A Cost-Utility Analysis of Liver Resection for Malignant Tumours: a Pilot Project

By

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VOULUME 1 of 2

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Abstract

This study is a pilot cost-utility analysis comparing hepatic resection, radiofrequency ablation (RFA), systemic chemotherapy, and symptom control only for the treatment of colorectal liver metastases. It is a prospective, non-randomized, observational study, which did not influence the type of treatment received. All patients with newly diagnosed liver malignancies of any type who were referred to a hepatobiliary surgeon or to medical oncologists at CancerCare Manitoba (CCMB) at the St. Boniface General Hospital (SBGH) were eligible. Quality of life, in terms of utility, was measured serially with the Health Utilities Index Mark II and III. Costs, in 2001 Canadian dollars, were captured from the viewpoint of society in general, including hospital costs, outpatient medical costs, and costs borne by patients themselves. A cost-utility analysis was then performed with the aid of decision analysis techniques.

Forty patients were enrolled in the study. Seven patients underwent hepatic resection, 7 patients underwent RFA (sometimes in combination with resection), 20 patients received systemic chemotherapy, and 6 patients received symptom control alone. The sample size is small and the treatments were not randomized. Liver resection was the most effective treatment, providing an average benefit of 2.51 quality-adjusted life years (QALY's) compared to 1.99 QALY's for RFA, and 1.18 QALY's for chemotherapy, and 0.82 QALY's for symptom control alone. The costs were $20,122, $ 15,845, $15,069, and $3,899, respectively. The cost-utilities of liver resection and RFA were similar at $8,027 and $7,965 per QALY, respectively, although patients receiving RFA generally had more advanced disease. The cost-utility of chemotherapy appears higher, at $12,751 per QALY. The cost-utility of symptom control alone was the lowest at $4,788, but it was

also the least effective treatment. RFA is still a relatively new treatment. However, if long-term survival proves as promising as the short-term data, it may prove to be a viable alternative to liver resection.

Chapter 1. Introduction

Malignant liver tumours are common in Canada and around the world. They affect large numbers of people and consume considerable health care resources. These diseases, along with their treatments, are responsible for many early deaths and significant reduction in life (QOL).

Worldwide, hepatocellular carcinoma (HCC) is one of the most common malignancies, in part related to the prevalence of chronic hepatitis B virus (HBV) infections(1;2). Its incidence is increasing in the western world due to the epidemics of the hepatitis C virus (HCV)(2).

In North America and Western Europe most liver malignancies are metastases, and colorectal cancer is responsible for the majority of these metastases(1). In Canada, an estimated 19,600 new cases of colorectal carcinoma will occur in 2005 with 8,400 deaths, making it the fourth most commonly diagnosed cancer and the second leading cause of cancer death in Canada(3). Nearly half of these patients will develop liver metastases at some point during the course of their disease, with 15% to 25% having metastases at the time of diagnosis(4;5).

Unfortunately, among all patients with metastatic liver disease only a small fraction will be candidates for curative resection, which currently offers the best chance for long-term survival(4-6). Only 20% to 25% of patients with liver metastases will have their metastases confined to the liver(1;7), and then only 8% to 27% of this subgroup will be candidates for resection of their hepatic metastases(8). For patients who do have resectable lesions, 5-year survival with hepatic resection is in the range of 24% to 38%(6). With careful patient selection this figure can reach 58%(9). On the other hand, 5-

year survival without resection is extremely rare(4). The complications of surgical resection are significant, however. A recent review found that reported morbidity rates average 23% and mortality averages 3.3%(10).

The majority of patients with liver metastases are not candidates for hepatic resection, but may undergo systemic chemotherapy. This generally results in median survivals of 10 to 14 months(1;11;12), although the addition of newer anti-angiogenesis agents has resulted in median survivals as high as 20 months(13). The side effects of systemic chemotherapy are also quite substantial. For patients with unresectable disease, other regional techniques such as hepatic cryosurgery and radiofrequency ablation (RFA) have been the subjects of ongoing research(6;14). The goal in developing such techniques is to achieve a similar survival as can be achieved with resection, but with less morbidity and greater quality of life. Longer follow-up is required to determine disease-free and overall survival rates as well as the gain in QOL that may be achieved. Hepatic arterial infusion (HAI) chemotherapy is another option that may improve survival, but is generally reserved for patients with disease limited to the liver(6). It allows higher doses of chemotherapeutic agents to be administered while limiting systemic complications, but complications related to the catheter are frequent and advantages over systemic chemotherapy are unproven. Trials using combinations of interventions are also currently being done. When feasible, hepatic resection remains the treatment of choice.

