MANAGEMENT OF COLORECTAL LIVER METASTASES IN OLDER PATIENTS: A DECISION ANALYSIS

by

Simon Yang

A thesis submitted in conformity with the requirements for the degree of Master of Science (Clinical Epidemiology)

Graduate Department of Health Policy, Management and Evaluation
University of Toronto

©Copyright by Simon Yang 2010
ABSTRACT

MANAGEMENT OF COLORECTAL LIVER METASTASES IN OLDER PATIENTS: A DECISION ANALYSIS

Simon Yang
Master of Science 2010
Graduate Department of Health Policy, Management and Evaluation
University of Toronto

BACKGROUND: The incidence of liver metastases from colorectal cancer (CLM) is on the rise. Older cancer patients are frequently subject to under-treatment.

METHODS: A Markov decision model was built to examine the effect on life expectancy (LE) and quality-adjusted life expectancy (QALE) of four strategies – best supportive care (BSC), systemic chemotherapy (SC), radiofrequency ablation (RFA), and hepatic resection (HR). The model was designed to account for both age and comorbidities.

RESULTS: In the base case analysis, BSC, SC, RFA, and HR yielded LEs of 11.9, 23.1, 34.8, and 37.0 months, respectively, and QALEs of 7.8, 13.2, 22.0, and 25.0 months, respectively. Model results were sensitive to several variables including age, comorbidity status, and length of model simulation.

CONCLUSION: Hepatic resection may be the optimal treatment strategy for healthy older patients with CLM. Treatment decisions in older cancer patients should be individualized and account for patient age, comorbidities, and values.
I would like to thank members of my thesis committee for their continued support over the past two years. This work could not have been undertaken without contributions from this excellent group of clinical and academic experts. In particular, I wish to thank Dr. Shabbir Alibhai for his assistance with model construction and modifications. Of course, thanks to Dr. Calvin Law not only for his supervisory efforts, but for his advice, encouragement, and mentorship in both my academic and personal lives.

Finally, I would also like to acknowledge the Department of Surgery at the University of Toronto for the financial support I have received through the Surgeon Scientist Program during my studies.
TABLE OF CONTENTS

LIST OF TABLES ........................................................................................................... v
LIST OF FIGURES ......................................................................................................... vi

1.  BACKGROUND ......................................................................................................................... 1
   1.1 Aging and Cancer ................................................................................................................. 1
   1.2 Colorectal Liver Metastases (CLM) in Older Patients......................................................... 11
   1.3 Decision Analysis ............................................................................................................... 23
   1.4 Summary ............................................................................................................................ 29

2.  OBJECTIVE ................................................................................................................................... 30

3.  METHODS ..................................................................................................................................... 31
   3.1 Model Structure .................................................................................................................. 31
   3.2 Model Data - Probabilities .................................................................................................. 40
   3.3 Model Data - Utilities ......................................................................................................... 49
   3.4 Outcome Measure .............................................................................................................. 52
   3.5 Model Validation ................................................................................................................ 52
   3.6 Expected Value Calculations ............................................................................................. 53
   3.7 Sensitivity Analysis ............................................................................................................ 53

4.  RESULTS ..................................................................................................................................... 55
   4.1 Model Validation ................................................................................................................ 55
   4.2 Expected Value Analysis ..................................................................................................... 55
   4.3 One-way Deterministic Sensitivity Analysis .................................................................... 56
   4.4 Two-way Deterministic Sensitivity Analysis ................................................................... 63
   4.4 Probabilistic Sensitivity Analysis (PSA) ............................................................................ 64

5.  DISCUSSION ............................................................................................................................... 67
   5.1 Interpretation of Results ..................................................................................................... 67
   5.2 Study Limitations .............................................................................................................. 73
   5.3 Implications of Study Findings .......................................................................................... 75

6.  SUMMARY .................................................................................................................................... 77

7.  REFERENCES ............................................................................................................................ 78

8.  APPENDIX A – SUPPLEMENTARY TABLES ........................................................................... 103

9.  APPENDIX B – SAMPLE CALCULATIONS ............................................................................. 110
LIST OF TABLES

Table 3.1 Calculation of comorbidity multiplier
Table 3.2 Baseline parameter estimates and ranges of all model variables
Table 4.1 External validation – comparison of model and published overall survival
Table 4.2 Results of deterministic base case analysis
Table 4.3 One-way sensitivity analysis of all model variables
Table A.1 Charlson comorbidity index
Table A.2 AJCC Tumour-Node-Metastasis (TNM) definitions for CRC
Table A.3 AJCC Tumour-Node-Metastasis (TNM) staging for CRC
Table A.4 Summary of studies of untreated CLM
Table A.5 Summary of literature examining percutaneous RFA for CLM.
Table A.6 Summary of literature examining HR for CLM in older adults
Table A.7 Summary of literature reporting true resectability at time of HR
**LIST OF FIGURES**

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 3.1</td>
<td>Schematic of decision tree</td>
</tr>
<tr>
<td>Figure 3.2</td>
<td>Schematic of health states in BSC</td>
</tr>
<tr>
<td>Figure 3.3</td>
<td>Schematic of health states in SC</td>
</tr>
<tr>
<td>Figure 3.4</td>
<td>Schematic of health states in RFA and HR</td>
</tr>
<tr>
<td>Figure 4.1</td>
<td>Effect of age at diagnosis on LE</td>
</tr>
<tr>
<td>Figure 4.2</td>
<td>Effect of age at diagnosis on LE</td>
</tr>
<tr>
<td>Figure 4.3</td>
<td>Effect of comorbidities on LE.</td>
</tr>
<tr>
<td>Figure 4.4</td>
<td>Effect of comorbidities on QALE</td>
</tr>
<tr>
<td>Figure 4.5</td>
<td>Effect of length of simulation on LE</td>
</tr>
<tr>
<td>Figure 4.6</td>
<td>Effect of utility of well after HR on QALE</td>
</tr>
<tr>
<td>Figure 4.7</td>
<td>Two-way sensitivity analysis: age at diagnosis and length of simulation</td>
</tr>
<tr>
<td>Figure 4.8</td>
<td>Two-way sensitivity analysis: age at diagnosis and utility after HR</td>
</tr>
<tr>
<td>Figure 4.9</td>
<td>Stochastic expected outcomes of LE and QALE</td>
</tr>
<tr>
<td>Figure 4.10</td>
<td>Distribution of preferred strategies to optimize LE in PSA by age</td>
</tr>
<tr>
<td>Figure 4.11</td>
<td>Distribution of preferred strategies to optimize QALE in PSA by age</td>
</tr>
</tbody>
</table>
1. **BACKGROUND**

Recent Canadian census data in 2006 enumerated over 4.3 million persons aged 65 or over. This represents an increase of 11.5% since 2001 (1). The population over age 80 dramatically increased by 25% over the same time period, totalling over 1 million for the first time. In fact, aging of the population has emerged as a significant demographic trend in most developed countries. Cancer is a significant health problem in the developed world and its incidence increases progressively with age (2). In Canada, the median age at cancer diagnosis is between 65 and 69 years and the median age at cancer-related death is between 70 and 74 years (3). In the United States, 54.7% of all cases of cancer are diagnosed in patients over the age of 65 (4). The age-related increase in cancer incidence combined with the growing geriatric population is leading to an increased absolute number of older patients with cancer. In order to provide comprehensive and sensible care, we must appreciate the unique challenges presented by this population of geriatric oncologic patients.

This study is a formal decision analysis performed specifically to examine the management of older adults diagnosed with liver metastases from colorectal cancer (CRC). The scope and rationale for the current study are presented in the following sections.

1.1 **Aging and Cancer**

Prior to any discussion regarding the specific management of metastatic CRC in older patients, one must consider some general issues in geriatric oncology. These are outlined in the following sections.

1.1.1 **Chronological Definition of ‘Elderly’**

While senescence is defined by the decreased ability of the body to deal with the gradual decline of one or more organ systems, no chronological age defines one as ‘elderly’. Nonetheless, any study of older adults necessitates a chronological definition. Within the literature, the ages of 65
and 70 seem to be used most often for this definition. The frequent use of 65 as the cut-off age in large epidemiological studies is largely due to its use in administrative databases. However, there is some evidence that a cut-off age of 70 better reflects the lower boundary of clinical senescence since age-related physiologic changes increase sharply between ages 70 and 75 (5). This is further supported by the widespread use of age 70 as the definition of ‘elderly’ in oncologic trials. In a review of 48 elderly-specific clinical trials of chemotherapy for advanced non-small cell lung cancer, the age of 70 years was used to define the lower limit of ‘elderly’ in 70% of trials (6). Another study surveyed 277 oncologists from 28 countries for their opinions on adjuvant chemotherapy use in older breast cancer patients. Over 60% of participants defined ‘elderly’ as patients over the age of 70 (7).

1.1.2 Aging and Tumour Biology

Both empirical and epidemiological evidence demonstrate the association between aging and increase in incidence of malignant tumours (8). Several mechanisms have been proposed to explain this association (9). First is the theory that carcinogenesis is heavily dependent on the duration of exposure to carcinogens. As such, aging provides a longer period of exposure which results in more cancers. A second theory proposes that aging comes with molecular changes that prime tissues to the harmful effects of carcinogens. The third theory is that age-related changes in the body’s microenvironment, including proliferative and immune senescence, favour cancer development. In reality, an age-related increase in cancer incidence is likely explained by a combination of these three hypotheses.

There is some evidence that tumour biology may be different between older and younger patients, especially for a number of specific tumours such as breast, ovarian, and several hematologic malignancies (8). The effect of advanced age on tumour biology and subsequent prognosis is believed to be two-pronged. In the case of acute myelogenous leukemia, there appears to be an increased expression of multi-drug resistance genes in neoplastic cells of older patients thus leading to worse prognosis in these patients (10). Older patients with Non-Hodgkin’s Lymphoma have increased circulating levels of interleukin-6 which is thought to contribute to worse prognosis (11-13). In contrast, breast cancer in older individuals is associated with better
prognosis, often attributed to the theory that senescent tissues may provide a microenvironment less capable of supporting rapid tumour growth (14). These examples illustrate the few cases in which differential tumour behaviours in younger and older patients have been elucidated. In many other malignancies such as ovarian cancer, the association between advanced age and tumour prognosis cannot be explained at present and likely involve multiple complex factors (15).

Tumours may also present differently in younger and older patients with variable signs, symptoms, and stage at presentation. Well-described examples of different anatomical presentations include gastric and CRC. Gastric cancer in older adults is more likely to be located in the distal portion of the stomach (16-18). Similarly, right-sided CRCs are twice as common in older patients as in younger counterparts (19,20). In both cases, patients present with significantly different clinical signs and symptoms due to these age-related anatomical variations. More importantly, the differences in clinical signs and symptoms lead to variation in the stage at diagnosis. For instance, gastric cancers in older patients are often smaller and better differentiated although lymph-node metastases are more common (21). However, the true association between age and stage at presentation is more complex and will be discussed in the following section.

1.1.3 Aging and Stage at Presentation

The effect of advanced age on tumour stage at presentation is largely disease-specific and dependent on multiple factors including tumour biology, generalized screening and barriers to diagnosis. In the case of CRC, younger age at diagnosis has been shown in multiple studies to be an independent risk factor for advanced stage and poorly differentiated disease (22,23). However, this was only true for patients diagnosed at ages younger than 50 or 55 years. Therefore, these age-specific differences in tumour stage may be attributed to universal screening programs for older patients that detect disease at earlier stages. Reasons for increased prevalence of poorly differentiated CRC in younger patients are likely related to tumour biology and are not well understood. In patients with breast cancer, advanced age appears to be a risk factor for more advanced stage and lower grade of disease at presentation (24,25). In one study, age over 65 is
associated with a doubling of the incidence of advanced stage at presentation (26). However, the same patients appear to have better differentiated and less aggressive disease.

The association of age with cancer stage at presentation is also affected by both suboptimal staging and patient delay in seeking medical attention. In a large population-based study, De Rijke et al. found a higher proportion of cancer cases without staging information or histological confirmation in older patients (27,28). This may reflect the common belief by both physicians and patients that older patients have such limited life expectancy that risks of diagnostic tests and subsequent cancer treatments outweigh any benefits. In addition, many older patients delay seeking care for medical problems, resulting in more undiagnosed cancers and more advanced stage disease at diagnosis (29).

1.1.4 Comorbidities and Cancer

Beyond normal age-related physiologic changes, a number of chronic medical conditions frequently coexist in older cancer patients. These medical comorbidities may limit an older patient’s life expectancy or predispose him/her to heightened risks from standard cancer treatments.

One study conducted by the National Institute on Aging (NIA) and National Cancer Institute (NCI) assessed the prevalence of comorbidities in a population of 7,600 cancer patients using the Surveillance, Epidemiology and End Results (SEER) database (30). The results showed that the most prevalent comorbidity among older cancer patients is hypertension, followed by diabetes, atherosclerotic disease, chronic respiratory diseases, and arthritis. In a separate SEER-based study, Ogle and colleagues reviewed 15,626 cancer patients in the Detroit area for comorbidities at the time of cancer diagnosis (31). Across all age groups, 67% of patients had at least 1 significant comorbidity, 33% had at least 2, and 10% had at least 3. As expected, the prevalence of comorbid conditions increases with older age groups. Given the prevalence of comorbidities in older cancer patients, a number of scoring systems have been used to evaluate the overall health status of individual patients. Of the numerous alternatives, the Charlson comorbidity index represents one of the best validated scales in oncology patients (32) [Table A.1].
The Charlson comorbidity index is one of the most commonly used scores in oncology studies. The index was initially developed to predict 1-year patient mortality using comorbidity data abstracted from hospital charts (33). In the initial study, it was derived from a cohort of medical inpatients and validated in a cohort of breast cancer patients. The overall score is calculated using 19 pre-defined comorbidities that are assigned weights based on results of the original Cox proportional hazards regression model. As the index already includes malignancy as a heavily-weighted comorbidity, any study of oncology patients using the index must exclude the primary cancer as a comorbidity. Since its initial development, the Charlson index has been validated in a variety of malignancies, including CRC, as a predictor of morbidity and mortality (32,34,35).

1.1.5 Aging and Cancer Treatment

While informed consent is important for all patients, it is particularly important when providing cancer treatment for older patients. For many such patients, their expectations of treatment may be very different from those of their caregivers. Thus, in order to allow full autonomy, older patients should be informed of all treatment options including the risks and benefits of each. Moreover, any treatment decision should take into consideration the baseline health status, quality of life (QoL), and life expectancy of the patient. In general, cancer treatments include surgery, radiation therapy, chemotherapy, or a combination of these strategies. The use of these modalities in older cancer patients will be briefly outlined below; a more specific review of treatments for CRC liver metastases will be presented in later sections.

Surgery in Older Cancer Patients

Although chronological age may not be a predictor of post-operative mortality in the surgical management of various malignancies, older surgical patients nonetheless require special considerations (36-41). Even in otherwise healthy individuals, physiological changes associated with aging pose unique challenges to safe and effective surgical care.

Greater than half of all post-operative deaths in older surgical patients are a result of cardiovascular complications (42,43). Changes in the cardiovascular system associated with
aging include inability to increase heart rate to the same extent as younger individuals under stress, dampened sensitivity to beta-adrenergic modulation, reduced diastolic filling rate, reduced ejection fraction, and impaired coronary perfusion (44-45). In synergy, these changes adversely affect the older patient’s ability to respond to the stress of surgery. As such, stresses such as peri-operative fluid depletion common to oncologic surgeries must be managed in a timely manner in this age group. In addition, the prevalence of cardiovascular diseases such as arrhythmias and conduction abnormalities also increases with age (46). Thus, risk stratification in older patients prior to surgery is particularly important to facilitate identification of high-risk groups who are unsuitable for surgery or require preoperative optimization (44).

Anatomical changes in the chest wall, respiratory musculature, lung parenchyma, and vasculature associated with aging result in depression of respiratory function in older patients (47). Combined, these factors predispose older surgical patients to post-operative atelectasis and respiratory infections (48). In fact, respiratory complications represent the second most common cause of post-operative mortality in older patients behind cardiovascular complications, accounting for up to 18% of all complications following non-cardiac surgery (49,50).

In addition to cardio-respiratory function, aging poses a myriad of other challenges to the surgical management of older patients. Aging-related reduction in total body water combined with decreased renal function impacts the distribution and clearance of both water- and fat-soluble drugs given during an operation (51). In addition, impairments in renal function secondary to reduction in renal cortical mass result in increased propensity for dehydration, acidosis, and acute renal failure in older patients under surgical stress (52). Changes in the skin and immune systems of older patients has been shown to delay wound healing (53). However, significant impairments in wound healing are often secondary to comorbid conditions such as diabetes and peripheral vascular disease and not chronological age alone. Finally, under-nourishment, common in older individuals, can result in a six-fold increase in post-operative complications (54,55).

In summary, the increased risks of surgery in older cancer patients are largely dependent on functional reserve and the ability to respond to the stress of a major operation. As such, complete preoperative evaluation of such patients accompanied by individualized risk stratification is especially important. This is evidenced by the drastically different outcomes of emergency
versus elective surgery in older patients. While operative outcomes are similar between older and younger patients undergoing elective non-cardiac surgery, old age is a significant predictor of morbidity and mortality following emergency surgery (56,57).

Radiation Therapy in Older Cancer Patients

Radiation therapy involves the use of ionizing radiation as an energy source to eradicate tumour cells or shrink tumours. It has been shown to be useful in the loco-regional management of a variety of malignancies as singular therapy or as an adjunct to other modalities (58). The goal of radiation therapy is to maximize toxicity to cancer cells while limiting injury to surrounding healthy tissues, and an individual’s sensitivity and tolerance to radiation therapy is determined by tumour factors as well as patient factors (59). The declining functional reserve of various organ systems associated with aging significantly impacts the older cancer patient’s tolerance to radiation therapy. In addition, common medical comorbidities associated with aging such as hypertension, diabetes, and hypercholesterolemia have been shown to predispose older patients to vascular radiation damage, which is most responsible for late toxicities following radiation therapy (60). Nonetheless, with careful pre-treatment assessment of functional reserve combined with necessary dose adjustments, radiation therapy had been shown to be safe and effective in older patients with tumours located in the brain, head and neck, thorax, and pelvis (58).

