The overall median survival for metastatic well differentiated NETs is a median of 33 months in comparison to 5 months for those with metastatic poorly differentiated NETs.[5,12,16]

I.4 Symptoms

Symptoms with NETs can be related to tumor burden or tumor hormonal secretion. NETs can secrete a variety of hormones including serotonin, somatostatin, gastrin, insulin and histamine.[17] For gastrointestinal NETs the NCCN and ENETS guidelines suggest that both serum CgA and urine 5-HIAA be assessed.[18,19] For pancreatic NETs the NCCN recommends that serum CgA, pancreatic polypeptide (PP), parathyroid hormone-related protein (PTH-rP) and growth hormone-releasing hormone (GHRH) should be assessed at diagnosis with further testing based on the presence of symptoms.[19]

Of the functional NETs, serotonin secretion is the most common and up to 20% of patients develop carcinoid syndrome which is characterized by flushing, diarrhea, abdominal

pain, bronchoconstriction and carcinoid heart disease.[17] Due to the significant consequences of carcinoid syndrome, such as carcinoid heart disease and carcinoid crisis, a large amount of literature is available regarding symptoms, diagnosis and treatment of carcinoid tumors. Other functional NETs have characteristic syndromes based upon the secreted hormone.

The majority of NETs however are non-functional and do not secrete hormones. In these patients symptoms are largely related to tumor burden and disease progression. Symptoms of locoregionally advanced and metastatic GEP-NETs can include abdominal pain, hepatobiliary obstruction and bowel obstruction. Non-advanced small bowel NETs can also exhibit symptoms of bowel obstruction secondary to the associated mesenteric fibrosis exhibited by NETs.

The NANETS 2017 guidelines for the management of small bowel NETs states that excision of primary tumor should be performed if patients exhibit symptoms of bowel obstruction, diarrhea, cramping or intestinal ischemia but this is not commonly adapted in clinical practice where patients are more so referred for surgical intervention only with significant symptoms of obstruction or ischemia alone. [12] Increased awareness of symptoms and best management of symptoms in NETs is necessary.

I.5 Treatment

The only curative treatment for NETs is radical surgical resection, which is largely for those without metastatic disease. For patients who are not candidates for curative resection treatment strategies must focus on symptom relief, disease stabilization and improving survival while balancing quality of life.

Systemic treatment options range from somatostatin analogs (SSAs), mTOR inhibitors, tyrosine kinase inhibitors (TKIs), interferon-α (IFN-α), PRRT and chemotherapy. There are no

randomized studies directly evaluating these therapeutic approaches in comparison and as such optimal treatment strategies and sequence are unknown.[1]

I.6 Surgery

Curative surgical resection is not limited to localized disease but also includes tumors resectable by radical resection for locoregional spread and resectable hepatic metastasis.[7,20] Careful patient surveillance is required in this population after radical resection due to recurrence patterns, liver metastases of GEP-NETs have high recurrence rates of up to 70% at 5 years.[20] For surgically unresectable metastatic well differentiated GEP-NETs surgery can still play a role in treatment as surgical resection without an complete R0 resection has been shown to increase overall survival.[21] The opinion regarding this surgical treatment of metastatic GEP-NETs is however controversial and does vary in the literature. Proponents for the resection of the GEP-NET primary cite symptom control and reduction or delay of potential consequences such as bowel obstruction due to tumor progression, mesenteric fibrosis, vascular occlusion, and biliary tract obstruction in addition to the controversial survival benefit demonstrated in the literature.[11,12,22] Opponents of surgical resection argue that the benefit is unclear in asymptomatic patients and that the literature largely consists of retrospective evidence and questioning if the improved survival is simply the result of selection bias.[12]

Multiple studies in the literature support that surgical intervention increases the survival of patients with metastatic GEP-NETs. Pape et al. in 2008 demonstrated an improved 5 year survival rate (5-YSR) in GEP-NETs treated with R1 and R2 resection (5-YSR 74%, P = 0.0042) and surgical debulking without curative intent (5-YSR 74%, P = 0.0007) in comparison to patients treated without any surgical intervention (5-YSR 54%, P = 0.0001).[21] A retrospective study by

Hellman et al. showed that resection of the primary tumor in patients with metastatic small bowel NETs was associated with a statistically significant improvement in median survival at 7.4 years compared to 4.0 years.[23]

With regards to potential selection bias a study by Hill et al. of patients with pancreatic NETs (PNETs) demonstrates a statistically significant survival advantage across all stages for patients treated with surgical resection in comparison to patients recommended for surgery who did not undergo surgery suggesting that surgical resection, and not patient selection, truly does confer a survival benefit.[24]

The role of surgery in poorly differentiated NETs is even more controversial. The European Society for Medical Oncology (ESMO) as well as ENETS and NANETS guidelines recommend that surgery should not be performed for debulking or metastatic disease in patients with high grade NETs.[15,22,25] However, with the rarity of high grade GEP-NETs the treatment guidelines are largely inferred from the evidence for high-grade pulmonary NETs and as such the true role and potential benefit of surgery in this population is unestablished.[5,8]

With the current level of evidence available evaluating the role of surgical therapy in advanced disease it is difficult to set criteria and guidelines for the role of surgery in metastatic GEP-NETs. However, the potential benefit of surgical resection demonstrated in the literature cannot be ignored and consideration should be made in multidisciplinary consultation for palliative resection.[12]

I.7 Systemic Therapy

I.7.1 Somatostatin Analogs

SSAs include octreotide or lanreotide and are commonly used to control disease and to treat carcinoid symptoms.[26] SSAs have been shown to control symptoms due to a reduction in hormone overproduction, inhibit tumor growth and to increase OS and progression free survival (PFS).[16,27]

The majority of all GEP-NETs express somatostatin receptors (SSR) and SSAs are the first line recommended treatment for SSR positive well differentiated GEP-NETs.[27–29] For tumors that are not somatostatin receptor positive it is still recommended that SSA therapy should be utilized.[30] Although there are high grade, poorly differentiated, NETs which express somatostatin receptors for this group the role of SSAs is not established and chemotherapy is recommended as first line treatment.[5]

The two landmark trials that established the role of octreotide and lanreotide with antitumor activity against metastatic G1 and G2 NETs are PROMID and CLARINET respectively.[26] The PROMID trial was double blind, placebo controlled, randomized controlled phase III trial evaluating octreotide LAR to placebo in 85 patients with locally inoperable or metastatic midgut primary NETs. 66.7% of patients had disease stabilization on octreotide LAR in comparison to 37.2% of patients receiving placebo with a median TTP of 14.3 months in the treatment group versus 6 months in placebo. Equivocal response rates to octreotide LAR treatment were seen in both functional and non-functional tumors. The CLARINET trial was a double blind, placebo controlled, randomized controlled phase III clinical trial evaluating lanreotide versus placebo.[31] Study results demonstrated that lanreotide was associated with a statistically significant increase in PFS.[31]

With regards to timing of treatment initiation recent results from the PROMID group evaluate OS in patients who were randomized to octreotide LAR at diagnosis versus those randomized to placebo who were consequently started on octreotide LAR at detection of disease progression.[32] Their results indicate that in asymptomatic patients with well differentiated tumors treatment with SSAs can be delayed until tumor progression is observed with no difference in OS; with OS of 84.7 months in those who receive treatment at diagnosis versus 83.7 months in those who receive treatment at detection of disease progression.[32]

I.7.2 mTOR Inhibitors

mTOR inhibitors such as everolimus have an established role in the treatment of GEP-NETs with the mutation and activation of the mTOR pathway being common in NETs.[17] The sentient trials in establishing the efficacy of mTOR inhibitors for treatment of NETs are the RADIANT-2 and RADIANT-3 trials.

