University of Alberta

The use of PET/CT scans in the assessment of resectability of colorectal liver metastases

by

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Dedication

To my husband, family, friends and colleagues for the encouragement that I received from both sides of the ocean; thank-you for the chance you've given me to realize my dreams both professionally and personally. I am indebted.

Abstract

Background: Surgical treatment of colorectal liver metastases (CLRM) depends on resectability that is currently based on the CT scan. With the PET/CT scan, a more accurate pre-operative assessment of resectability may be possible.

Methods: A Cochrane-based diagnostic test systematic review and a systematic review of cost-effectiveness studies on PET scans were conducted. Lastly, a diagnostic decision analysis model was created to assess the cost-effectiveness of the technology.

Results: PET/CT scans was equally sensitive for hepatic metastases and more sensitive for extra-hepatic metastases compared to CT scans. A cost-savings of PET scans for CRLM is identified; with decision modelling demonstrating a cost-savings with the addition of PET/CT scans to the current clinical algorithm.

Conclusion: There is cautious support for the addition of PET/CT scans to the pre-operative assessment in CRLM. Unnecessary surgery may be prevented, thus decreasing wait times. Future endeavours include finding, evaluating and validating methodology for appropriate effectiveness measures.

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To Dr. Bigam and Dr. Ohinmaa for believing that it is possible for a surgeon to implicate herself in the realms of economics and technology, for your support in providing the supervison, funding, expert counsel and faith, even when the ocean separated the completion of this project.

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List of Abbreviations

AU	Australian
CEA	Cost effectiveness analysis
CI	Confidence Intervals
CT scan	Computed Tomography Scan
CIP	Clinical Investigator Program
CND	Canadian
FDG	fluro-deoxyglucose
KeV	kilo Electrovolts
PET	Positron Emission Tomography
PET/CT	Positron Emission Tomography combined with CT scan
SPN	Solitary Pulmonary Nodule
US	United States of America

1. Introduction

Motivation and Historical Development

Time magazine hailed it as the Medical Science Invention of the Year in 2000. The product of a joint effort by physicist David Townsend and engineer Ron Nutt, the fusion of the positron emission tomography (PET) and computed tomography (CT) scans into one machine (PET/CT) in 1992, enables clinicians and radiologists to pinpoint, on the anatomically precise CT scan, the hyper-functioning lesions seen on a PET scan (1). The first PET/CT prototype was introduced at the University of Pittsburgh in 1998, after which the technology became available widely in 2002 through Philips, Siemens and other major diagnostic imaging companies. The technology was especially sought after in oncologic assessment where the functional imaging provided by the PET scan and the precise anatomic reference provided by the CT scan could directly impact therapeutic decisions. However, its utility from the health technology assessment perspective is still unclear and research is needed to provide timely information in the context of rapidly expanding worldwide demand for these machines.

University of Alberta and The Edmonton Institute of Health Economics

A non-profit organization founded in 1994, the Institute of Health Economics (IHE) was initially named the Institute of Pharmaco-Economics (IPE). The organization was established as a joint venture between the University of Alberta

and the Government of Alberta. In 2003 the IHE began serving as the secretariat for the only health technology society the Health Technology Assessment International. In 2005 the organization became involved in the provision of provincial health technology assessments. In 2008 the Institute opened its decision analytic modelling unit with the goal of promoting the use of these techniques by healthcare professionals and related organizations (1). The institute's board of directors consists of members of the government, public authorities, academia and industry.

The objectives of this thesis were initially formulated in the clinical domain with **Dr. David Bigam,** surgeon and Chair of the Clinical Investigator Program (CIP) at the University of Alberta. The need for a health technology and particularly health economics expertise, brought **Dr. Philip Jacobs** and **Dr. Arto Ohinmaa** to the discussion and resulted in establishment of a thesis subject. Finally, the addition of oncologic and nuclear medicine expertise through collaboration with **Dr. Charlie Butts** and **Dr. Sandy McEwen**, provided the necessary background and resources to complete our team.

Access to the IHE's experts resulted in assistance on a few smaller projects within the Institute. The systematic reviews in this work were completed with two key systematic review research librarians, **Ms. Liz Dennett** and **Ms. Leanne Topfer,** as well as with University of Alberta systematic review expert and professor, **Dr. Donna Dryden**.

Later, funding from the Faculty of Graduate Studies resulted in the opportunity to participate in the San Francisco-based healthcare training workshops on decision modelling. This allowed us to encompass a decision-model into this work.

A multidisciplinary team was developed and co-ordinated by the author that extended from the surgical domain of the hepatobiliary, nuclear medicine and oncology units at the University of Alberta Hospitals, the Department of Public Health Services and the non-profit Institute of Health Economics. Among its achievements, this team effectuated the first diagnostic accuracy systematic review following recently published Cochrane-based guidelines, at the University of Alberta.

Summary of Contents

This thesis comprises the major stages of a health technology assessment. Each stage, despite its limitations, is successful in providing information to further assess the appropriate utilization of the PET/CT scan in the context of pre-operative surgical planning. The social, legal and ethical domains are discussed only briefly. The core chapters stem from academic articles that have either been accepted, or are in the process of submission for publication by the author.

Systematic Review of Clinical Effectiveness

This stage, Chapter 3, identifies the first step in determining the appropriate use of PET/CT scans. Before the discussion of feasibility or cost, the diagnostic test in question must meet certain measures of clinical effectiveness that may be measured by its sensitivity and specificity. This measure alone, does not take into account the many additional limitations this poses in the realm of *radiologic* diagnostic imaging. However, these two measures do provide a baseline quantitative value that can be compared to other centres and technologies. The objective of this work was to determine whether PET/CT scans were, in fact, accurate in their diagnosis of colorectal liver metastases compared to the currently used CT scan.

In January 2010 the Cochrane Database of Systematic Reviews launched their Diagnostic Test Accuracy Working Group, with the unique goal of tackling the clinically based diagnostic questions. The Cochrane Collaboration identified the intrinsic shortcomings of the radiologic and surgical literature, namely the lack of randomized controlled trials, and conferred a framework through which clinicians and academics could systematically study this data.

The major contribution of our work is presented in the associated publication 'PET/CT scans compared to CT scans for detecting colorectal liver metastases: A diagnostic systematic review' in the *Annals of Surgery* (3). Through a systematic

search of the literature, this work analyses the clinical effectiveness of the use of PET/CT scans in the assessment of colorectal liver metastases.

Systematic Review of Cost-Effectiveness

This next stage outlined in Chapter 4, assesses the historical economic data available for the predecessors of PET/CT scans. Cost-effectiveness data of PET/CT scans are scarce, as the technology is currently undergoing investigation. Hence, to further the understanding of the associated costs, our group performed a systematic review and critical appraisal of the body of cost-effectiveness data.

Technology advances very quickly; in particular, in the domain of medical imaging, therefore, accurate and timely assessments are often difficult. For radiologic diagnostic test accuracy, the task is even more difficult because long-term effectiveness measures may not apply (4). Nevertheless, the quality of cost-effectiveness literature is advancing as more emphasis is placed on the evaluation of the data based on valid technology-assessment principles. The second objective of this research was to evaluate the quality of cost-effectiveness literature for PET technology; the predecessor to PET/CT scans, for the same clinical indication.

The contribution of this work was to demonstrate the current knowledge of cost-effectiveness of the predecessor to PET/CT scans. We also discuss the variability in the results of the cost-effectiveness literature and the innate difficulties of

finding an appropriate effectiveness measure for radiologic diagnostic accuracy studies.

Decision Modeling Techniques

The last stage of our research is outlined in Chapter 5. The most difficult of the stages, that of decision modelling required the compilation of information from the previous chapters and beyond. This work could not have been completed without the help of **Dr. Anderson Chuck**, decision-modelling expert at the IHE (5). This particular decision model was simplified and restricted to a precise, short period of time of interest within the total duration of disease. This in itself presented many challenges that are discussed.

A retrospective look at the literature demonstrated a number of influential academic papers. The research of others, particularly by Kenneth Park and Catherine Lejeune on PET scans for colorectal metastases was particularly useful and provided the framework for our model (6,7). The author is grateful to these two academics for their thoughtful insights and discussions that contributed to the improvements in our current model. This last work contributes to body of literature on PET/CT scans for the assessment of resectability of colorectal metastases by performing with a cost-effectiveness analysis based on a systematic review of clinical effectiveness addressing the issues of the use of intermediate measures in decision analysis.

Conclusions

To conclude the thesis, a discussion of the historical and current challenges of the stages of technology assessments, in particular of the clinical and cost-effectiveness are outlined. A recurring theme through this research is that despite an imperfect literature with limitations to utilization, both theoretical and practical, the clinical value of these three stages can still exploited.

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2. Background

Social and System Demographics

Epidemiology and Pathogenesis of Colorectal Cancer

Cancers of the colon and rectum affected 22 500 Canadians in 2010, with an age-standardized incidence rate of 62 per 100,000 males and 41 per 100,000 females (1). In total 9100 deaths resulted from this disease (1). There is discussion that environmental factors may play a role, with developed nations having a higher prevalence of cancer than underdeveloped nations.

The prevalence of colorectal carcinoma (CRC) increases with age (1) and 90% of cases are seen in patients 50 years or older. Colorectal cancer survival has increased with early surveillance through screening guidelines (1,2). These guidelines were updated in April 2008 in Alberta (Table 2.1).

Table 2.1: Current Alberta colorectal cancer screening guidelines

Fecal Occult Blood Test	Flexible Sigmoidoscopy	Double Contrast Barium Enema	Colonoscopy
• q 1 – 2 years • three step guaiac-based home test • abnormal→ colonoscopy	• q 5 years • + FOBT • if abnormal → colonoscopy	• not recommended • q 5 years • if abnormal→ colonoscopy	• q 10 years • if negative no further screening test for 10 years

*Alberta Health Services: Clinical Practice Guideline: Screening for Colorectal Cancer. Alberta Health Services, Edmonton, Alberta, Canada, Also available online, April 2008.

The adenoma-carcinoma sequence describes the pathophysiology of colorectal carcinoma and outlines the series of known mutations that transform a normal cell to an adenoma and later, to a carcinoma. The preliminary genetic mutations can be seen in bowel polyps that are microscopically classified as hyperplastic and adenomatous. The latter contain atypical cells that, through multiple mutations in the DNA sequence, result in cancer. The lesion can further be microscopically classified into well-differentiated, moderately differentiated and poorly differentiated cells. Macroscopically, CRC growths are classified as sessile, pedunculated, mass or stricture-like (3). Histologically, the tissue is classified into adenocarcinoma, scirrhous and neuroendocrine tumours (3). Prognosis is generally better with more differentiated lesions. Clinical presentation can include weight loss, change in bowel habits, bleeding, or abdominal pain. Often, one of the fecal occult blood tests, digital rectal exam or sigmoidoscopy will reveal pathology in the context of normal clinical function. A colonoscopy or a virtual colonoscopy usually follows and visualised masses are biopsied. This allows the clinician to plan for therapeutic options. Work-up of colorectal carcinoma initially involves colonoscopy, blood work including liver tests and a carcinoma embryonic antigen (CEA), chest x-ray and an abdominal CT scan.

The treatment plan depends on the location and stage of tumour. Colorectal carcinoma follows the TNM classification guidelines (Table 2.2) (3). To assess nodal status, at least 12 nodes must be assessed. These are utilized to stage for

treatment decisions. Stage I and II have no nodal disease, Stage III and its subtypes have nodal disease and Stage IV is classified as metastatic (1).

Table 2.2: TMN staging classification of colorectal carcinoma

Primary (T)		Regional Lymph Nodes (N)		Distant metastasis (M)	
To	No tumour	Nx	Cannot assess	Mx	Cannot assess
Tis	Carcinoma in situ	No	No nodes	M0	No distant metastasis
T1	Invades submucosa	N1	Metastasis 1-3	M1	Distant metastasis
T2	Invades muscularis propria	N2	Metastasis >4		
T3	Invades through muscularis propria into subserosa				
T4	Invades into adjacent structures				

Primary surgical therapy is warranted in patients with localized disease. Adjuvant chemotherapy for stage II disease is controversial, however, for stage III disease both 5 fluorouracil and leucovorin as well as capecitabine are used with benefit[4]. Radiation therapy is not well defined but has been attempted for colon cancer in patients with T4 lesions, immobile tumours, local perforation, obstruction and post-resection residual disease. Nevertheless, a phase III randomized trial demonstrated no benefit (5).

For surveillance, the American Society of Clinical Oncology guidelines 2005 were created based on three meta-analyses of randomized controlled trials. After primary treatment, annual chest and abdominal CT scans for each year for three years in high-risk patients were recommended. Sigmoidoscopy should be done every 6 months for 5 years in patients with resected rectal cancer without pelvic radiation. For patients with colon cancer, carcinoma embryonic antigen (CEA)

should be done every three months for three years after diagnosis in candidates for surgical or systemic therapy and colonoscopy should be done at 3 years after operation and then every 5 years. All patients should undergo a clinical examination every 3-6 months for the first 3 years and every 6 months in years 4 and 5. Chest x-ray, and other blood work are not recommended (6).

Metastatic Colorectal Cancer

Twenty percent of patients with colorectal cancer have liver metastases *on presentation alone* and 25% will have isolated liver metastases that are potentially resectable. The mean survival for untreated liver metastases is 9 months (7). Combining initial and surveillance visits, approximately 50% of patients will present with liver metastases; of whom, a small percentage is amenable to surgical resection with a 5-year survival benefit of 25-40% (8). Management of metastatic spread of colorectal carcinoma can involve surgical resection of the primary tumour, bypass of the primary tumour, surgical resection of liver or pulmonary metastases, adjuvant chemotherapy, radiation therapy or clinical trial treatments. Patients with unresectable metastases can undergo resection with ablation therapies, though clear evidence for this is lacking (9). Otherwise, ablation therapies can be used without resection and can include radiofrequency ablation, cryosurgical ablation, embolization and interstitial radiation therapy (10,11).