Chemotherapy in Older Cancer Patients

Chemotherapy, an integral component of cancer treatment for many malignancies, is associated with potentially severe side effects even at therapeutic doses. As such, standardized tools have been developed to facilitate assessment and reporting of chemotherapy-associated toxicities. Of these, the Common Terminology Criteria for Adverse Events (previously termed Common Toxicity Criteria) scale developed by NCI is one of the most frequently used in clinical as well as research settings (61,62). This scale classifies adverse events into 24 categories and assigns a grade of 0 to 5 for each event.
Normal physiologic changes of aging result in significant changes in drug absorption, distribution, metabolism, and excretion. Aging-related reductions in the small bowel absorptive surface area, splanchnic circulation, gastric motility, and gastric secretions combine to lessen the absorption of oral chemotherapeutic agents (63). The increase in body fat and decrease in total body water associated with aging significantly affect the distribution of both fat- and water-soluble agents (64). Since most agents are metabolized in the liver and excreted by the kidneys, declining hepatic and renal function are important considerations in chemotherapy dose adjustments in older patients (65,66). Aside from physiologic changes, the existence of comorbidities may further lead to chemotherapy-induced toxicities. Several studies have demonstrated a positive correlation between the existence of comorbidities and incidence of severe toxicities (67-69). Another challenge associated with older patients is the prevalence of poly-pharmacy secondary to multiple comorbidities. Not surprisingly, studies have suggested that the risk of adverse drug reactions is increased significantly in patients aged 70 years or older (70).

Conflicting evidence exists regarding the incidence and severity of chemotherapy-related toxicities in older cancer patients compared to younger counterparts. While some have demonstrated increased toxicities in older patients (71-73), others have argued that toxicities in older and younger patients are equivalent as long as doses are appropriately adjusted for renal function (74,75). In reality, there is a lack of high quality evidence in the current literature to determine the true relationship between age, comorbidities, and tolerance of chemotherapy (76). For this reason, there has historically been a tendency to exclude older patients from clinical trials of chemotherapy treatments. Unfortunately this tendency only leads to a greater deficiency of knowledge in the field of chemotherapy for seniors.

1.1.6 Under-treatment of the Older Patients with Cancer

Despite the prevalence of older individuals with malignancies, current evidence suggests that cancer treatments may be under-utilized in this population. In a study of patients over the age of 70 diagnosed with cancer in Ontario, Canada, Townsley and colleagues demonstrated that older cancer patients were less likely to be referred to cancer centres than younger patients (77). After
controlling for possible confounders such as tumour stage, patient comorbidities, and year of diagnosis, age ≥ 70 was an independent negative predictor of receipt of any cancer-related treatment including chemotherapy, radiation therapy, and surgery (odds ratio 0.50). Importantly, due to the universality of the Canadian health care system, the age-related disparity cannot be explained by financial barriers. Similar findings of general under-treatment have been reported in specific malignancies including lung, prostate, and rectal cancer (78-80). In the case of rectal cancer, one population-based study using the SEER database examined 21,390 patients with a diagnosis of rectal cancer (81). Overall, age ≥ 70 was independently associated with decreased receipt of cancer-directed surgery and radiation therapy.

In another SEER-based study of all patients diagnosed with one of 9 localized solid tumours over 10 years, rates of cancer-directed surgery were compared across age groups (82). This study demonstrated steadily declining rates of cancer-directed surgery across all tumour groups, except primary CRC, with increasing age. Moreover, the most significant age-related disparities in surgery utilization were observed in tumours of the esophagus, stomach, pancreas, liver and lungs. Disparities were least apparent in the management of breast cancer and CRC. Interestingly, this study also collected data on reasons for not undergoing cancer-directed surgery. Of all patients who did not undergo surgery, surgery was ‘not recommended’ in 49% of cases, ‘contraindicated’ in 16% of cases, and ‘refused’ in 10% of cases. In a separate multivariate analysis, advanced age beyond 70 was a strong independent predictor of cancer-directed surgery being ‘not recommended’.

One important factor contributing to the under-utilization of targeted cancer treatments in older patients is the lack of evidence to guide decision making in this age group. Most clinicians are aware of the heightened risk associated with cancer treatment in older patients, who often have other comorbidities on top of normal age-related changes in pharmacokinetics, pharmacodynamics, and tolerance to invasive therapies. However, due to the lack of sound evidence, many are unaware that simple alterations such as chemotherapy dose reduction can render a treatment safe and effective in the older patient. This lack of evidence is partly secondary to age-related disparities in enrolment in cancer clinical trials.

In 1993, the National Institute of Health (NIH) Revitalization Act was passed to address the under-enrolment of women and minorities in clinical trials (83). However, recommendations for
enrolment of older patients were missing from this act. Hutchins and colleagues reviewed patient enrolment in 164 cancer-treatment trials conducted by the Southwest Oncology Group (SWOG) from 1993 to 1996 (84). Participant demographics from these trials, which included 15 malignancies, were compared to demographics of the general population of patients with cancer derived from the SEER database. The study found that while 63% of the general population with cancer were over 65 years old, only 25% of trial participants were of the same age group. In a similar study, all Clinical Trial Cooperative Group (CTCC) trials sponsored by the NCI from 1996 to 2002 were examined for enrolment disparities (85). Again, an inverse relationship was found to exist between age and trial enrolment. These demonstrations of age-related disparities in clinical trial enrolment prompted a policy change in 2000 by Medicare to include coverage of routine patient care costs of clinical trials for those aged 65 and over (86). Following the policy change, Hutchins and colleagues re-evaluated the participant demographics in SWOG clinical trials (87). Among other findings, this study demonstrated a significant increase in enrolment rates of older patients, although this age group was still under-represented in trials. Specific to surgical treatment, Stewart and colleagues reviewed participants of NCI CTCC surgical oncology trials from 2000-2002 (88). Not surprisingly, patients aged 65 and over were again under-represented in these trials.

1.1.7 Importance of Quality of Life in Older Patients with Cancer

Traditionally, the primary goal of cancer management has been to prolong survival. However, absolute survival benefits of cancer treatment generally decline with age while the risks of various therapies increase with age. As such, increasingly more attention has been given to the improvement or preservation of QoL in this age group (89-91). The trade-off between QoL and survival frequently influence the choice between more aggressive therapies versus palliative treatments. In addition, some studies have demonstrated that older cancer patients place more value in QoL when compared with younger ones (92-94). The increased focus in QoL outcomes has prompted the assessment of this parameter in clinical trials (95,96). Nonetheless, QoL measurements in older patients are limited by the underrepresentation of this age group in such trials.
In summary, the rapid aging of our population emphasizes the pressing need to understand cancer epidemiology, biology, diagnosis, and management in the older patient. In reality, clinicians often avoid aggressive therapies for older cancer patients based on the lack of high quality evidence and the assumption of elevated risks of treatment. While the changing physiology and comorbidities associated with aging pose unique challenges to the delivery of cancer-directed therapy in older patients, risks of cancer treatment can generally be minimized with careful pre-treatment risk stratification. In addition, there is evidence to suggest that the majority of older cancer patients are willing to undertake aggressive therapy and are actually more compliant with therapeutic regimens than younger patients (97). Therefore, older cancer patients should be offered the same potentially curative treatment options offered to their younger counterparts. High-quality evidence that is age-specific is urgently required to determine the most efficacious and safe therapies in older individuals diagnosed with cancer. The following sections will continue to discuss cancer diagnosis and treatment with particular focus on metastatic CRC.

1.2 Colorectal Liver Metastases (CLM) in Older Patients

The following sections will describe the epidemiology and management of CLM with specific emphasis on the older age group. The discussion will begin with a brief introduction to CRC in older patients.

1.2.1 CRC in Older Patients

CRC is the second leading cause of cancer deaths in Canada, with 22,000 new cases and 9,100 CRC-related deaths reported in 2009 (3). Although relative mortality rates from CRC continue to decline, likely due to better treatment options, crude mortality is still on the rise secondary to increasing incidence. This increasing incidence is attributable to the aging of the population, as CRC incidence has been shown to increase with age, peaking in the 70-79 year-old age group. In
fact, Canadians aged 70 or older account for 53% of all newly diagnosed CRC and 65% of all CRC-related deaths (3).

The prognosis of any patient with CRC is highly dependent on staging information. CRC is most commonly staged using the American Joint Committee on Cancer (AJCC) Tumour-Node-Metastasis (TNM) system (98). This system stages CRC based on depth of tumour invasion into bowel wall, extent of regional nodal involvement, and presence of distant metastases [Appendix Tables A.2, A.3]. The relationship between age and CRC prognosis is complex and often complicated by differences in stage at presentation, baseline health status, and types of treatment received. Studies have showed that older patients with CRC have more comorbidities, are more likely to present with later-stage disease, are more likely to undergo emergency surgery, and are less likely to undergo curative surgery (36).

Recent results from the EUROCare-4 study included over 180,000 individuals diagnosed with CRC and found 5-year relative survival rates decreased with age (99). Similar trends have been observed among CRC patients in Canada (3). However, the gap between relative survival rates of older and younger patients has narrowed considerably in recent years, a result of more treatment options offered to older patients (100).

Surgical resection represents an important step towards cure for the majority of patients with stage I, II, or III CRC. The safety and efficacy of surgery in the treatment of older patients with CRC has been examined in several studies. In a population-based study of 6,457 patients with CRC from the Rotterdam Cancer Registry, a positive correlation was reported between age and operative mortality (101). Among this cohort, operative mortality increased with age from 1% in those younger than 60 up to 10% in those older than 80. Similar results were observed in a French cohort of 5,874 patients with CRC, where operative mortality increased from 1.7% in patient under 60 to 12% in those over 75 (102). In addition, the current literature seems to indicate a positive correlation between age and the incidence of post-operative respiratory and cardiovascular complications following CRC resection (36).

In a systematic review of 28 independent studies including 34,194 patients, overall survival of those who had undergone CRC resection was significantly lower in patients older than 65 than in those younger than 65 (36). However, the same investigators reported that the difference in
Overall survival is largely mitigated by examining only those patients who underwent elective curative surgery. In addition, age-related differences in cancer-specific survival were much less significant in the study, suggesting that other competing causes of mortality are mainly responsible for the decreased overall survival in older patients. This is further supported by evidence that following surgical resection, there is no difference in rates of local or systemic recurrence between older and younger CRC patients (103). Even when not curative, surgery can significantly improve QoL by minimizing potential complications of unresected CRC including pain, change in bowel habit, bleeding, and obstruction.

Due to the proven safety and efficacy of surgical management in older patients with CRC, recently published guidelines by the International Society of Geriatric Oncology (SIOG) stress the importance of not denying resection surgery on the basis of chronological age alone (104). It was concluded that for older CRC patients, “elective surgery with a prospective analysis of the peri-operative variables and careful treatment planning should be the pathway of choice”. In this respect, recent data from Ontario, Canada suggested appropriate management of CRC patient with little age-related bias. Overall, 85.4% of CRC patients over age of 70 received resection surgery, which was comparable to 89.9% of those under age 70 (105).

Despite advances in surgical technique and adjuvant therapies, CRC recurs in up to 50% of patients after primary resection (106). Most recurrences occur within the first 3 years following resection. Common sites of recurrence include liver, lung, and loco-regional structures. The management of such recurrences is largely dependent on the location and extent of recurrence. While curative therapies in the setting of recurrent CRC are often restricted to those with limited disease, effective treatment using multiple modalities can offer benefits in both quality and quantity of life.

From this point on, the management of metastatic CRC in older patients will be discussed in the context of liver metastases. Not only is the liver by far the most common site of CRC recurrence, hepatic recurrence also represents an area where the most significant advancements in the management of metastatic CRC have occurred.
1.2.2 Epidemiology and Natural History of CLM

Colorectal liver metastases (CLM) develop in 50-60% of all CRC patients and are responsible for two-thirds of CRC mortality (107,108). Up to 19.6% of patients present with synchronous CLM at the time of CRC diagnosis (109). In patients who have received resection for primary CRC, metachronous CLM represents up to 71% of all disease recurrence and is most frequently the first site of recurrence (110,111). According to a population-based study of 3,655 patients who had primary CRC resection, the 5-year cumulative rate of metachronous CLM was 14.5% (108). Since CRC is largely a disease of older individuals, it follows that the incidence of CLM peaks in the 70 to 80 year-old age group (107,108).

The vast majority of patients with untreated CLM will die of liver failure within the first year after diagnosis. Due to the emergence of multiple therapeutic options, studies examining the natural history of untreated CLM are relatively dated. A 1989 study by Chang and colleagues reviewed 14 single-centre series totalling more than 1,800 patients with untreated CLM (81) [Appendix Table A.4]. Among these series, reported median overall survival ranged from 4 to 15 months.

1.2.3 Treatment Modalities for CLM

While hepatic resection remains the treatment option with the highest cure rate for patients with CLM, novel strategies such as ablative therapies and the continued evolution of chemotherapy agents have also been shown to be effective. The management of older patients with CLM further complicate clinical decision making due to the need to balance comorbidities, QoL, and risks of therapy. At present, the primary modalities for CLM management include best supportive care (BSC), systemic chemotherapy (SC), radiofrequency ablation (RFA), and hepatic resection (HR).

Best Supportive Care

BSC in oncology can be generally defined as the optimum treatment administered with the intent to maximize QoL without specific anti-neoplastic therapies (112,113). Despite the frequent use
of BSC in oncology trials as a control arm, no specific criteria exist to describe what treatments might actually be considered BSC (114). In reality, the scope of BSC is often at the discretion of the clinician, but may include analgesics, antibiotics, anti-diarrheals, corticosteroids, anti-emetics, blood transfusions, nutritional support, and external-beam radiation for the control of pain, cough, dyspnea, or hemoptysis (115). Moreover, modern supportive care has broadened to involve non-tumour specific treatments such as social, psychological, and spiritual support. Regardless of the actual combination of care provided, the goal of BSC is to optimize comfort and function while minimizing suffering.

There is little evidence in the literature to describe the outcomes of BSC specifically for older patients with CLM. Most data regarding BSC effectiveness are derived from randomized trials of anti-cancer therapies that contain a BSC treatment arm. A recent Cochrane review examined the effectiveness and outcomes of BSC interventions in trials of gastrointestinal cancer therapies (116). Investigators concluded that in cases of metastatic CRC, overall survival is significantly longer in patients treated with combination chemotherapy versus BSC alone. Importantly, in two trials of metastatic CRC treatment that measured QoL, the addition of combination chemotherapy to BSC either had no effect on QoL or improved it (117,118). Nonetheless, investigators recognized that patients over the age of 75 were significantly under-represented in all included trials. Therefore, the true outcomes in older patients remain unknown, since side effect profiles of chemotherapy treatments may be different across age groups.

Systemic Chemotherapy

Historically, 5-fluorouracil (5FU) had been the only drug with any proven clinical effectiveness in the treatment of metastatic CRC (119-122). First synthesized in 1957, 5FU is a pyrimidine analogue that exerts its cytotoxic effects through anti-metabolic mechanisms, including inhibition of thymidylate synthase and incorporation into RNA/DNA (121). 5FU has traditionally been administered in combination with leucovorin (LV), or folinic acid, due to their synergistic anti-neoplastic effect. The past decade has witnessed the emergence of several new classes of cytotoxic and biological agents. As a result, median overall survival rates have improved from an average of 10-12 months on 5FU-only therapy to almost 24 months with modern regimens (122).
The benefits of 5FU have been clearly demonstrated in the treatment of older patients with metastatic CRC. A pooled analysis of 22 European trials reviewed a total of 629 older patients aged 70 or older and found equal response rates and overall survival in older versus younger patients treated with 5FU-based therapy (123). The same study confirmed that across all age groups, infusional compared with bolus administration of 5FU resulted in higher response rates.

The introduction of new cytotoxic agents, specifically irinotecan (IRI) and oxaliplatin (OX), in combination with 5FU, has dramatically improved outcomes in the management of metastatic CRC. Initial trials using IRI as second-line therapy concluded that the increased levels of toxicity observed with combination therapy justified dose reduction in older patients (117,124). However, several follow-up trials specifically examining IRI use in older patients reported equal toxicity profiles in younger and older patients (125,126). A recent pooled analysis of four randomized controlled trials (RCTs) included 599 patients, aged 70 and over, with metastatic CRC who received either 5FU/LV or 5FU/LV/IRI (127). The study found the addition of IRI to be beneficial across all age groups in terms of response rates and survival. More importantly, the study showed that toxicity associated with 5FU/LV/IRI combination therapy was no different between the age groups. In a further subgroup analysis of patients aged 75 and over, there was a marginally higher incidence of severe neutropenia in the older group. The data for combination therapy of 5FU/LV/OX is similarly positive for older patients with metastatic CRC. In an age-based, pooled analysis of 1,881 patients treated with 5FU/LV/OX from four RCTs, 16% of all patients were 70 or older (128). The study concluded that the addition of OX improved response rate and survival independent of age group. Nonetheless, age over 70 was associated with higher rates of severe hematologic toxicity and thrombocytopenia.

Recently, several new biological agents – namely bevacizumab, cetuximab, and panitumumab – have emerged as potential adjuncts to the already standard-of-care combinations of 5FU/LV/IRI or 5FU/LV/OX. Of these agents, only bevacizumab has accumulated sufficient evidence to support its use as an adjunct to first-line chemotherapy for metastatic CRC (129). Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF), a factor which controls angiogenesis and tumour growth. It has been shown in randomized trials to improve overall survival in combination with 5FU/LV (130,131), 5FU/LV/IRI (132,133), and 5FU/LV/OX (134). However, data supporting its safety and efficacy in older patients have been
limited. Initial studies found the incidence of arterial thromboembolism to be significantly higher in older compared to younger patients (135,136).