The RADIANT-3 trial is a phase III trial in 410 patients consisting of a double-blind crossover format evaluating monotherapy with everolimus to placebo. Patients treated with everolimus have a significant increase in PFS (11.4 months versus 5.4 months, $p < 0.0001$).[33] Following the results of the RADIANT-3 trial everolimus was approved for use in progressive advanced NETs by the US Food and Drug Administration (FDA) and the European Medical Agency (EMA).[1]

Trials evaluating the use of mTOR inhibitors in combination with SSAs do not show any conclusive benefit and as such at present combination therapy can only be recommended for patients with functioning NETs in with a SSA is indicated for symptom control.[1]

I.7.3 Interferon-α

The use of IFN-α in treatment relies on its anti-tumoral role of angiogenesis inhibition and apoptosis.[20] Treatment has a symptomatic response rate of 40 to 70%, disease stabilization rate of up to 65% and even tumor reduction rate of up to 10%.[6,11] Studies evaluating the potential of combined IFN and SSA have not been able to demonstrate any superiority to treatment with SSA alone.[34] The toxicity profile of IFN-α also limits its use clinically as a primary treatment. As such, IFN-α is largely indicated only for patients who have failed first line therapy or are somatostatin receptor negative.[20]

I.7.4 Angiogenesis Inhibitors

The utility of tyrosine kinase inhibitors (TKIs) in NETs initially became of interest due to the vascular nature of these tumors.[34] TKIs are currently approved for the treatment of advanced NETs.[34] A phase II trial conducted by Hobday et al. on sorafenib shows a 17% response rate and 32% partial response rate in GEP-NETs.[35] This response rate is lesser than that of other agents such as SSAs thus limiting the role of TKIs as first line monotherapy, but raising the question of a role in combination therapy.[17] Monoclonal antibodies against vascular endothelial growth factor (VEGF) can also be utilized as angiogenesis inhibitors. Studies evaluating Bevacizumab show equivalent or superior PFS in comparison to treatment with IFN. Studies show promising improvements in PFS utilizing VEGF monoclonal antibodies in combination and require further investigation.[34]

I.7.5 Peptide Receptor Radiotargeted Therapy (PRRT)

PRRT works to deliver targeted radiotherapy to tumor cells by selective uptake and internalization of the somatostatin analog bound radioisotope utilizing somatostatin receptors expressed on NETs.[36] The utilization of ^{90}Y-DOTATOC and ^{177}Lutetium in the treatment of NETs

has been of increasing utilization over the past decade with ^{177}Lutetium being the most widely approved agent.[37]

With regards to response to PRRT GEP-NETs have objective response rates of 15 to 35% and complete response rates in the literature of up to 6% with PFS of 16 to 33 months and OS from 22 to 46 months.[27,29] The PFS and OS rates for PRRT compare favorably with that of SSAs and other treatment modalities including chemotherapy and everolimus.[29,37] The median time to disease progression in patients with responsive tumors is 40months with more extensive disease at treatment initiation decreasing PFS.[29]

The landmark trial for ^{177}Lutetium PRRT treatment is the NETTER-1 open label phase III randomized trial which evaluates the use of octreotide LAR and ^{177}Lutetium to octreotide LAR alone.[38] NETTER-1 found overall that ^{177}Lutetium has a 79% lower risk of death than octreotide LAR alone with 65.2% PFS at 20 months and 18% response rate in the ^{177}Lutetium group in comparison to 10.8% PFS and 3% response rate in the control group.[38] Further evaluation of the NETTER group is ongoing to assess overall survival.

With regards to the timing of integration of PRRT into the treatment of NETs it must be assessed if early treatment confers greater PFS and OS. Current guidelines list PRRT as an end-line treatment as the current literature evaluates the use of PRRT as salvage therapy yet with the promising outcomes evaluation of earlier initiation in treatment algorithms should be assessed.[37] Further investigations into PRRT are also evaluating the potential role of chemotherapeutic agents as radiosensitizing agents for PRRT in addition to the potential benefit of using a combination of radionuclides in combined therapy.[29,39,40] Additionally with

the function of some patients exhibiting decrease in tumor burden and up to 6% of patients having complete response the role of PRRT as neoadjuvant therapy should also be evaluated.[29] While PRRT is promising, not all patients are suitable for treatment with SSA-Rs. Renal function must be evaluated prior to treatment consideration in all patients as both ^{90}Y-DOTATOC and ^{177}Lutetium are eliminated by the kidney and renal protection is required with all treatment.[27] Concerns regarding hepatotoxicity and radiation hepatitis are relatively limited. It has been documented that a normal liver can recover from 30Gy of radiation and the radiation dose delivered to the liver in treatment with ^{177}Lutetium is below this threshold.[41] Special consideration however must be made for patients with hepatic metastases as liver failure with treatment is most often associated with disease progression in addition to higher incidence of hepatotoxicity in patients who received liver directed therapies prior to PRRT.[41]

I.7.6 Chemotherapy

The role of chemotherapy in the treatment of GEP-NETs is largely as the primary treatment for G3 tumors although chemotherapy can also be considered as salvage therapy in progressive well differentiated tumors.[11]

I.8 Thesis Statement

Overall as increasing therapeutic options become available, the question of how to manage metastatic GEP-NETs is evolving. With the increasing number of available treatment strategies for GEP-NETs, it is important that prognostic factors are well established so that they can aid in guiding treatment strategies.

Further investigation into lutetium treatment—specifically treatment regimens, duration, and outcomes—are necessary to help guide treatment decisions.

Improvements in overall survival are important. However, we must also take into consideration patient quality of life (QOL) to truly judge new treatment strategies. There is very limited literature available assessing QOL in NETs. To better assess the impact of lutetium treatment, changes in quality of life over treatment course should be assessed.

The treatments available for the treatment of GEP-NETs are evolving and there are promising strategies for increased overall survival. In this thesis, I hope to add some insight into the best patient specific treatment strategies considering patient specific prognostic factors and quality of life in the differential benefit of lutetium PRRT.

II. Chapter Two: Lutetium Therapy for NETs – Meta-Analysis

The available literature regarding ^{177}Lutetium therapy includes many publications evaluating disease response. However, the majority of all studies are of small size and consist of cohort studies[42,43]. In 2014 ^{177}Lutetium was approved for use in clinical trials and was then approved for clinical treatment by the FDA in 2018[44,45]. The last published review and meta-analysis of ^{177}Lutetium treatment for NETs was published in 2015, prior to the publication of many studies including the seminal NETTER-1 phase III RCT[42,43,46].

This meta-analysis provides an up to date statement of the efficacy of ^{177}Lu-labelled PRRT for patients with unresectable NETs.

II.1 Methods

A systematic literature search of PubMed, Medline, EMBASE and Ovid was performed in accordance with PRISMA guidelines (PRISMA Group. PRISMA Group. preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement). All databases were searched from inception to June 2019 with the key terms of “lutetium”, “PRRT”, “^{177}Lu”, and “neuroendocrine.” The electronic search was supplemented with manual searches of the references for all relevant publications.

Inclusion criteria were studies assessing ^{177}Lutetium treatment of NETs in human participants including assessment of response by Response Evaluation Criteria in Solid Tumors (RECIST) or Southwest Oncology Group (SWOG) criteria. Only cohort and randomized controls trials (RCTs) were included for assessment with review articles, abstracts and case series being excluded.

All studies were assessed independently by two reviewers with disagreement resolved by consensus.

All data was extracted into a standardized database by both reviewers. Demographic parameters of interest included: study title, first author, year of publication, country, study design, sample size, dose of radiopharmaceutical, number of treatment cycles, cumulative activity of treatment, follow-up, type of NETs included and adverse events. Outcomes of interest included disease response and disease control rates as measured by RECIST and SWOG criteria. Disease response was defined as those exhibiting complete response and partial response on imaging at follow-up. Disease control was defined as those demonstrating disease response in addition to those with stable disease on imaging at follow-up.