Both pulmonary and liver metastases may be resected for cure. Criteria for resection depend on the presence of less than 4 metastases, tumour size and

resection margin of 1 cm. Recent work has not shown a difference in survival with 1-3 tumours and 4 or more tumours; tumour size was not been proven as a reliable predictive factor either (12). A microscopically negative resection margin continues to be a significant predictor of long-term outcome, however, it does not always correlate with a 1 cm margin (12). Pawlik et al. describe new criteria for liver resection that focuses on negative margins, in the context of adequate volume of remnant liver. They state that an R0 resection must be achieved, with 2 adjacent liver segments being spared. Vascular inflow and outflow, as well as biliary drainage must be preserved. The liver remnant must be at least 20% of the total estimated liver volume of normal parenchyma (30-60% with chemotherapy/steatosis/hepatitis and 40-70% with cirrhosis) (12).

PET imaging demographics in Alberta

There are 26 PET & PET/CT scanners in Canada (Appendix 2). In Edmonton, The Cross Cancer Institute currently supports the use of two PET scanners for its catchment area. The first is located at the Cross Cancer Institute and the second scanner is housed at the associated University of Alberta Hospital. The site has a cyclotron to generate positrons and a laboratory to manufacture the fluorine-18-deoxyglucose.

On an annual basis our institution performs 2,900 scans. Of these 500 are done for research purposes. The marginal cost per scan at this frequency is approximately CND $276[13].The total cost per scan was $1,320 at the current annual output (research and clinical). At maximum capacity, the total cost would be $1,100 (13).

Technology Effects and Effectiveness

Positron Imaging Technology

Positron Emission Technology utilizes a positron-emitting radioisotope called fluorine-18-deoxyglucose (FDG), a glucose analogue. This is injected intravenously and the glucose transporter facilitates the isotope's uptake into cells. At the cellular level the positrons are released from the FDG and collide with electrons to release 511keV energy that is detected by the scanner (14). This data is then collected and the region in question is displayed on a diagrammatic representation of a human body as an area of increased cellular activity. Cells with high turnover preferentially take up the isotope. PET scans are limited by their inability to provide anatomic detail, but provide functional information about tissue for both diagnosis and response to therapy (14). The PET scan has a low false positive rate compared to CT scan(14).

PET scans are acquired during free breathing and the relative motion during the 20-60 minute scan blurs images. CT scan must be adapted to this breathing as the diaphragm, lungs and abdominal organs will also be displaced (15). Integration with the images through software fusion is possible but wrought with logistic complications, lengthy time to create and registration errors (15). The second option, hybrid scanners, introduces joint CT and PET scans where image acquisition happens without repositioning and at a 35% time reduction (15). Nevertheless the issue of free breathing, bladder filling, bowel motions still presents a problem (15). Furthermore, previous contrast from a CT and in situ metal can create false hotspots (15).

Hardware integrated PET/CT appears to improve diagnostic accuracy over stand alone PET and CT. Alternatively, software fusion is prone to errors and its use should proceed cautiously (15). The use of joint PET/CT implies the need for multidisciplinary readings with nuclear medicine, radiology, oncology and surgery (15). The combination of PET/MRI, in the future could provide soft tissue localization with low radiation and should be available clinically in the next five years (15).

The indications for PET scans in our institution include work-up for cancers of the brain, breast, colorectal, oesophagus, head and neck, thyroid, lung, ovary, cervix, endometrial, testicle, kidney, bladder and stomach. PET is also used for lymphoma, melanoma, cholangiocarcinoma, neuroendocrine, sarcoma and primary unknown tumours. There is a need to judiciously include FDG-PET into therapeutic trials to test the appropriate positioning of PET into algorithms for most effective patient management (7,16).

Indications for PET imaging in colorectal cancer

The oncologic indications of the PET/CT are currently being researched. Here we retrospectively consider the present indications for the simple PET scan, understanding that PET/CT would likely be sought for the same reasons.

The diagnosis of colorectal cancer is relatively straightforward with the use of CT scans and colonoscopy. Most patients with resectable disease are surgically

treated resulting in modified anatomy and inflammatory changes that challenge the interpretation of post-operative imaging, particularly for the research of recurrence. The PET scan may be useful initial test in the search for suspected recurrent colorectal carcinoma as it can attempt to differentiate post-operative changes from tumour, highlight malignant lesions and evaluate patients with rising tumour markers (17). Of note, PET is limited by normal physiologic uptake of 18F-FDG in the liver and colon, making detection of lesions < 1cm difficult (18).

In a 1997 retrospective analysis of 51 patients with suspected recurrence of colorectal carcinoma presented on 61 occasions and underwent PET, CT and CT portography scans. Pathologic diagnosis was report in 44 patients and clinical follow-up was reported in 17 patients. Of the total 166 suspicious lesions, 127 were hepatic and 104 of these hepatic lesions were malignant. The 39 extra hepatic lesions had 34 malignancies. Accuracy rates were reported as 92% PET, 78% CT and 80% CT portography scans. The PET scan was the most accurate non-invasive test for informed management decisions (19). A meta-analyses done in 2000 found that PET scans had a 97% sensitivity for detection of metastatic colorectal cancer in the whole body (20).

With the use of PET to aid in decision for the appropriate surgical procedures improvements in patient survival rates in colorectal liver metastases can be seen as the target population changed (21).

In a prospective study of 24 patients with recurrent liver metastases, suspected based on CT scans or by elevated tumour markers, underwent PET scans at least one year after their last surgery. Nineteen patients were found to have recurrence. Sixteen of these were diagnosed on operative resection, 2 at intraoperative biopsy, 1 on percutaneous biopsy and 5 were followed clinically. There were discrepancies between imaging in 6 patients, where the PET scan identified all but one single liver lesion <1cm. PET changed the planned pre-operative surgical management in 6 of 24 patients (22).

The dramatic change in treatment plans in these studies suggests that PET might be useful to add to the clinical algorithm. In some institutions they are being routinely performed on patients being evaluated for liver resection for colorectal liver cancer (23). However, this is not the standard clinical practice.

While the use of PET for recurrence was being evaluated, in 2002 a prospective study by Kalff et al. suggested that some clinical algorithms might require PET scans to make an initial treatment decision. Interestingly, in those patients who would not routinely need a PET scan but received one in the trial, 56% had an altered treatment plan based on their PET findings (18). The most common change in treatment plan was a modification in the type of surgery, as opposed to cancellation of the surgical treatment (18).

The addition of PET scans to the surgical decision-making algorithm appears to improve clinical decision-making. The newer technology of PET/CT scans may make even greater leaps. Now, by combining the two procedures, the disadvantages of PET scans are decreased. To this end one study compared PET/CT scans to PET scans in 2003 and found that diagnosis by PET/CT scans reduced the number of lesions with uncertain location by 55% compared to diagnosis by PET scans alone (25). Diagnosis by PET/CT scans also resulted in a treatment change compared to diagnosis by PET scans alone (10 non-operable, 6 positive hepato-duodenal nodes—liver resection + removal of peri-portal nodes= 16/60 patients) in 21% of patients presenting for possible liver resection. No change in treatment plan was seen in 79% of patients (23). PET/CT scan is significantly more sensitive to CT scan to detect recurrence of metastatic liver disease after liver resection for metastatic colorectal cancer (23).

Economic Evaluation of Diagnostic PET

Colorectal Cancer

The treatments for colorectal cancer have clinical importance and pre-operative surgical decision-making plays a large role. Tools to improve this decision-making process include new technology. The question then remains whether or not it is feasible to introduce these technologies, such as PET, into the diagnostic algorithm, and determine who would benefit and at what cost to the system. To this end our group conducted a systematic review and critical appraisal of the available data, the results of which are present in Chapter 4.

Other Cancers

To date, lung cancer and solitary pulmonary nodules have been targeted for economic evaluations around the world. Numerous studies have found that PET imaging has utility in in the diagnosis of metastatic non-small cell lung cancer and also demonstrates cost-effectiveness (37,38). With respect to solitary pulmonary nodules (SPN), PET imaging has become the new standard of care for work-up (39).

For the field of lung cancer numerous competing strategies were examined including basic work-up with chest x-ray and another strategy with mediastinoscopy. In the early 2000's a UK randomized controlled trial of 22 hospitals studied 465 patients with clinical suspicion of lung cancer from history, physical and chest x-ray. The patients were randomized to receive routine work-up vs. routine work-up and a PET scan with follow-up for 6-12months. Significantly fewer patients required mediastinoscopy in the PET arm, but there were no differences in direct medical costs (tests, outpatient visits, hospital admissions) (40).

In another study, a cost savings of AU $2,128 was identified by the routine use of PET scans and mediastinoscopy compared with mediastinoscopy alone in preoperative work-up for non-small cell lung cancer. The study looked at costs and clinical outcomes (avoidance of unnecessary procedures, prevalence of

disease, sensitivity and specificity of PET), using effectiveness evidence from published data in Australian decision model. The study supported the routine use of PET to avoid unnecessary mediastinoscopy with a cost savings of AU $ 2128 (41).

Within the Canadian system, a decision tree calculation suggests a cost savings of US $4,689 in patients with non-small cell lung cancer. Creating a budget impact of US $ 8 million based on the prevalence of disease. This was reviewed by CRD (42). Clearly, this impact is significant.

The detection of primary tumour is just one facet where PET imaging is utilized. With respect to the determination of metastatic nodal disease in lung cancer and in previous colon resections, it is difficult to differentiate reactive (inflammatory or metastasitc) lymph nodes on CT scan or MRI from non-reactive lymph nodes, leading to the necessity of nodal biopsy for confirmation (43). PET imaging was 92% accurate in making this distinction, and changed therapeutic management in 18% of patients leading to cost savings documented in both decision analysis and randomized control trials (43).

A Missouri based study performed a decision analysis on patients with stage I lung disease discovered on CT scan and PET scan. Seventy-four percent of these patients had diagnostic mediastinoscopy at a cost of $250, 989/ life-years gained and a 0.008 years of increased life expectancy. The authors found that with the

CT scan and PET scan diagnosis of stage I cancer, little benefit was derived from mediastinoscopy (44).

Primary brain cancer can be diagnosed and graded for prognosis. This is particularly important in heterogeneous glioma and can also aid in more directed biopsy of metabolically active areas (39). Pet imaging is particularly useful here to differentiate tissue.

The use of PET imaging spans many facets of oncologic disease that is demonstrated in these few examples. For some cancers, a significant body of literature is already present, whereas for others, new literature is just being published.

Cost Effectiveness Analysis for Diagnostic Procedures

Health economics is a complex study of statistics and theory. Of particular importance is the attention to detail required when valuing health outcomes. Another important factor in health economics is cost analysis, defined by the analysis of the comparative costs of alternative treatments or health care programmes (45). This analysis is common to all economic evaluations.

Cost effectiveness, in particular, looks at the comparison of at least two alternatives with respect to both cost and consequences. For example, a study looking at PET scans vs. CT scans for colorectal carcinoma, showed an average

savings of $5269 with addition to PET to the clinical algorithm over current management. By measuring only costs but not consequences this study would be considered a cost study (33). Alternatively, by including differences in an outcome measure such as ‘life years gained’, ‘treatment plan change’ or ‘death’, a study would be considered a cost effectiveness study.

Specifically, with the analysis of diagnostic procedures the cost of the diagnostic tool and the cost of the resulting interventions must be considered.

Conclusion

Colorectal cancer is a pertinent problem of developed countries that has seen dramatic declines in cancer-related deaths secondary to early screening programs. With the addition of new diagnostic tools to improve pre-operative surgical planning, appropriate and timely treatments are possible.

Throughout the developed world PET scans are becoming an important tool in oncology diagnostics. As the drive to build new facilities continues, the various potential uses for PET scans are highlighted, bringing with it an increased desire to utilize the technology in research endeavours. Over time, this translates into increased clinical interest. It is at this point that the optimum usage endpoints become important.

From the perspective of the imaging department's fiscal needs before lobbying for funding a new PET facility one must determine if the catchment area of the facility validates the significant down payment. Second, the cost per study at optimum usage is determined to comprehend the ongoing cost. Third, the cost of doing any additional studies must be considered.

Health care is often emotionally charged, a 'right' of all citizens. Which also makes the cost of care a secondary objective on the list of most primary caregivers. Instead, from their perspective, these clinicians and researchers are more concerned about access to the use of PET scans. With respect to the competing needs of oncology patients to those without cancer are more easily addressed. However, within oncology, the competing needs of pulmonologists, thoracic surgeons, hepatologists, hepatobiliary surgeons, gastroenterologists and colorectal surgeons become a contentious issue. Some believe these problems are a result of lack of health care dollars and that the answer is the provision of more PET facilities. In reality, it is likely a problem of effectiveness—how best can the resource be used to make the most difference to the most patient outcomes, at the most efficient cost?

To justify, the costs of a continuously operating a PET facility, a given number of cases per year must be compared to the patient outcomes achieved. Outcomes can range from intermediate outcomes that include 'number of new lesions found' and final outcomes that can include death, change in treatment plan, surgery or

palliation. These variables all have an associated cost. It is the comparison of the PET intervention cost and the outcome cost that can answer the question.

Often access to imaging comes down to availability of imaging time, technicians, FDG, and doctors. Sometimes it comes down to money and availability of funds. In the Canadian system, where public health care supports all citizens, the necessity for the best value for each health care dollar is paramount and herein comes the necessity for careful analysis of the cost-effectiveness of PET imaging in the pre-operative assessment of resectability of colorectal liver metastases.

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3. PET/CT scans vs. CT scans for detecting colorectal liver metastases: A diagnostic systematic review

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Introduction

Colorectal cancer is the third leading cause of cancer in men and women in Canada (1). Metastatic spread to the liver is common, for which the overall survival without treatment is nine months (2). If the liver is amenable to a surgical resection, five-year survival of 25 to 40% can be expected (3).

Surgical treatment is possible, but the intra-operative discovery of extra-hepatic disease means that the patient undergoes a non-beneficial operation (laparotomy without resection) and requires a hospital stay. This results in substantial and unnecessary health care costs (4).

The hybrid positron emission tomography/computed tomography (PET/CT) scanner provides anatomic and functional information on body tissue. The PET component uses FDG-glucose to highlight areas of increased glucose metabolism and the subsequent increased metabolic rate as in neoplastic tissue. It is limited, however, by poor anatomic delineation. Software and hardware fusion of non-integrated PET and CT images can be done but may introduce error as a result of patient movement, breathing and positioning. The integrated PET/CT scan positions the patient once and performs both tests. It is currently used for lung cancer, lymphoma, imaging-negative cancers (thyroid, germ cell, colorectal cancer), brain imaging, and myocardial viability studies (5). There are limitations of using PET/CT for colorectal metastases. In particular, PET/CT cannot detect

tumours less than 5mm. Furthermore; the use of chemotherapy less than one month prior to the scan can result in high false negative results (6).