In summary, combination regimens of 5FU/LV/OX and 5FU/LV/IRI represent two of the safest and most effective choices for treating metastatic CRC in older patients. While the newer additions of biological agents have demonstrated improved survival, data on their effectiveness and safety in older patients have been limited.

Radiofrequency Ablation

A variety of modalities have been developed as localized liver-directed therapy for CLM. These include trans-arterial chemotherapy, ethanol injection, microwave ablation, cryoablation, and radiofrequency ablation (RFA). By far the most extensively studied and widely utilized of these modalities is RFA (137). This technique uses radiofrequency generators to produce an alternating low-voltage current which in turn induces localized thermal injury (138). RFA may be delivered via percutaneous, laparoscopic, or open surgical approaches. In the absence of concurrent hepatic surgery, most institutions now administer RFA through a percutaneous approach with intravenous sedation and appropriate monitoring (139). During such procedures, lesion targeting is generally performed under the guidance of ultrasound, computed tomography fluoroscopy, or open magnetic resonance systems. Initial reports of RFA treatment of CLM demonstrated significant local failure rates, with up to a third of patients presenting with local recurrence (140-143). This was thought to be a result of several inherent limitations to the RFA technique.

First, the induction of thermal injury via RFA is highly dependent on electrical and thermal conductance through tissue. Unfortunately, tissue composition within and around lesions is heterogeneous, resulting in uneven heat distribution and ultimately leads to unpredictably irregular zones of ablation (143). This is further compounded by the inability to accurately monitor ablation zones in real time. Since larger tumours require accurate overlap of such irregular ablation zones, tumour size limitations have long been the Achilles’ heel of RFA for CLM management. Several studies have examined the outcomes of RFA used for lesions greater than or less than 3 cm in maximum diameter (142,144-147). Such studies have demonstrated
significantly lower recurrence rates and improved survival when RFA is applied to smaller lesions. Recent improvements in the technology have permitted RFA application in lesions up to 5 cm with favourable results (137,148,149). A second limitation of RFA involves the so-called “heat sink” and “energy sink” effects of large vascular structures near lesions of interest. The former describes the tendency of intravascular blood flow to dissipate heat while the latter reflects the tendency of vascular tissue to dissipate electrical current due to its lower resistance (150). However, the effect of this second limitation is theoretical and has not been shown in clinical studies to alter recurrence or survival rates.

Many studies have reported long-term outcomes of percutaneous RFA for CLM although none have specifically examined outcomes in older patients [Appendix Table A.5]. In general, this modality is associated with relatively low procedural morbidity or mortality. The most common causes of mortality include sepsis, colon perforation, and portal vein thrombosis. Procedure morbidity most frequently results from intra-peritoneal bleeding, bile duct injury, peri-hepatic abscess, and grounding pad burns. Importantly, long-term results in terms of survival rates appear to compare favourably with survival on chemotherapy and are approaching survival rates reported after hepatic resection. However, since RFA is a relatively novel procedure, available data have been limited to cohort studies and case series. As such, results likely reflect significant selection bias where younger and healthier patients represent the majority of study subjects.

With careful patient selection, RFA can provide effective treatment of patients with CLM with good long-term outcomes. Its low morbidity and mortality has made RFA an attractive option in the treatment of older patients and those with significant comorbidities.

*Hepatic Resection*

Hepatic resection (HR) has remained the mainstay of curative therapy for CLM for several decades and has been extensively studied over the years. In general, the purpose of HR is the complete removal of all malignant lesions with negative margins while ensuring sufficient liver volume remains for adequate post-operative function.
A recent systematic review of HR for CLM included 49 studies that contained more than 100 patients and involved follow-up periods greater than 24 months (151). Twenty-five of such studies involved retrospective cohorts while 11 were conducted prospectively, of which three were RCTs. Overall, reported post-operative mortality ranged from 0 to 6.6%. The most frequent fatal complications were hepatic failure, post-operative hemorrhage, sepsis, and cardiac failure. The most common sources of morbidity included wound infection, sepsis, bile leak, peri-hepatic abscess, pleural effusion, and hepatic failure. Among patients who received surgery, reported 5-year overall survival rates ranged from 9 to 63% with a median of 32%. Among 13 studies that reported recurrence, median disease-free survival ranged from 10.8 to 37.4 months with median of 17.2 months.

The high variability observed within published data reflects not only diversity in study design, but also heterogeneity in study subjects. As a result, many attempts have been made to risk stratify patients according to clinical variables using prognostic scoring systems (152-154). One of the most validated scales was developed by Fong and colleagues in a retrospective analysis of a large series of patients from a single institution (155-157). Using multivariate regression analysis, a clinical risk score was developed including 5 independent negative predictors of long-term survival: nodal metastases for primary CRC, short disease-free interval before CLM, CLM size larger than 5 cm, greater than one CLM, and CEA over 200 ng/mL (153).

As improvements in knowledge of hepatic anatomy and surgical technique have continued to lower operative risks, some investigators have turned their attention to the use of HR to treat older patients with CLM, in whom major surgery was often deemed too risky. To date, 14 studies have specifically investigated the use of HR to treat CLM in older patients [Appendix Table A.6]. All were retrospective cohort studies of patients from single centres. Eleven studies compared outcomes of HR in older patients to unmatched control cohorts of younger patients (158-168). Of these, all but the investigation by Figueras and colleagues found no significant difference between age groups in terms of operative morbidity, mortality, and survival. Figueras et al. further divided their cohort into those who received HR before 1998 and since 1998. While they found overall morbidity and mortality of HR was significantly higher among older patients, this difference was not observed when only analyzing operations performed after 1998 (165).
Given the currently available data, HR appears to be safe and effective in older patients with CLM. Nonetheless, one must recognize that these conclusions are based on relatively poor quality evidence from single-centre retrospective series.

**Special Considerations**

At present, the management of CLM is one of the fastest evolving areas of CRC care. Continuous developments in SC, RFA and HR have led to recent application of these modalities in increasingly aggressive ways.

The management of synchronous presentation of primary CRC and CLM has traditionally involved a staged approach with initial primary CRC resection followed by HR. Recent studies have suggested that simultaneous resection of colorectal and hepatic tumours may be preferable to staged approaches (172-175). However, others have warned against increased risks of morbidity and mortality in the simultaneous approach and have instead suggested resection of CLM prior to primary CRC resection in order to better select for patients who may benefit from surgery (176). A systematic review of 16 studies addressing the surgical management of synchronous CLM concluded that simultaneous resections should be undertaken only in select situations, in healthy patients with limited hepatic involvement and at institutions with both colorectal and hepatobiliary expertise (177).

Traditionally, patients were deemed unresectable based on number and size of metastases, hilar adenopathy, proximity to major veins, or extra-hepatic disease. More recently, surgical technique and adjuvant therapies have improved so much that a recent consensus statement only specifies four criteria to define resectability: the ability to (1) preserve two contiguous hepatic segments, (2) preserve adequate vascular inflow and outflow as well as biliary drainage, (3) preserve adequate future liver remnant, and (4) achieve margin-negative resection of all intra- and extra-hepatic metastases (178). In this respect, multiple combinations of treatment modalities have been demonstrated to effectively improve long-term survival in previously unresectable patients. These strategies include but are not limited to: pre-operative portal vein embolization to promote future liver remnant hypertrophy (179,180), two-stage HR for multi-lobar disease (181-183),
concurrent use of HR and RFA for multiple lesions (184,185), and neoadjuvant chemotherapy to improve resectability (143,186-191).

While these strategies have been used in a variety of clinical settings, data supporting their use in older patients CLM have been non-existent, as studies examining such therapies are generally limited to young and healthy patients.

1.2.4 Comparing Treatment Options for CLM

With the emergence of new modalities for CLM treatment, the comparative effectiveness of each strategy must be determined to support one modality over another. To date, no randomized trials have been conducted to compare two or more of the main strategies, namely BSC, SC, RFA and HR. This is largely due to the lack of clinical equipoise secondary to the early establishment of surgery as the only ‘curative’ therapy for CLM (81). However, it has become evident that long-term results of modern SC and RFA are continuing to improve, almost equal to those of HR, with careful patient selection. This has made direct comparisons of strategies increasingly important.

Several studies have compared RFA with HR specifically for the treatment of CLM (140,141,170,171,192). All but one study limited patient inclusion to only those with solitary lesions (192). All studies reported significantly higher rates of recurrence and worse overall survival in those who received RFA. Importantly, what was consistent across all studies is the fact that most patients who received RFA did so because their disease was deemed surgically unresectable. This represents a significant confounder in any comparative study since patients undergoing RFA generally have poorer prognosis simply due to selection bias.

Some authors have suggested that the majority of bias in the comparisons of RFA versus HR in the current literature favours HR (193). As such, they believe there is enough evidence of clinical equipoise between RFA and HR to conduct RCTs. However, this does not seem to be the consensus among others, evidenced by the closure of one recent randomized trial comparing the two modalities due to poor patient recruitment (194).
A recent randomized study conducted by the European Organization for Research and Treatment of Cancer (EORTC) group compared chemotherapy alone to chemotherapy with RFA for unresectable CLM (195). In the study, 59 patients received SC alone while 60 received RFA + SC. At a median follow-up of 4.4 years, median overall survival was 9.9 months in the SC arm and 16.8 months in the RFA + SC arm. However, due to limitations in study design, investigators were not able to perform formal comparisons between treatment arms.

1.2.5 Older Patients with CLM – Rationale for Current Study

In the absence of high quality evidence to support other modalities, most clinicians still consider HR to be the best therapy choice in the average (i.e. middle-aged) patient presenting with CLM. However, largely due to the risks of HR, most are less sure of the best therapeutic choice when presented with the same scenario in an older patient, especially in the presence of comorbidities. While conventional wisdom suggests an upper age limit exists beyond which age-related morbidity and mortality become unacceptable, newer evidence has questioned the independent correlation between chronological age and outcomes. The rapid evolution of chemotherapy agents and local modalities such as RFA has further complicated the clinical decision making process. In addition, research has shown that compared to younger patients, older cancer patients tend to place particular emphasis on QoL after treatment (92,94,196). Thus, the trade-off between quality and quantity of life involved in each treatment strategy is especially important in older patients. Finally, the rapid aging of our population will predictably result in higher incidences of both CRC and CLM among older individuals. For these reasons, the question of “what is the optimal treatment for older patients with CLM” must be addressed in a comprehensive and timely manner.

While informed consent is important for all management decisions in the clinical setting, it is of particular importance in the context of complex therapy choices that can significantly impact both quality and quantity of life. Such is the case with the management of CLM in older patients, where informed decision making is further complicated by the lack of specific evidence. In order to make truly informed decisions, patients should be presented with the best unbiased data available, then apply their own value systems (197). However, this is very difficult to achieve in
real-life complex clinical scenarios. Research has shown that patients are easily overwhelmed by having to consider more than a few options in making choices and as a result, tend to resort to simplifying choices by ignoring important information provided to them and/or rely on recommendations of their clinicians (198).

Decision analysis (DA) represents a method of incorporating clinical evidence and patients’ values in a rational framework in an effort to direct good medical decision making. At the patient level, DA is particularly useful in the evaluation of complex clinical decisions that involve: (1) incorporation of complex information from a variety of sources, (2) absence of specific or high quality data, (3) uncertainty intrinsic to medical decisions, and (4) complex interactions between the patient and physician where each has different values and expectations. From a societal or systemic perspective, DA techniques can also address the need to balance cost and effectiveness of therapeutic options (199).

To summarize, due to the complexity of the clinical scenario and the merits of DA, we believe that decision analytic techniques can be used to guide decision making in the management of older patients with CLM. A brief outline of the concepts and theory behind DA as well as an introduction to specific techniques is presented in the following section.

1.3 Decision Analysis

The concept of medical DA originated more than half a century ago, when Meehl and colleagues suggested that a formal statistical approach to clinical judgements can improve decision making (200). The application of DA in the clinical setting did not truly gain acceptance until the 1980s and 1990s, around the same period as the emergence of evidence-based medicine (EBM) (201-204). In fact, both DA and EBM are deeply rooted in the use of quantitative approaches to guide clinical decision making. However, these two entities have since diverged such that today, EBM has become deeply rooted in both academic and clinical medicine while DA is being applied almost exclusively in health policy development, guideline development, and cost-effectiveness analyses (205,206). In reality, since most modern applications of DA take a societal perspective, clinicians often find the results impractical in everyday patient care. Therefore, in order to re-
establish the use of DA in the clinical setting, studies must adopt a patient perspective to address specific clinical dilemmas.

**1.3.1 Markov Models**

At the core of the DA methodology is the decision tree, a rational framework from which the prognosis of a patient subsequent to the choice of management strategy can be modelled. Due to fixed time horizons for analysis, conventional DA models do not allow probability values to change over time or account for variable life-spans of theoretical patients. Markov models, first described by Beck and Pauker in 1983, have been used to overcome these limitations and provide a more convenient method for modeling ongoing risk as well as life expectancy (207,208). These characteristics make Markov modeling an attractive option for studying oncologic treatments with associated risks of complications, recurrence, and death.

The Markov model consists of a finite number of health states and assumes that the simulated patient is always in one of these Markov states. Clinically important events such as death from surgery or cancer recurrence are modeled as transitions between states. Each Markov state is then assigned a utility value which can eventually be used to calculate expected values. The time horizon for any Markov model is divided into equal increments named Markov cycles. Transitions between health states may only occur once per cycle. Generally, death is represented by an absorbing health state, and as such, can be used to calculate survival for simulated patients. Expected values of Markov models are evaluated by adding up the average time simulated patients spend in individual health states over the entire time horizon. Quality adjusted expected values are obtained by summing up time spent in each health state weighed by the utility assigned to each state.

**1.3.2 Data Identification and Incorporation**

Proper identification of the best available data permits the translation of evidence-based knowledge into DA models. Generally, data required to populate a patient-perspective DA model include event probabilities and utilities. In principle, every parameter input in a model should
represent the most up-to-date and complete evidence. However, this may not be resource-sensitive in practice; instead, experts have recommended that modellers should reserve systematic reviews of the literature for key model inputs (209). Furthermore, data should not be rejected based on inability to achieve statistical significance, often defined rather arbitrarily by a p-value < 0.05. In the absence of higher quality evidence, expert opinion is an acceptable method for data identification.

In reality, one major difference between EBM and DA is the emphasis placed on quality of evidence. While critical appraisal plays a central role in EBM, DA relies heavily on sensitivity analysis to identify those variables within a complex model that have significant impact on model outcomes since not all point estimates for model parameters can be derived from highest quality evidence.

1.3.3 Utility Assessment

Decision analysis is based on expected utility theory, first described and applied in the field of economics. Based on this theory, individuals always make choices that maximize expected utility (i.e. the weighted sums obtained by adding the utility values of outcomes multiplied by their respective probabilities) (210). In economics, utility is defined by what a decision maker expects to gain from consumption of a good or service. Extended to health care, utility is generally defined by the individual’s state of well-being derived from the preference one placed on being in that particular health state (211). Health state utilities are generally assigned a scale varying from 0 for death, to 1 for perfect health. The quality-adjusted life year (QALY) was developed as a method of incorporating QoL with quantity of life in DA. Utility measures represent ‘weights’ which must be multiplied by time spent in particular health states in order to obtain QALYs.

In accordance with expected utility theory, utility measures must be obtained using preference-based methods under conditions of uncertainty (212). However, in practice, all methods of utility assessment except for the standard gamble method are conducted under certainty. Several commonly used methods of utility valuation are briefly described below.
Standard Gamble

The standard gamble approach has been regarded as the gold standard for utility measurement largely due to its consistency with expected utility theory (212,213). This method involves presenting a patient with a choice between two alternatives: (1) a health state that is certain and (2) a gamble that can result in a better outcome (e.g. cure) or a worse outcome (e.g. death). The goal is to determine what probability of the better outcome would make the patient indifferent between remaining in the certain health state or taking the gamble. This resulting point of indifferent represents the patient’s utility measure for that particular health state.

Criticisms of the standard gamble method revolve around two issues. First, the approach is dependent on an individual’s risk-taking tendencies. In general, individuals are averse to taking risks, thus resulting in commonly higher utility scores compared to other methods. Second, this method not only requires interviews to be conducted by a trained individual but also a general understanding of probability theory by the patient (213,214).

Time trade-off

The time trade-off approach involves asking patients to consider the duration of time in perfect health that they consider as equivalent to time spent in the impaired health state (215). The ratio of these two time durations is the utility measure. Therefore, while this method does force patients to make a choice, there is no uncertainty or risk associated with the choice.

Visual Analogue Scale

The visual analogue scale is a rating scale consisting of a single line with anchors representing best possible health and death. Patients are then asked to place each health state on the line such that intervals between the placements reflect their perceived differences between health states (216). As such, this approach entails neither an element of choice nor decisions under uncertainty and thus deviates significantly from expected utility theory. However, unlike standard gamble and time trade-off, this method is relatively easy to administer.
**Indirect Methods**

The above methods all involve presenting subjects with detailed descriptions of various specific health states and obtaining preference-based utilities. Since this direct approach is both time- and resource-consuming, an alternative approach of using generic utility instruments to obtain preference weights is often chosen. Such instruments are based on models developed from the valuation of a set of non-disease-specific health states by a general public sample of subjects. In specific studies, patients with certain health conditions then complete a questionnaire which defines the generic health state they are in. By mapping these results to population-based weights derived from a reference population, the appropriate utility measurements can be obtained (217). Examples of generic utility instruments include the EQ-5D (EuroQol five dimensions), SF-6D (Short Form six dimensions), and the HUI (Health Utilities Index). Despite their simplicity of use, indirect methods of utility assessment have been criticized because they: (1) lack sensitivity when applied to specific health states, (2) are insensitive to small differences in utility, and (3) often generate variable results for the same health state (218,219).