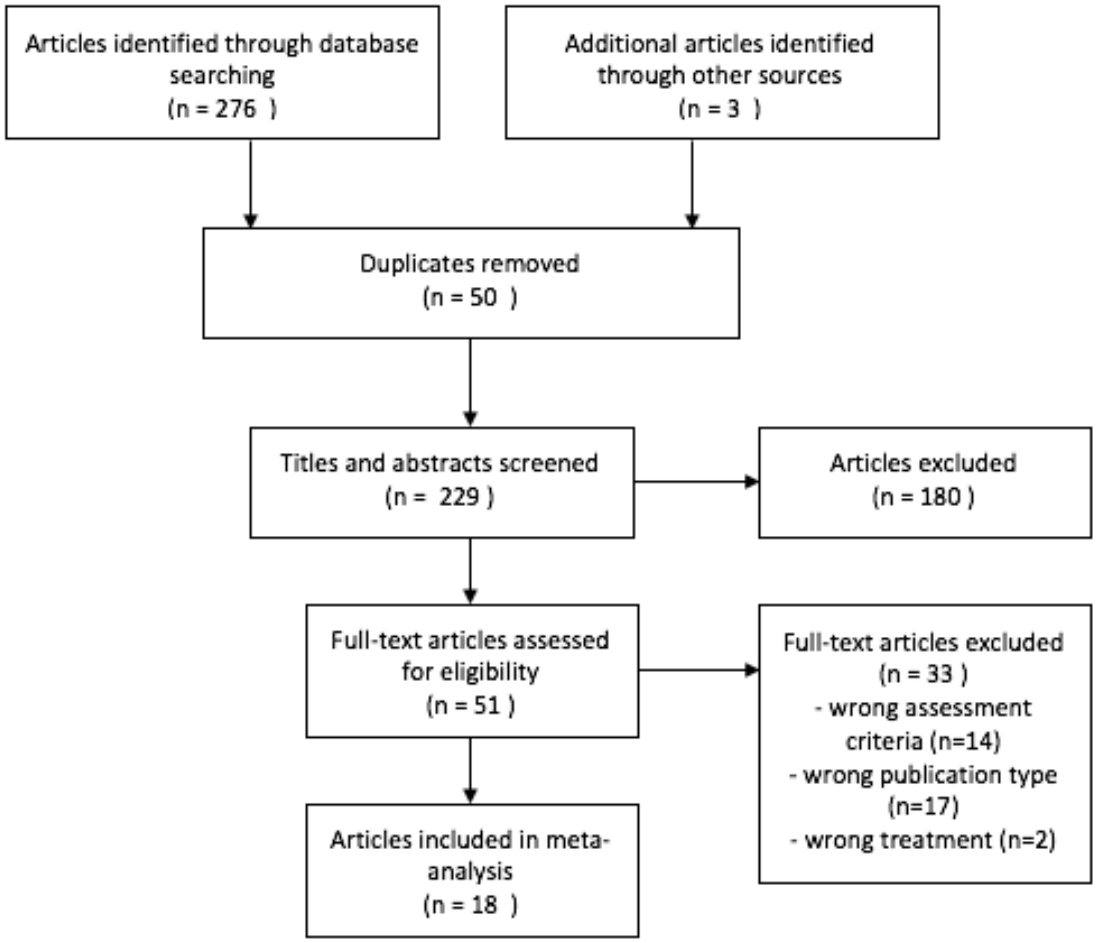
Statistical analysis was performed using MedCalc Statistical Software 14.12.0 (MedCalc Software, Ostend, Belgium). Pooled disease response and control rates were estimated by pooled proportion by RECIST and SWOG criteria. Both a fixed-effects and random-effects model were used, and appropriate model selected based on statistical heterogeneity. Both Cochran's Q-test and Higgins I^2 statistic to measure inconsistency[47]. With regards to Cochran's Q, heterogeneity was considered significant with a p value of < 0.1. With regards to the I^2 value, heterogeneity was considered high with $I^2 > 75\%$, moderate with I^2 of 50% and low with $I^2 < 25\%$[47]. Accordingly, with high heterogeneity a random-effects model was selected and if heterogeneity was low a fixed-effects model was used.

The methodological quality of all articles was also assessed. For cohort studies quality was assessed using the Newcastle-Ottawa Quality Assessment Scale for cohort studies[48]. For RCTs quality was assessed using the Cochrane Collaboration's tool for assessing risk of bias[49].

II. Results

The initial database search revealed a total of 276 relevant articles with an additional 3 articles identified through hand search. Through title and abstract screening, a total of 230 articles were excluded, including 50 duplicate articles. On full text assessment for eligibility a total of 33 articles were excluded leaving 18 articles with a total of 1920 patients meeting inclusion criteria as outlined in Figure 1.

Figure 1. PRISMA Study Selection



All studies included, with the exception of 1, consisted of cohort studies with publication date ranging from 2008 to 2018. Further study characteristics are outlined in Table 2.

Table 2. Study Characteristics

First Author	Year	Country	No. of Patients	Compound	Activity (GBq)	^{177}Lu Cycles	Cumulative Activity (GBq)	Primary Endpoint	Tumor Location
Kwekkeboom	2008	Netherlands	310	Lu-DOTATATE	3.7/7.4	4	27.8-29.6	DRR DCR	GEP-NETs
Bodei	2011	Italy	51	Lu-DOTATATE	3.7-5.2	1-7	3.7-29.2	DRR DCR	All NETs
Campana	2013	Italy	20	Lu-DOTATATE	5.3	4	25.2	DRR DCR	GEP-NETs
Romer	2013	Switzerland	16	Lu-DOTATOC	-	1-5	13.5	DRR DCR	-
Sansovini	2013	Italy	52	Lu-DOTATATE	3.7/5.5	5	11.1-27.8	DRR DCR	Pancreatic NETs
Van Vliet	2013	Netherlands	268	Lu-DOTATATE	3.7/7.4	4	22.2-29.6	DRR DCR	GEP and thoracic NETs
Ezziddin	2014	Germany	68	Lu-DOTATATE	8.0	3.4	-	DRR DCR	Pancreatic NETs
Ezziddin	2014	Germany	74	Lu-DOTATATE	7.9	4	-	DRR DCR	GEP-NETs
Delpassand	2014	USA	32	Lu-DOTATATE	7.4	4	29.6	DRR DCR	GEP-NETs
Paganelli	2014	Italy	43	Lu-DOTATATE	3.7/5.5	5	14.4-27.8	DRR DCR	GI NETs
Marinello	2015	Italy	443	Lu-DOTATATE	-	5/8	27.6/29.6	DRR DCR	Bronchopulmonary Carcinoids
Baum	2016	Germany	56	Lu-DOTATOC	3.5-10.0	1-4	29.2	DRR DCR	All NETs
Ianniello	2016	Italy	34	Lu-DOTATATE	3.7/5.5	5	12.9-27.8	DRR DCR	Bronchial Carcinoids
Brabander	2017	Netherlands	443	Lu-DOTATATE	5.2-7.4	4	5.6-28.9	DRR DCR	GEP-NETs
Hamiditabar	2017	USA	143	Lu-DOTATATE	7.3	1-6	29.6	DRR DCR	All NETs
Pencharz	2017	UK	79	Lu-DOTATATE	7.4	4	-	DRR DCR	GEP and Thoracic NETs
Strosberg	2017	USA	111	Lu-DOTATATE	7.4	4	29.6	DRR	Midgut NETs
Bodei	2018	Germany	72	Lu-DOTATATE	3.7-6.5	4	14.8-27.8	DCR	GEP and Bronchopulmonary NETs
			44	Lu-DOTATATE	-	4	-	DCR	GEP and Bronchopulmonary NETs
			42	Lu-DOTATATE	7.4	4	29.6	DCR	GEP and Bronchopulmonary NETs

With regards to quality assessment overall the single RCT was of high quality and the cohort studies were of fair to good quality of evidence as outlined in table 3.

Table 3. Quality assessment of included studies

First Author	Year	Study Type	Study Design	Follow-up Months median (Range)	Quality
Kwekkeboom	2008	Prospective	Cohort	19	4*
Bodei	2011	Prospective	Cohort	29 (4-66)	4*
Campana	2013	Retrospective	Cohort	6	3*
Romer	2013	Prospective	Cohort	9 (1-80)	5*
Sansovini	2013	Prospective	Cohort	26/29 (6-42)	6*
Van Vliet	2013	Retrospective	Cohort	-	5*
Ezziddin	2014	Retrospective	Cohort	58 (4-112)	5*
Ezziddin	2014	Retrospective	Cohort	47 (44.5-49.5)	5*
Delpassand	2014	Prospective	Cohort	14.3 (0.3-26.9)	5*
Paganelli	2014	Prospective	Cohort	38 (11-59)	6*
Marinello	2015	Retrospective	Cohort	45.1 (3-191)	4*
Baum	2016	Retrospective	Cohort	16.1	5*
Ianniello	2016	Prospective	Cohort	29 (7-69)	5*
Brabander	2017	Retrospective	Cohort	78	6*
Hamiditabar	2017	Prospective	Cohort	13.1 (2.5-49)	5*
Pencharz	2017	Retrospective	Cohort	23 (12-40)	6*
Strosberg	2017	Prospective	RCT	14	High
Bodei	2018	Retrospective and Prospective	Cohort	1-33	5*

*Assessed by Newcastle-Ottawa Quality Assessment Scale

II. 1. Disease Response and Control Rates

The pooled disease response control rates according to response criteria are outlined in table 4.