Bipat et al. conducted a meta-analysis in 2005 to assess the diagnostic accuracy of various imaging techniques to identify hepatic metastases (7). They reported a pooled sensitivity of 95% for PET (non-integrated) and 64% for CT for identification of hepatic lesions. On a lesion-by-lesion basis, they found sensitivity of 76% and 64% for PET and CT, respectively. They did not examine extra-hepatic disease or PET/CT integrated scanners. In 2007, researchers from the Netherlands developed evidence-based guidelines for the evaluation of colorectal liver and extra-hepatic metastases. For extra-hepatic disease they recommended that abdominal and chest CT scans be performed; based on the CT findings, the decision to use a PET scan can be made (8).

The objective of this systematic review was to assess the diagnostic accuracy of an integrated PET/CT scan compared to CT scan for the pre-operative evaluation of patients with suspected colorectal liver metastases to identify the presence of hepatic and extra-hepatic metastatic disease verified by biopsy.

Methods

Data Sources

We searched the following electronic databases: Medline (1950-2009), EMBASE (1980-2009), Scopus (February 2009), Web of Science (February 2009), Cochrane Library (Issue 1, 2009), PubMed (limited to the last 6 months), and

DARE. Searches are current to March 30, 2009. We conducted extensive searches of the grey literature including: Conference Papers Index (2003 to 2009), American College of Radiology (2001-2009), American College of Surgeons (2002-2009), Royal College of Radiologists (2003 to 2009), Canadian Association of General Surgeons (2003 to 2009), and American Society of Clinical Oncology (2003-2009). We also searched Google Scholar, Clinical Trials Registry, and health technology websites (Appendix 1). We hand searched the reference lists of all included studies.

Search strategies were developed in consultation with a research librarian. Key search terms included: (PET or PET/CT or "PET/CT" or FDG-PET or FDGPET or FDG PET) AND (colorectal or colo-rectal or colon or rectal) AND (sarcoma or carcinoma or lymphoma or oncolog* or malignan* or tumor* or tumour* or cancer* or neoplasm*) AND (liver or hepatic) AND (metastases or metastatic). A detailed search strategy is available from the authors. The studies were not limited by study design, publication type, or language.

Study Selection

One reviewer (SP) reviewed the titles and abstracts of all citations using broad screening criteria to exclude studies that were clearly irrelevant. Two reviewers (SP, MM) independently reviewed the full text of potentially relevant studies that assessed the diagnostic accuracy of PET/CT scans for colorectal metastases. Both investigators used a standard data collection form and applied eligibility criteria

that were defined a priori (Appendix 2). Disagreements were resolved by consensus.

For inclusion, studies had to be reports of primary research of adults (≥ 18 years) with colorectal liver metastases being assessed for liver resection with a 2-18-F-fluoro-2-deoxyglucose PET/CT scan and a CT scan with histological gold standard. All studies had to report sufficient data to populate a 2x2 table.

We excluded studies if they included patients with intact primary tumors, previous hepatic therapy for cancer, or who were pregnant. Studies were also excluded if they used an alternate radio-compound or assessed fused images of separate PET and CT scans (Appendix 3).

Data Extraction and Assessment of Methodological Quality

Two reviewers (SP, MM) extracted all data independently using a standardized form. The reviewers were not blinded for journal name or authors.

Two reviewers (SP, MM) independently assessed the methodological quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. Using Whiting et al.'s published guidelines to apply the QUADAS tool, decision rules were developed for each question. In general, if the study met the criteria it received a 'yes', if it was not reported, but didn't likely

effect the results it was reported as 'unclear', if it was not reported but likely effected the results, it was reported as 'no' (9). QUADAS is the tool recommended by the Cochrane Collaboration for reviews for diagnostic test accuracy (9,10). The tool assesses the selection and spectrum of patients as well as the characteristics, timing and completeness of the use of the reference standard (CT) and the index test (PET/CT). The two tests must be independent and described in adequate detail to be replicable. Also, the reporting of results of the reference and index tests should be done independently to uphold quality standards. Finally, withdrawals and uninterpretable results must be reported (9).

Data Analysis

True positive, true negative, false positive and false negative data are presented for each study. Assessments of heterogeneity and reporting bias were planned but not executed because of the small number of studies. Forest plots of sensitivity and specificity with 95% confidence intervals (CI) were generated. Planned pooled analyses were not performed given the heterogeneity in the studies.

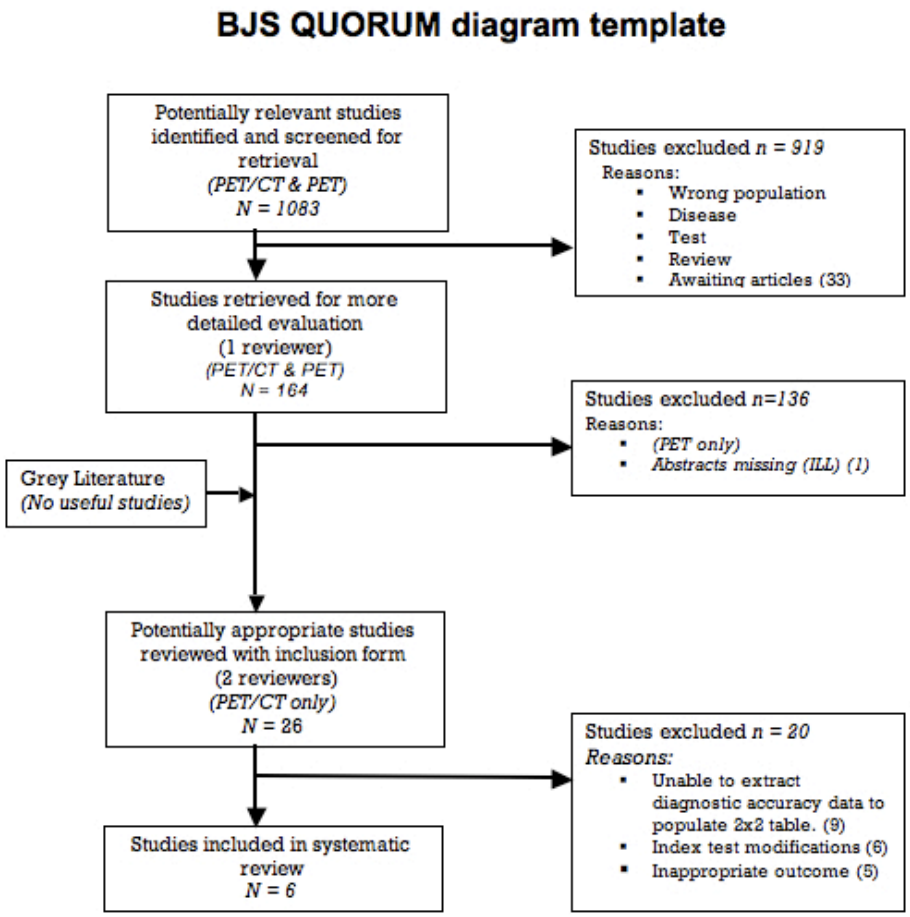
Results

Description of Included Studies

Our search identified a total of 1,083 unique citations of which 26 met the inclusion criteria. Of these, 20 of 26 studies were further excluded because of insufficient data to calculate sensitivity and specificity (n=9), modifications to

routine PET/CT protocol (n=6) and lack of sufficient histological outcomes (n=5) (5, 11-30). Six studies were included in the review (6, 31-35) (Figure 3.1).

Figure 3.1: Workflow of included studies (QUORUM)



All six studies used a prospective or retrospective cross-sectional design (Table 1.0). Only one study reported consecutive recruitment of patients. Five of studies reported patient demographics; one study did not describe their population. Sample sizes ranged from 35 to 131. All studies used PET/CT scans following the routine protocol for their institutions. Five studies reported detection of liver metastases as an outcome (6,32-35). Three studies reported detection of extra-

hepatic metastases (6, 33,34). Follow-up ranged from 6 to 24 months. The specific study and patient characteristics and results are summarized in Table 3.1.

Table 3.1 Characteristics of included studies

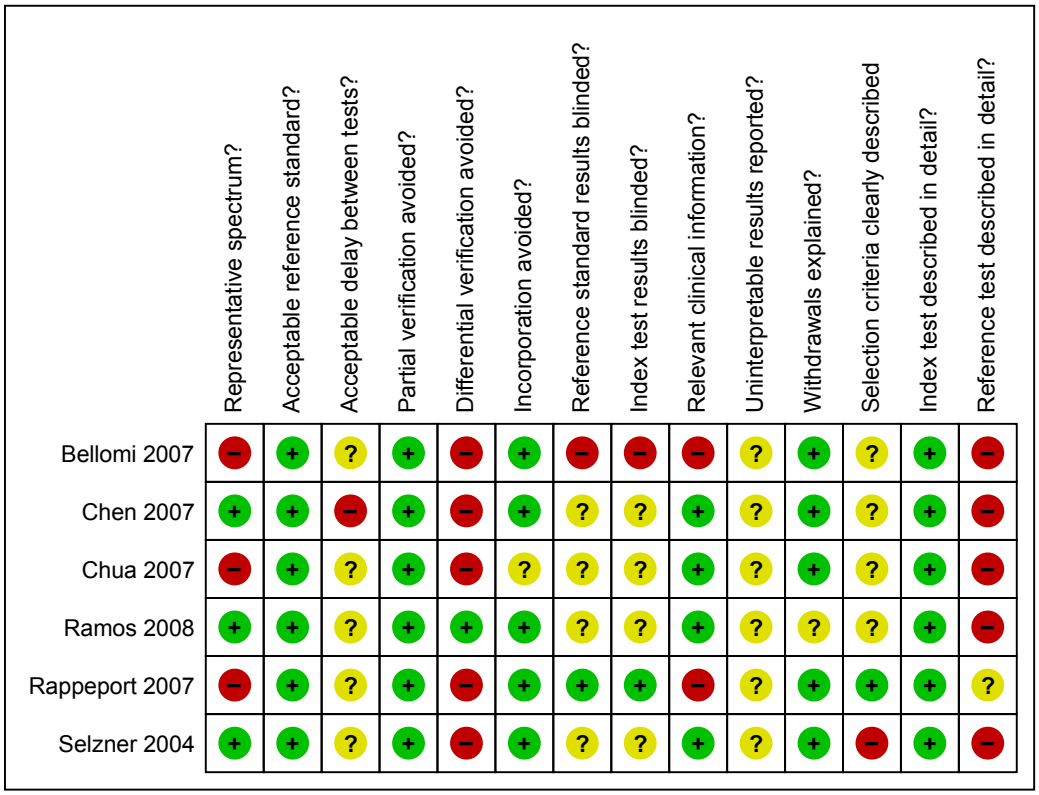
Author	Design	Duration (mo)	Setting	Total N	# male	Age (ave)	Fasting glucose	Cancer Type	# with Chemo, RT, both	Timing of PET/CT & chemo	Index Test	Alt. Test	Gold Standard
Bellomi, 2007	RCS*	24	tertiary	67	n/a	n/a	n/a	rectal	23, 25, 19	4 weeks	iPET/CT	CT	Biopsy
Chen, 2007	RCS	24	tertiary	68	48	58.1	6.6	CRC	n/a, n/a,n/a	n/a	iPET/CT	CT+	n/a
Chua, 2007	RCS	n/a	tertiary	131	67	62	n/a	CRC	n/a, n/a, n/a	6weeks	iPET/CT	CT	Biopsy
Ramos, 2008	PCS**	14	tertiary	63	41	62 (median)	n/a	CRC	17, 0, 0	4 weeks	iPET/CT	CT	Biopsy
Rappeport, 2007	PCS	8	tertiary	35	16	62 (median)	n/a	CRC	4, 0, 0	4 weeks	PET/CT	CT	Biopsy
Selzner, 2004	PCS	6	tertiary	76	52	63 (median)	n/a	CRC	62, 0, 0	12 weeks	PET/CT	CT	Biopsy

* RCS= retrospective case series, PCS = prospective case series, Alt. = alternative test arm

Assessment of methodological quality

The methodological quality of each study is summarized in Figure 3.2. Overall the quality of the studies was moderate. Well-documented items included acceptable reference standard, partial verification avoided, incorporation avoided, withdrawals explained, index test described in detail. Items that unclear in more than half of the studies included acceptable delay between tests, blinding of reference standards, blinding of index test results, reporting of uninterpretable results, clear description of selection criteria. Of concern is the possibility of differential verification bias (no blinding of reference test and index test results).

Figure 3.2: Methodological quality assessment of included studies

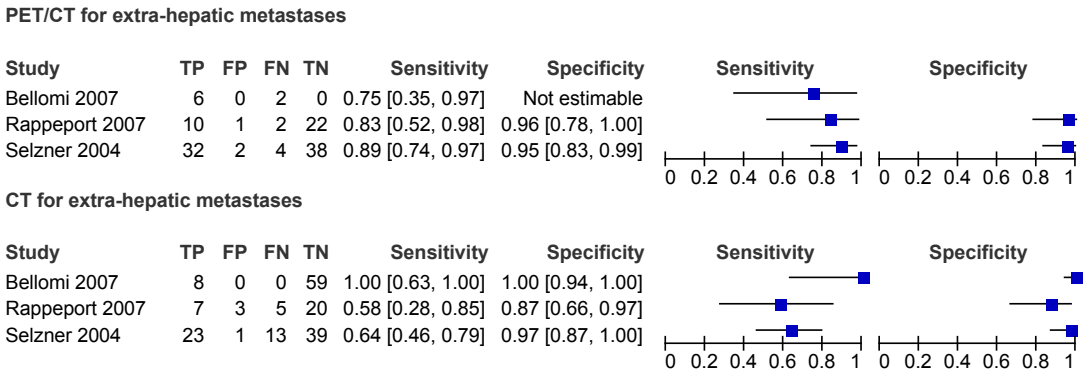


Qualitative Synthesis

Extra-hepatic Disease

Three studies provided data on extra-hepatic disease (6,33,34). The sensitivities and specificities were either directly reported in the papers or derived from the data presented in the paper (Figure 3.3). The sensitivities ranged from 75% to 89% for PET/CT and 58% to 100% for CT. The specificities ranged from 95% to 96% for PET/CT and 87% to 100% for CT. The 95% CI for each test overlapped and the differences among the studies were not significant.