There are two therapies considered optimal for HCC, resection and transplantation(15;16). Resection can provide 5-year survival rates of 15% to 30%(1), but only a minority of patients are potential candidates. Orthotopic liver transplantation may be preferable to hepatectomy in patients with hepatic insufficiency and in patients with

more than one tumour(15). 4-year survival rates of 75% may be achieved, but only in selected patients(1). In small HCC's, percutaneous ethanol injection (PEI) is an option, and transarterial chemoembolization (TACE) is a palliative procedure that may offer a small survival benefit(16). Again, other local treatments are currently being evaluated, including radiofrequency ablation(14).

For some medical conditions, the best available treatments also carry significant morbidity and mortality. Malignant liver diseases are excellent examples of such conditions. Even with the best available treatments, 5-year survival is not very high (E.g. For colorectal metastases to the liver, the 5-year survival is on the magnitude of 24 to 38%(6)) and the treatments themselves cause significant mortality and morbidity. The choice of treatment is often dictated by both the potential survival offered and by the potential morbidity. Quality of life after treatment is an extremely important factor.

Unfortunately, quality of life after treatments for liver metastases is not well described in clinical studies and patients must often rely mainly on anecdotal information. The ability to accurately describe this outcome is impaired by a scarcity of published reports and by the lack of a common scoring system among studies. No single scoring system to describe health-related quality of life has been uniformly accepted among investigators, and the few studies that do exist often used different scoring systems. As a result, it is difficult to make comparisons between different treatments and to draw broad conclusions about quality of life. Another drawback of such scoring systems is that it is often unclear as to what magnitude of change in QOL score from these instruments reflects a clinically significant change(17). An important aspect of the

present study is the description and comparison of both the survival and the quality of life offered by the various treatments for malignant liver diseases.

The high costs associated with treatment of liver metastases create a great burden to the healthcare system and to society as a whole, and the amount of resources available to the healthcare system is limited. Because resources are limited, the decision to spend resources to combat one disease often means a choice not to spend the same resources to treat another disease, making it difficult to determine the best way to spend a particular resource. The term, *opportunity cost*, is used to represent the value of the alternative that must be foregone when resources are consumed to provide an intervention(18). This notion is especially important in medicine where limited resources dictate that the provision of one treatment often means foregoing the provision of another. The costs of a particular treatment, the survival offered, and the quality of that survival are all important factors that go into these decisions. Thus, it is important to compare the cost-utility of various interventions for hepatic malignancies.

The present study was a pilot project to compare different available treatments for colorectal liver metastases. Because colorectal cancer is responsible for most liver malignancies in North America, hepatic colorectal metastases were the primary focus of the study. Patients with all forms of hepatic malignancy were eligible, as it was hoped that by including more patients, more hypothesis data would be generated. Although the initial results of RFA appear promising, this technique is still relatively new and long-term survival has not yet been reported. The treatment of choice for metastatic liver disease is surgical resection when feasible(4-6). It is hoped that RFA will be able to offer similar survival with less morbidity and mortality and if longer-term follow-up suggests

this may be true then randomized controlled trials would be indicated. The present study was designed to generate hypothesis data as to whether the cost-utility of RFA and hepatic resection are similar enough to justify such a trial. Systemic chemotherapy and symptom control alone (i.e. palliative treatment) were included in the study because the costs and quality of life after all treatments for liver metastases are poorly described and the cost-utility of all treatment options should be within an acceptable range(19) if physicians are to continue to recommend them.

First, the current status of the available treatments for colorectal liver metastases will be reviewed, along with a summary of the limited existing cost-effectiveness and quality of life data. This background information will help explain the rationale for the current study.

Chapter 2. Existing Survival Data for Treatments of Colorectal Liver Metastases

A. Surgical Resection of Colorectal Metastases

Liver metastases are present in 15% to 25% of patients with colorectal cancer at the time of diagnosis, and another 25% of patients will develop metachronous lesions(4;5;20). Presently, surgical resection, when feasible, offers these patients the only chance for long-term survival(4-6).

The type of resection performed depends on the size, number, and location of the lesions(1). Smaller lesions may be removed with wedge resections or segmental resections when feasible, with a goal of 1 cm margins. Larger lesions and lesions close to major vascular structures within the liver often require formal lobectomies. This may entail formal left or right hepatectomies where half the liver is removed, or extended lobectomies where the left or right lobes are removed along with a portion of the opposite lobe.