II. 1.1 Disease Response

A total of 11 studies with 1268 patients were included in assessment of disease response by RECIST criteria[50,51,60,52–59]. Statistical heterogeneity was significant between studies with an I^2 of 91.5% (95% CI 86.8 – 94.5 %) and Cochran's Q of 117.5 ($p<0.0001$) and accordingly a random-

effects model was used. Pooled disease response rate was 29.1% (95% CI 20.2 – 38.9 %) to ^{177}Lutetium PRRT when assessed by RECIST criteria.

A total of 6 studies with 804 patients were included in assessment of disease response rate by SWOG criteria[54,60–64]. Statistical heterogeneity was significant between studies with I^2 of 89.1% (95% CI 78.8 – 94.4 %) and Cochran's Q of 45.7 ($p<0.0001$). Pooled proportion was obtained by random-effects model revealing a pooled disease response rate of 30.6% (95% CI 20.7 – 41.5 %) to ^{177}Lutetium PRRT by SWOG criteria.

II. 1.2 Disease Control

A total of 13 studies with 1410 patients were included in the assessment of disease control by RECIST criteria[50,51,65–67,52–58,60]. Statistical heterogeneity was significant between studies with an I^2 statistic of 83.2% (95% CI 73.6 – 89.3 %) and Cochran's Q of 83.3 ($p<0.0001$) indicating that a random-effects model should be used. The pooled disease control rate was 74.1% (95% CI 67.8 – 80.0 %) by RECIST criteria with ^{177}Lutetium PRRT.

A total of 6 studies with 804 patients were included in assessment of disease control rate by SWOG criteria[54,60–64]. Statistical heterogeneity was significant with I^2 of 55.4% (95% CI .0 – 82.1 %) and Cochran's Q of 11.2 ($p=0.0473$) and a random-effects model was used. Pooled proportion revealed pooled disease control rate of ^{177}Lutetium PRRT by SWOG criteria of 81.1% (95% CI 76.4 – 85.4 %).

Table 4. Disease response and control rates

Criteria	Effects	No. of Studies	No. of Patients	Models	Pooled Proportion % (95% CI)	I^2% (95% CI)	Q (p)
RECIST	Response rate	11	1268	Fixed-effects Random-effects	29.2 (26.7 – 31.8) 29.1 (20.2 – 38.9)	91.5 (86.8 – 94.5)	117.5 (<0.0001)
	Control rate	15	1410	Fixed-effects Random-effects	75.2 (72.9 – 77.4) 74.1 (67.8 – 80.0)	83.2 (73.6 – 89.3)	83.3 (<0.0001)
SWOG	Response rate	6	804	Fixed-effects Random-effects	29.8 (26.6 – 33.0) 30.6 (20.7 – 41.5)	89.1 (78.8 – 94.4)	45.7 (<0.0001)
	Control rate	6	804	Fixed-effects Random-effects	79.9 (76.8 – 82.4) 81.1 (76.4 – 85.4)	55.4 (0.0 – 82.1)	11.2 (0.0473)

III. Discussion

The disease response and control rates of this meta-analysis are similar to those of the original and only other meta-analysis assessing ^{177}Lutetium treatment of NETs by Kim et al. published in 2015[42]. Kim et al. had a total of 6 studies for inclusion with 473 patients of which 4 studies used RECIST criteria and 3 studies used SWOG criteria and demonstrated pooled disease response rate of 29% (95% CI 24-34 %) by RECIST and 23% (95% CI 11-38 %) by SWOG criteria[42]. The pooled disease control rate was 81% (95% CI 71-91 %) by RECIST and 82% (95% CI 71-91 %) by SWOG criteria[42].

Our analysis included 18 studies with a total of 1920 patients with 15 studies using RECIST criteria and 6 studies using SWOG criteria. As such, our meta-analysis represents a fourfold increase in sample size over the 2015 meta-analysis and most importantly includes the results of the seminal trial, and only RCT on the subject, the NETTER-1 trial[46]. Our results reveal a pooled disease response rate of 29% (95% CI 20 – 39 %) by RECIST and 31% (95% CI 21 – 42 %)

by SWOG criteria. Pooled disease control rate was 74% (95% CI 68 – 80 %) by RECIST and 81% (95% CI 76 – 85 %) by SWOG criteria.

The response rate by RECIST criteria remained consistent, at 29% and 29%, whereas the response rate by SWOG criteria improved from 23% to 31%. This may reflect that in the original meta-analysis by Kim et al. the small number of studies, 3 with 374 patients, utilizing SWOG criteria did not allow for a comprehensive assessment of disease response to ^{177}Lutetium PRRT by SWOG criteria. This meta-analysis with 6 studies and 804 patients includes a more representative patient cohort and as such identifies response rates similar to RECIST criteria although these two methods cannot be directly compared as discussed later.

The lower average disease control rate seen in the RECIST group in this meta-analysis in comparison to that of Kim et. al, 81% compared to74%, may be the result that this study includes 1410 patients from 15 studies with the majority of these studies being published with increased use of inclusion criteria for ^{177}Lutetium PRRT being documented disease progression[42]. Accordingly, the spectrum of disease included in this study is more heterogeneous but also more inclusive of the more severe spectrum of NETs. Thereby as these more extreme cases are likely less responsive this comparatively lowers the disease control rate. The disease control rate per SWOG criteria remains comparable as the majority of the 6 studies and 804 patients evaluated by SWOG criteria are relatively older studies where disease progression, more significant disease, was not necessarily required for inclusion. This phenomenon was not reflected in the response group as those more likely to respond to treatment are likely to be those without necessarily significantly progressive disease and as such were well represented in older studies and still included in more contemporary studies.

Limitations of this study include the large amount of statistical heterogeneity between studies. Such heterogeneity is likely in part due to clinical differences between studies including variable primary tumor location and variable inclusion criteria including disease severity. Of note management with regards to cycles and dose of ^{177}Lutetium therapy was relatively consistent between studies and thereby not a large source of heterogeneity. Methodological issues likely contribute significantly to this large heterogeneity, especially as only a single RCT was available for inclusion and all other studies are cohort studies. As the sources of heterogeneity are largely methodological and could not be controlled for in analysis random effects models were used.

^{177}Lutetium PRRT seems to be an effective treatment strategy for patients with progressive and metastatic NETs with impressive and consistent disease control and response rates. The appropriate integration of ^{177}Lutetium PRRT into treatment protocols with regards to timing is not yet established. In order to better provide rationale for preferential and timely treatment with ^{177}Lutetium PRRT an understanding of the impact of treatment on patient QoL is necessary.

III. Chapter Three: Quality of Life after Lutetium Induction Therapy

III.1 Introduction

Few studies have evaluated the effect of ^{177}Lutetium treatment in NETs with regards to the outcome of QoL. It is crucial to establish the overall role of ^{177}Lutetium in the palliative treatment of NETs in order to help identify areas for potential preferential use with regards to patient and disease profile.

The current evidence in the literature does suggest beneficial effects of ^{177}Lutetium treatment with regards to QoL. There are four cohort studies that document QoL change after treatment all of which use the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)–core module (C30) and all demonstrate a statistical improvement in global health status[68–71]. Marinova et al. evaluated 53 patients, the majority being PNETs, and documented additional statistical improvement in social functioning, fatigue and appetite[68]. Teunissen et al. evaluated 50 patients with GEPNETs and documented additional statistical improvement in role functioning, emotional functioning, social functioning, fatigue, pain and insomnia[69]. However, the majority of previously published studies did not necessarily require documentation of disease progression for inclusion in QoL assessment and as such this limits the generalizability of these results to the clinical environment.