Figure 3.3: Forest plot of extra-hepatic metastases



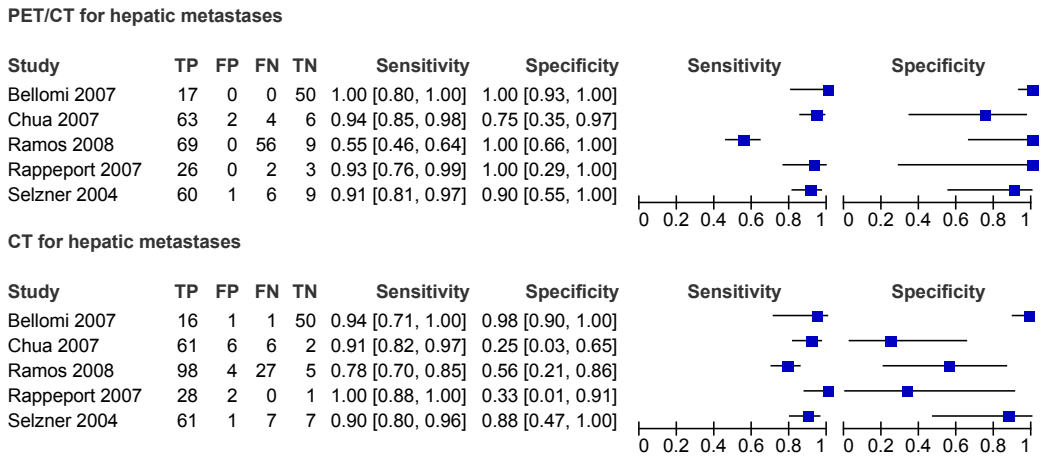
In a fourth study, Chen et al. reported combined hepatic and extra-hepatic disease. They demonstrated a sensitivity of 95% and specificity 83% for PET/CT (31). This study did not conduct biopsies of lesions that were PET/CT positive; however, they conducted follow-up on patients over 5 to 28 months (31). Therefore, there may be unidentified false positive patients in the cohort.

Hepatic Disease

Five studies provided data on the detection of hepatic metastases (Figure 3.4) (6,32-35). Sensitivities ranged from 55% to 100% for PET/CT and 78% to 100% for CT. The Ramos et al. study was significantly different from the others based on the 95% CI (32). The sensitivity of CT ranged from 78% to 100%, and there were no significant differences between studies.

The specificities of PET/CT ranged from 75% to 100% with no significant differences between studies. There was considerable heterogeneity for specificity that ranged from 25% to 98% for CT scan with very wide confidence intervals.

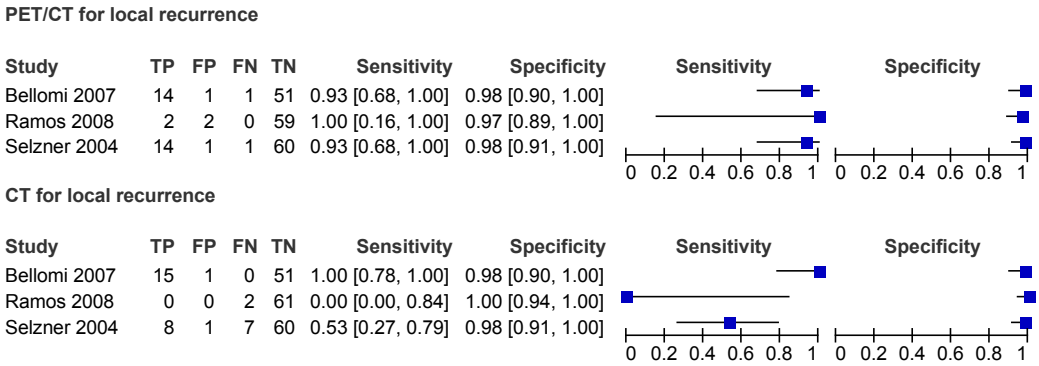
Figure 3.4: Forest plot of hepatic disease



Local Recurrence

We conducted a post hoc analysis of local recurrence, which was reported in three studies (Figure 3.5) (6,32,34). In the Bellomi et al. study, the CT specificity was very high (34). This was explained by the authors by a potential difference in senior level experience of the radiologist compared with the nuclear medicine physicians who had just started to report PET/CT (34). Ramos et al. showed very high PET/CT sensitivity and very low CT sensitivity in their analysis (32). Selzner et al. found the opposite: PET/CT was more accurate than CT (sensitivity and specificity of 93% and 95%, compared with 53% and 98%) (6).

Figure 3.5: Forest plot of local recurrence



Chemotherapy effect

A post hoc comparison of the effect of chemotherapy on the detection of metastases was conducted. Research has shown that chemotherapy within one month of PET may decrease the sensitivity of the tests results, however, no studies had performed a PET/CT at less then one month post-chemotherapy(6). Chua et al. reported that the PET/CT sensitivity was 98% and specificity was 100% in the chemotherapy group, and 95% and 60% in the patients without chemotherapy (35). Patients who did not have histological confirmation had close radiologic monitoring. Lesions were considered metastatic based on their rate of growth (35). Chemotherapy did not confound the PET/CT accuracy for hepatic metastases in the study by Rappeport et al (33).

Selzner et al. found extra-hepatic metastases in 9 of 18 patients with recent chemotherapy (6). Of these, three (66%) did not have FDG uptake. In the group with no chemotherapy only one of twelve patients were FDG negative with local recurrence diagnosed by a large and obvious tumour in the sacrum (6).

Change in treatment plan

The definition of 'change in treatment plan' includes patients having a different type of surgery (likely more aggressive) or avoiding surgery altogether. Since there are no firm guidelines for hepatic CRC resectability, these treatment decisions are based on individual and regional practices. Chua et al. found that 10 of 15 patients (66%) avoided surgery (35). In Chen et al., 4 of 56 (13%) patients had a change in surgery and 7 of 56 (20%) patients avoided surgery based on the PET/CT.[31] Similarly, 5 of 63 (9%) people had a change in treatment plan in the Ramos et al. study; 4 false positive patients were not included (32). Selzner et al. found that PET/CT resulted in a change in treatment plan in 16 of 76 (20%) patients.[6] Lastly, Rappeport et al. found that 3 of 35 (9%) patients avoided surgery, but no patient had a change in the surgical procedure (33). Overall, all studies reported that the use of PET/CT affected clinical practice in 8% to 20% of patients.

Discussion

The use of CT alone to determine resectability of colorectal liver metastases could lead to under diagnosis of invasive disease and unnecessary operations. The PET/CT scan has been used to improve pre-operative identification.

Using a comprehensive search strategy and concerted efforts to avoid publication and selection bias, this review identified all the available evidence to assess the

effectiveness of PET/CT compared with CT for colorectal liver metastases. Overall we identified six studies that met our inclusion criteria involving between 35 and 131 participants. Due to the small number of studies we were not able to derive pooled estimates. However, the results of the studies suggest that PET/CT is sensitive and specific for extra-hepatic disease. CT with contrast appears to be sufficient to identify intra-hepatic disease. Evidence suggests that PET/CT is better able to detect local recurrence of tumours and effect of chemotherapy. Finally, there appears to be a trend favoring a change in treatment plan based on the PET/CT. These results must be interpreted with caution. Overall, the methodological quality of the studies was moderate.

The added effective radiation of 13-30 mSv with (PET/CT) compared with 7mSv (CT) and 10 mSv (PET) is marginal for patients with metastatic cancer, especially since the lifetime risk of radiation is 0.2% to 0.5% (36). However, if it is possible to offer dual reporting of both techniques, this may be of benefit for patient outcomes in the search for extra-hepatic disease. These clinical implications are reason enough that research be continued in this field.

Sources of clinical heterogeneity could not be assessed in the small number of studies; however, two studies stand out. One study showed significantly higher sensitivity in detecting extra-hepatic disease by CT than the other studies (34). Aside from being limited to patients with rectal cancer, these patients were referred for numerous reasons (CT finding, colonoscopy findings or clinical

findings). Aggressive tumours are more likely to have colonographic or clinical findings from rectal cancer, and hence the patient population in this study could be representative of more advanced disease. Ramos et al. had poor PET/CT sensitivity for detecting hepatic disease (32). Their unit of analysis was lesion-based as opposed to patient-based. Without individual patient data we could not determine how many patients had more than one metastatic lesion and it is likely that patients were counted more than once in this analysis. Therefore, the results of Ramos et al. may not be comparable to the other studies in this review.

There are many methodological considerations when undertaking a systematic review of the diagnostic literature. First, there is the possibility of publication bias. The impact of publication bias on the results of diagnostic test accuracy reviews is not well understood nor have the tools to investigate publication bias in these reviews been developed (37). We conducted a comprehensive search of the published literature for potentially relevant studies. Search strategies included combinations of subject heading and free text words. These searches were supplemented by hand searching for grey literature (i.e., unpublished or hard to find studies). Furthermore, there were no restrictions on publication type, study design or language. Despite these efforts, we recognize that we may have missed some studies. Thirty-three abstracts could not be retrieved despite efforts to obtain them through our University interlibrary loan service; however, only one title referred to the integrated PET/CT and the others to PET alone. Therefore, it is unlikely that major studies on the integrated technology were missed.

There is also the possibility of selection bias. However, we employed two independent reviewers to identify potentially relevant studies and feel confident that the studies that were excluded from this review were done so for consistent and appropriate reasons.

There were numerous limitations to the review imposed by the study design, study reporting and the technology. Because PET/CT became more available in the early 2000's the body of literature is small (36). Secondly, all studies were case series with inadequate reporting of the patient selection process and elements of the demographics. A number of studies did not have adequate reference standard measures. Lastly, the reporting of true positive, false positive, false negative, true negative sensitivity and specificity data was poor.

This review systematically assessed the data on diagnostic accuracy of PET/CT compared with CT scan for colorectal liver metastases and extra-hepatic metastases. There appears to be evidence for the use of PET/CT scans for the detection of extra-hepatic metastases and the possible avoidance of surgery. This suggests the PET/CT scan has added value over a CT scan alone in avoiding surgery. No studies provided adequate follow-up to demonstrate a change in life expectancy of those undergoing surgery. The quantity of data is minimal in this field and the studies are at risk of several sources of bias. Well-designed prospective studies are needed to provide evidence about the diagnostic test

characteristics of PET/CT. More research in the form of prospective randomized trials is required to decrease the bias and increase the quality of data on PET/CT scans.

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4. Systematic review and critical appraisal of cost-effectiveness studies on PET scans compared to CT scans for the assessment of resectability of colorectal liver metastases.

Background

Treatment of hepatic metastases from colorectal cancer can involve surgery, chemotherapy, ablation or radiation therapy. Surgery is most common and requires an evaluation for extra-hepatic disease, done by chest x-ray and an abdominal CT scan. Once extra-hepatic disease is ruled out, surgical treatment can proceed(23). Unfortunately, in 30-40% of patients taken for operation, extra-hepatic disease is discovered, the patient undergoes a laparotomy without resection, requires a hospital stay and incurs significant health care costs—all with the added risk of post-operative complications without the benefit of treatment(24).

With the availability of positron emission technology (PET) scans, the diagnostic algorithm for colorectal liver metastases is being challenged. Software and hardware fusion of PET and CT scan images can be done to efficiently combine the higher sensitivity of PET scans and the anatomic detail of CT scans. The PET technology is limited by poor anatomic delineation and so a CT scan with contrast is still required.

PET scans have been shown to have 89% sensitivity compared to 64% sensitivity of CT ($p=0.02$) in the detection of metastatic colorectal cancer(15). This has shown a change in the treatment plan in 30% of patients(15). By using PET to more accurately find extra-hepatic disease before unnecessary surgical

intervention, changes to patient outcomes, wait times and cost could be impacted. Prospective trials are emerging to investigate the utility of this PET technique for clinicians. The limiting step is generally the high costs associated with a PET facility. To this effect, decision modeling has been used to answer cost-effectiveness questions in the attempt to determine the financial feasibility of the PET technology.

The objective of this paper is to identify and critically appraise the available cost-effectiveness literature for the use of PET scans compared to CT scans in the assessment of colorectal liver metastases.

Methods

A thorough systematic review of the literature was performed and identified economic evaluation studies on PET and CT scans for liver metastases in patients treated for colorectal carcinoma. The search strategy was created in conjunction with our research librarian using recognized economic keywords and MeSH terms used by CADTH (Canadian Agencies for Drugs and Technologies in Health). Articles were selected if they reported economic data and outcomes on patients with colorectal liver metastases who underwent PET and CT scans. The type of outcome data was not specified as significant diversity was expected.

A search strategy was applied to the following databases: OVID Medline 1980-2009, Embase, Web of Science, AMA Clinical Practice Guidelines (March 2009),

CMA Infobase (March 2009), National Guideline Clearinghouse (March 2009), ClinicalTrials.gov (US) (March 2009), CenterWatch Clinical Trials Listing Service (March 2009), metaRegister of Controlled Trials (*m*RCT) [Trial as of 2005-11-21], National Research Register (March 2009), AHRQ Clinical Trials Registry, Trip Database, CRD DARE (March 2009), CRD NHS EED, CRD HTA Database, AHRQ Evidence Based Reports http://www.ahrq.gov/clinic/epcix.htm (March 2009), AHRQ Technology Assessment (March 2009), Nice Technology (March 2009) and Google (March 2009). The search was carried out using the following main keywords: colorectal cancer, liver metastases, PET, CT and cost-effectiveness. The main topics were exploded and associated terms were used to ensure that a complete search of the literature was undertaken (Appendix 5).

Two reviewers (SP and AC) eliminated clearly irrelevant articles based on their titles and abstracts. Of the remaining references the full text articles were retrieved and inclusion criteria were applied. References for review articles were searched, but reviews were not included. Disagreements were resolved by consensus. Data extraction was done by two reviewers (SP, AC) using a data extraction form. Data analysis was expressed with an incremental cost-effectiveness ratio and quality was assessed by Drummond's guidelines for economic evaluation(1).

Results

Search Results

Of the 73 discrete citations identified, 64 were excluded based on the title and abstract search because they were reviews or because they lacked cost or outcome data (Figure 4.1). The grey literature provided only one study of interest (2). Of the 9 studies, 5 studies were excluded for the following reasons (Table 4.1): lack of original data (3, 4), provided only cost data (5) and were written in Japanese, translation for which was not feasible (6, 7). Hence, four studies were included for review (2,8, 9, 10).