In summary, the ability to combine quality and quantity of life measures into the same model is one of the main strengths of the decision analytical technique. Therefore, utility assessment is a central part of the DA methodology. However, there is considerable variability in the way utility measurement is conducted due to the advantages and shortcomings of each method. In the field of health economics, some institutions have attempted to standardize the assessment of utilities. In the UK, the National Institute for Health and Clinical Excellence (NICE) has identified the EQ-5D as the preferred method for utility measurement in clinical trials (220). In the meantime, most other institutions have focused on ensuring that whatever methods used are applied in a robust manner.

**1.3.4 Previous DA Studies of CLM**

Several previous studies have used the DA method to evaluate the management of CLM (221-224).
A group of investigators from the United Kingdom performed a cost-effective analysis on the management of potentially resectable CLM (223). The analysis was based on a conventional non-state transition decision model assessing two strategies: referral to a liver surgeon or non-surgical treatment. Simulated patients in the surgical referral arm received one of three downstream options at predetermined proportions: curative HR, palliative HR followed by SC, or SC alone. Recurrences after curative HR were modeled in a constant and non-time-dependent manner. Overall, the study reported that considering a time horizon of 5 years, surgical referral with the intention of curative HR is cost effective, with an incremental benefit of 1.6 life-years at the cost of £6,742. This study did not consider alternative therapies such as RFA or systemic chemotherapy alone for the management of CLM. In terms of methodology, investigators constructed a conventional model which failed to account for variations in patient characteristics such as age or comorbidities.

A more recent study originating in Canada evaluated HR, RFA, SC and BSC for the management of CLM in a cost-utility analysis (222). A Markov state transition model was built to incorporate survival data from available literature without specific modelling of recurrence rates or patient baseline health status. In addition to DA modeling, investigators conducted a prospective study of 40 patients with a variety of hepatic malignancies who eventually received one of the four therapies. Cost data were derived from average costs incurred by patients in each strategy. Utilities were measured from each patient using generic HUI questionnaires. The study reported that over 5 years, HR, RFA, SC, and BSC strategies were associated with benefits of 2.58, 1.95, 1.18, and 0.82 QALYs, respectively. Moreover, investigators concluded that HR and RFA are both cost-effective modalities in the treatment of CLM, with cost-utility ratios of $7,792 and $8,056, respectively.

Gazelle and colleagues presented an alternative approach to DA modeling of CLM in their cost-effectiveness analysis of HR for CLM (221,224). The investigators developed a state-transition model that tracks up to 15 individual lesions in a patient. The presence, number, size, location, and growth of each individual lesion were incorporated in the model in the form of distributions in order to estimate radiologic detectability and surgical resectability. Every resected lesion was associated with a specific recurrence rate depending on its characteristics. After consideration of cost data, the study concluded that HR is a cost-effective option for patients with CLM. Clearly,
the model relied heavily on the assumption that the characteristics – distribution, size, growth, and natural history – of CLM are well understood. Nonetheless, the authors had presented a novel approach to the modeling of solid organ tumours.

These previous studies all adopted a societal perspective by focusing on cost analyses. As such, results of these analyses cannot be easily applied to the patient-level where complex clinical decisions must be made. In addition, no study has accounted for the impact of patient age and comorbidity status, two essential variables to consider in the management of CLM as illustrated in the previous sections.

1.4 Summary

Older patients diagnosed with CLM following resection of primary CRC pose a clinical dilemma. While surgery may offer the best survival benefit, the significant morbidity of a major abdominal operation influences patients and surgeons to choose less invasive strategies. However, traditional non-invasive therapies of BSC or SC offer no chance of cure. Ablative therapies such as RFA have emerged in recent years as a possible alternative to major surgery. Randomized comparative trials of various therapies for CLM have not been conducted although lesser quality data suggests that HR provides a greater survival benefit. Furthermore, no study has compared treatment strategies for CLM specifically for older patients, in whom both chronological age and existing comorbidities can affect the choice of treatment.
2. **OBJECTIVE**

The objective of this study is to determine, from a patient perspective, the optimal strategy for the management of older patients (age $\geq 70$) who present with liver metastases following primary CRC surgery. A decision analytical approach will be used to determine gains in life expectancy and quality-adjusted life expectancy associated with: (1) best supportive care, (2) systemic chemotherapy, (3) radiofrequency ablation, and (4) hepatic resection.
3. METHODS

3.1 Model Structure

A Markov state transition model was developed using TreeAge Pro software (TreeAge Software, Inc. Williamstown, MA, USA v2009) to evaluate the effectiveness of various strategies for treating CLM in older patients [Figure 3.1]. Strategies evaluated in the decision analysis included: best supportive care (BSC), systemic chemotherapy (SC), radiofrequency ablation (RFA), and hepatic resection (HR).

Figure 3.1 Schematic of decision tree

Cycle length of the model was set to 1 month. Since the most rigorous follow-up in research settings involve surveillance studies no more than 3 months apart (225), it was assumed that tumour recurrence, the main event being modeled, will not be detected in shorter than 1-month intervals. The model was run until one of four conditions was met: (1) all simulated patients have died, (2) all simulated patients reach 100 years of age, (3) incremental benefits gained per cycle have become < 0.001/cycle, or (4) 60 cycles (5 years) have passed. The upper age limit of 100
years was necessary given the paucity of reliable mortality data for patients older than 100. An incremental utility gain of less than 0.001 per cycle was defined as negligible in order to improve model efficiency. The 60-cycle (5-year) limit was placed on our model in order to enhance clinical relevance, since the lack of recurrence by 5 years following treatment generally defines cure (226). Another reason for this limit is the scarcity of data on survival and recurrence rates after 5 years after RFA or HR. The half-cycle correction was applied to all health states in order to improve the accuracy of expected value estimates (227).

### 3.1.1 Age and Comorbidities

A chronological age of ≥ 70 was used to define older patients. This chronological definition was chosen due to its common use in geriatric oncology studies (6,7). Patient comorbidities were defined using the Charlson score, a weighted scoring system validated for predicting morbidity and mortality in CRC patients with liver metastases (33). According to the overall score, patients were identified as having: low (0), medium (1), or high (≥ 2) comorbidity. Our model accounts for the effect of comorbidities in several ways.

First, the level of comorbidity alters the probability of dying from an invasive procedure (RFA or HR). Previous studies in surgical oncology have demonstrated increased post-procedural mortality associated with increasing comorbidity (228-230). Second, patients with high comorbidity (Charlson score ≥ 2) were excluded from receiving any systemic chemotherapy. Finally, our model accounts for the effect of comorbidity burden on life expectancy by applying a comorbidity multiplier to standard life table mortality estimates. We used a method first described by Welch et al., which used the declining exponential approximation for life expectancy (DEALE) model to quantify the effect of comorbidities on annual mortality (231). The DEALE approximation assumes that, across any short period of time, life expectancy is equal to the inverse of annual mortality rate (208). By extension, one can calculate the average annual mortality rate given any specific start age by referring to standard life tables [Table 3.1]. Welch’s method then assumed that healthier individuals have a longer life expectancy and lower annual mortality rates than the average person. Conversely, sicker individuals have shorter life expectancy and thus higher mortality rates. For our model, we assumed that our defined
categories of low, medium, and high comorbidity translate to 75th, 50th, and 25th percentiles of life expectancy from census data. We then calculated annual mortality using the DEALE model described earlier. Life expectancy values were derived from U.S. census data specific to a 70 year-old individual (232). Finally, a comorbidity multiplier was derived using the medium comorbidity level (and thus median life expectancy) as the reference [Table 3.1]. This application of the Welch method has been used in other studies to approximate the impact of comorbidities on life expectancies (233,234).

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Years</th>
<th>Mortality</th>
<th>Charlson Index</th>
<th>Level of Comorbidity</th>
<th>Comorbidity Multiplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>75th</td>
<td>19.65</td>
<td>0.051</td>
<td>0</td>
<td>Low</td>
<td>0.715</td>
</tr>
<tr>
<td>50th</td>
<td>14.05</td>
<td>0.071</td>
<td>1</td>
<td>Medium</td>
<td>1</td>
</tr>
<tr>
<td>25th</td>
<td>8.1</td>
<td>0.123</td>
<td>≥2</td>
<td>High</td>
<td>1.735</td>
</tr>
</tbody>
</table>

*Percentiles and life expectancy derived from Life Tables of the United States.

### 3.1.2 Strategies and Markov Health States

In our analysis, it is assumed that all patients present with CLM following resection of the primary colorectal lesion. This represents the majority of patients who present with resectable CLMs (109,235). We also assumed that patients entering the analysis have CLMs that are amenable to all treatment options. This assumption allows fair comparison between strategies since the invasive strategies each have their own limitations such as the size of lesions for RFA and distribution of lesions for HR. In reality, patients who are not amenable to all treatment options at presentation represent a heterogeneous group for whom therapeutic choices are often limited.

Each strategy in the model contained a set of specific health states which simulated patients can stay in or transition between. All events of interest were modeled as transitions between health states and, as described earlier, transitions were assumed to occur no more frequently than once
every month. Utility values were assigned to each state and used to calculate expected values. Death was an absorbing state present in all strategies and represents mortality from all causes. We did not model cancer-related and non-cancer-related deaths separately because distinguishing between the two in a study population with metastatic disease is almost impossible. Since HR has traditionally been regarded as the only curative therapy, reports on other treatment modalities rarely separate cancer-specific from non-cancer specific deaths.

**Best supportive Care:**

In the BSC arm, all CRC liver metastases are left untreated and patients are provided supportive care only. Under this strategy, all patients begin in the Well state [Figure 3.2]. For each subsequent cycle, patients may either stay well or die and enter the Death state at a fixed probability.

**Figure 3.2** Schematic of health states in BSC

![Schematic of health states in BSC](image)

**Systemic chemotherapy:**

In the SC arm, all patients receive repeated cycles of 5-FU, leucovorin (LV), and irinotecan (IRI). Combination of irinotecan or oxaliplatin with 5-FU/LV is currently the standard of care in
patients with metastatic CRC, supported by multiple randomized trials showing improved overall survival over the traditional 5-FU/LV combination alone (236-239). The combination of 5-FU/LV/IRI has been shown to be safe and effective in older patients (127). Patients with a high comorbidity level (Charlson ≥ 2) were excluded from receiving any chemotherapy. This assumption is supported by evidence that systemic chemotherapy may not be safe in patients with multiple significant comorbidities (67,69,240,241). In our model, patients receiving chemotherapy could either have low toxicity or high toxicity. The latter is defined as any grade ≥ 3 toxicity according to the Common Terminology Criteria for Adverse Events (previously termed Common Toxicity Criteria) scale (61,62).

There are 4 health states in the SC arm: Chemotherapy with low toxicity, Chemotherapy with high toxicity, Well on BSC, and Death [Figure 3.3]. As patients enter the strategy, anyone with high comorbidity does not receive any chemotherapy and thus enters the Well on BSC state. This state is identical to the Well state in the BSC arm of the model and can only transition into the Death state at a fixed probability per cycle. All patients with low or medium comorbidity proceed to the Chemotherapy with low toxicity state. In each cycle following commencement of chemotherapy, patients may transition between states of high and low/no toxicity representing development or resolution of ≥ grade 3 toxic side effects. While the two chemotherapy states incur different utilities, both states can transition to the Death state with the same probability of death. In our study population, no literature on chemotherapy outcomes has investigated the impact of toxicity severity on survival. Although patients with higher toxicities are intuitively more likely to die on therapy, there is evidence to show that higher toxicities may, in fact, predict better survival (242).
As the only invasive and potentially curative options for CLM treatment, the RFA and HR strategies in our model were built with similar structure to ensure model balance [Figure 3.4]. Repeat treatments of RFA were regarded as a single strategy since multiple sessions of RFA are often planned to remove all lesions (143). It was assumed that RFA is administered in a percutaneous manner as it is the most frequently used route in patients not receiving surgery for other lesions (138). HR was assumed to be performed through an open rather than laparoscopic approach since at most centres the laparoscopic technique is presently limited to selected patients and lesion locations (243). Any neoadjuvant or adjuvant chemotherapy in the RFA or HR arms was not modeled as separate strategies and was included in the analysis as part of RFA or HR strategies. This is due to the heterogeneity of pre- and post-operative chemotherapy given to patients in clinical trials.

Both strategies begin with patients distributed among two temporary health states: Effective treatment / Ineffective treatment for RFA, and Resectable / Unresectable for HR. Many large
series of RFA treatment for CLM have highlighted a significant proportion of patients in whom RFA is ineffective despite sometimes repeated attempts at ablation (137,146,169,171,244,245). This generally reflects inability to obtain complete ablation and thus poor oncologic control. For the present model, a proportion of patients entering the RFA strategy receive ineffective treatment. We assumed that these patients are exposed to the risks and disutility of RFA, but proceed to be treated with systemic chemotherapy. Analogous to ineffective treatment in RFA trials is the proportion of patients in HR trials who are determined to have unresectable disease at the time of operation. This is typically a result of the inability of preoperative imaging to accurately detect the location and extent of metastatic lesions. In our model, we assumed that patients with intra-operatively determined unresectable disease are exposed to the risks and disutility of a laparotomy, but proceed to be treated with systemic chemotherapy. In all cases, the efficacy and toxicity of chemotherapy are unaffected by previous unsuccessful RFA or surgery.

Whether the invasive treatment was effective/resectable or ineffective/unresectable, patients may die from the procedure within the first cycle or survive. We defined death from this period as operative mortality, as our cycle length of 1 month is in agreement with the general definition of 30-day mortality as operative mortality (246). For the patients who survive, they may transition to the Well state or alternatively proceed to the Complication state according to the probability of post-operative complications for the procedure.

While complication rates differ between RFA and HR, we assumed that the impact of complications on patient QoL and survival is the same between these strategies. This is based on the similarity in types of complications experienced by patients after both procedures. The impact of complications from both RFA and HR were modeled in two ways. First, having a complication imparts a disutility on the patient for an average of 3 months after surgery. In our model, this was implemented by designating the Complication state as a tunnel state where every patient with complications must stay for 3 cycles prior to recovering and transitioning to the Well state. Preference-based utility studies conducted on patients following such procedures show recovery of QoL indicators to pre-procedural baseline levels within this time frame (247). Second, those patients who experienced complications will have increased baseline all-cause mortality for up to 24 months after the procedure. This assumption is supported by previous studies of the long-term effects of complications following non-cardiac surgery (248). To
account for this, our model applied hazard ratios to adjust all-cause mortality probabilities for patients who experienced a post-procedural complication. In order to make our model ‘remember’ which patients experienced complications, patients with and without complications transitioned through the rest of the model via paths that were mirror images of one another. As an example, Well and Well After Complications were modeled as separate health states in order to account for increased mortality that patients are exposed to after experiencing a complication.

Recurrence after RFA or HR is defined as any evidence of metastatic CRC in the patient. We did not make the distinction between local and systemic recurrence as differentiating between the two is often challenging based on our review of the literature. More importantly, in our study population of older patients, there is presently no evidence that repeated invasive treatments for local disease can improve survival (249). We also assumed that all patients with recurrences after RFA or HR proceeded to receive SC, or BSC (in cases of high comorbidity). This is based on the logic, supported by clinical experience, that patients and their physicians who choose invasive strategies such as ablation or surgery will likely also choose chemotherapy over supportive care if indicated. In our model, patients may recur during any cycle after the first month; this is true even if patients are in the Complication tunnel state. All such events result in transition to the Chemotherapy state or BSC state (in cases of high comorbidity). Subsequent downstream model structure is identical to that of SC and BSC strategies. The only modification is an additional per-cycle hazard of dying from long-term effects of post-procedural complications if these occurred.
3.1.3 Stochastic Model

Once our primary model structure was finalized, a duplicate model was created to enable stochastic baseline and sensitivity analyses. In this stochastic model, all model parameters were defined as distributions rather than point estimates. This modification allows for analysis based on the joint uncertainty of multiple model parameters, often referred to in the literature as probabilistic sensitivity analysis. Specific details of distributions used for individual parameters are detailed in a later section.

3.1.4 Base Case Definition

The base case for primary analysis was a 70 year-old patient with Charlson comorbidity index of 0 (low comorbidity), presenting with CLM following CRC resection. As tumour-specific criteria for RFA and HR are different and often poorly supported by evidence (143), only patients with tumours potentially treatable by either strategy were included in the analysis.
3.2 Model Data - Probabilities

Event and transitional probabilities were obtained from a comprehensive review of the available literature. To identify probabilities associated with each strategy, the MEDLINE and EMBASE health-related electronic databases were searched from 1950 to the time of this publication. The literature search was limited to the English language. Studies specific to older patients were used when available. Where parameter estimates were obtained from a single source, 95% confidence intervals were used as ranges for sensitivity analyses. If confidence intervals were not available, ranges were defined as +/- 50% of the point estimate. Where multiple sources of data were available, studies with the highest grade evidence were used for baseline probabilities and all sources were used to establish the range for sensitivity analysis. In cases where multiple studies had equal grade evidence, probabilities were derived using an inverse variance-weighted pooling method. This method is commonly employed in meta-analyses where the weight given to each study is the inverse of the variance of the effect estimate from each study. This method gives heavier weight to larger as well as more precise studies (i.e. with smaller standard errors). This generally produces more accurate pooled estimates than weighting by sample size alone. It has been shown that for each study with standard error, SE, optimal weights (w) to be used for meta-analysis can be calculated as:

\[
w = \frac{1}{SE^2}
\]

For studies that do not report SE, we estimate it from variance (var) derived from sample size (n), proportion of patients experiencing an event (p), and proportion of patients not experiencing an event (q). Assuming a binomial distribution of event outcomes, we calculate w from:

\[
w = \frac{1}{SE^2} = \frac{1}{var} = \frac{1}{pq/n} = \frac{n}{pq}
\]

Using this weight for each study, we calculated the weighted mean effect size (\( \bar{ES} \)) from individual effect sizes (ES) from each study using the following formula:

\[
\bar{ES} = \frac{\sum(w \times ES)}{\sum w}
\]
This weighted mean effect size was used as the baseline point estimate in our model. Ranges for sensitivity analysis were derived using the standard error of the above mean effect size as calculated below:

\[
SE_{ES} = \sqrt{\frac{1}{\sum w}}
\]

Data extracted from the literature review were transformed to fit the model as detailed below [Appendix B]. All transformations assume an exponential distribution with constant rates over time. In order to apply hazard ratios, proportional hazards over time are assumed.