Most recently in September 2018 further results from the NETTER-1 trial, which required disease progression for inclusion, with regards to quality of life were released. These results demonstrate clinically and statistically significant improvement in time to deterioration of global health status and physical functioning with ^{177}Lutetium in comparison to high dose octreotide[46].

The populations included in these studies vary and no studies have investigated QoL assessment in clinical contexts or variables preferentially associated with ^{177}Lutetium associated QoL benefit. Accordingly, we seek to establish in our study a consistency in QoL improvement, best methods for QoL assessment in translation to clinical practice and prognostic factors for QoL improvement.

III.2. Methods

III.2.1 Study Design

This study was conducted as a part of the Phase II open label clinical trial at the Cross Cancer Institute (CCI) in Edmonton as a planned interim analysis of quality of life as a secondary objective.

Patient enrollment began in March of 2014 and is ongoing with a total of 229 patients enrolled to September of 2017. Study participants are divided into two separate groups: Group A and Group B. Group A consists of subjects receiving primary PRRT therapy and Group B includes subjects who have been previously treated with Lu-DOTA-TATE under Special Access Programs (SAP) at the CCI or at other institutions. As such, only patients in group A are included in QoL assessment as patients in Group B started treatment outside of the study and accordingly do not have a baseline QoL questionnaire.

Inclusion criteria for Group A were: (1) age ≥ 14 to 90 years of age; (2) presence of a somatostatin receptor positive tumor with at least one tumor site reliably visualized on imaging of at least 1.5cm within 26 weeks of enrolment; (3) OctreoScan® demonstrating target lesion uptake equivalent to or greater than hepatic uptake within 1 year of enrollment; (4) life expectancy greater than 12 weeks; (5) serum creatinine ≤ 150 mol/L with estimated glomerular

filtration rate (eGFR) ≥ 50 mL/min; (6) hemoglobin ≥ 90 g/L, white blood cell (WBC) ≥ 2 x 10^9/L and platelets ≥ 100 x 10^9/L; (7) serum albumin, total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) ≤ five times the upper limit of normal; (8) Eastern Cooperative Oncology Group (ECOG) of ≤ 2; and (9) written informed consent given prior to enrollment. As patients with any somatostatin receptor positive tumor were eligible for inclusion in the trial and the purpose of this study is to assess QoL with regards to treatment of NETs inclusion was limited to GEP-NETs. The inclusion of NETs was limited to GEP-NETs to reduce heterogeneity within the study population as NETs can arise throughout the body with more variable characteristics and prognosis. Additionally, as this study looks to evaluate change in quality of life after initial induction therapy, or 4 cycles of treatment, only patients who had completed 4 treatment cycles were eligible for inclusion.

Exclusion criteria for group A participants were: (1) previous Lu-DOTA-TATE therapy; (2) potential for surgery with curative intent; (3) surgery within 12 weeks of enrollment; (4) radioisotope therapy within 12 weeks of enrollment; (5) systemic therapy of mTOR or tyrosine kinase inhibitor within 6 weeks or chemotherapy or interferon within 8 weeks of enrollment; (6) change in long acting somatostatin analogue therapy regimen within 12 weeks of enrollment; (7) localized external beam irradiation with target lesion in radiation field; (8) known brain metastases unless treated and stable for at least 4 months; (9) uncontrolled diabetes mellitus within 12 weeks of enrollment; (10) significant medical, psychiatric or surgical condition which may interfere with completion or conduct of study; (11) pregnancy; (12) breastfeeding; or (13) prior radiation therapy to greater than 25 percent of the bone marrow.

III.2.1 PRRT Treatment Protocol

The treatment regimen was of ^{177}Lutetium DOTATATE with an average dose of 5.55 GBq, range 2.50 GBq to 6.11 GBq, depending on patient risk factors for treatment toxicity. administered at four treatments, 10 weeks apart. The treatment was run over a slow infusion of 1 to 2 hours. An amino acid infusion (2.5% arginine and 2.5% lysine in 1 L of saline) was started prior to each Lu-DOTA-TATE therapy for renal protection. As planned in the study protocol for those patients who completed the induction treatment of 4 cycles without toxicity or progression a maintenance phase therapy was then entered. This maintenance treatment consisted of on average 2.78 GBq, range of 1.67 to 4.07 GBq, with exact dose dependent on patient risk factors for treatment toxicity. Maintenance treatments were administered every 6 months for up to 4 years or a maximum of 12 treatments.

III. 2. 2 QoL Evaluation

Quality of life was assessed with the EORTC QLQ-C30 Version 2.0, QLQ-GI.NET 21, and ESAS-r. The QLQ-C30 is a validated questionnaire for the assessment of QoL in cancer care. The questionnaire is patient based and consists of 30 questions and assesses a series of parameters through either single or multi item questions which are then converted into 100 point scores for each parameter. The parameters assessed by the QLQ-C30 are global health status, functional scales – physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning – and symptom scales – fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties.

Once the question scores are converted to the 100 point scale with regards to global health status and functional scales higher scores relate to improved quality of life. In contrast, for symptom scales lower score corresponds to improved quality of life[72]. The QLQ-GI.NET 21 is a

validated QOL assessment tool which is an add on questionnaire to the QLQ-C30 which specifically evaluates GI related NET symptoms with an additional 21 questions[73].

The Edmonton Symptom Assessment System Revised (ESAS-r) form is a validated QoL assessment tool for QoL assessment in palliative and general oncology clinical practice[74,75]. The ESAS-r assesses 9 symptoms – pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, feeling of well-being and shortness of breath – in addition to including an optional space for patients to self report another area of concern[76]. Each symptom parameter is scored on a numerical scale from 0 to 10 with a higher score indicating greater symptomology[77]. Scoring for the ESAS-r is straightforward and requires no conversions or calculations but is simply used as reported by patients on the 10 point scale[76]. Overall scores of total symptom distress, emotional symptoms and physical symptoms can also be simply summated. The total symptom distress score is out of 90 and is the result of the sum of all 9 parameters. The emotional symptom score is out of 20 and is the sum of the 2 emotional parameters of anxiety and depression[75,78]. The physical symptom score is out of 60 and is the sum of the 6 physical parameters of pain, fatigue, drowsiness, nausea, appetite and dyspnea.

Questionnaires were administered to patients participating in the study at baseline prior to first treatment and subsequently prior to each treatment. Of note the QLQ-GI.NET 21 questionnaire was not included and approved for use in the study protocol until May 2014 and as such patients enrolled prior to this date do not have a baseline QLQ-GI.NET 21 for assessment.

Clinical significance of changes in QoL parameters were used as established in the literature. For the EORTC QLQ-C30 clinically significant change in QoL was established by Osaba

et al. to be a mean change in score of at least 5 to 10 points[79–81]. For ESAS-r clinically significant values were established by Hui et al. with a cut-off of 1 point for improvement and deterioration of single scores[82]. For total symptom distress and physical scores, a minimally clinical important difference (MCID) of decrease in score by 3 points is noted for symptom improvement and a MCID for deterioration being an increase in score by 4 points. For emotional symptom distress score the MCID for improvement is a score decrease of 2 points and a score increase of 1 point for deterioration[78].

III. 2. 3 Study Size

Marinova et al. found the mean difference in global health status to be 11.1 points with a standard deviation of 21.2 to 33.2.[68] Teunissen et al. noted the mean difference in global health status to be 9.2 points with a standard deviation of 16.9 to 20.0.[69] While the NETTER-1 secondary outcomes reported do not report the mean difference in global health status, a standard deviation of 20 was found.

Accordingly, a study size was calculated using a 95% confidence interval, power of 80% and 1:1 ratio of groups, as patients would function in both groups as their own comparison from baseline to after completion of induction therapy, for the primary outcome of mean difference in global health status or overall QoL. A mean difference of 10 was used and a standard deviation of 20 for both baseline and post induction therapy measures. This calculation, as outlined in Figure 2, detected a minimum required sample size of 63 patients per group.

III. 2. 4 Data Analysis

The questionnaires were completed by patients prior to treatment and subsequently entered manually into Research Electronic Data Capture interface (REDCap). Provisions were taken in

administering and collecting questionnaires to optimize full completion. Any missing data was treated with imputation as established by the EORTC scoring manual and guidelines for missing data[72].