Figure 4.1: Quorum flow diagram of economic evaluation studies for PET scans for colorectal cancer

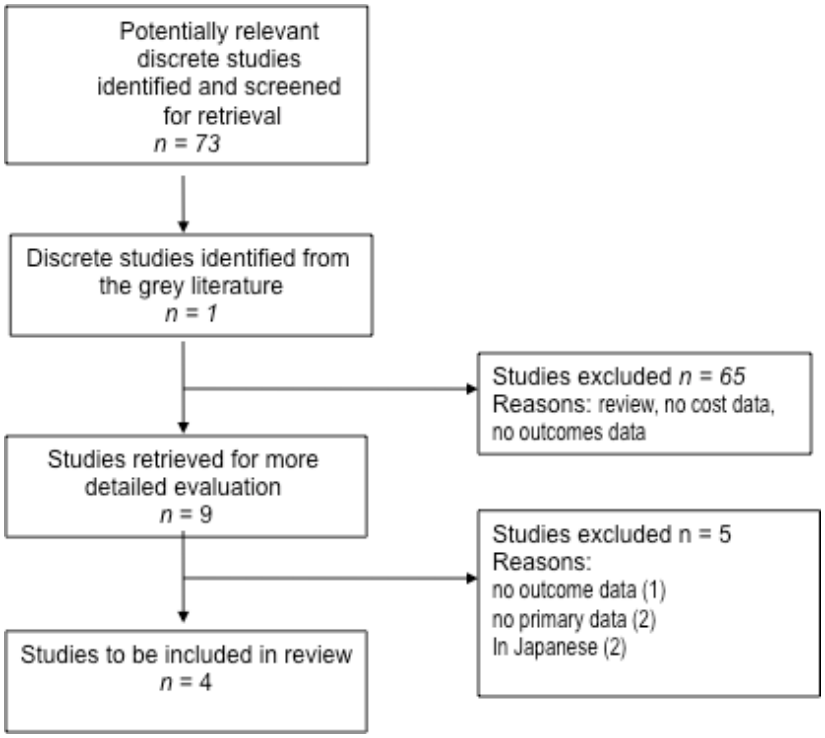

Table 4.1: Studies excluded from systematic review of economic evaluation of PET scans for colorectal cancer

Arulamplam et al	2001	Br.J.Surg	Review article, no primary data
Facey et al	2007	Health Tech Assess	Review article, no primary data
Zubeldia et al.	2005	Canc Biother Rad	Cost data only, no outcome data
Ito et al.	2002	Nippon Igaku Hosha	Japanese. No translation
Kato et al	2002	[Japanese title]	Japanese. No translation

Study Design

Drummond's criteria 1, 2, 8 and 10 relate to study design elements and specifically addresses the definition of the question, the appropriateness of the alternate outcomes and the discussion of the limitations (Table 4.2). Of the studies reviewed, one study was a prospective blinded trial and the other three were decision models.

Valk et. al. (1999) published a prospective-blinded trial comparing PET scans to CT scans for the assessment of colorectal liver metastases using the outcome of number of operations avoided as their outcome measure(10). A decision model-based study that modeled the diagnostic work-up of metastases in patients known for colorectal cancer, presenting with elevated carcinoembryonic antigens levels comparing PET&CT scans to CT scans alone to identify metastatic disease was published in 2001(9). The study had a number of well-defined alternative groups including a "do-nothing" approach. Three years later, a Canadian decision model compared PET&CT scans to CT scans alone from the viewpoint of the hospital(2). The two arms were described in a decision model, where a do-nothing approach was not considered. The most recent contribution to the literature, a

French decision-model (2005) studied the cost-effectiveness of PET&CT scans compared to CT scans in patients with colorectal liver metastases from the national insurance perspective and used the outcome measure of change in life expectancy(8). Both arms of the trial were described, however, a do-nothing approach, where neither a diagnostic test nor a treatment were effectuated, was not considered.

Costing

In Valk et al, the authors provided one total cost number that covered the range of costs (hospital, physician and histological) using Medicare reimbursement. However, the inclusion of capital costs, overhead costs and discounting were not clearly stated (10). Park et al, also included hospital and physician costs, but did not clarify the cost of the hospital stay(9). Sloka et al included capital and operational costs for PET, and quoted fee schedules and literature for CT and surgery per diem costs(2). The authors omitted other overhead costs citing that these costs would be included in the diagnostic imaging budget, however, as they are joint costs it may be appropriate to put them into a shared budget and add them to the total cost of the PET arm(2). Palliative costs were omitted as they were likely similar between the two arms.

The range of costs reported in the Lejeune study included fixed costs for procedures, equipment and per diem hospital costs for laboratory tests and surgery(8). Although the physician fees for diagnostic tests were presented, the

surgeon operating fees were not clearly stated, which could significantly change the costing picture(8). Fee schedules and national databases were appropriately used to determine costs and expert opinion was used to determine utilization(8). Costing is often a controversial issue, and greatly dependent on the administrative landscape and the goals of the study. Although societal and indirect costs were not considered in the studies reviewed, given their relatively small contribution to overall costs, one can argue that these costs do not significantly impact the overall cost. Certain omissions described in the costing parameters in these papers, may be potentially misleading as the cost components may be hidden in a total cost number, nevertheless, if these additional significant costs were not included, the total cost of each arm may significantly differ, affecting the ability of the cost-effectiveness analysis to make fiscally and medically appropriate decisions.

Choice of effectiveness

Life expectancy, life-years-saved and change in treatment plan were the three outcomes used in the reviewed studies. The first two were based on evidence from an abstract on colorectal cancer. The effectiveness measure in Lejeune et al was measured based on change in life expectancy and, quoting the decision analysis done by Park et al. in 2001, avoidance of surgery as a secondary outcome(8). Park et al. used an abstract on colorectal cancer and a study for the effectiveness of PET scans in pulmonary disease published in 1998(14).

Sloka et al. did not find a significant difference in outcomes between the two arms(2). Incremental ratios were not calculated, as there was no change in life expectancy(2). The authors also measured the intermediate outcome of number of surgeries prevented (125/1000) in the PET arm(2). By being less expensive and avoiding surgeries, they concluded that the PET demonstrated a cost-savings of $1,758 CDN(2). Discounting, at 6%, was done for capital and operational PET costs only, and a justification of the discount rate was not provided(2). There was no evidence of discounting for other costs or for outcomes. One reason for this might be that the time interval for the tests and outcomes was too short.

In the Lejeune study there were no significant differences in the outcome of life expectancy between the two arms (8). The authors instead reported a cost-savings of $3, 213 US with the PET & CT strategy(8). One-way sensitivity analysis was done.

In that last study 25/78 (32%) of patients avoided surgery after having a positive PET scan, the outcome measure of interest was “avoidance of surgery”(10). Being a prospective trial, there were no associated modeling parameters.

Incremental cost-effectiveness ratios

All studies showed at least a cost-savings using PET technology, and one study was able to calculate an incremental cost-effectiveness ratio (ICER). Valk et al. showed a cost-savings of $3003/ patient with the PET arm and reported a 32 %

change in treatment plan, however the data for the CT arm was not available and an ICER could not be calculated(10). Lejeune et al. found a cost saving in the PET&CT arm of $3213 US dollars and Sloka et al. found a savings of $1758 CND, in the PET&CT arm, however, these latter two studies did not find a difference in their effectiveness measures and hence ICERs could not be calculated(8),(2). Park et al. demonstrated a change in the effectiveness measure and calculated an incremental cost-effectiveness ratio (ICER) of $16, 437 US dollars/per life-year-gained(9).

Awareness of study limitations

In Sloka et al, the conclusions described as cost-effective, though effectiveness was not established. However, the authors discuss other study limitations, including the omission of overhead and palliative costs; the assumption of full utilization and the assumption of 100% sensitivity and specificity for the biopsy(2).

Valk et al. discussed the issue of selection bias in this type of prospective cohort study, as well as the verification bias associated if only newly identified lesions were biopsied. They also discussed the limitations of test parameters like sensitivity and specificity(10). The issue of number of patients with disease versus the number of diseased lesions is unclear. Many patients did not receive CT scans, hence, only the patients that had both tests were included in the analysis and could result in selection bias. Furthermore, compared to others, a low specificity was

seen (16). Also, not all sites had histological confirmation; however, it is unclear if all patients had histological confirmation.

The Park et al study population is generalizable and the various treatment options are clinically relevant. It is limited in design because PET scans are not performed for negative CT scans in the clinical setting. Although costing is limited, the article fulfilled many elements of an economic evaluation and provides some information to the clinician.

The discussion in Lejeune et al. outlines the limitations of PET placement in the algorithm as an issue of generalizability as well as the uncertainty of the test parameters(8). The study was limited by the outcome measure appropriateness and the limited costing details of the surgery arm(8). This study shows agreement with previous work in that PET scans &CT scans appears to be more cost saving than CT scans for the pre-operative assessment of colorectal carcinoma (8).

Table 4.2: Critical appraisal of studies included in systematic review of economic evaluation studies on PET scans for colorectal liver metastases

Criteria	Sloka.	Lejeune.	Park.	Valk.
1.Well-defined question?	Yes. PET&CT vs. CT in CRCLM, change LE. Hospital Perspective	YES. PET&CT vs. CT change LE in CRCLM. NHI Perspective	YES. PET&CT vs. CT in CEA to change LYS. Payer persepective	YES. PET vs. CT in CRCLM for tmt plan. payer perspective
2. Alternatives described?	YES. Both arms well detailed. No MRI option or do-nothing option	YES. Well detailed. No MRI option or do-nothing.	YES. Well detailed. No MRI option or do-nothing option	UNCLEAR. Variation in the alternative. No decision model flow
3. Evidence of effectiveness?	YES. Measured LE and # of OR prevented in cohort studies No SR	Unclear Cite two abstract for LE. No SR.	Unclear. One decision analysis for LE. No SR.	Unclear. PET's high S&S = avoidance of surgery. No SR. Diff. verification bias: pts with + CT more likely to get PET
4. Broad costs (range, viewpoints, capital)?	UNCLEAR. Limited. Partial operating costs (PET only), hospital days and physician fees.	UNCLEAR. Imaging, dailly hospital costs (NGAP), surgeon fee. Expert opinion for utilization. No capital	No. Poor detail.No capital/overhead. Values and ranges are from Medline & Medicare for imaging, OR, chemo.	UNCLEAR. No detail. Surgical fees for hospital, physician and biopsy. No capital.Medicare for PET. Utilization not given.
5. Appropriate cost units, sources, omitted items?	YES. $, days (LYS). Fee schedules, literature. Used lung chemo costs. Overhead not discussed.	YES. Days and by patient. Fee schedule for tests & national database for hospital costs. Missing CT costs (dye, injection). No Indirect	YES. Appropriate units. Values and ranges (Medline & Medicare). No omitted items.	YES. Dollars, # of OR avoided. No costing table. Medicare.
6. Evidence for costs and outcomes values?	NO. Fee schedules & lit. Outcomes (LE, OR avoided) were not separately valued.	UNCLEAR. From fee schedules and databases. Outcomes not valued	UNCLEAR. Costs (from reimbursement rates--not actual). Outcome valuation not done.	UNCLEAR. Cost (from Medicare), # OR avoided not valued.
7. Timing of costs and outcomes discounted?	NO. Capital costs were discounted at a rate of 6% for capital costs for PET. No justification for rate. The authors did not state for other costs. Outcomes were not discounted.	NO.Not costs. Outcomes at 5%, citing literature	YES. Life expectancy and costs were discounted, but rate and justification not provided.	NO. No discounting done for cost or effect.
8. Incremental analysis?	NO. Non-significant difference in effectiveness. CT $9,523/pt. PET/CT $7,765/pt. Savings $1758/pt	NO. No change outcome. Savings by PET ($3,213 US).	YES. ICER $16,437/life year saved (PET over CT) Avoided surgery in 2.77% of patients	UNCLEAR. Savings by PET of $3003/pt. Total cost of avoided surgery $374 596 in 25 (32%)patients. Don't present CT arm costs. ICER not calculable.
9. Uncertainty in costs and ourcomes tested?	YES. Threshold sensitivity analysis(imaging, cost, disease probability, resectable rate etc). CT dominates if PET sens/spec is 74% & 68%, if PET cost >$2,787 CAN.	YES. One-way sensitivity analysis, with predetermined thresholds was done. Detailed. Cost sensitive (PET >$10, 817 US)	YES. Multi-way sensitivity analysis.	NO. No sensitivity analysis done
10. Discussion considers all issues of relevance?	UNCLEAR. Canadian. Full utilization, probability selection, biopsy accuracy, omitted (overhead & QOL), chemo, palliative costs addressed. No discussion on limited choice of outcome measure or ICER.	UNCLEAR. PET & CT cost-saving compared to CT. No diff in effectiveness (little evidence). Limited costing not addressed. Not generalizable (biopsies based on CT scans).	YES. Discussed evidence for change in treatment, (not original outcome--LE). Discussed limitations of imaging & f/u. Arms not mutually exclusive (CT -ve pts have PET) = overestimated costs	UNCLEAR. Not CEA--ignores alt. arm. Poor costing. Outcome is clinically significant (3 supporting articles). No ICER. A savings of $3,003 US (PET arm). Limitations of PET (tumour size, tracer accumulation), wait time (+24 days), selection bias and veri

**CRLM= colorectal liver metastases, LE (life expectancy), LYG (life years gained), OR (operative), SR (systematic review)

Discussion

A thorough search of the literature resulted in a four key articles of moderate quality. In general, appropriate valuation of costs and effects was present in 0/4 articles, appropriate timing and/or discounting in 1/4 articles and use of incremental analysis in 1/4 articles. A significant problem in all studies was the lack of availability of quality-of-life outcomes for PET scans. Finally, a systematic review was not performed in any of the studies to determine the appropriate effectiveness measures. The studies relied on single-study or abstract evidence, often for other cancers using PET technology, limiting the validity of cost-effectiveness studies.

All studies used the hospital perspective. Unfortunately, capital costs and overhead cost were not well documented. Though appropriate costing units were used, detailed costing data was missing in all four studies. Generally, costing data came from fee schedules and capital costs were not clearly discussed. Only one study described discounting (9). The issue of short time intervals (< 1year) may have been the reason for the exclusion of discounting. Sensitivity analysis were only performed in the Park et al. study where discounting of both costs and effectiveness was done, although the discount rate used is not given(9).