- All rates extracted were converted to per-cycle probabilities using the TreeAge function RATETOPROB. This effectively performs the following mathematical conversion:

\[
P = 1 - e^{-RT} = 1 - e^{-R \left( \frac{\text{length of cycle}}{\text{length of rate period}} \right)}
\]

For the above equation, P represents probability and R represents rate. T is calculated by dividing the length of each cycle (1 month in our case) by the duration of the rate period.

- Time-dependent probabilities such as the probability of cancer recurrence were converted to per-cycle transitional probabilities. Probabilities were first converted to rates using the TreeAge function PROBTORATE which performs the following mathematical conversion:

\[
R = - \left( \frac{\ln(1 - P)}{T} \right)
\]

Rates were then adjusted for our cycle length before they were converted back to per-cycle transitional probabilities using the TreeAge function RATETOPROB described above.
• Time-independent probabilities such as operative mortality and morbidity did not require any conversion and were incorporated into the model at the cycle where the procedure was performed.

• Odds ratios (OR) were applied to probabilities by first converting probabilities ($P_1$) to odds ($O_1$). After applying the OR, the new odds ($O_2$) is then converted back to a new probability ($P_2$). This was accomplished with the TreeAge function PROBFACTOR and is demonstrated below:

\[
O_1 = \frac{P_1}{1 - P_1}
\]

\[
O_2 = O_1 \times \text{OR}
\]

\[
P_2 = \frac{O_2}{1 + O_2}
\]

• Hazard ratios (HzR) were applied to transitional probabilities by first converting probabilities to rates, applying the HzR, then changing back to a probability. This was performed with the TreeAge function PROBTOPROB.

• Data in the form of median time-to-event were treated as the length of time after which the probability of an event is 50%. For example, a median time to recurrence of 10 months was assumed to equal a probability of recurrence of 50% over 10 months. This probability is then converted to per-cycle probabilities by an intermediate conversion to a rate, then back to a probability.

It should be noted that under ideal circumstances, probability estimates used for different strategies in decision analytic models should originate from randomized, comparative studies conducted in subjects similar to the model population. However, at the time of this study, no randomized study exists to compare HR versus RFA or either strategy with SC for patients of any age group. As such, we have attempted to gather the highest grade evidence available from literature with older patients as subjects. The following sections will describe in detail the event/transition probabilities and odds/hazard ratios present in our model.
3.2.1 Probability of death from other causes

The probability of dying from causes other than CLM or related treatments was estimated from standard life table mortality. We used the most recent Canadian Life Tables from Statistics Canada published in 2006 (251). This publicly available report contains data constructed from age-sex-specific mortality rates observed in Canada in the 2000 to 2002 period. The life tables used a model which assumes that a cohort of 100,000 individuals born at the same time is subject to age-sex-specific mortality rates experienced by the actual population. Among other statistics, the life tables provide the probability that a person aged exactly x years will die before reaching age x+1. As such, these tables are extremely useful for Markov modeling in providing age-specific probabilities of surviving year to year. In order to use the life tables for our model population, we used an average of the female and male mortality probabilities. These annual probabilities were then converted to monthly values for use in our model. As mentioned earlier, comorbidity multipliers were applied to the probabilities given by life tables. This serves to adjust for patients who are healthier or sicker than the average population.

3.2.2 BSC – mortality

Since BSC involves no active anti-tumour treatments, the mortality of patients while on BSC should depend solely on the natural history of CLM from CRC. Chang et al. reviewed 14 single-centre series (including one under the author’s supervision) and Table A.4 is an adaptation from the published review (81). We converted median overall survival to per-cycle probability of death prior to pooled analysis. The resulting inverse variance-weighted pooled estimate of monthly probability of dying on BSC was 0.0803 with a SE of 0.0084. This point estimate corresponds to median overall survival of 8.3 months.

3.2.3 SC – mortality, toxicity

While the use of 5-FU/LV/IRI chemotherapy for metastatic CRC has been studied extensively in randomized controlled trials, no trials have been designed specifically for older patients. Our literature search found a recent pooled analysis of all older patients who participated in 1 of 4
RCTs with a therapeutic arm of 5-FU/LV/IRI (127,236-239). Overall survival data of older patients enrolled in these studies were used to derive the probability of dying in the SC arm of our model. This combined analysis included 599 patients over the age of 70 with metastatic CRC. Median overall survival was 17.6 months among these patients, with a 95% confidence interval of 15.5 to 19.7 months. This converts to a monthly probability of death of 0.0386 with confidence interval 0.0346 to 0.0437. These were used in our model as the baseline probability of dying while on SC with a corresponding range for sensitivity analyses.

While we did not allow patients with high comorbidity to receive SC in our model, we assumed no difference in mortality on chemotherapy between low and medium comorbidity patients. Multiple studies have shown no association between comorbidity and overall survival on 5FU/LV/IRI as long as patients with very poor performance status are excluded (237,238). As such, patients entering SC experienced a constant per-cycle probability of dying regardless of age or comorbidity level.

Toxicity information from the above pooled analysis was not used in our model since the study analyzed toxicity data in a very specific manner, separately reporting incidences of 11 categories of adverse events. In order to derive data for the overall risk of severe toxicity while on chemotherapy, we turned to a retrospective study by Pentheroudakis et al. which included patients over age 65 who received chemotherapy for metastatic breast, lung, or CRC (252). A total of 621 patients with metastatic CRC were included in this study and all received modern 5-FU-based chemotherapy. Overall, severe toxicities were observed in 25% of patients. We used this as our base-case probability of having severe toxicity while on SC and a +/- 50% range, 0.125 to 0.375, for sensitivity analysis.

3.2.4 **RFA – effectiveness, mortality, morbidity, recurrence**

Many studies have examined the use of percutaneous RFA in the treatment of CLM from CRC. However, as RFA is a relatively new technique applied to this disease, most such studies have short follow-up times and focused on safety and efficacy. At the present time, there are no studies regarding RFA for CLM specific to the older population. In our literature review, we found 11 studies of percutaneous RFA with follow-up periods over 12 months [Appendix Table
A.5] (137,145,146,149,169-171,244,245,253,254). All studies were of prospective or retrospective cohort designs.

We defined the effectiveness of RFA as the ability for single or staged RFA treatments to achieve complete radiologic destruction of all lesions. Six of 11 studies report treatment effectiveness ranging from 60% to 98%. These yielded a pooled point estimate of 92.9% with SE of 0.9%. Complication rates were reported in 9 of 11 studies and yielded a pooled probability of 3.6% with a SE of 0.6%.

Operative mortality was reported in only 8 of 11 studies of which only 1 post-operative death was observed. However, we recognized that within the 8 studies that did report mortality, it is likely that this mortality was too low (yet still non-zero) to be detected in the relatively small sample sizes. As such, we resorted to non-age-specific data from a study by Livraghi et al., which represented the largest multi-centre prospective series of percutaneous RFA to date (255). In a total of 2,320 patients, a post-procedure mortality of 0.3% was observed. Thus, we used 0.3% as our point estimate and the range of 0% to 1% in our literature review was used in sensitivity analyses. This mortality was further modified based on comorbidity level-stratified odds ratios stratified by comorbidity level, which will be discussed in a later section. Complication rates were reported in all but 2 studies and ranged from 0% to 16.7%. Pooling these data, we calculated a point estimate of 3.6% with a SE of 0.6%.

Finally, reported recurrence after RFA was standardized to per-cycle probabilities for pooled estimates. Only 5 of 11 studies reported overall recurrences, ranging from 0.0421 to 0.1091 per month. The resulting pooled probability used in our model was 0.0642 with a SE of 0.0124. Again, overall survival data were not used to generate model inputs but were instead used in external validation.

3.2.5 HR – resectability, mortality, morbidity, recurrence

Our review of the literature yielded a total of 39 studies which examined hepatic resection in older individuals. Of these, we excluded 11 studies that looked at HR for hepatocellular carcinoma (256-266), and 14 that looked at HR for mixed liver pathology (267-280). These
studies were excluded since resectability and disease recurrence from such studies would be irrelevant to our study population with CLM from CRC. Even mortality and morbidity data from such studies were not useful as a large proportion of patients from the excluded studies had pre-existing cirrhosis and/or viral hepatitis, both significantly impacting morbidity and mortality. The 14 remaining studies all examined HR in older patients with CLM from CRC [Appendix Table A.6] (158-168,281-283). As is evident from this list, studies specific to the older population are limited to single-centre retrospective cohorts. However, using inverse variance weights, we can combine all existing studies to provide reasonably reliable estimates. Note that data for overall survival from these published studies were only used for validation of the model since the Markov model is designed to predict survival based on other data such as operative mortality, morbidity, and recurrence rates.

All studies examined patients over the age of 60 and most used age 70 as the cut-off to study older patients. Two studies only examined the older age group in subgroup survival analysis and thus did not report specific mortality, morbidity, and recurrence data for this age group (163,168). Due to time and resource constraints, attempts were not made to contact investigators to obtain more specific data.

Studies of HR generally exclude subjects who received surgery but were eventually determined to have unresectable disease. This was true for all 14 studies retrieved in our review. In order to obtain an estimate for the proportion of patients who would be exposed to the risks of laparotomy but never receive HR, we explored literature examining outcomes of patients with preoperative imaging-proven CLM from CRC. Our review yielded 8 studies examining outcomes of patients with a preoperative diagnosis of resectable CLM from CRC who proceeded to have HR [Appendix Table A.7] (284-291). These studies included all patients with imaging diagnoses of CLM and did not specifically include only older patients. These studies reported true resectability percentages of 79 to 100% determined at the time of operation. Using these studies, the inverse variance-weighted pooled estimate for resectability was 90.8% with a SE of 0.8%

Operative mortality data was reported in 12 of 14 studies and ranged from 0 to 7.3%. All studies defined operative mortality as 30-day post-operative mortality. Using the inverse variance-
weighted method, this yielded a pooled estimate of 4.1% with a SE of 0.70%. This mortality was further modified by odds ratios stratified by comorbidity level.

Complications after surgery ranged from 10-42% among 11 studies reporting this data. While most studies included all minor and major post-operative complications, 3 studies only reported major complications. Given our definition of complications in the model as all complications experienced after surgery, the remaining 8 studies reporting all major and minor complications were used to generate the pooled estimate of 35% with a SE of 1.7%. Finally, disease recurrence was reported in 9 of 14 studies. These were converted to per-cycle probabilities according the methods presented earlier. Pooling of these probabilities yielded a point estimate of 0.0248 with a SE of 0.0056.

3.2.6 Laparotomy – mortality and morbidity

For patients who were determined to have unresectable disease at the time of HR, we assumed that they will be exposed to operative risks similar to those of the average non-cardiac surgery patient requiring general anaesthesia. As such, data for mortality and morbidity following laparotomy were extracted from a study by Leung et al. regarding older patients undergoing non-cardiac surgery (292). This study reviewed 544 consecutive patients over the age of 70 who received non-cardiac surgery requiring general anaesthesia at a single centre over a 1 year period. Patients in the study had a mean age of 78 with 93% classified as American Society of Anesthesiologist (ASA) class II or III. Under the ASA physical status classification system, ASA II and III are defined as the existence of mild to severe systemic disease that is not a constant threat to life (293). This population is therefore relatively similar to our study population both in terms of age and comorbidity status. In total, patients from this study experienced post-operative mortality of 3.7% and a complication rate of 22.4%. These estimates were used as our baseline probabilities for death and complication after HR. Ranges for sensitivity analysis were set at +/- 50% of the point estimates. Similar to the post-operative mortality after HR, this mortality after laparotomy was also modified based on comorbidity level-stratified odds ratios.
3.2.7 *Odds ratio of death from HR/laparotomy/RFA based on comorbidity*

The previous sections have alluded to a modifier used to adjust post-operative mortality stratified by comorbidity level. We assumed that the impact of comorbidity on mortality is equal for all invasive procedures in our model. Specific odds ratios were derived from a study by Simons *et al.* of in-hospital mortality for the treatment of CLM (294). In this population-based study using administrative databases, a total of 50,537 adults who received invasive treatment for hepatic metastases were included. Risk factors studied included Charlson score, derived from International Classification of Diseases 9th edition (ICD-9) codes in patient discharge records. Of these, 34% received RFA and the rest received HR. Multivariable logistic regression modeling the risk of in-hospital mortality yielded significant odds ratios of 1 (reference), 1.50, 2.46, and 7.15 for Charlson scores 0, 1, 2, and ≥3, respectively. These were entered into our model in a look-up table such that patients were exposed to adjusted risks of post-operative mortality according to their Charlson comorbidity score.

3.2.8 *Hazard ratio of death after complications*

In our model, complications after procedures not only cause short-term disutility but also exert a lasting impact on long-term survival. Data to quantify this long-term impact were derived from a study examining the prognostic significance of post-operative in-hospital complications in older patients (248). This prospective cohort study of 517 patients included only individuals over the age of 70 who had non-cardiac surgery. The study focused on long-term outcomes up to 36 months after surgery and excluded patients who died within 30 days of surgery (considered operative mortality). Age- and gender-specific death rates in the general population were used as controls. Complications examined included cardiac, respiratory, renal, neurologic, infectious, gastrointestinal, and thrombo-embolic events of varying severity. Survival analysis concluded that for patients who suffered any post-operative complication, their relative risk of death compared with controls were 7.3, 2.4, and 1.9 in 0-3 months, 3-12 months, and 12-36 months after surgery, respectively. For our model, these relative risks were entered in a table so that patients who suffered complications were exposed to elevated overall mortality according to length of time since their procedure date. Specifically, this hazard ratio was applied to the
following transitional probabilities in RFA and HR arms: probability of non-cancer death, probability of dying while on SC, and probability of dying while on BSC.

### 3.3 Model Data - Utilities

In order to model both LE and QALE, we created two separate models that only differ in utility parameter inputs. In our primary model used to estimate LE, we assigned all health states except for Death a value of 1. Our secondary model accounted for QoL estimates by assigning each health state a different utility estimate based on the best available evidence. The Death state was valued at 0 for both models. Since single studies were used in all cases to derived utility values, ranges used in sensitivity analysis were set as +/- 20% of the point estimates. However, given the paucity of utility data, we performed secondary sensitivity analyses on all utility parameters with the full range of 0 to 1.

We reviewed the literature for sources of utility values for health states present in our model. Few studies contained QoL data specifically for patients with liver metastases, and none used a standard gamble approach to elicit utilities. In addition, it is often problematic to pool utility data from different studies due to the variation in utility study methods. Thus, we selected a single study by Ruers et al. for our baseline parameter estimates as it was the only one comparing QoL following different treatments for CLM (247). This prospective study obtained health-related QoL data from 109 patients with CLM before and after treatment with HR (53 patients), ablation (29 patients), and SC (27 patients). Patients were asked to complete the EQ-5D visual analog scale (VAS) pre-treatment, 2-3 weeks post-treatment, and every 3 months until 1 year post-treatment.

As mentioned earlier, health-state classification systems such as the EQ-5D represent an indirect preference-based measure of health-state utilities. This instrument has been used extensively in cost-utility research and is in fact the preferred health state utility measure for the National Institute for Health and Clinical Excellence (NICE) in the UK (220). Specifically, the EQ-5D VAS contains a 20cm visual scale ranging from 0 to 100, representing the worst to the best imaginable health states (295). The resulting score is divided by 100 to give a utility value from 0 to 1. In the Ruers et al. study, there was no difference between preoperative EQ-5D VAS
scores across different therapies. Following an initial post-treatment drop in utility scores, scores reached a steady state after 3 months in all treatment arms. These steady state utility scores of 0.72, 0.72, and 0.60 were used as utility parameters for well states in HR, RFA, and SC in our model, respectively.

Utilities for complications after procedures were assumed to be 0.60. These were derived from the lowest utility values recorded in the first 3 post-operative months after HR or RFA in the Ruers et al. study. In the absence of more specific data, we assumed that the lowest utilities reported after these invasive procedures were a result of complications. We also assumed that utilities for complications after HR, RFA and laparotomy were the same since most post-operative complications are cardiac, respiratory, or infectious in this age-group while specific hepatic complications such as bile leaks and hepatic insufficiency are less common (269).