Data was analyzed with both Stata Version 15 (Stata Corp, Lakeway Drive College Station, USA) and SPSS. As a planned interim analysis repeated measure analysis of variance was performed comparing patients' QoL ratings from baseline to post treatment cycle four. The data met the assumptions of normality by sufficient sample size and equal variance was also established. Additionally, as repeated measures was performed the assumption of sphericity was also verified prior to analysis. A p value of ≤ 0.05 was considered statistically significant. Overall significance was considered in terms of both statistical and clinical significance.

For EORTC a threshold of score change of ≥5 to 10 points was the MCID indicating improvement[79–81]. For ESAS-r a score decrease of ≤1 for individual scores, ≤3 for physical and total symptom distress score, and ≤2 for emotional score was considered to be of MCID for symptom improvement.

Table 5 Baseline Patient Demographics

Demographic Characteristics of Study Population		
85 patients included for analysis		
Characteristic	**Number**	**Percent %**
Age		
20-49	10	11
50-59	30	35
60-69	19	22
70-79	23	27
80-90	3	4
Sex		
Male	49	58
Female	36	42
ECOG Prior to Treatment		
0	54	64
1	27	32
2	4	5

III. 3. Results

III. 3. 1 Baseline Patient Characteristics

From study commencement to September of 2018 a total of 229 patients were enrolled. Of these patients 61 patients had prior ^{177}Lutetium therapy and as such were enrolled in Group B and were not eligible for inclusion in QoL analysis as no baseline QoL questionnaire was

available. Into group A 168 patients were enrolled and were potentially eligible for inclusion in this analysis. When restricted to patients with GEP-NETs a total of 160 patients were eligible for inclusion. Within this group 28 patients had completed fewer than 4 cycles and were excluded for this analysis of QoL change after induction therapy consisting of 4 cycles. A total of 36 patients were enrolled and started treatment prior to the introduction of the QLQ-GI.NET 21 and ESAS-r into the study protocol and consequently did not have baseline QoL questionnaires for comparison for these QoL forms. An additional 11 subjects had insufficient questionnaire completion for inclusion and were excluded. In total 85 patients were then eligible for inclusion in QoL analysis of GEP-NETs after completion of induction therapy.

Table 6 Characteristics of Primary Tumor and Metastasis

NET Diagnosis		
Site of Primary	Number	Percent %
Pancreas	20	24
GI	58	68
Unknown Primary (presumptive GNET)	7	8
Metastasis	Number	Percent %
Yes	85	100
No	0	0
Site of Metastasis	Number	Percent %
Liver	77	91
Bone	19	22
Mesentery	18	21
Lymph Nodes	20	24
Ki-67	Number	Percent %
<2%	26	31
2-20%	33	39
>20%	3	4
Unknown	23	27%

Within the study group 64% of patients has a GI primary, 24% had a pancreatic primary and 11% had a primary of unknown origin but were suspected to be of GEP origin. The mean age of the study population was 61 years with a range from 26 to 86 years. A total of 49 participants were male and 36 were female.

Almost all patients had received other treatment prior to inclusion with the exception of 5 patients whose initial treatment for the NET consisted of ^{177}Lutetium therapy. Regardless, all patients had documented disease progression prior to initiation of ^{177}Lutetium therapy. Of the 80 patients who had received other treatment prior to study enrollment 73% had undergone surgery, 72% had been treated with SSAs, 14% had chemotherapy, 1% had radiotherapy, 6% had treatment with mTOR inhibitors or TKI and 7% had locoregional therapy. Further baseline patient characteristics are outlined in table 5 with NET and tumor characteristics outlined in table 6.

III. 3. 2 EORTC Quality of Life Outcomes

As measured by the EORTC QLQ-C30 and GI-NET.21 the mean global health score of patients at baseline prior to treatment was 68.1(95%CI 60.57, 75.62) and was 66.4(95%CI 57.33, 75.52) after 4 treatment cycles with ^{177}Lutetium therapy. This change in global health status was not statistically significant with p=0.68 and as such treatment demonstrated no improvement but also no deterioration in overall QoL status in patients.

With regards to individual symptom scales assessed by the EORTC QLQ-C30 and GI-NET.21 statistically significant change, $p \leq 0.05$, was observed in endocrine symptoms, GI symptoms and insomnia. The mean score for endocrine symptoms decreased from 20.37(13.58, 27.16) to 14.81(9.37, 20.26**)** with p=0.05 with a mean change of 5.56 indicating a statistically

and clinically significant improvement in endocrine symptoms. The mean score of GI symptoms decreased from 22.28(16.16, 28.39) to 16.67(12.17, 21.17) with p=0.05 with a mean change in GI symptoms of 5.61. This represents a statistically and clinically significant improvement in GI symptoms after induction therapy. The mean score for insomnia decreased from 36.43(26.47, 46.40) to 25.58(16.96, 34.20), p=0.03, with a mean change of 10.85 representing a statistically and clinically significant improvement in insomnia.

In evaluating the summative scores, a marginally significant change was detected in social functioning alone. The mean score for social functioning changed from 76.85(95%CI 68.09, 85.62) to 83.33(75.02, 91.64), p=0.07, giving a mean change of 6.48. This change is only marginally statistically significant but is clinically significant. All other parameters had no significant change and therefore QoL was maintained with regards to these aspects and are outlined in table 7.

Table 7. EORTC QLQ C-30 and GI-NET.21 Scores

EORTC scale	**Mean (95%CI)**	
	Baseline	**Post Treatment 4**
Global Health Status	68.10 (60.57, 75.62)	66.40 (57.33, 75.52)
Functional Scales		
Physical Functioning	80.50 (73.76, 87.25)	82.13 (75.86, 88.41)
Role Functioning	76.74 (68.14, 85.35)	77.13 (67.9, 86.36)
Emotional Functioning	70.14 (62.15, 78.13)	73.15 (64.51, 81.78)
Cognitive Functioning	75.00 (65.52, 84.48)	76.39 (66.45, 86.33)
Social Functioning	**76.85** **(68.09, 85.62)**	**83.33**** **(75.02, 91.64)**
Symptom Scales		

Fatigue	32.56 (24.78, 40.36)	30.36 (22.57, 38.15)
Nausea and Vomiting	5.04 (1.77, 8.31)	6.98 (1.47, 12.49)
Pain	24.81 (16.40, 33.21)	22.48 (13.68, 31.29)
Dyspnea	19.38 (10.36, 28.40)	21.71 (13.99, 29.42)
Insomnia	**36.43** **(26.47, 46.40)**	**25.58*** **(16.96, 34.20)**
Appetite Loss	12.40 (6.06, 18.74)	11.63 (5.76, 17.50)
Constipation	13.18 (6.05, 20.31)	11.63 (2.30, 20.26)
Diarrhea	36.19 (26.42, 45.96)	31.43 (21.83, 41.03)
Financial Difficulties	20.00 (10.71, 29.29)	20.95 (11.71, 30.20)
Endocrine Symptoms	**20.37** **(13.58, 27.16)**	**14.81*** **(9.37, 20.26)**
GI Symptoms	**22.28** **(16.16, 28.39)**	**16.67*** **(12.17, 21.17)**

*statistically significant, p≤0.05

**marginally statistically significant, p 0.05-0.07

III. 3. 3 ESAS-r Quality of Life Outcomes

As measured by ESAS-r the mean total symptom distress score at baseline was 18.16 (95% CI 12.95, 23.37) and 15.36 (95% 10.90, 19.83) after the induction treatment of 4 cycles of ^{177}Lutetium. This change in QoL was not statistically significant, p=0.11, thereby again indicating no overall improvement nor deterioration in QoL after induction therapy.

With regards to individual symptoms a statistically significant change was detected in anxiety alone. Mean anxiety changed from 3.07 at baseline to 2.36, p=0.04, post induction therapy. This change in score while statistically significant was not clinically significant as it did not meet the MCID of 1 point and as such is clinically equivalent to maintained anxiety.

From the summative scores only emotional functioning was found to have a statistically significant change from 4.80 to 3.88, p=0.04. This change is not clinically significant as it does not meet the MCID of 2 points and as such is clinically equivalent to maintained emotional functioning after induction therapy.