The outcome measures ranged from change in life expectancy, number of life-years-saved and change-in-treatment plan. None of the studies performed a systematic review to validate their use of outcome measure. Sloka cited two

clinical studies for life-years-saved(2). As with the other studies in the PET scan literature, the validity of the effectiveness measure was not proven (9). Although many studies are quoted to show a diagnostic superiority of PET to CT, no clinical studies specifically describe the improvement in life expectancy with PET scans for colorectal cancer or liver metastases. For the third outcome measure, a prospective clinical study published in 2004 by Selzner et. al. demonstrates that PET&CT scans can significantly change the treatment plan in patients with colorectal metastases, by changing the type of surgery or avoiding unnecessary surgery compared to CT scans (15). This may then indirectly change the life expectancy as a different population is being assessed.

The paucity of literature on effectiveness measures for PET scans is shared by many diagnostic studies because an imaging technology is only an intermediate intervention followed by different treatment options that also affect outcomes. The final measures of life-expectancy and life-years-saved are not necessarily affected by the diagnostic test and so, an intermediate measure such as "change-in-treatment plan" probably more accurately reflects the utility of PET scans in the clinical setting(1).

The ICER was calculated for only 1 of 4 studies. The availability of ICERs was inconsistent in two studies as the outcome measures were not clinically significant and in last study the alternate arm (CT scan) cost data was not available. The results suggest that although there is interest and some data available, better-

designed economic evaluation studies are needed to provide useful information to the clinicians and the hospitals. One way to improve this may be to engage physicians in the discussion of important outcome measures prior to creation of the decision model.

Conclusion

Even with different costing strategies, different diagnostic algorithms and different national health plans the results suggest a cost-savings for the addition of PET&CT scans to the diagnostic algorithm of colorectal liver metastases. Caution, however, is needed to interpret these results because of limited costing data and concerns of the appropriateness of the outcome variables. By changing the type of outcome measure used, it may be possible to calculate an incremental cost-effectiveness ratio to truly compare the two arms of the studies. Nevertheless, with the finding of cost-dominance in all of the studies, there appears to be value in continuing to assess the effectiveness of using PET&CT scans to assess resectability of colorectal liver metastases.

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5. Decision-modelling of PET/CT compared to CT scans.

Background

The positron emission tomography (PET) scan has been available for the last 30 years, but it continues to garner renewed interest, particularly in oncology. Currently health care providers are struggling to make decisions about the clinical indications for funding PET scans. The lack of anatomic delineation is the biggest obstacle of the PET scans and for this reason the technology has evolved into the integrated PET/CT scan. This method combines the anatomic advantages of CT scan with the functional advantages of PET scan and has been attempted by using both software fusion (superimposing images of PET on to images of CT acquired at two separate times) and hardware fusion (acquisition of both images at the same time) to provide anatomic detail (2,3). With this improvement, the integrated PET/CT scan is rapidly replacing and currently outnumbers the number of PET scans available in Canada(1).

There were approximately 22 public PET centers and 5 private PET centers as of November 2007 in Canada(4). In Alberta alone, as of March 2009 four machines (1 PET, 3 PET/CT) and 1 cyclotron were in use, with an anticipated 3,500 scans performed in 2008(4). The province of Ontario utilizes three PET and nine PET/CT scans and two current cyclotrons. Two more cyclotrons are anticipated

and the ensemble of nuclear imaging is used to perform approximately 2,000 scans in the last published data in 2007/2008(4).

Given this vast expansion, the indications of use of PET/CT scans need to be rapidly assessed. This is particularly important in the oncologic domain where functional data is often used to identify recurrence and metastases. Particularly, in colorectal carcinoma, this technology has been used in a number of recent publications and appears to be more sensitive for the detection of extra-hepatic metastases and equally sensitive for the detection of hepatic metastases, helping prove its clinical effectiveness (6,7,8,9).

Nevertheless, for successful, widespread utilization to occur, the economic feasibility of such a venture must be determined. In this regard, preliminary studies have been done on the PET scan and describe a cost-savings with the use of the PET scan vs. the CT scan for the detection of colorectal metastases, however, no economic evaluation literature exists on the use of PET/CT scans for the detection of colorectal metastases (6,7,8). The objective of this study is to identify and compare the cost-effectiveness of PET/CT scans to CT scans for the detection of colorectal metastases.

Methods

Economic Parameters

Costing of PET scans involves a careful examination of the fixed and variable costs, and this data has been recently published by Chuck et al in 2005 (5). Costing of PET/CT scans need to consider capital costs and operational costs. Facility costs are very high given the immense start up costs and include the annual fixed, variable and total cost of the Alberta PET Centre at typical volume outputs(5) (Table 5.1). Capital expenditures included construction, FDG Synthesis, FDG preparation and Clinical Imaging (PET scanner and PET/CT Scanner). The original cost of a PET scanner is $2,206,110, amortized over 7 years is $381,260/annually. The original cost of a PET/CT scanner is $2,800,000 amortized over 7 years is $483,896 annually (based on a 10% discount rate).

Table 5.1: Fixed, variable and total costs of a PET center, Alberta, Canada

Resource	Cost ($)		
	Fixed	Variable	Total
FDG Synthesis	905'142	151'345	1'056'487
FDG Preparation	352'822	0	352'822
Clinical Imaging	1'380'829	631'824	2'012'653
cGCP	273'103	0	273'103
TOTAL	2'911'896	783'169	3'695'065

Chuck et al, 2005
* cost values include construction, equipment, personnel (physicist, physician, technologist, managers, nursing), supplies and overhead

The regulatory environment for FDG plays a significant role. The radiolabelled FDG must meet rigid technical and safety standards, resulting in a significant percentage of operational costs going to regulatory boards (Good Clinical Practice Guidelines and Good Manufacturing Practice Guidelines)(5). Different centers could share a single cyclotron, hence, decreasing capital and operational costs related to this center. This is the current trend in Canada.

The average cost per PET scan in Alberta is $1300-$1540(5). A PET scan in Ontario costs $1000-1200/scan (radioisotope, physician fee). The costs paid by Alberta Health & Wellness is $776 (direct, indirect and physician fees) (Personal Correspondence, Alberta Health and Wellness), while under development, a separate fee schedule has not been instituted. These numbers might be different if remuneration is coming from multiple sources, and is not clearly outlined to date.

From the economic standpoint, very few economic evaluation studies exist in the field of colorectal liver metastases. Four studies have been published on PET scans for colorectal carcinoma assessment, all of which demonstrated a cost-savings using PET technology over CT scans alone (6-9). One study was able to calculate an incremental cost-effectiveness ratio demonstrating the dominance of the addition of PET scans to CT scans alone(6).

The cost parameters for this study were retrieved from Alberta Health and Wellness medical costing report as well as Alberta Health Insurance Plan data from December 2008 (Table 5.2). Direct costs are provided for some data and include salaries, drugs, medical and surgical supplies. Indirect costs included finance, material management, facilities management, registration, patient food services and health records. Building amortization, leaseholds positions were not included in these costs. If costing data could not be obtained from government documents, published literature and expert opinion were sought

Table 5.2: Baseline costing parameters of diagnostic decision model

Diagnostic and Surgical Costs	Direct cost ($)	Indirect cost ($)	LoS (days)	Total Cost/unit ($	Reference
CT imaging cost	492	95	.	587	Alberta Health costing 2006 pg 282 CT
CT Physican cost	n/a		.	n/a	
PET/CT imaging cost	795	133	.	928	Alberta Health costing 2006 pg 282 nuc med
PET/CT Physician cost	219.2		.	219.2	SOBM Medical Procedures 2008-GI nuc med pg 207
PET-CT total cost	1014.2	133	.	1147.2	.
Hospital day: laparotomy	6830	1940	7.7	8770	Alberta Health care costing 2006, pg 90
Hospital day: liver resection	13000	3287	9.3	16287	Alberta Health care costing 2006, pg 94
Percutaneous liver biospy	413	114	.	527	Alberta Health care costing 2006, pg 285

**all costs in CDN dollars, amortization and leasehold costs not included. Direct costs refer to salaries, drugs, medical and surgical supplies. Indirect costs include finance, material management, facilities management, registration, food services and health records.

Imaging Parameters

In an earlier study, we performed a systematic review that assessed the diagnostic accuracy of PET/CT scan and CT scans for identifying metastatic colorectal cancer (Patel et al, in press). Of the 1083 citations, six studies were identified and the clinical accuracy of the PET/CT scan suggests that it is more sensitive and specific for extra-hepatic lesions then CT scans (PET/CT sens.: 75-89% and spec.: 95-6%, CT sens.: 58-64% and spec.: 87-97%). For hepatic lesions, PET/CT scan is equally sensitive and specific compared to CT scan (PET/CT 91-100% and 75-100%; CT 78-94% and 25-98%). For local bowel recurrence, PET/CT scan again appears to more sensitive and specific than CT scan (PET/CT sens.: 93-100% and spec.: 97-98%). Data was extrapolated from these results for the baseline parameters of the decision model (Table 5.3).

Table 5.3: Baseline imaging parameters for diagnostic decision model

Diagnostic Characteristics	Baseline	Range	Source
CT sensitivity for liver	0.79	0.75-0.842	Park et al, 2001
CT specificity for liver	0.883	0.778-0.948	Park et al, 2001
CT sensitivity for EH mets	0.64	0.46-0.79	Selzner et al, 2004
CT specificity for EH mets	0.97	0.87-1.00	Selzner et al, 2004
FDG PET/CT sensitivity for liver	0.91	0.80-0.97	Selzner et al, 2004
FDG PET/CT specificity for liver	0.9	0.55-1.00	Selzner et al, 2004
FDG PET/CT sensitivity for EH mets	0.89	0.74-0.97	Selzner et al, 2004
FDG PET/CT specificity for EH mets	0.95	0.83-0.99	Selzner et al, 2004
Biopsy sensitivity	0.85	0.70-0.95	Lejeune et al, 2005
Biopsy specificity	1	.	Lejeune et al, 2005
Surgical specimen sensitivity	1	.	.
Surgical specimen specificity	1	.	.

Effectiveness Parameters

Gazelle et. al. discusses the complexities of finding appropriate effectiveness measures for diagnostic decision models (21). In principle, diagnostic tests are followed by numerous other events that are difficult to control. Thus the direct impact of the diagnostic modality on the final outcomes is difficult to quantify.

Change in Treatment Plan

The study by Chua et al. found that 11 people avoided surgery (66%)(10). In Chen et. al. 4 (12.5%) people had a change in surgery and 7 (19.6%) avoided surgery based on the PET/CT(11). Again, caution should be noted for this study's results since the treatment plan was based on the PET/CT and the presence of malignancy was not confirmed with biopsy (something not noted until data extraction)(11). Similarly, 14% of patients had a change in treatment plan in the Ramos et. al. study(12). While Selzner et al. found that PET/CT scan resulted in a change in treatment plan in 16/76 (20%) of patients(13). Lastly, in Rappeport,

3/35 (8.5%) of patients avoided surgery, but no patient had a change in the surgical procedure (14).

The change in treatment plan for patients assessed with PET/CT scan or CT scan varies between 8.5% and 66% (10-14). The Selzner et al. data was utilized, for our outcome parameters for multiple reasons (13). First the well-designed prospective study design, for their clinical protocol that closely resembles our own and for the moderateness of the findings with respect to the findings of other studies.

The definition of 'change in treatment plan' considered the situation in which PET/CT scan prevented a planned surgical resection based on a positive finding of extra-hepatic metastases. For the model, we adopted a binary measure of effectiveness for change in treatment plan. If the imaging of choice (CT scan in the CT arm and PET/CT scan in the alternate arm) correctly identifies extra-hepatic disease, it is identified as an effectiveness of 1. A '0' is assigned if the imaging modality does not identify extra-hepatic disease (true negative) or incorrectly identifies extra-hepatic disease (false positive or false negative).

Life Expectancy

A second model was created using the final outcome measure of life expectancy. Others have used this effectiveness measure in diagnostic decision models of PET scans for colorectal liver metastases (6,7,8). However, of the three articles using

this final outcome measure, only one found a difference in effectiveness by 9 days in favour of the PET arm (6) (Table 5.4).

Table 5.4: Baseline life expectancy values for diagnostic decision model

Life expectancy	Years
Normal postsurgical patient	5.681
Life expectancy recurrent patient (no treatment)	2
Life expectancy recurrent patient (surgical cure)	3.804
Life expectancy recurrent patient (chemotherapy)	2.663

* Park et al, 2001

Model Description

A decision analysis tree was constructed to depict the possible diagnostic and treatment options for the management of colorectal metastases, including a 'no treatment' arm using a hospital perspective. Each alternative arm represented a management strategy and stemmed from having a clinical suspicion for colorectal metastases. The clinical alternatives were constructed using our institutions current clinical practice. A systematic review done in our institution provided the baseline variables for imaging, costs and effectiveness measures. The modeling and sensitivity analyses were performed using decision-modeling software (TreeAge Software, Inc., Williamstown, MA).

A patient would enter the model with a clinical, laboratory or external imaging suspicion of recurrence. The patient can choose to refuse (no treatment arm) or to undergo further investigation and treatment. If a decision is made to undergo investigation, the patient is referred for surgical consultation. The model

compares a CT scan only arm vs. a CT scan + PET/CT scan arm. Initially, both groups are treated equally and a CT scan is performed. If extra-hepatic disease is found on the CT scan (CT EH+), the lesion is biopsied for pathological confirmation. If the biopsy is positive (bx EH +), the patient leaves the model. If the biopsy is negative (bx EH -), hepatic resection is scheduled. If extra-hepatic disease is not seen (CT EH-), but resectable hepatic disease is seen (CT liver +), the patient is scheduled for hepatic resection. If no metastatic disease is seen, the patient leaves the model.

In the CT+PET/CT arm, if extra-hepatic disease is not seen on CT scan, a PET/CT scan is performed. If the PET/CT is negative (PET/CT EH -) the patient leaves the model. If the PET/CT is positive (PET/CT EH +), the patient undergoes percutaneous biopsy. If the biopsy confirms the tumour spread (bx EH +), the patient is considered unresectable with potential for chemotherapy but not surgery and the treatment strategy is ended. If the PET/CT is negative for extra-hepatic (PET/CT EH -) disease, and resectable hepatic metastases exist, the patient is booked for surgery. At surgery if no extra-hepatic metastases are seen (surg liver only), a hepatic resection is completed, otherwise, if extra-hepatic disease is discovered, a confirmatory surgical biopsy is done and a laparotomy without resection realized.