Unfortunately, no utility study specifically examined the QoL while on BSC. As such, we made the assumption that the utility of being on BSC was 0.66, halfway between well states for HR/RFA and SC. Likewise, the utility for chemotherapy with moderate to severe toxicity was not available and was assumed to be 0.8 times the utility for chemotherapy with mild or no toxicity. Importantly, these utilities were linked by this multiplier in order to preserve the integrity of the model during sensitivity analyses.
Table 3.2 Baseline parameter estimates and ranges of all model variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline*</th>
<th>Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>70</td>
<td>70-90</td>
</tr>
<tr>
<td>Comorbidity by Charlson Index</td>
<td>0</td>
<td>0-3</td>
</tr>
<tr>
<td>Length of simulation (months)</td>
<td>60</td>
<td>12-120</td>
</tr>
<tr>
<td><strong>Probabilities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure Success</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFA (Effectiveness)</td>
<td>0.929</td>
<td>0.920-0.938</td>
</tr>
<tr>
<td>HR (Resectability)</td>
<td>0.908</td>
<td>0.900-0.916</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cancer death</td>
<td>Life Tables**</td>
<td>0.5-1.5 x Table</td>
</tr>
<tr>
<td>On BSC</td>
<td>0.0803</td>
<td>0.0719-0.0887</td>
</tr>
<tr>
<td>On SC</td>
<td>0.0386</td>
<td>0.0346-0.0437</td>
</tr>
<tr>
<td>RFA (operative)</td>
<td>0.003</td>
<td>0-0.01</td>
</tr>
<tr>
<td>HR (operative)</td>
<td>0.041</td>
<td>0.034-0.048</td>
</tr>
<tr>
<td>Laparotomy (operative)</td>
<td>0.037</td>
<td>0.019-0.056</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFA</td>
<td>0.0642</td>
<td>0.0518-0.0766</td>
</tr>
<tr>
<td>HR</td>
<td>0.0248</td>
<td>0.0192-0.0304</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFA</td>
<td>0.036</td>
<td>0.030-0.042</td>
</tr>
<tr>
<td>HR</td>
<td>0.350</td>
<td>0.333-0.367</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>0.224</td>
<td>0.112-0.448</td>
</tr>
<tr>
<td>Severe toxicity on SC</td>
<td>0.25</td>
<td>0.125-0.375</td>
</tr>
<tr>
<td><strong>Modifying ratios</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cancer death (by comorbidity)</td>
<td>Table**</td>
<td>0.5-1.5 x Table</td>
</tr>
<tr>
<td>Procedural mortality (by comorbidity)</td>
<td>Table**</td>
<td>0.5-1.5 x Table</td>
</tr>
<tr>
<td>Mortality after complications (by time)</td>
<td>Table**</td>
<td>0.5-1.5 x Table</td>
</tr>
<tr>
<td><strong>Utilities</strong>†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>0.66</td>
<td>0.53-0.79</td>
</tr>
<tr>
<td>SC (no/mild toxicity)</td>
<td>0.60</td>
<td>0.48-0.72</td>
</tr>
<tr>
<td>SC (mod/severe toxicity)</td>
<td>0.48††</td>
<td>***</td>
</tr>
<tr>
<td>RFA</td>
<td>0.72</td>
<td>0.58-0.86</td>
</tr>
<tr>
<td>HR</td>
<td>0.72</td>
<td>0.58-0.86</td>
</tr>
<tr>
<td>Complications after HR/RFA/Laparotomy</td>
<td>0.60</td>
<td>0.48-0.72</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>***</td>
</tr>
</tbody>
</table>

* All transitional probabilities listed as per-month equivalents.

** All variables derived from tables were varied at +/- 50% of the values retrieved from tables.

† Ranges for all utilities given as +/- 20% of baseline.

‡‡ This utility is always linked to chemotherapy with no/mild toxicity by a factor of 0.8X.
3.4 **Outcome Measure**

Outcomes were measured in life expectancy (LE) and quality-adjusted life expectancy (QALE). We defined any incremental LE or QALE benefit between strategies of over 1 month as a significant difference. Measuring QALEs allowed us to incorporate health-related QoL into the model in the form of utility values. This is particularly important in older individuals since morbidity from interventions may be more detrimental to older patients than younger ones. As such, QALE represents an important outcome for our target population.

3.5 **Model Validation**

3.5.1 **Internal Validation**

Once our final model was constructed, we performed rigorous internal testing to ensure its integrity and internal validity. We began by examining each branch of the model for syntax errors. Following this, all variables were tested using null to extreme inputs (0 to 1 for probabilities and utilities) to ensure that obvious and predictable outputs were produced.

3.5.2 **External Validation**

Our model was built on the assumption that recurrences after invasive treatments account for all cancer-related deaths. Therefore, only recurrence data were derived from our literature review, whereas overall survival statistics were left out of the model. Instead, overall survival after hepatic resection reported in our literature review served as data for external validation.

Using baseline cohort analysis, survival curves for each strategy of our model were generated using the Declining Exponential Approximation of Life Expectancy (DEALE) technique outlined earlier. The resulting median overall survival data produced by the model were compared to published overall survival data from our literature review. This validation was not performed with the SC and BSC strategies since overall survival data from the literature were used in our modelling of those strategies.
3.6 Expected Value Calculations

Expected value (EV) calculations were performed in a deterministic as well as stochastic manner for both LE and QALE outcomes. In this manner, the model evaluates the preferred strategy based on maximum LE or QALE.

In deterministic analysis of the LE model, base case point estimates for all model variables were used. Expected values were calculated by the proportion of the simulated cohort in each health states summed over all cycles. In the QALE model, proportions of simulated cohorts are further weighted by the utility of each health state. The calculations are performed as below:

\[
EV_{LE} = \sum_{\text{All Cycles}} (\text{proportion of cohort in each state})
\]

\[
EV_{QALE} = \sum_{\text{All Cycles}} (\text{proportion of cohort in each state} \times \text{utility weight per cycle})
\]

3.7 Sensitivity Analysis

3.7.1 Deterministic Sensitivity Analysis

One-way deterministic sensitivity analysis was performed for all model parameters based on the base case model. For all parameters except utilities, one-way analyses were performed on the LE model, whereas analyses for utilities used the QALE model. Each one-way sensitivity analysis varies a single parameter input within a pre-determined range while all other parameters are held constant at their respective baseline estimates. Variables are considered sensitive if the preferred strategy (one with maximum LE or QALE) changes when the variable is changed within the specified range. For sensitive variables in one-way analysis, threshold values are calculated to represent the value beyond which a different strategy would be preferred. Ranges for sensitivity analysis were alluded to in previous sections and are presented in Table 4.3. In order to vary parameters in the form of tables such as probability of non-cancer deaths, a multiplier set to a baseline of 1 was applied to such parameters to be used in the sensitivity analysis.
Two-way sensitivity analysis follows the same principles as one-way analyses except that two parameters are varied through their specified ranges while all others remain constant. These provide additional information regarding the effects of uncertainty on the model outputs. However, due to the sheer number of combinatorial pairs of variables available for analysis, two-way sensitivity analyses were reserved for continuous variables that were sensitive in the one-way analyses as well as variables hypothesized to be clinically important.

3.7.2 Probabilistic Sensitivity Analysis (PSA)

Stochastic analysis was performed on the probabilistic versions of our model where parameter estimates were assigned distributions in order to evaluate their uncertainty simultaneously. Distributions were assigned to model parameters based on the type of input parameter modeled (296). All probabilities and utility inputs were assigned beta distributions which range from 0 to 1. All odds ratios and hazard ratios in our model were derived from tables. These were then multiplied by fudge factors to account for uncertainty. These factors were assigned a normal distribution with mean 1 and standard deviation of 0.2. The Charlson Index was assigned a set distribution with 75.2%, 18.0%, 3.6%, and 3.1% representing Charlson scores of 0, 1, 2, and ≥ 3, respectively. These frequencies were derived from a population-based study of over 50,000 patients with CLM requiring HR or RFA (294). The age at diagnosis was not varied as a distribution. Instead, PSAs were performed at different ages in order to assess the impact of age on strategy choices.

This analysis was conducted using second-order Monte Carlo simulation, where values for each model parameter were simultaneously and randomly sampled prior to EV calculation (296). A total of 10,000 iterations of this process were conducted and the final output consisted of mean EV calculations for each strategy as well as the error associated with such calculations. Ninety-five percent confidence intervals were derived using the 2.5th percentile EV for the lower limit and 97.5th percentile EV for the upper limit. Other outputs from the PSA include strategy selection percentages for each strategy representing the proportion of simulations where a specific strategy was preferred. PSA was performed on both LE and QALE models.
4. RESULTS

4.1 Model Validation

Our model was tested rigorously with all possible ranges for all variables while checking for obvious and predictable outcomes. This served to ensure internal validity of the model. In order to evaluate external validity, the LE model was used to predict median, 3-year, and 5-year overall survival for HR and RFA using the DEALE method. These are reproduced in Table 4.1 with comparable values from our literature review. Predicted overall survival results from our model all fall within the range of published data.

Table 4.1 External validation – comparison of model and published overall survival

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Overall Survival – Model</th>
<th>Overall Survival – Published Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>3-year</td>
</tr>
<tr>
<td><strong>RFA</strong></td>
<td>33 mos</td>
<td>45%</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>37 mos</td>
<td>51%</td>
</tr>
</tbody>
</table>

4.2 Expected Value Analysis

Results from deterministic base case expected value calculations for both LE and QALE outcomes are presented in Table 4.2. Based on a 70 year-old patient with no comorbidities and base case estimations of each parameter input, HR offered the most LE and QALE over a 5-year period. All incremental gains between strategies were over 1 month, and thus were considered to be significant. Specifically, HR provided an incremental benefit of 2.2 months of LE and 3 months of QALE over RFA over 5 years. In addition, the ranking of preferred strategies does not change between LE and QALE analyses.
Table 4.2 Results of deterministic base case analysis

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Total Expected Value</th>
<th>Incremental Expected Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LE (months)</td>
<td>QALE (months)</td>
</tr>
<tr>
<td>BSC</td>
<td>11.9</td>
<td>7.8</td>
</tr>
<tr>
<td>SC</td>
<td>23.1</td>
<td>13.2</td>
</tr>
<tr>
<td>RFA</td>
<td>34.8</td>
<td>22.0</td>
</tr>
<tr>
<td>HR</td>
<td>37.0</td>
<td>25.0</td>
</tr>
</tbody>
</table>

4.3 One-way Deterministic Sensitivity Analysis

The results of one-way deterministic sensitivity analyses on model parameters are presented in Table 4.3. Utilities were varied using the QALE model while all other variables were varied using the LE model. All parameters were tested within the plausible range as well as through the entire range of 0 to 1 to account for the lack of reliable data sources.

Our results indicate that the model is sensitive to 4 parameters within the plausible ranges: age at diagnosis, comorbidity (by the Charlson Index), length of simulation, and utility of the well state after HR. Four additional variables, recurrence after RFA, recurrence after HR, utility while on SC and utility of well state after RFA, produced sensitivity analysis threshold values very close to but still outside their plausible ranges. An outline of all sensitive variables is detailed in the following sections.
Table 4.3 One-way sensitivity analysis of all model variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range*</th>
<th>Threshold within (outside of) range**</th>
<th>Strategy Preferred below/above Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>70-90</td>
<td>79.4</td>
<td>HR/RFA</td>
</tr>
<tr>
<td>Comorbidity by Charlson Index</td>
<td>0-3</td>
<td>&gt;2</td>
<td>HR/RFA</td>
</tr>
<tr>
<td>Length of simulation (months)</td>
<td>12-120</td>
<td>39.3</td>
<td>RFA/HR</td>
</tr>
<tr>
<td><strong>Probabilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure Success</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFA (Effectiveness)*</td>
<td>0.920-0.938</td>
<td>NT (NT)</td>
<td>(HR/RFA)</td>
</tr>
<tr>
<td>HR (Resectability)*</td>
<td>0.900-0.916</td>
<td>NT (0.790)</td>
<td>(RFA/HR)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cancer death*</td>
<td>0.5-1.5 x Table</td>
<td>NT (2.7 x Table)</td>
<td>(HR/RFA)</td>
</tr>
<tr>
<td>On BSC*</td>
<td>0.0719-0.0887</td>
<td>NT (0.0178)</td>
<td>(BSC/HR)</td>
</tr>
<tr>
<td>On SC*</td>
<td>0.0346-0.0437</td>
<td>NT (0.0270)</td>
<td>(RFA/HR)</td>
</tr>
<tr>
<td>RFA (operative)</td>
<td>0-0.01</td>
<td>NT (NT)</td>
<td>---</td>
</tr>
<tr>
<td>HR (operative)</td>
<td>0.034-0.048</td>
<td>NT (0.104)</td>
<td>(HR/RFA)</td>
</tr>
<tr>
<td>Laparotomy (operative)</td>
<td>0.019-0.056</td>
<td>NT (NT)</td>
<td>---</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFA*</td>
<td>0.0518-0.0766</td>
<td>NT (0.0496)</td>
<td>(RFA/HR)</td>
</tr>
<tr>
<td>HR*</td>
<td>0.0192-0.0304</td>
<td>NT (0.0318)</td>
<td>(HR/RFA)</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFA</td>
<td>0.030-0.042</td>
<td>NT (NT)</td>
<td>---</td>
</tr>
<tr>
<td>HR</td>
<td>0.333-0.367</td>
<td>NT (0.553)</td>
<td>(HR/RFA)</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>0.112-0.448</td>
<td>NT (NT)</td>
<td>---</td>
</tr>
<tr>
<td>Severe toxicity on SC</td>
<td>0.125-0.375</td>
<td>NT (NT)</td>
<td>---</td>
</tr>
<tr>
<td><strong>Modifying ratios</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cancer death (by comorbidity)</td>
<td>0.5-1.5 x Table</td>
<td>NT (2.7 x Table)</td>
<td>(HR/RFA)</td>
</tr>
<tr>
<td>Procedural mortality (by comorbidity)</td>
<td>0.5-1.5 x Table</td>
<td>NT (2.8 x Table)</td>
<td>(HR/RFA)</td>
</tr>
<tr>
<td>Mortality after complications (by time)</td>
<td>0.5-1.5 x Table</td>
<td>NT (2.6 x Table)</td>
<td>(HR/RFA)</td>
</tr>
<tr>
<td><strong>Utilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC</td>
<td>0.53-0.79</td>
<td>NT (NT)</td>
<td>---</td>
</tr>
<tr>
<td>SC (no/mild toxicity)</td>
<td>0.48-0.72</td>
<td>NT (0.90)</td>
<td>(HR/RFA)</td>
</tr>
<tr>
<td>SC (mod/severe toxicity)††</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>RFA</td>
<td>0.58-0.86</td>
<td>NT (0.90)</td>
<td>(HR/RFA)</td>
</tr>
<tr>
<td>HR</td>
<td>0.58-0.86</td>
<td>0.60</td>
<td>RFA/HR</td>
</tr>
<tr>
<td>Complications after HR/RFA/Laparotomy</td>
<td>0.48-0.72</td>
<td>NT (NT)</td>
<td>---</td>
</tr>
<tr>
<td>Death</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

NT = no threshold

* All transitional probabilities listed as per-month equivalents.

** Probabilities and utilities were varied within the plausible range as well as full range of 0 to 1.

*** All variables derived from tables were varied at +/- 50% of the values retrieved from tables.

† Ranges for all utilities given as +/- 20% of baseline.

†† This utility is always linked to chemotherapy with no/mild toxicity by a factor of 0.8X.
4.3.1 Effect of Age at Diagnosis

Figures 4.1 and 4.2 represent the effect of varying the age at diagnosis of CLM from ages 70 to 90. Our model predicts that HR is the preferred strategy for patients up 79.4 years old after which RFA becomes preferred. In fact, the difference between LE offered by HR versus RFA ranges from an incremental gain of 2.3 months for 70 year-old patients to a loss of 3.7 months for 90 year-old patients. This overall 6-month change in incremental LE represents the significant impact of age at diagnosis on model outputs.

Figure 4.1 Effect of age at diagnosis on LE

*BSC and SC are both inferior strategies with LE < 25 months.
Figure 4.2 Effect of age at diagnosis on LE

4.3.2 Effect of Comorbidities

The effect of comorbidities on our model outputs was examined by recalculating expected values for simulated patients with Charlson Index scores of up to 3. Results of these analyses are presented in Figure 4.3 and 4.4 for LE and QALE outcomes, respectively. As was described in the Methods section, patients with a high comorbidity level (Charlson ≥ 2) do not receive systemic chemotherapy. In addition, survival in the SC and BSC arms of the model are not varied with comorbidity level as there is no evidence to support this approach. Overall, these results illustrate that while HR is the preferred strategy in healthier patients, patients with high comorbidity may benefit more from RFA in both LE and QALE gains. However, the benefit of RFA over HR in patients with high comorbidity was only 0.8 months of LE and 0.2 months of QALE, and thus did not reach significance according to our definitions.
Figure 4.3 Effect of comorbidities on LE

![Graph showing effect of comorbidities on LE]

Figure 4.4 Effect of comorbidities on QALE

![Graph showing effect of comorbidities on QALE]
4.3.3 **Effect of Length of Simulation**

Performing one-way sensitivity analysis on the length of simulation of the model serves to demonstrate changes in incremental gains between strategies over time. Figure 4.5 illustrates the effect of changing the length of simulation from 12 months to 120 months. While a threshold value was technically identified at 39.3 months, it is evident that LE gains from RFA and HR are practically identical under the threshold. In fact, only beyond 50 months of simulation does the incremental LE gain of HR over RFA become significant (i.e. > 1 month). This gap continues to widen until at 120 months, at which point the model predicts a benefit of 8.3 months provided by HR over RFA.

**Figure 4.5** Effect of length of simulation on LE

4.3.4 **Effect of Probabilities of Recurrence**

Although the probabilities of recurrence after RFA and HR were not sensitive variables in initial sensitivity analyses using plausible ranges, further analyses showed a trend towards both parameters having an impact on model outcomes [Table 4.3]. Our analysis demonstrated that at a
per-cycle probability of recurrence after RFA of 0.0496, RFA and HR provided equivalent outcomes. This threshold value is only within 4.2% of the lowest published post-RFA recurrence data. Likewise, the threshold value associated with the probability of recurrence after HR was 0.0318, merely 1.3% greater than the highest published post-HR recurrence value.

### 4.3.5 Effect of Utilities

Within our pre-defined ranges for one-way sensitivity analyses, the only sensitive utility variable was the utility of the Well state after HR. However, despite a calculated threshold value of 0.60, the maximum incremental benefit of RFA over HR in the analysis was 0.5 months and thus not significant [Figure 4.6]. In further extended analysis allowing ranges of 0 to 1 for all utilities, the utility of Well state after RFA and the utility while on SC were sensitive variables. While both were associated with threshold values of 0.9, incremental benefits did not reach our definition of significance beyond this threshold in either case.