All other QoL factors assessed by ESAS-r has no statistically significant change and were maintained over treatment as outlined in table 8.

Table 8. ESAS-r Scores

ESAS-r	**Mean (95%CI)**	
	Baseline	**Post Treatment 4**
Pain	1.61 (0.94, 2.28)	1.46 (0.82, 2.09)
Tiredness	3.25 (2.56, 4.14)	2.73 (1.99, 3.47)
Drowsiness	2.07 (1.22, 2.92)	1.46 (0.78, 2.13)
Nausea	0.80 (0.33, 1.26)	0.77 (0.28, 1.26)
Lack of Appetite	1.32 (0.66, 1.97)	1.09 (0.59, 1.59)
Dyspnea	1.61 (0.84, 2.39)	1.75 (1.1, 2.4)
Depression	1.73 (0.94, 2.52)	1.41 (0.77, 2.05)
Anxiety	**3.07** **(2.15, 3.40)**	**2.36*** **(1.59, 3.13)**
Overall Wellbeing	2.72 (1.92, 3.53)	2.40 (1.68, 3.12)
Physical Score	10.66 (7.31, 14.01)	9.25 (6.39, 12.11)
Emotional Score	**4.80** **(3.23, 6.37)**	**3.77*** **(2.44, 5.10)**
Total Symptom Distress Score	18.16 (12.95, 23.37)	15.36 (10.90, 19.83)

*statistically significant, p≤0.05

III. 4. Conclusion

One of the most important outcomes to consider in the treatment of patients receiving palliative care is QoL.[83]. With regards to patient perspective a preference towards optimizing QoL over life expectancy has been demonstrated[84].

Quality of life is assessed using patient interactive modalities as it is a patient-measured outcome. The measures used to assess QoL can vary based on the environment, research or clinical practice. It is important to assess QoL in research to establish the potential benefit of a treatment for the patient population. However, as individual patient responses may vary it is equally as important to assess QoL in the clinical setting such that individual response and concerns can be measured.

The EORTC QLQ-C30 is a validated QoL questionnaire designed for use in clinical trials assessing oncology patients[72]. There is a supplementary questionnaire to the EORTC QLQ-C30 the GI.NET-21 which allows for more comprehensive assessment of NET symptomology[72]. The QLQ C-30, sometimes with the addition of the GI.NET-21 supplement, has been standardly used in the assessment of NETs in research and studies have demonstrated a benefit with regards to ^{177}Lutetium therapy[68–71]. The results of the NETTER-1 RCT have revealed statistically and clinically improved time to deterioration in global health scores and physical functioning with ^{177}Lutetium therapy when compared to treatment with octreotide long-acting repeatable[85]. With the exception of the NETTER-1 trial however the other available studies evaluating the QoL in NETs treated with ^{177}Lutetium therapy are of generally small sample size and did not outline criteria of disease progression as a requirement for study inclusion[68–71,86,87]. Because of this inconsistency with regards to disease progression for ^{177}Lutetium therapy initiation this limits the clinical applicability of these studies. In contrast this study required documentation of

disease progression on imaging for study enrollment, representing a population similar to that in clinical practice.

This study in keeping with the current literature finds that patients with unresectable and metastatic NETs have a relatively high baseline QoL with baseline global health status of 68.10, in comparison to 67.0 in the NETTER-1 trial[85]. Comparatively, the mean global health status cited for cancer patients with advanced cancer is 61.5 and the mean global health status cited for the general population is 71.2 [88]. Our results demonstrate a statistically significant change in insomnia, endocrine symptoms and GI symptoms with a marginally significant change in social functioning from baseline to post induction therapy. Most importantly all statistically significant changes also met the MCID for clinical significance, of change in score by 5 to 10 points as established by Osaba et al., and thereby represented a clinical improvement in these QoL domains[79].

The overall or global health status of patients from baseline to post completion of induction therapy demonstrated no statistically significant change indicating that overall global health status was maintained over treatment course. In consideration of the relatively high baseline QoL this supports maintenance of a good QoL standard for patients with ^{177}Lutetium therapy.

However, in consideration of applicability to individual patients in clinical practice QoL in response to ^{177}Lutetium therapy can vary and as such should be measured individually to assess patient response and to identify areas of concern. The EORTC QLQ-C30 together with the GI.NET-21 addition while designed and validated for research use with its 51 questions and requirements for score conversions and varying calculation formulas dependent on parameter

may be cumbersome for clinicians and intimidating for patient in the clinical setting as opposed to the ideal questionnaire which is brief and easy for patients to complete and physicians to interpret [89,90]. The use of the EORTC questionnaire set for NETs has not been evaluated in a clinical context.

The ESAS-r in contrast to the EORTC QoL questionnaire is designed and validated for QoL assessment of palliative care patients in the clinical environment [74,75]. Consisting of only 10 questions with direct conversion to scoring from the patient responses the ESAS-r is comfortable for patients to complete and time efficient and simple for clinicians to employ and track over time [91]. The ESAS-r has not been assessed in use for patients with NETs and as such in this study we evaluate the ability of the ESAS-r to assess change in QoL in patients with NETs treated with ^{177}Lutetium therapy.

The mean overall QoL or total symptom distress score measured by the ESAS-r was 18.16, out of a total potential score of 90. Again, the ESAS-r similar to the EORTC questionnaires demonstrates a relatively high baseline QoL for patients with metastatic unresectable NETs as the mean total symptom distress score for advanced cancer patients is cited at 38.4 for patients under the age of 60 and 38.9 for patients over the age 60[92]. There was no statistically significant change in the total symptom distress score indicating maintained overall QoL over induction treatment.

The ESAS-r detected statistically significant changes in emotional functioning and anxiety. However, the improvement in these QoL parameters did not meet the MCID for clinical significance as established by Hui et al. [82]. As such the EORTC QLQ-C30 with GI.NET 21 in comparison to the ESAS-r is better capable of detecting changes in symptomology and QoL in

patients with NETs during ^{177}Lutetium therapy, especially with regards to endocrine and GI symptoms. The EORTC questionnaires appear to be more sensitive than the ESAS-r to detecting changes in QoL with regards to the NET population.

This difference in ability to detect changes in QoL in NET patients between the two QoL assessment methods may in part reflect the relatively high baseline QoL of this patient population. As a result of this higher QoL changes in QoL for this population may be smaller than that demonstrated in most oncology populations and thereby may potentially require NET specific rather than general QoL assessment tools to detect these changes in QoL.

These findings indicate that the EORTC QLQ-C30 assessment method should be used preferentially in the clinical setting if possible to quantify and track QoL of patients with NETs over their treatment course. However, adaptation of EORTC QLQ-C30 into the clinical context may be limited for the aforementioned difficulties in using this questionnaire outside of the research setting where time and resources are limited for clinicians and where patient uptake may be decreased. With regards to patient uptake the ESAS-r with its 10 questions is less intimidating for patient use compared to the 51 questions in the EORTC assessment, this cannot be easily rectified without reformulation of the EORTC questionnaire for clinical use. However, with regards to limitations of difficulty in scoring and clinician interpretation these concerns could be addressed by computerized assessment allowing for easy scoring and tracking of QoL over treatment course [89]. This solution could also potentially increase patient uptake as research has demonstrated that not only clinicians but also patients believe that computerized QoL collection allows for better assessment in clinical practice[89].

Overall, the EORTC QLQ-C30 and GI.NET-21 allow for the most sensitive assessment of QoL in patients with NETs treated with ^{177}Lutetium therapy. However, some QoL assessment may be preferential to no QoL assessment as it promotes patient-physician communication and identification of key patient concerns and improve patient care [9193]. Accordingly, if the EORTC questionnaire is too cumbersome for incorporation into a physician's clinical practice the findings of this study should not discourage use of other QoL assessment parameters such as the ESAS-r. Further research into the utilization of QoL tools in the clinical care of patients with NETs is needed in order to identify the ideal tool and administration method.