Sensitivity analysis was performed to test the robustness of the model. The range of sensitivities and specificities of PET/CT scans and CT scans for the assessment

of colorectal cancer discussed earlier were used. To determine whether prevalence of hepatic or extrahepatic metastases changed the results of the decision model, a 20% reduction and augmentation in the prevalence of disease was applied. Twenty percent was used, as we believe this number would largely account for the difference in prevalence of metastases of colorectal cancer.

Results

Our analysis revealed a cost-savings of $ 3064.83 with the PET/CT scan arm compared to the alternative CT scan arm (Figures 5.1, 5.2). The outcomes measure of 'change in treatment plan' and life expectancy were not significantly different between the two arms. Hence, an incremental cost-effectiveness ratio could not be calculated. A 'no treatment' arm was the dominant strategy in this study.

All cost values were reported in Canadian dollars. One cost could not be clearly identified, using published data—the physician cost of interpreting a CT scan. This cost appears in both arms of the tree and therefore, significant change to the costing results is not anticipated.

The preliminary model was run using a 'no treatment arm'. Essentially, once a suspicion for recurrence was suggested, the patient decided not to undergo further investigation. The CT only arm and the PET/CT + CT arm completed the model. As can be expected, the 'no treatment' arm was favoured in the rollback analysis.

Since data on the costs of palliative care are difficult to find for this population, a zero cost value had been assigned from the hospital perspective. Clearly, from a societal perspective over time the costs would be significant, and the no treatment strategy may prove to be less cost-effective.

The second model looked at the two arms of interest (CT alone vs. PET/CT) with the effectiveness measure of 'change in treatment plan'. The change in treatment plan was a binary outcome: if the imaging modality of choice treatment plan changed based on surgical or biopsy specimen a '0' was recorded, no change was recorded as a correct pre-operative diagnosis and a '1' was recorded. The results of the study show that PET/CT has a cost savings compared to the CT only arm. A cost-savings of $3064.83 was found in favour of the PET/CT arm, however, a difference in effectiveness was not found between the two arms (Figures 5.1).

The third variation of the model looked at the same two arms, with the effectiveness measure of life expectancy (Figure 5.2). The effectiveness parameters were derived from previous studies in the literature (6). Again, a cost-savings of $3064.83 was found, without a difference in effectiveness measure.

Figure 5.1: Diagnostic decision model for PET/CT vs. CT scans and change in treatment plan.

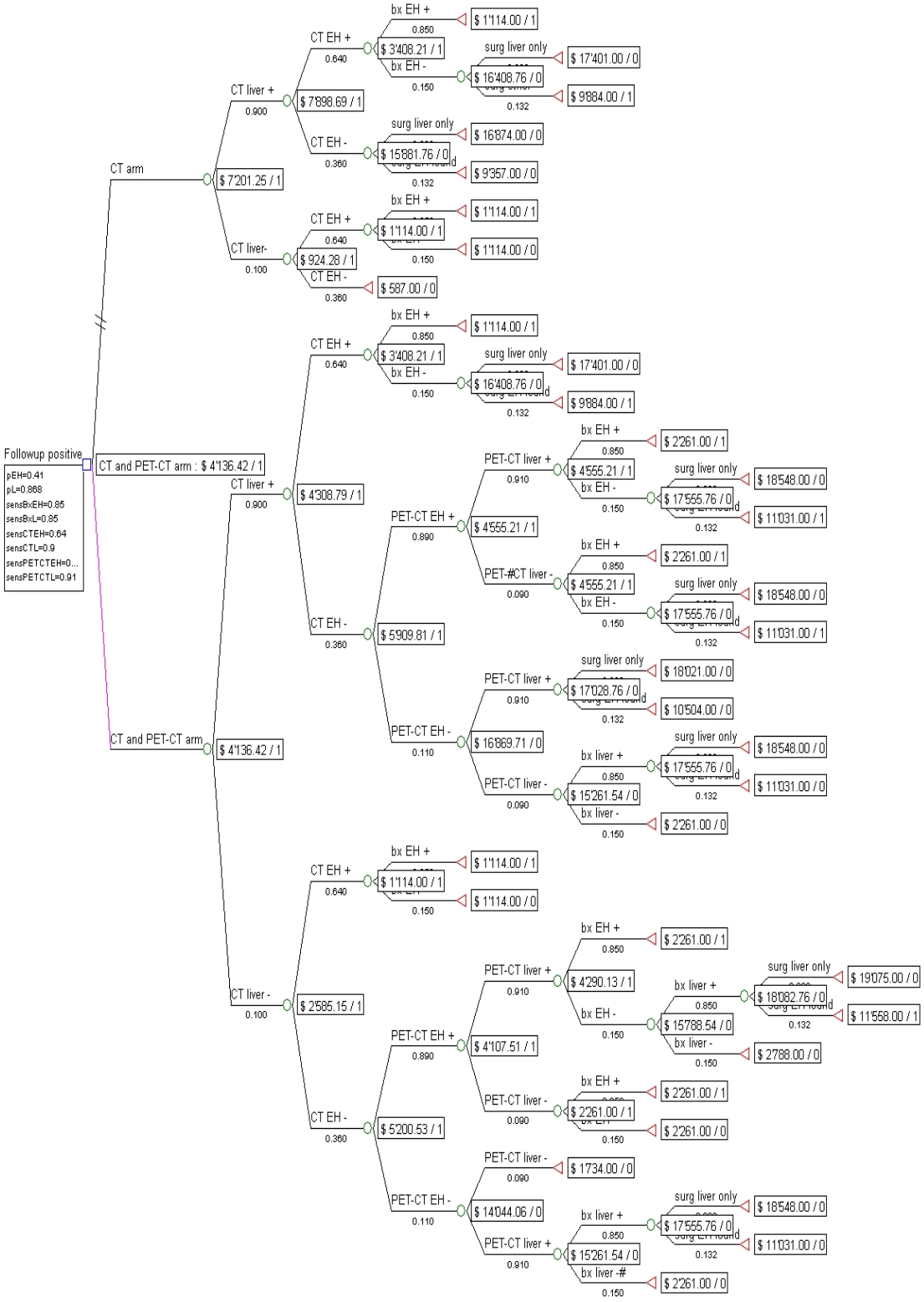
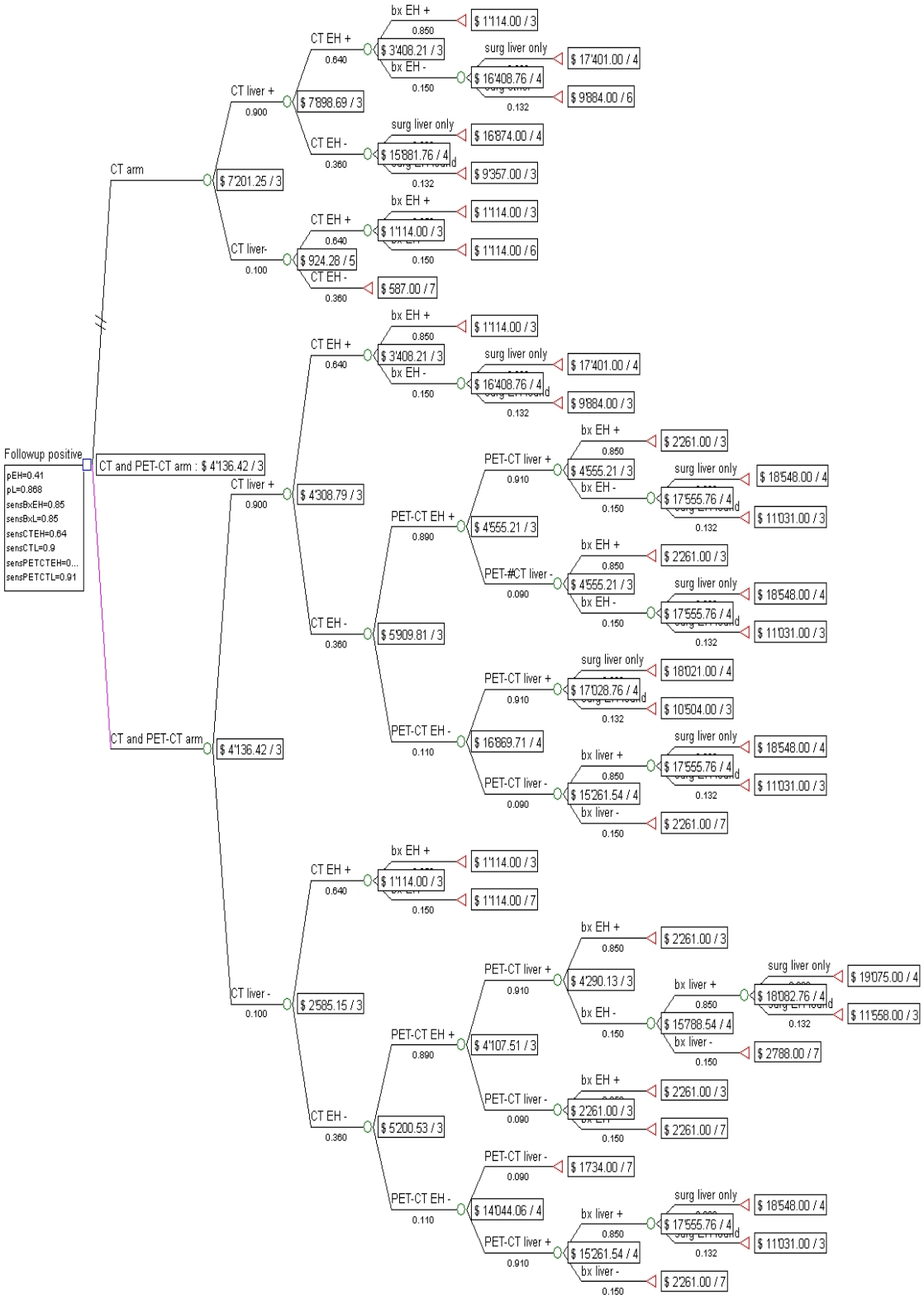


Figure 5.2: Diagnostic decision model for PET/CT vs. CT scans for life expectancy



A one-way sensitivity analysis on the prevalence of hepatic and extra-hepatic disease using prevalence values of 20% more cases and 20% fewer cases did not show a difference in the results. If sensitivity and specificity of CT scan and PET/CT scan using the range of values found in the literature showed a dominant PET/CT arm in all cases. Markov modelling was not performed.

Discussion

The results of this diagnostic decision model of PET/CT scan vs. CT scans for assessment of resectability of colorectal metastases demonstrates a cost savings with the PET/CT arm of $3064.83. This echoes the findings of others for the sister technology PET scans, with the exception of Park et al, in that we were not able to demonstrate a difference in life expectancy between the two arms, for the model using PET/CT scans in the place of PET scans. The likely explanation for this discrepancy is the difference in the parameters of cost and prevalence, but also in the differences within the algorithms. Park et al, consider patients with elevated carcinoembryonic antigen levels alone, whereas these levels maybe negative, with the presence of metastatic disease, as demonstrated by Lee et al. in their study detecting the presence of metastases in patients with normal antigen levels and elevated CA 19-9 levels, where 63.3% of patients were found to have metastatic disease, with normal carcinoembryonic antigen levels (23).

Our algorithm reflects the current ideal clinical practice in our institution and includes any patient referred to the hepatobiliary surgeon for a suspicion of metastases, either through clinical exam, laboratory analysis or outside imaging. Whereas Park et. al. used elevation of CEA values, in their decision model of PET vs. CT scans; we did not limit our patients to this. Furthermore, a recent article by Lee et al showed that on follow-up of patients with normal CEA levels but elevated CA 19-9 levels, PET/CT showed true positive recurrence or metastatic lesions in 63% of patients (22). Hence, it is possible that only a subgroup of patients was included using the criterion of elevated CEA levels for entering into the algorithm.

The use of biopsy as a gold standard in our algorithm could be argued as biopsy still has a margin of error compared to a surgical specimen. Nevertheless, surgical specimens are not available in all cases, for example, if palliative treatment was planned; biopsy is the sole option for confirmation of disease. The inclusion of a CT first in the PET/CT arm, may seem redundant, but accounts for the work-up in numerous patients that arrive in our clinical practice having just had a CT scan in anticipation of the surgical consult.. Based on each case, a PET/CT might be requested. In order to generalize these complex decision processes, we decided to include an initial CT followed by a PET/CT. Our decision reflects the true and sometimes redundant cost of pre-operative imaging. Clearly, if only a PET/CT is arranged at the onset of the pre-operative work-up the cost of the PET/CT arm would be lower than that of our current algorithm. This, however, is subject to

societal factors, and institutional factors of access to FDG and PET/CT facilities that are currently being discussed. To simplify the model post-operative complications, radiation and chemotherapy were not assessed.

The definition of surgically resectable disease is hard to pinpoint. In some institutions, limited extra-hepatic disease would be resected, however, prevalence of this thinking is limited and far from the standard of care. As guidelines become established the creation of resectability stages may improve reporting of CT scans and PET/CT scans by radiologist, improving the communication pathways and clarifying treatment options which in turn will improve the validity of these types of decision models.

Accessibility and wait times need to be considered with insurance that patients are receiving PET/CT scans in a timely manner, should this algorithm be accepted. This issue of accessibility will become important for administrators and policy issues to ensure a smooth transition for PET/CT scans incorporation into the clinical algorithm of colorectal cancer.

There are a number of limitations and cautions associated with decision models. The first is in its applicability to other institutional settings, particularly with respect to the clinical algorithm. We have attempted to be as realistic as possible in our patient selection, allowing for a more case-by-case approach, as opposed to applying rigid inclusion criteria and restrictive protocols to our model. Clearly

this provides a less clean cut model, but hopefully one that is more realistic. One particular critique of our model is that patients with suspicion of recurrence may already have an external CT scan. Hence our model might select for a subgroup of patients that are already predisposed to having a positive scan. These patients were not excluded for fear that the model would not appropriately reflect our clinical situation.