**Figure 4.6** Effect of utility of well after HR on QALE
4.4 Two-way Deterministic Sensitivity Analysis

Two-way deterministic sensitivity analyses for two pairs of variables are reported here. These are reported in graphic form with the variables plotted on the horizontal and vertical axes. Regions of these plots represent conditions under which competing strategies are preferred. Lines separating regions demonstrate points of indifference analogous to threshold values in one-way sensitivity analysis.

4.4.1 Age at diagnosis and length of simulation

Figure 4.7 demonstrates the interaction of uncertainties associated with age at diagnosis and length of simulation. The plot area is split between RFA and HR, while neither BSC nor SC was preferred under any conditions. Overall, the distribution of this graph illustrates that HR is preferred over RFA in younger patients especially when long-term outcomes are studied.

Figure 4.7 Two-way sensitivity analysis: age at diagnosis and length of simulation
4.4.2 Age at diagnosis and utility after HR

The simultaneous analysis of age at diagnosis and utility after HR yielded results shown in Figure 4.8. Again, BSC and SC are inferior strategies in all combinations of these variables. The plot suggests that as the age increases, the threshold level for utility after HR increases accordingly. In other words, older patients should receive HR only if the utility after HR is sufficiently high.

Figure 4.8 Two-way sensitivity analysis: age at diagnosis and utility after HR

4.4 Probabilistic Sensitivity Analysis (PSA)

PSA involved expected value analysis performed in a stochastic manner where all uncertainties in the model are accounted for. This form of analysis produces estimations of expected value as well as standard deviations around the estimate [Figure 4.9]. Our results show that given a starting age of 70 at diagnosis, while the ranking of preferred strategies to maximize LE and QALE did not change, there appeared to be no significant difference between outcomes offered
by RFA and HR. Nonetheless, both RFA and HR remain significantly better strategies than SC and BSC.

Another significant output from the PSA was an analysis of strategy selection frequency. While considering all parameter uncertainties, the proportion of hypothetical cases in which each particular strategy would be preferred is calculated as a percentage. In cases where competing strategies provided less than our predefined incremental gain of 1 month, the strategy choice was defined as ‘indifferent’. We performed this analysis through a range of ages in order to elicit the interaction between strategy preference and age at diagnosis [Figures 4.10 and 4.11]. Overall, SC and BSC were never the optimal strategy while HR was preferred over RFA. Specifically, given an age at diagnosis of 70, HR and RFA are preferred in 62.7% and 15.1% of cases, respectively, when assessing LE. The same analysis for QALE outcomes showed HR and RFA to be preferred 64.6% and 21.4% of the time, respectively.

**Figure 4.9** Stochastic expected outcomes of LE and QALE

*Analysis performed for age at diagnosis = 70
**Error bars represent 95% confidence intervals*
Figure 4.10 Distribution of preferred strategies to optimize LE in PSA by age

*Indifferent = difference between strategies < 1 month
**BSC and SC were never the preferred strategy

Figure 4.11 Distribution of preferred strategies to optimize QALE in PSA by age

*Indifferent = difference between strategies < 1 month
**BSC and SC were never the preferred strategy
Older patients diagnosed with CLM following resection of primary CRC pose a difficult clinical scenario for both the patient and the treating clinician. Traditional therapies of surgical resection and 5-FU-based chemotherapy have improved vastly in recent years and have become both safe and effective in older patients (297). The recent emergence of ablative therapies such as RFA has been associated with minimal morbidity and mortality, although its effectiveness as a stand-alone therapy for CLM is questionable (298). In addition, supportive care without anti-neoplastic therapies remains an option that may provide good QoL without exposing the patient to the toxicities of cancer treatment.

Traditionally, clinicians have been cautious when offering aggressive treatments to older patients with cancer. However, increasing evidence has demonstrated that patients should not be denied such treatments on the basis of chronological age alone (77-80). Nonetheless, clinical judgements in the age group remain complex and must consider normal physiological changes associated with aging, additional comorbidities of some older patients, and patient values. There are currently no randomized data to support any particular therapy in the management of older patients with CLM. In this study, we have built a Markov transition-state decision analytic model to estimate the outcomes of BSC, SC, RFA, and HR when used in the treatment of CLM in older patients.

5.1 Interpretation of Results

The results of our base case analysis indicate that HR is the optimum therapy for the treatment of healthy 70 year-old patients who present with CLM after primary CRC resection. While RFA offered slightly lower benefits than HR, both were superior to SC or BSC. The order of preferred strategies was the same in both LE and QALE analyses. Specifically, HR provided incremental benefits of 2.2 months of LE and 3.0 months of QALE over RFA in our 5-year analysis. In addition, our results showed that while SC was preferred to BSC, it was never the preferred strategy in base case or sensitivity analyses.
5.1.1 Clinical Significance

For the purposes of our model, we had defined an incremental difference of 1 month of LE or QALE to be technically significant. According to this definition, HR was a significantly better strategy than RFA providing gains of 2.2 months of LE and 3.0 months of QALE. However, true clinical significance of the magnitude of difference between strategies from decision analysis studies is often difficult to determine. In order to give our results clinical context, one must (1) consider the clinical meaning of LE and (2) compare these results with other reported gains for intervention in the same target population.

In the clinical setting, a gain in LE is often misinterpreted by clinicians and patients as an increase in life span. Construed this way, there is a tendency to minimize or disregard small absolute potential gains in LE as a long-term consequence. In reality, LE is defined as the average future life span of a cohort of individuals with similar characteristics. As such, LE can be regarded as the area under a survival curve, in which the probability of survival is plotted against time (299). By extension, a gain in LE can simply be defined as a shift of the survival to the right. Thus, a gain in LE should not be viewed as an extension of life span, but rather as an increase in the probability of survival over time. Importantly, this positive impact is immediate rather than long-term. Therefore, although incremental gains found in our study may be small, they nonetheless represent immediate increases in the probability of survival. Another important consideration when estimating clinical significance is how a study’s results compare with other studies. Such comparison must be performed using studies involving similar patient and disease characteristics since any therapeutic benefit must be interpreted within the context of the natural history of a given disease (300). For the present study, we will compare our results to those of other studies specific to CLM treatment.

The current practice of adding IRI or OX in combination with traditional 5FU/LV in the setting of metastatic CRC is largely based on the results of several RCTs showing clinically significant survival benefits of combination therapy. Two trials comparing 5FU/LV with and without IRI reported absolute increases in median overall survival of 3.3 months and 3.2 months associated with the addition of IRI (237,239). One trial investigating the impact of adding OX to 5FU/LV reported an increase of 2.5 months in median overall survival with the addition of OX (301). In comparison, the benefits of HR over RFA found in our study are similar in magnitude to the
incremental benefits reported in the above RCTs – results deemed significant enough to broadly change clinical practice. Therefore, the results of our expected value analysis are likely to be clinically significant.

5.1.2 Chronological age

One-way sensitivity analyses of our model yielded several significant results. First, when the age at diagnosis was varied from the baseline of 70 to 90, RFA eventually became the preferred strategy, with an incremental benefit of 3.7 months of LE over HR for patients diagnosed at age 90. Our model predicts that the shift of preference from HR to RFA occurs at the age of 79.4 years. This precise figure should not be interpreted at face value, since individual variation exists in real-life clinical scenarios. Nonetheless, our results suggest that the choice between these invasive strategies should be considered in the context of chronological age alone. This represents a contradiction to the modern notion that in the absence of comorbidity differences, patients should receive identical treatment options regardless of chronological age. As such, we explored our model for reasons of this finding.

First, our results reflect significant improvements in RFA efficacy in recent years. Although initially a technique developed for the palliative treatment of unresectable liver tumours, RFA has been shown to provide median survival of up to 37 months (170). Compared to HR, RFA remains superior in terms of safety, as evidenced by the minimal procedural mortality observed in most studies (138). Although HR still provided better efficacy, the combined safety and efficacy of RFA has made it an attractive alternative to HR in our model. As we considered increasingly older patients, the short-term benefits of RFA in terms of safety outweighed the long-term benefits of increased effectiveness of HR.

Another explanation for the independent impact of chronological age on model outcomes is important role that cancer recurrence plays in both quality and quantity of life. Since post-procedural mortality and morbidity have improved significantly for both HR and RFA, recurrence represents the most important cause of cancer-related deaths in patients undergoing either therapy. Recurrences, both intra- or extra-hepatic, invariably result in decreased quality of life secondary to local symptoms, systemic effects of metastatic CRC, and in many cases, the
toxic side effects of salvage chemotherapy (302). Life expectancy is also significantly shortened in events of tumour recurrence. Current literature suggests that recurrence rates following RFA are significantly higher than after HR for CLM treatment (303). This may explain the advantage of HR over RFA in our model predictions at age 70. However, given that the life expectancy decreases with age such that the average 90 year-old Canadian has a LE of 4 years, it is conceivable that the reduced recurrence rates associated with HR does not result in significant long-term benefits in these oldest patients.

5.1.3 Comorbidities

In our model, patient comorbidities in the form of the Charlson Index impacted post-RFA/HR mortality, the receipt of SC, and non-cancer mortality. As a result, altering the comorbidity level of simulated patients independent of other variables significantly influence the choice of optimal therapy [Figures 4.3 and 4.4]. Specifically, our results suggested that while HR is preferred over RFA in healthy patients, the benefits of HR over RFA decreases gradually with increasing comorbidities. In fact, HR is equivalent to RFA in offering LE and QALE benefits to patients with Charlson Index > 2. Again, these results may be secondary to two factors. First, the short-term advantages of RFA over HR in terms of post-operative morbidity and mortality are exaggerated in patients with more comorbidity. Second, the long-term advantages of reduced recurrence rates become less significant in less healthy patients since these patients already have limited LE based on comorbidity status. Overall, these findings have significant implications in clinical practice as therapy choices must be made in the context of an older patient’s overall health status.

5.1.4 Length of simulation

The outcome of our model was sensitive to changes in the number of cycles we allowed it to run (i.e. length of simulation). Specifically, the incremental benefit of HR over RFA was demonstrated to increase over time. Our results showed that a significant difference in predicted LE between RFA and HR only existed when the model was analyzed beyond 50 months [Figure
This phenomenon can likely be attributed to the relative long-term benefits of HR over RFA in terms of lower rates of recurrence. However, this sensitivity analysis must be taken in the context of important model assumptions. In particular, our model assumes that recurrence can be represented as a constant hazard function. As such, simulated patients are at a constant risk of recurrence for as long as they are alive. This assumption is valid for our base case analyses since recurrence probabilities were largely extracted from studies reporting 5-year survival. In our age group of interest, there has been no study with sufficient follow-up to estimate recurrence rates beyond 5 years. Therefore, extrapolation of our analysis beyond 60 months should be interpreted in the context of this limitation.

Nonetheless, the observation that significant differences between RFA and HR only become evident after 50 months of simulation has significant implications in the research setting. Our results suggest that future studies of RFA and HR efficacy, especially comparative studies, should have sufficient follow-up times of greater than 4 years in order to show meaningful results. Although not significant by our definition, our model demonstrated a trend of preference for RFA prior to 39 months. As such, comparative trials with less than 39 months follow-up may unfairly favour RFA over HR. In addition, results from two-way sensitivity analysis with age at diagnosis and length of simulation demonstrated that as we consider increasingly old patients, even longer follow-up times are necessary to observe a meaningful difference between RFA and HR outcomes [Figure 4.7].

5.1.5 Utilities

With the exception of the utility of being well after HR, our model was not impacted by variations in utility inputs. Even in the case of utility after HR, no significant difference in the outcomes of RFA and HR was observed through the plausible range of utility values [Figure 4.6]. Therefore, we can conclude that as independent variables, utilities do not significantly alter the outcomes of our model. Nonetheless, when we analyzed the utility of well after HR with age in a two-way analysis, the resulting trend indicates that the utility estimate becomes more important as we consider older patients. Practically, this suggests that utilities become increasingly
important as the presenting patient becomes older. As such, clinicians managing very old patients should pay particular attention to the values and expectations of the individual patient.

5.1.6 Likelihood of recurrence

Extensive analysis demonstrated a trend towards the probabilities of recurrence after RFA and HR being sensitive variables in our model. Specifically, the threshold probability of recurrence after RFA was only slightly lower than reported values while the threshold for HR recurrence was slightly higher than reported values. These observations illustrate the potential dependence of our model on data pertaining to recurrence rates. This implies that our model outcomes are susceptible to any biases in the available data. As such, our results underscore the importance of future randomized trials that specifically investigate rates of recurrence after therapy.

5.1.7 Probabilistic Sensitivity Analysis

In our PSAs, we treated most model parameter inputs as distributions in order to assess the effects of the joint uncertainty of these variables. As an exception, we treated age at diagnosis as a variable free of uncertainty for two reasons. First, in the practical setting, the age of the presenting patient is always known with certainty. Second, by isolating age as a variable without uncertainty, we were able to further investigate the effect of age (beyond deterministic analysis) on strategy choices while incorporating the joint uncertainty of other important parameters.

Given the start age of 70, our results from stochastic expected value analysis indicate that while RFA and HR were better than BSC or SC, the two strategies were not significantly different. In fact, the joint uncertainty of model parameters resulted in considerable errors associated with the EV estimates [Figure 4.9]. This suggests that neither HR nor RFA is clearly superior to one another. Therefore, in the clinical setting, each older patient with CLM should be evaluated on an individual basis in the context of patient characteristics, tumour factors, as well as patient values.

Our analysis of preferred treatment strategies using PSA at different starting ages produces interesting results. First, when considering both LE and QALE, RFA became the preferred
strategy as the presenting age of patients became older. Second, this gradual preference for RFA over HR with age was more prominent when LE outcomes are concerned [Figure 4.10 and 4.11]. This suggests that HR provides better QoL to older patients, such that analysis of QALE (in contrast to LE) results in a more gradual preference for RFA with age. Again, BSC and SC were never the preferred strategy in the analyses.

5.2 Study Limitations

5.2.1 Model Structure

The state-transition structure of our model allowed for explicit modeling of procedural mortality and mortality, survival on BSC/SC, and tumour recurrence. In addition, the incorporation of patient age and comorbidity in the model makes our model unique among other decision analytical studies of CLM treatment (221-224). While we have attempted to structure the model in such a way that reflects the underlying disease processes, there are some important limitations we recognize.

First, we have only included four mutually exclusive strategies into our model. In reality, there has been an increased focus on multi-modal management of CLM in recent years. Strategies such as the use of pre-operative chemotherapy to downsize tumours and the concurrent use of RFA and HR for multiple lesions have been shown to be effective in the literature (181-186,188,190). However, these studies are generally non-randomized with significant selection biases. As such, these strategies are currently reserved for select cases and certainly have not been studied among older patients with CLM. More importantly, the goal of our study was not to consider and model every possible treatment or combination of treatments. Instead, our objective was to evaluate the four most commonly used modalities for CLM management and develop a structural framework upon which future models of oncologic management can be built.

One major task of our analysis was to model treatment outcomes while taking age and comorbidities into consideration. Previous studies have demonstrated that comorbidities are more responsible for poor outcomes of oncologic treatment than chronological age (228-230,304,305). As such, we have incorporated comorbidities in two manners: as a modifier of
post-procedural mortality and of non-cancer mortality. The latter was accomplished using a previously described method of matching levels of comorbidity with quartiles of LE derived from life tables (231,233,234). However, these methods are not without their limitations. While the impact of comorbidity on post-HR and RFA mortality could be derived from studies with multivariate regression models, no such data exists for SC or BSC (294). As such, we did not model the effects of comorbidity in the SC and BSC arms. Nonetheless, if these assumptions biased the SC and BSC strategies, inclusion of comorbidity effects should have made these strategies less favourable and thus not change the ranking of preferred strategies.

5.2.2 Model Data

The quality of any decision analytic model depends heavily on the quality of data used to populate it. Despite our best efforts to identify the best evidence available, we recognize that the quality of input data represents a significant weakness in our study.

Data used for parameters in the BSC arm were derived from relatively outdated literature consisting of retrospective series of patients with untreated CLM. While some may argue that supportive care has evolved in recent years to improve outcomes, most improvements are made to QoL rather than survival (114,116). In fact, using relatively old data in this respect may be advantageous. Due to the adoption of HR as the primary option for patients with CLM, any recent studies examining patients BSC would consist of mostly patients with unresectable disease. In contrast, studies contained in our literature search of BSC were conducted at a time before surgery was widespread, thus resulting in a sample of patients who may have resectable disease (especially by modern standards) but were untreated. Therefore, the patient population from these studies may better represent the target population that our decision analysis was designed to evaluate. A further concern is the lack of specific BSC data for older patients. Nonetheless, there is some evidence in the literature that age is not a significant predictor of overall survival with untreated CLM (306). This suggests that most older patients with CLM die of their cancer and not age-related non-cancer causes.

Data used for the SC strategy were mostly derived from pooled analyses of RCTs and thus were of good quality. However, as described in an earlier section, older patients remain under-
represented in chemotherapy trials despite recent improvements in enrolment. In particular, patients with significant comorbidities are even less likely to be enrolled in trials (84,85,87,88). The pooled analysis by Folprecht et al. used as our primary source of SC data reviewed 599 patients aged 70 or above (127). Of these, 69% were aged 70-74, 27% were aged 75-79, and only 4% were aged 80 or above. In addition, 90% of these older patients had a performance status of 0 or 1. Therefore, while this data serves our base case analysis well, extrapolation to even older ages should be done with caution. In addition, we excluded all patients with a high level of comorbidity from receiving SC in our model to reflect the general practice of restricting chemotherapy to healthier individuals.

At the time of this study, there are no randomized trial data in the RFA literature to support its use in CLM treatment (303). Thus, studies included in our data identification are restricted to non-randomized cohorts of patients from all age groups. This may have impacted our analysis in two ways. First, present studies have generally selected for healthy patients with favourable disease characteristics. Second, studies to date of RFA as single therapy for CLM have almost exclusively been restricted to patients who have disease deemed to be surgically unresectable. While these two factors may bias our study in opposite directions, the true impact of these biases is unknown. To obtain probability estimates for the HR strategy, we relied heavily on data from retrospective cohort studies. While results from these studies are specific to older patients, selection bias for healthier and relatively younger patients may still exist.