IV. Chapter Four: Predictors for QoL change with Lutetium Therapy

IV.1 Introduction

Currently the treatment algorithm or ideal sequence of treatment for unresectable GEP-NETs is uncertain[94]. First line treatment for is somatostatin analogs (SSA)[95] but the best course for second line therapy after failure and progression on SSAs is not clearly established. This ambiguity persists with regards to initiation of ^{177}Lutetium as select studies or guidelines suggest initiation only after the failure of other available medical therapies others suggesting initiation potentially after progression on SSA [94,96]. This ambiguity in where to introduce ^{177}Lutetium therapy into the treatment algorithm may be in part due to the uncertainty of clearly predicting which patients will response to PRRT [97,98]. Furthermore, the relationship between disease response and symptom response is unpredictable and seemingly independent of tumor response as assessed by imaging or even biomarkers[99].

Due to the overall burden of symptoms, the importance of QoL in palliative care and the potential of ^{177}Lutetium therapy to improve QoL we raise the consideration that QoL be considered in the timing of ^{177}Lu therapy. In this analysis we aim to identify which patients may gain greater benefit from ^{177}Lu therapy with regard to QoL and thereby help prioritize ^{177}Lu therapy earlier in the treatment course of these patients.

IV.2 Methods

This study was a planned sub-analysis of the ongoing Phase II open label clinical trial at the CCI in Edmonton of the efficacy of ^{177}Lutetium therapy in treatment of somatostatin receptor positive tumors. Full details of study design, treatment protocol, and QoL evaluation are outlined in chapter III.

IV.2. 1 Statistical Analysis

Data analysis was conducted with STATA version 13 (StataCorp LP, Texas, USA). A linear regression model was fit for the change in mean global health status score by EORTC QLQ-C30 from baseline to after completion of induction therapy to identify factors related to change in QoL after induction therapy with ^{177}Lutetium. Variables controlled for were age and sex. The explanatory variables evaluated in the analysis were ECOG at enrollment, baseline global health score, treatment prior to enrollment, primary site of tumor, presence of metastasis, Ki-67, cumulative ^{177}Lu dose and time from diagnosis to treatment with ^{177}Lu. A univariate analysis of all the explanatory variables was first performed run and variables subsequently included in the regression model if an initial univariate significance of p value of 0.20 or less was met. Once the combined model was created, explanatory variables were then excluded if their individual p value did not meet a significance of p value of 0.05 or less, given that they were not confounders for the remaining variables.

IV.3 Results

A total of 85 patients with GEP-NETs were included for analysis. Further patient characteristics are outlined in table 5 and table 6.

Overall 34% of patients had a decrease and 43% of patients had an increase in global health score in comparison to 23% who had a maintained global health score after induction therapy. In the purposeful selection linear regression model adjusting for age and sex, global health score at baseline ($p<0.01$) and time from diagnosis to treatment with ^{177}Lu therapy ($p=0.04$) were found to be statistically significant. The presence of metastatic disease ($p=0.078$) was a

marginally significant variable. No predictors of global health score met clinical significance with a change in change in global health score of 5 or more points as outlined in table 9.

Table 9. Purposeful selection linear regression model – final model

Variable	Coefficient (95%CI)	P value
Age	0.455 (-0.011 – 0.920)	0.055
Sex	-0.921 (-9.745 – 7.903)	0.836
Metastatic disease	37.986 (-4.425 – 80.398)	0.078
Ki-67		
	4.250 (-7.661 – 16.151)	0.480
	-8.521 (-20.697 – 3.656)	0.168
Time from diagnosis to ^{177}Lu therapy	-0.928 (-1.810 - -0.046)	0.039
Baseline global health score	0.319 (0.104 – 0.535)	0.004

For every point increase in global health at baseline, the mean change in global health from baseline to post treatment 4 increased by 0.319 points (95% CI 0.104 to 0.535) given age, sex, Ki-67, presence of metastatic disease and time from diagnosis to treatment with ^{177}Lu therapy. For every year increase in time from diagnosis to initiation of treatment with ^{177}Lu therapy mean global health from baseline to post treatment 4 decreased by -0.928 points (95% CI -1.810 to -0.046) given age, sex, Ki-67, presence of metastatic disease and baseline global health score. Patients without metastatic disease had a mean global health score that was 37.986 points (95%CI -4.425 to 80.398) higher than patients with metastatic disease given age, sex, Ki-67, presence of metastatic disease, global health score and time from diagnosis to treatment with ^{177}Lu therapy.

IV.4 Discussion

The goal of this study was to assess and identify unique factors, both patient and tumor factors, that result in a more pronounced response to ^{177}Lutetium in patients with GEP-NETs with regards to QoL. To our knowledge this is the only study that investigates this relationship.

The univariate and multivariate analysis demonstrates that the factors of baseline global health score and time from diagnosis to ^{177}Lutetium therapy significantly relate to overall

quality of life after induction therapy. For every one point higher global health score at baseline patients had a score increase of 0.32 points greater after induction therapy. This indicates that patients with a higher baseline QoL will have a statistically significantly greater benefit from ^{177}Lutetium induction therapy. This does not imply that patients with lower baseline QoL do not achieve benefit from ^{177}Lutetium therapy but that patients with a higher baseline QoL have a greater magnitude of benefit with regards to global health score after induction treatment. Of note this difference of 0.32 points does not meet the MCID for improvement of 5 points and as such is not clinically significant. However, a clinically significant difference would be evident in patients with a baseline global health score of 15.6 points greater at baseline.

The significance of this finding applies to patients with high global health status, or overall QoL, but lower life expectancy due to either their tumor burden or other etiology. In these patients an earlier incorporation of ^{177}Lutetium therapy may be considered at an earlier point in their individual treatment algorithm to facilitate maintenance and improvement of terminal QoL. This finding should also be considered in patients with a high global health status who then have a functional and symptomatic decline in whom earlier treatment with ^{177}Lutetium therapy could provide significant improvement in QoL.

With regards to the influence of time from diagnosis to treatment with ^{177}Lutetium therapy for every year increase from diagnosis to ^{177}Lutetium treatment there is a 0.93 point statistically significant decrease in global health status. This decline is not clinically significant in the context of a single year but does meet clinical significance when a delay of 5.4 years or more is reached. Thus, in the timing of PRRT into patient treatment one should consider that significant delay in initiation can negatively influence the potential benefit of ^{177}Lutetium

therapy with regards to quality of life. This is most important to consider in the treatment of patients with low baseline QoL in whom deterioration can be functionally significant and in whom ^{177}Lutetium therapy could be potentially important to patients with regards to improving or even delaying time to deterioration of QoL.

Future studies are needed to evaluate other patient and disease parameters not available in this study, such as the emerging ^{68}Gallium DOTATATE PET, and their prognostic relation to ^{177}Lutetium therapy for patients with GEP-NETs. treatment. With further results fully inclusive models for predicting QoL in patients with GEP-NETs in respect to ^{177}Lutetium therapy can be developed.

Limitations of the QoL analysis in this study are largely represented by subjectivity in assessment modality and potentially small sample size. Although QoL is standardly collected through patient based questionnaires this form of assessment does have its inherent flaws which contribute to bias, in the form of participation bias, which influences reported outcomes. We attempted to minimize this potential bias by encouraging full participation by all patients and filling in missing data by standardized imputation however there were still 11 patients excluded from analysis due to incomplete questionnaire completion. If this subset of patient did not report findings due to particularly adverse or beneficial outcomes their exclusion from analysis unduly influences the results.

The other notable limitation of this study is the sample size of the study population. While out study size was calculated referencing the standard mean difference and standard deviation in reported in studies of global health status the mean difference in our study was lower, by over half, and the standard deviation of our population higher by double. Accordingly,

in reflection of the mean difference and standard deviation of this population the study is underpowered to detect a difference and as such we may have not detected more subtle differences and changes in QoL. As this study was performed as an interim analysis of the ongoing Phase III trial assessing ^{177}Lutetium therapy at the CCI to address this another analysis of QoL will be performed at study completion at which accruement will have reached 400 patients.

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Appendices

Figure 2: Sample-size estimation

Sample Size for Comparing Two Means

Input Data

Confidence Interval (2-sided)	95%
Power	80%
Ratio of sample size (Group 2/Group 1)	1

	Group 1	Group 2	Difference*
Mean			10
Standard deviation	20	20	
Variance	400	400	

Sample size of Group 1	63
Sample size of Group 2	63
Total sample size	126

*Difference between the means

http://www.openepi.com/SampleSize/SSMean.htm