Most of the survival literature involves large case series that are often retrospective. The survival figures for resection of colorectal liver metastases vary between series, but recent papers have reported 5-year survival rates ranging from 21% to 54%(20-57) (See Table 1). Patients who are candidates for repeat hepatic resections after disease recurrence can have similar survival compared to patients undergoing their first resection(21;24;25;47;48;58-63). Advances in surgical technique and technology, in addition to advances in anaesthesia and intensive care practices have resulted in improvements in survival. Recent advances in imaging technology may improve survival rates even further with improved patient selection by detecting more patients with occult

extra-hepatic disease and excluding them from resection. Newer computed tomography and magnetic resonance imaging equipment has improved resolution to detect smaller lesions. Positron emission tomography (PET) is particularly promising (9;64-66). Fernandez et al recently reported a 5-year survival of 58% after hepatic resection for colorectal metastases in patients screened with PET Scans(9). A possible consequence of this improved screening process is that even fewer patients may be considered candidates for hepatic resection.

There are many variables that have been associated with poor outcomes. Patients with extra-hepatic disease and with positive resection margins have significantly worse survival(22;26;27;32;38;40;46;67). Patients with synchronous lesions fare worse than patients with metachronous lesions(26;32;33;37;40;46;68). Other independent poor prognostic factors that have been reported include stage of the primary tumour, number of liver lesions, size of lesions, requiring a more extensive resection, intra-operative blood loss, and elevated carcinoembryonic antigen (CEA) levels(22;23;26;27;29;32;35;37-39;41;46;47;50;52;53;68;69). Hepatic surgery is a major undertaking and carries with it significant chance of both operative mortality and of postoperative morbidity (see Table 2). The average of the reported mortality rates from several recent series is 3% with a range from 0%to 11%(20-26;28-57;70). The average of the reported overall morbidity rates was 26.5%. Although hepatic resection offers the best chance of long-term survival(4-6), it should be kept in mind that the associated morbidity and mortality are significant.

Table 1. Reported Survival Rates Following Hepatic Resection for Colorectal Metastases (%)(20-26;28-57;70).

Author	Date	N	5Y DFS	5Yr Surv	10Yr Surv
Hananel(33)	1995	24		30.5	
Jatzko(39)	1995	66	13.9	29.6	
Doci(31)	1995	219	18.0	24.0	
Nordlinger(46)	1996	1568	15.0	28.0	
Pinson(48)	1996	95	16.0	38.0	
Wade(20)	1996	161		26.0	
Wanebo(54)	1996	74		24.0	13.0
Wang(55)	1996	54		25.5	
Chu(21)	1997	74		28.0	
Jenkins(40)	1997	131	16.0	25.0	
Nadig(43)	1997	275		26.0	
Jamison(38)	1997	280		27.0	20.0
Fong(32)	1997	456	19.0	38.0	
Taylor(52)	1997	123	20.0	34.0	26.0
Lorenz(42)	1997	37		25.0	
Rees(49)	1997	114		30.0	
Shirabe(51)	1997	31		39.0	
Ohlsson(47)	1998	111	19.0	25.0	17.0
Kin(24)	1998	67		31.7	
Nitti(45)	1998	69		32.6	
Sato(50)	1998	36		43.1	
Hardy(34)	1998	52		30.3	
Fong(22)	1999	1001		37.0	
Nakamura(25)	1999	79		49.0	33.0
Irie(37)	1999	77		24.1	
Jourdan(41)	1999	53		27.2	
Ambiru(27)	1999	168		26.0	
Bradley(29)	1999	134	16.0	36.0	23.0
Harmon(35)	1999	110	28.0	46.0	27.0
Yamamoto(57)	1999	96		51.0	
Bolton(28)	2000	165		36.0	
Brand(30)	2000	126		21.0	
Ueno(53)	2000	85	20.5	27.9	
Sugawara(26)	2001	330		45.9	
Ishizuka(23)	2001	46		42.0	
Weber(56)	2001	221	20.0	34.0	
Heslin(36)	2001	52		54.0	
Nagakura(44)	2001	85		34.1	
Mean			**19.5**	**32.9**	**22.7**

Table 2. Range of Reported Incidences of Postoperative Mortality and Complications Following Hepatic Resection for Colorectal Metastases(20-26;28-57;70).