To summarize, there is a general paucity of literature regarding the treatment of CLM in older patients. Nonetheless, we have attempted to utilize the best available evidence in the construction of our model. Aware of the potential inaccuracy of data used, we performed extensive sensitivity analyses around variable estimates. This included probabilistic sensitivity analysis to evaluate the magnitude of joint uncertainty in our model.

5.3 Implications of Study Findings

There are several significant implications of our current study. First, we have demonstrated the importance of individualized care for older patients with CLM. While HR may be beneficial for a healthy 70 year-old patient with CLM, RFA may be an equally preferable strategy in other
older patients with significant comorbidities. From a patient’s perspective, our results suggest that both chronological age and comorbidity can determine the optimal treatment strategy for such patients. Furthermore, sensitivity analyses of our model have highlighted the importance of sufficient follow-up in any future studies of RFA and HR. According to model predictions, clinically significant differences in the long-term effectiveness of RFA and HR may not be measureable within the first 4 years following treatment. In the construction of our model, we have also recognized the scarcity of high quality data that is specific to older patients. In particular, controlled trials of both RFA and HR should be conducted in the future to guide clinical decision making. Emphasis should also be placed on measurement of health-related QoL using standardized methodology.

The present study has illustrated the value of a patient-centered decision analytical approach to complex medical problems. While the majority of recent DA research has taken a societal perspective and revolve around cost-effectiveness, patient-centered models such as ours can potentially be applied to the clinical setting. Ultimately, older adults have the same right as younger individuals to take part in the decision making process regarding their health care. More so than their younger counterparts, older patients with cancer are faced with their own mortality while considering their past experiences and their personal set of values. As such, significant heterogeneity exists among older cancer patients with respect to their preferences for quantity and quality of life. Future refinements of our model may involve development of a clinical decision aid that patients and clinicians can use in the clinic to guide the decision making process while considering individual patient preferences and values.
6. SUMMARY

Decision analysis is particularly useful in the approach to older cancer patients due to its ability to incorporate patient-specific factors such as age and comorbidity, treatment-specific factors, as well as patient values into a comprehensive model. It is often the lack of high-quality, randomized evidence that necessitates the use of decision analysis as a synthesis of available evidence in a rational, quantitative structure. This study used a detailed decision analytic model populated with current clinical data to evaluate the use of BSC, SC, RFA, and HR in the management of older patients with CLM after primary CRC resection. Our results suggest that RFA and HR are superior to BSC and SC in terms of both LE and QALE outcomes. Moreover, our results highlight the importance of considering both chronological age and comorbidity status when choosing between RFA and HR. HR may provide a marginal benefit over RFA in healthy older patients while RFA may be more appropriate for older patients with significant comorbidities. The outcome of our analysis has the potential to improve patient-physician communication and inform decision making in the clinical setting.
7. REFERENCES


(70) Maggiore RJ, Gross CP, Hurria A. Polypharmacy in Older Adults with Cancer. Oncologist 2010 Apr 24.


(143) Abdalla EK. Radiofrequency ablation for colorectal liver metastases: do not blame the biology when it is the technology. Am.J.Surg. 2008 Sep 11.


(218) Ferreira PL, Ferreira LN, Pereira LN. How consistent are health utility values? Qual.Life Res. 2008 Sep;17(7):1031-1042.


### Table A.1  Charlson comorbidity index

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Relative Weight Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarct</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td>1</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>1</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>1</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe renal disease</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes with end organ damage</td>
<td>2</td>
</tr>
<tr>
<td>Any tumor</td>
<td>2</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>3</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>6</td>
</tr>
<tr>
<td>AIDS</td>
<td>6</td>
</tr>
</tbody>
</table>

*Total score is obtained by adding the relative weight of each comorbidity.*
<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TX</strong> Primary tumour cannot be assessed</td>
</tr>
<tr>
<td><strong>T0</strong> No evidence of primary tumour</td>
</tr>
<tr>
<td><strong>Tis</strong> Carcinoma in situ</td>
</tr>
<tr>
<td><strong>T1</strong> Tumour invades submucosa</td>
</tr>
<tr>
<td><strong>T2</strong> Tumour invades muscularis propria</td>
</tr>
<tr>
<td><strong>T3</strong> Tumour invades pericolectal tissues</td>
</tr>
<tr>
<td><strong>T3a</strong> Tumour invades through muscularis propria into subserosa or into non-peritonealised pericolic or perirectal tissues</td>
</tr>
<tr>
<td><strong>T3b</strong> T1 or T2 tumour with satellite deposits in pericolectal tissues</td>
</tr>
<tr>
<td><strong>T4a</strong> Tumour penetrates visceral peritoneum</td>
</tr>
<tr>
<td><strong>T4b</strong> Tumour directly invades or is adherent to other organs or structures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymph Nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NX</strong> Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td><strong>N0</strong> No regional lymph node metastasis</td>
</tr>
<tr>
<td><strong>N1</strong> Metastasis in 1 to 3 regional lymph nodes</td>
</tr>
<tr>
<td><strong>N1a</strong> Metastasis in 1 regional lymph node</td>
</tr>
<tr>
<td><strong>N1b</strong> Metastasis in 2-3 regional lymph nodes</td>
</tr>
<tr>
<td><strong>N2</strong> Metastasis in 4 or more regional lymph nodes</td>
</tr>
<tr>
<td><strong>N2a</strong> Metastasis in 4 to 6 regional lymph nodes</td>
</tr>
<tr>
<td><strong>N2b</strong> Metastasis in 7 or more regional lymph nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MX</strong> Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td><strong>cM0</strong> No distant metastasis</td>
</tr>
<tr>
<td><strong>M1</strong> Distant metastasis</td>
</tr>
<tr>
<td><strong>M1a</strong> Metastasis confined to one organ or site</td>
</tr>
<tr>
<td><strong>M1b</strong> Metastases in more than one organ/site or the peritoneum</td>
</tr>
</tbody>
</table>

AJCC = American Joint Committee on Cancer  
Adapted from AJCC Cancer Staging Manual 7th Edition
<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIC</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3-T4a</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2-T3</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-T2</td>
<td>N2b</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC</td>
<td>T4a</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3-T4a</td>
<td>N2b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>N1-N2</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

AJCC = American Joint Committee on Cancer
Adapted from AJCC Cancer Staging Manual 7th Edition
**Table A.4** Summary of studies of untreated CLM

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample Size</th>
<th>Median Survival (months)</th>
<th>Probability of Death on BSC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaffe <em>et al.</em></td>
<td>1968</td>
<td>177</td>
<td>4.9</td>
<td>0.1319</td>
</tr>
<tr>
<td>Bengmark <em>et al.</em></td>
<td>1969</td>
<td>38</td>
<td>4.0</td>
<td>0.1591</td>
</tr>
<tr>
<td>Abrams <em>et al.</em></td>
<td>1971</td>
<td>58</td>
<td>5.9</td>
<td>0.1108</td>
</tr>
<tr>
<td>Wood <em>et al.</em></td>
<td>1976</td>
<td>113</td>
<td>6.6</td>
<td>0.0997</td>
</tr>
<tr>
<td>Bengtsson <em>et al.</em></td>
<td>1981</td>
<td>155</td>
<td>4.5</td>
<td>0.1428</td>
</tr>
<tr>
<td>Boey <em>et al.</em></td>
<td>1981</td>
<td>73</td>
<td>7.5</td>
<td>0.0883</td>
</tr>
<tr>
<td>Goslin <em>et al.</em></td>
<td>1982</td>
<td>125</td>
<td>12.5</td>
<td>0.0539</td>
</tr>
<tr>
<td>Lahr <em>et al.</em></td>
<td>1983</td>
<td>175</td>
<td>6.1</td>
<td>0.1074</td>
</tr>
<tr>
<td>Fortner <em>et al.</em></td>
<td>1984</td>
<td>109</td>
<td>11.5</td>
<td>0.0585</td>
</tr>
<tr>
<td>Arnaud <em>et al.</em></td>
<td>1984</td>
<td>56</td>
<td>7.0</td>
<td>0.0943</td>
</tr>
<tr>
<td>Finan <em>et al.</em></td>
<td>1985</td>
<td>90</td>
<td>10.3</td>
<td>0.0651</td>
</tr>
<tr>
<td>Ekberg <em>et al.</em></td>
<td>1986</td>
<td>73</td>
<td>11.0</td>
<td>0.0611</td>
</tr>
<tr>
<td>DeBrauw <em>et al.</em></td>
<td>1987</td>
<td>69</td>
<td>8.4</td>
<td>0.0792</td>
</tr>
<tr>
<td>Chang <em>et al.</em></td>
<td>1989</td>
<td>67</td>
<td>15.1</td>
<td>0.0449</td>
</tr>
</tbody>
</table>

*monthly probability

Table adopted from Chang *et al.*
### Table A.5 Summary of literature examining percutaneous RFA for CLM

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Type</th>
<th>Centre</th>
<th>Sample Size</th>
<th>Effective (%)</th>
<th>Operative Mortality (%)</th>
<th>Complication Rate (%)</th>
<th>Probability of recurrence*</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solbiati et al.</td>
<td>2001</td>
<td>Prospective Cohort</td>
<td>Two</td>
<td>117</td>
<td>98</td>
<td>0</td>
<td>1.7</td>
<td>0.0561</td>
<td>36mos median</td>
</tr>
<tr>
<td>Livraghi et al.</td>
<td>2003</td>
<td>Prospective Cohort</td>
<td>Two</td>
<td>88</td>
<td>60</td>
<td>0</td>
<td>3.4</td>
<td>0.0421</td>
<td>NR</td>
</tr>
<tr>
<td>Oshowo et al.</td>
<td>2003</td>
<td>Retrospective Cohort</td>
<td>Single</td>
<td>25</td>
<td>NR</td>
<td>0</td>
<td>4</td>
<td>NR</td>
<td>37mos median</td>
</tr>
<tr>
<td>Lencioni et al.</td>
<td>2004</td>
<td>Prospective Cohort</td>
<td>Multi</td>
<td>423</td>
<td>85.4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>24% 5-year</td>
</tr>
<tr>
<td>White et al.</td>
<td>2004</td>
<td>Prospective Cohort</td>
<td>Single</td>
<td>30</td>
<td>68</td>
<td>0</td>
<td>5</td>
<td>0.0741</td>
<td>22mos median</td>
</tr>
<tr>
<td>Berber et al.</td>
<td>2005</td>
<td>Prospective Cohort</td>
<td>Single</td>
<td>135</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.1091</td>
<td>28.9mos median</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>2005</td>
<td>Retrospective Cohort</td>
<td>Single</td>
<td>96</td>
<td>96.7</td>
<td>1</td>
<td>2.5</td>
<td>NR</td>
<td>25% 3-year</td>
</tr>
<tr>
<td>Jakobs et al.</td>
<td>2006</td>
<td>Retrospective Cohort</td>
<td>Single</td>
<td>68</td>
<td>NR</td>
<td>NR</td>
<td>5.9</td>
<td>NR</td>
<td>68% 3-year</td>
</tr>
<tr>
<td>Schindera et al.</td>
<td>2006</td>
<td>Retrospective Cohort</td>
<td>Single</td>
<td>14</td>
<td>88.5</td>
<td>0</td>
<td>16.7</td>
<td>0.0620</td>
<td>NR</td>
</tr>
<tr>
<td>Sorensen et al.</td>
<td>2007</td>
<td>Retrospective Cohort</td>
<td>Single</td>
<td>102</td>
<td>NR</td>
<td>0</td>
<td>6.9</td>
<td>NR</td>
<td>32mos median</td>
</tr>
<tr>
<td>Gillams et al.</td>
<td>2009</td>
<td>Prospective Cohort</td>
<td>Single</td>
<td>309</td>
<td>NR</td>
<td>0</td>
<td>4.7</td>
<td>NR</td>
<td>27mos median</td>
</tr>
</tbody>
</table>

* monthly probability

NR = not reported
Table A.6 Summary of literature examining HR for CLM in older adults

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Type</th>
<th>Centre</th>
<th>Age Group</th>
<th>Sample Size</th>
<th>Operative Mortality (%)</th>
<th>Complication Rate (%)</th>
<th>Probability of recurrence*</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gayowski et al.</td>
<td>1994</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>&gt;60</td>
<td>108</td>
<td>0</td>
<td>NR</td>
<td>0.0238</td>
<td>28% 5-year</td>
</tr>
<tr>
<td>Zieren et al.</td>
<td>1994</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>≥70</td>
<td>18</td>
<td>6</td>
<td>16***</td>
<td>NR</td>
<td>18mos median</td>
</tr>
<tr>
<td>Fong et al.</td>
<td>1995</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>≥70</td>
<td>128</td>
<td>4</td>
<td>42</td>
<td>NR</td>
<td>35% 5-year</td>
</tr>
<tr>
<td>Doci et al.</td>
<td>1995</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>≥66</td>
<td>46</td>
<td>4</td>
<td>35</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Brand et al.</td>
<td>2000</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>≥70</td>
<td>41</td>
<td>7.3</td>
<td>29***</td>
<td>0.0663</td>
<td>21.9mos median</td>
</tr>
<tr>
<td>Tocchi et al.</td>
<td>2004</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>≥65</td>
<td>29</td>
<td>NR**</td>
<td>NR</td>
<td>NR</td>
<td>42.5mos median</td>
</tr>
<tr>
<td>Zacharias et al.</td>
<td>2004</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>≥70</td>
<td>56</td>
<td>0</td>
<td>39</td>
<td>0.0561</td>
<td>28mos median</td>
</tr>
<tr>
<td>Nagano et al.</td>
<td>2005</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>≥70</td>
<td>62</td>
<td>0</td>
<td>19.7</td>
<td>0.0113</td>
<td>34% 5-year</td>
</tr>
<tr>
<td>Figuerras et al.</td>
<td>2007</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>≥70</td>
<td>160</td>
<td>8</td>
<td>41</td>
<td>0.0253</td>
<td>38% 5-year</td>
</tr>
<tr>
<td>Mazzoni et al.</td>
<td>2007</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>≥70</td>
<td>53</td>
<td>6</td>
<td>21</td>
<td>0.0273</td>
<td>28mos median</td>
</tr>
<tr>
<td>De Liguori et al.</td>
<td>2008</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>≥70</td>
<td>178</td>
<td>4.9</td>
<td>38.5</td>
<td>0.0301</td>
<td>31.5% 5-year</td>
</tr>
<tr>
<td>Mann et al.</td>
<td>2008</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>≥70</td>
<td>49</td>
<td>0</td>
<td>31</td>
<td>0.0204</td>
<td>31% 5-year</td>
</tr>
<tr>
<td>Rees et al.</td>
<td>2008</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>&gt;70</td>
<td>236</td>
<td>NR**</td>
<td>NR</td>
<td>NR</td>
<td>37.9mos median</td>
</tr>
<tr>
<td>Bockhorn et al.</td>
<td>2009</td>
<td>Retrospective cohort</td>
<td>Single</td>
<td>≥75</td>
<td>59</td>
<td>3</td>
<td>10***</td>
<td>0.0210</td>
<td>23mos median</td>
</tr>
</tbody>
</table>

* monthly probability
** no specific data presented for the elderly group
*** only major complications reported; NR = not reported
Table A.7 Summary of literature reporting true resectability at time of HR

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample Size</th>
<th>True Resectability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jarnagin et al.</td>
<td>1999</td>
<td>416</td>
<td>79%</td>
</tr>
<tr>
<td>Schmidt et al.</td>
<td>2000</td>
<td>33</td>
<td>79%</td>
</tr>
<tr>
<td>Wallace et al.</td>
<td>2001</td>
<td>179</td>
<td>81%</td>
</tr>
<tr>
<td>Valls et al.</td>
<td>2001</td>
<td>157</td>
<td>94%</td>
</tr>
<tr>
<td>Zacherl et al.</td>
<td>2002</td>
<td>61</td>
<td>87%</td>
</tr>
<tr>
<td>Bhattacharjya et al.</td>
<td>2004</td>
<td>120</td>
<td>83%</td>
</tr>
<tr>
<td>Soyer et al.</td>
<td>2004</td>
<td>60</td>
<td>100%</td>
</tr>
<tr>
<td>Bennett et al.</td>
<td>2005</td>
<td>146</td>
<td>85%</td>
</tr>
</tbody>
</table>
9. APPENDIX B – SAMPLE CALCULATIONS

Conversion of rates to probabilities

TreeAge Function: RATETOPROB

Equation:

Example: “The annual rate of mortality was 0.137.” To calculate probability per 1 month cycle:

\[ P = 1 - e^{-0.137 \left( \frac{1 \text{ month}}{12 \text{ months}} \right)} = 1 - 0.9886 = 0.0114 \]

Conversion of probabilities to rates

TreeAge Function: PROBTORATE

Equation: \[ R = - \left( \frac{\ln(1-P)}{T} \right) \]

Example: “40% of patients have recurred at 5 years.” To calculate the hazard rate over 1 month:

\[ R = - \left( \frac{\ln(1-0.4)}{60 \text{ months}} \right) = 8.514 \times 10^{-3} \]
Conversion of probabilities over any time period to per-cycle probabilities

TreeAge Functions: PROBTORATE, RATETOPROB

Equations: \[ R = -\left( \frac{\ln(1-p)}{T} \right), \quad P = 1 - e^{-RT} \]

Example: “50% of patients are dead at 3 years” To calculate the probability of death per cycle (1 month):

\[ \therefore R = -\left( \frac{\ln(1-0.5)}{36 \text{ months}} \right) = 0.01925 \]

\[ \therefore P = 1 - e^{-0.01925 \times 1} = 1 - 0.9809 = 0.01907 \]