A second and more difficult dilemma is in the intrinsic limits of diagnostic decision models. In general diagnostic technologies do not directly affect long-term patient outcomes, thus making evaluation of their effectiveness difficult. Even if long-term outcomes are affected, to provide evidence of this requires long-term follow-up of 5 or 10 years that can delay the diffusion of innovative technologies and do not meet the immediate needs of decision makers (22). Furthermore, the use of utility-based index measures such as health-related quality of life measures were not available in the literature for this population.

Intermediate outcomes have been suggested, the reason for which we assessed effectiveness using 'change in treatment plan'. This has been addressed at numerous reprises, however, for the moment a solution is not yet clear. Imaging-based decision models are even more complex compared to traditional diagnostic test. Imaging often comprises many elements (number of lesions, location, size, associated effects of external compression etc.) compared to a simple numeric laboratory test (21). Imaging is also susceptible to different interpretations based

on the radiologist and different institutional protocols (MRI sequences, contrast injection) that quickly make a simple test result much more complex.

There are several special features of diagnostic decision analysis models. The most important is the indirect relationship between the diagnostic test and the health outcome making it difficult to identify a health effectiveness measure. Imaging tests are also multi-dimensional (considers the presence or absence of lesions, but also the size, location, functionality etc.), often based on likelihood of occurrence, can identify other associated abnormalities that effect the decision-making task, have individual risks of radiation and are sometimes associated with very high costs (21).

Conclusion

Our study provided some evidence for the cost-savings associated with the addition of PET/CT scans into the clinical algorithm for the assessment of resectability of colorectal liver metastases. Many limitations exist in the use of decision modeling and the validity of these findings in other centers is often difficult to prove.

Nevertheless, modeling data can provide a method to attribute imaging test outcomes to clinical outcomes avoiding the long follow-up periods required in a standard clinical trial, thus allowing technologies to, at least, be assessed rapidly,

prior to diffusion. Already, as we write this paper, institutional research in PET-MRI scans has started and once clinical data on the diagnostic properties of the imaging are available, this is anticipated to become the next realm of interest in the clinical algorithm of assessment of resectability. To increase the value of these modeling studies, discussion between biomathmeticians, statisticians, clinicians, policy-makers and health technology assessment agencies must be encouraged to establish guidelines for diagnostic decision models.

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6. General Discussion and Conclusions

Introduction

The major stages utilized in the analysis of the assessment of the PET-CT technology in the context of surgical assessment of resectability of colorectal metastases are discussed. In particular the advantages and difficulties of the different elements of each stage are discussed. Here we take the opportunity to summarize the historical challenges and our attempted improvements and the 'lessons' learned from this research for future improvements.

Clinical effectiveness

The first step to the assessment of a new technology is to determine its clinical effectiveness, or its ability to measure what we intend it to measure. Historically individual study results determined the usefulness of diagnostic tests. This is problematic because study design, population differences and methodological variance are present. Because of the need for timely decision-making, clinicians often make decisions based on prior experience or an incomplete assessment of the literature. This problem is compounded by the fact that it is often ethically difficult to perform randomized controlled trials on radiologic and surgical research. With the recent advances the new Cochrane protocols for diagnostic accuracy systematically assess the quality of clinical effectiveness data (1). This methodology was applied to systematically review the use of the PET/CT scans for the assessment of colorectal metastases. The study results showed

that PET/CT scans was more sensitive for assessing extra-hepatic metastases, and remained equally sensitive and specific compared to CT scan for the assessment of hepatic metastases (2).

Cost-effectiveness

Having established the clinical effectiveness of the PET/CT scan for the assessment of colorectal liver metastases, attention turned to the literature on cost-effectiveness. As formal studies of the cost-effectiveness of the PET/CT scan in this clinical context did not yet exist there was utility in assessing its close counterpart the PET scan in the same clinical context. Hence, a systematic review, assessing the evidence for cost-effectiveness of including PET scans into the algorithm of assessment for colorectal liver metastases, was performed. Quality was assessed using the well-established qualitative criteria from Drummond et. al. The results of this proved that keeping in mind the moderate quality of the cost-effectiveness data, all studies showed at least a cost-savings using PET scans in the clinical algorithm (3). Life expectancy was used as the effectiveness measure and only one study was able to find a difference in effectiveness. Interestingly, several studies also described a change in treatment plan ranging from 2-6% using PET scans, a variable that was also cited in the systematic review of clinical effectiveness of PET/CT scans (4,5,6)

Decision modelling

Having established the clinical effectiveness of PET/CT scans for the assessment of colorectal liver metastases through a systematic review of the literature, followed by a systematic assessment of the quality of cost-effectiveness studies from its sister technology the PET scan, the final stage of the research was realized through the application of these findings to the creation of a decision model for assessment of cost-effectiveness of PET/CT scans for the assessment of resectability of colorectal liver metastases.

Three variations of a diagnostic decision model were performed that reflect our current clinical practice and were based on previously published models (4,5,6). The models demonstrated a cost-savings of $3064.83, in favour of the PET/CT arm. A cost-effectiveness ratio was not obtained as there was no difference in the 'change in treatment plan' nor in the life expectancy variables that had been used as effectiveness measures. These results are supported by similar findings in the literature on models of PET scans vs. CT scans for colorectal liver metastases.

The difficulties associated with the use of clinical decision models are compounded in diagnostic decision models. Diagnostic tests may not have direct and significant impact on the patient outcome, but through a correct diagnosis, appropriate treatments can be administered that can then directly affect patient outcomes. To model this is difficult, and is made more complex because imaging decision models as compared to diagnostic decision models in general are associated not with a binary results, test positive or

negative, but with a myriad of information about the number and size of lesions, but also, their changes over time and their associated findings (7)

The research on diagnostic decision modelling continually improves, fuelled by a desire for this information by policy-makers, device companies and physicians. The future will likely demonstrate greater awareness and eventual acceptance in the clinical community of the limitations and power of modelling and cost-effectiveness analysis. From the clinical perspective by establishing that a diagnostic test can affect even intermediate outcomes, the surgeon is guided in their pre-operative assessments, at least for the moment from the economic perspective.

Conclusions and Future Work

This technology assessment of PET/CT scans for colorectal metastases demonstrates the power of this tool, in the radiological and surgical domains. Theoretical and practical limitations exist and can result in significant criticisms of this data. Especially when global accordance is present, even in the context of slightly differing methodology this data can be valuable to the clinician and policy maker.

1. Clinical Effectiveness

- **Historical Challenge:** Lack of randomized controlled trials to perform systematic reviews
- **Recent Advances:** Evolution and creation of methodology for systematic review of diagnostic accuracy, using non-randomized trials. Publication of a Diagnostic

Accuracy Systematic Review of PET/CT scans for the assessment of resectability of colorectal metastases (2).

2. Systematic Review of Economic Analysis

- **Historical Challenge:** Lack of critical appraisal techniques for cost-effectiveness studies
- **Recent Advances:** Progression over time with advancements in cost-effectiveness theory, in particular establishment of Drummond's criterion for evaluation of cost-effectiveness studies.

3. Decision modelling

- **Historical Challenges:** The use of long-term outcome measures to determine the cost-effectiveness of diagnostic tests, when these long-term measures are affected by many variables and decisions made after the diagnostic test.
- **Recent Advances:** Utilization of intermediate measures of effectiveness in attempts to measure the role of diagnostic tests in the clinical algorithm.

The first two stages of this research are naturally progressing as the demand increases for summarized information of accuracy and economic impact of diagnostic tests, and particularly, radiological imaging. The future challenges lie in finding, testing and evaluating a practical and user-friendly measure of effectiveness, that can be performed in a timely fashion that allows health economists to respond to the pressing concerns of decision makers and clinicians. Finally, these results can be applied to the future

technology of PET-MRI that will likely supersede the use of PET/CT scans in the coming years.

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7. Appendices

Appendix 1: Literature search strategy for systematic review of clinical effectiveness

Database	Edition or date searched	Search Terms ††
The Cochrane Database of Systematic Reviews http://www.thecochranelibrary.com		PET or positron emission tomography in Title Abstract Keywords (0 results)
MEDLINE OVID Licensed Resource (February 2009)		1. exp Colorectal Neoplasms/ 2. ((colorectal or colo-rectal or colon or rectal) and (sarcoma or carcinoma or lymphoma or oncolog* or malignan* or tumor* or tumour* or cancer* or neoplasm*)).mp. 3. 1 or 2 4. (liver or hepatic or metast*).mp. 5. 3 and 4 6. exp Tomography, Emission-Computed/ or exp Positron-Emission Tomography/ 7. (PET or PET-CT or "PET/CT" or FDG-PET or FDGPET or FDG PET).mp. 8. positron emission tomography.mp. 9. 6 or 7 or 8 10. 5 and 9
Pubmed (www.pubmed.org) (last 180 day from March 2009)		**PET/CT AND colorectal cancer (0/3)**
CRD Databases (DARE, HTA & NHS EED) http://nhscrd.york.ac.uk		Positron emission tomography AND colorectal cancer (2/9, ¾, 1/3 included in intial search)
EMBASE Licensed Resouce (Ovid Platform) (February 2009)		1.large intestine cancer/ or anus cancer/ or anus carcinoma/ or cecum cancer/ or cecum carcinoma/ or colon cancer/ or colon adenocarcinoma/ or colon carcinogenesis/ or colon carcinoma/ or colorectal cancer/ or colorectal carcinoma/ or sigmoid carcinoma/ or rectum cancer/ or

		rectum carcinoma/ 2.((colorectal or colo-rectal or colon or rectal) and (sarcoma or carcinoma or lymphoma or oncolog* or malignan* or cancer* or neoplasm*)).mp. 3.1 or 2 4.Liver Metastasis/ or ((liver or hepatic) adj3 metast*).mp. 5.3 and 4 6.computer assisted emission tomography/ or positron emission tomography/ or whole body pet/ 7.(PET or PET-CT or "PET/CT" or FDG-PET or FDGPET or FDG PET).mp. 8.positron emission tomography.mp. 9.6 or 7 or 8 10.5 and 9 11.colorectal tumor/ or rectum tumor/ or cecum tumor/ or anal tumor/ 12.((colorectal or colo-rectal or colon or rectal) and (tumor* or tumour*)).mp. 13.11 or 12 14.13 and 4 and 9 15.(liver or hepatic or metast*).mp. 16.3 and 15 and 9 17.16 not (10 or 14)	
Web of Science ISI Interface Licensed Resource (February 2009)	371	Topic=(PET or PET-CT or "PET/CT" or FDG-PET or FDGPET or FDG PET) AND Topic=(colorectal or colo-rectal or colon or rectal) AND Topic=(sarcoma or carcinoma or lymphoma or oncolog* or malignan* or tumor* or tumour* or cancer* or neoplasm*) AND Topic=(liver or hepatic) AND Topic=(metastases or metastatic) *Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years*	
Scopus? Licensed Resource (February 2009)		TITLE-ABS-KEY(**pet** OR **pet-ct** OR **"PET/CT"** OR **fdg-pet** OR **fdgpet** OR **fdg pet**) AND TITLE-ABS-KEY(**liver** OR **hepatic** OR **metast**) AND TITLE-ABS-KEY(**colorectal** OR **colo-rectal** OR **colon** OR **rectal**) AND TITLE-ABS-KEY(**sarcoma** OR **carcinoma** OR **lymphoma** OR **oncolog*** OR **malignan*** OR **tumor*** OR **tumour*** OR **cancer*** OR **neoplasm***)	
NEOS LIbrary http://www.library.ualberta.ca/catalogue (February 2009)		n/a	
Clinical Practice Guidelines			
AMA Clinical Practice Guidelines		Hand search of 2009 CPG	

http://www.topalbertadoctors.org/cpg.html (March 2009)		
CMA Infobase http://mdm.ca/cpgsnew/cpgs/index.asp (March 2009)		PET AND CT AND Colorectal cancer 0
National Guideline Clearinghouse http://www.ngc.gov (March 2009)		PET AND CT AND colorectal cancer 2/6 of interest
Clinical Trials		
ClinicalTrials.gov (US) http://clinicaltrials.gov/ (March 2009)		PET and CT and colorectal cancer 3/41 ongoing trials of interest
CenterWatch Clinical Trials Listing Service http://www.centerwatch.com/ (March 2009)		Hand searched onclology trials
metaRegister of Controlled Trials (*m*RCT) [Trial as of 2005-11-21]		n/a
National Research Register http://www.nrr.nhs.uk/search.htm (March 2009)		PET AND CT AND colorectal liver 0/8 of interest
AHRQ Evidence Based Reports http://www.ahrq.gov/clinic/epcix.htm (March 2009)		Positron emission tomography AND colorectal (hand-search) 0/0 relevant
AHRQ Technology Assessment (March 2009)		Positron emission tomography AND colorectal cancer 1/1 relevant
Nice Technology http://www.nice.org.uk/search/advsearch.jsp?guidancesearch=1 (March 2009)		Positron emission tomography AND colorectal cancer 0/2 relevant
Conference Proceedings		
Conference Papers Index		PET/CT AND colorectal cancer (0/95)
Associations (dates based on websites limits)		American College of Radiollogists (2001-2009) American College of Surgeons (2002-2009) Royal College of Radiologists (earliest-2009) Canadian Association of General Surgeons American Society of Clinical Oncologists (2003-209)
Internet		
Google Scholar (March 2009)		PET AND CT AND colorectal liver metastases

Note:

†† "*", "# ", and "?" are truncation characters that retrieve all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc.

Appendix 2: Inclusion criteria form for systematic review of clinical effectiveness

Review Title: PET/CT for Resectable Colorectal Liver Metastases

Article Title:_____ Study ID #: _____
Author/Yr: _____ Date: _____
Reviewer _____

Notes:

_____
_____
_____
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_____

Inclusion/Exclusion Criteria:

Criteria	Yes	No	Unclear
1. Publication Design A) Primary research reported	☐	☐	☐
2. Study Design a) RCT b) Prospective cohort c) Retrospective cohort d) Case-control e) case series	☐	☐	☐
3. Population a) patients greater than 18years of age with colorectal liver metastases with resected primary cancers prior to chemotherapy	☐	☐	☐
4. Index test a) PET/CT b) PET	☐	☐	☐
5. Reference Standard a) Contrast enhanced computer tomography b) histological confirmation	☐	☐	☐
6. Outcome a) numeric data sufficient to populate 2 x 2 table or calculation of sensitivity, specificity, PPV or NPV	☐	☐	☐
7. Language a) English, German or French	☐	☐	☐
REVIEWERS DECISION:	☐	☐	☐
FINAL DECISION:	☐	☐	☐