Type of Complication	Range (%)*
Mortality	**0-11.0**
Overall Morbidity	14.0-67.0
Haemorrhage	0.9-7.0
Bile Leak/Fistula	1.0-37.5
Anastamotic Leak	3.0-3.6
Abscess	0.8-11.0
Wound Infection	2.0-13
Liver Failure	0.9-8.5
Sepsis	0.9-6.7
Pneumonia	1.0-8.3
Pleural Effusion	1.9-7.0
Cardiac	0.9-6.8
CVA	0.2-1.7
DVT	0.2-4.2
PE	0.4-4.3
Other	4.5-16.7

* This refers to the range of reported values from these case series.

B. Systemic Chemotherapy for Colorectal Liver Metastases

Because untreated liver metastases from colorectal cancer are uniformly fatal, much research has been performed evaluating chemotherapy in hopes of prolonging survival. A meta-analysis of randomized controlled trials where patients with inoperable colorectal metastases received chemotherapy or best supportive care alone was recently published(71). It demonstrated that the increase in median survival offered by chemotherapy over is approximately 6 months, with a range of 0 to 8 months. The seven trials included in this meta-analysis used different agents, doses, and routes of administration, although all regimens contained either 5-fluorouracil (5-FU) or its analogue, fluorodeoxyuridine (FUDR).

Today, the most widely used agent in the treatment of metastatic colorectal cancer is 5-Fluorouracil (5-FU). Fluorouracil was developed more than 40 years ago, and has become the standard treatment to which other agents are compared, offering a median overall survival of about 11 months(72). Several attempts have been made to improve the efficacy of 5-FU by modifying the dosing schedule and biomodulation with other agents such as leucovorin (LV). While such clinical trials modifying the regimen have often demonstrated increased tumour response rates, many have either shown only a modest survival improvement (less then 1.5 months) (73;74)or no survival improvement at all(72;75-78).

A few randomized trials comparing 5-FU and LV to 5-FU alone, however, have shown a benefit to the inclusion of LV. Poon et al have shown a significant survival advantage of 5-FU plus low-dose LV (in a dosing schedule that is now generally referred

to as the Mayo Clinic Regimen) over 5-FU alone(79;80). In these two randomized trials, patients randomized to 5-FU alone had median survivals of 7.7 and 8.4 months compared to 12.0 and 12.7 months for patients receiving 5-FU plus low-dose LV. There was no survival benefit observed for using high-dose LV instead of low-dose LV seen. In fact, high-dose LV may be associated with higher levels of treatment-related toxicity(81). Another recent phase III trial which randomized 310 patients with inoperable or metastatic colorectal cancer to receive monthly 5-FU with or without low-dose LV has also shown a significant survival advantage with low-dose LV (median survival of 10.0 months versus 12.4 months)(82).

Although there is no internationally accepted gold standard, 5-FU/LV according to the Mayo Clinic regimen (bolus 5-FU at a dose of 425 mg/m^2 per day and low-dose LV at 20 mg/m^2 per day for 5 days, given in a 28-day cycle) has become the standard in North America and is commonly used as a reference in phase III trials(83;84). Studies have shown that weekly or bimonthly dosing schedules may offer lower toxicity with no change in survival(75;85).

Several studies have since looked to improve on this standard. The addition of agents such as interferon and hydroxyurea offered no survival advantage compared to 5-FU/LV, and often increased toxicity(86-88).

Investigators have also attempted to increase survival by altering the routes of delivery for chemotherapeutic agents. Delivery of chemotherapy via catheters placed in the common hepatic artery has been proposed on the premise that high concentrations of drug are needed in the liver to achieve adequate responses. Because of a high first-pass arterial extraction, concentrations of 5-FU delivered in this fashion can reach 80 to 100

times the concentrations in the liver that are achieved with conventional intravenous administration(89). Unfortunately, this technique has not resulted in improved overall median survival, although increased tumour response rates have been found(89-92).

Other studies have examined the efficacy of adding oxaliplatin or cisplatin to 5-FU/LV regimens(83;84;93-96). These trials have shown some promise in that response rates and progression-free survival increased, but overall survival did not statistically increase. The increase in progression free-survival came at the expense of toxicity, although chronomodulation of the dosing schedules increased progression-free survival with acceptable levels of toxicity.

Another promising agent is capecitabine. When given orally, it is absorbed as an intact molecule and then metabolized to 5-FU in 3 steps. Each of these steps occurs with successively greater specificity within tumour cells(97). Thus systemic exposure to 5-FU is reduced while increasing the dose-intensity within tumour tissue. In randomized trials comparing capecitabine to the Mayo Clinic regimen of 5-FU/LV, capecitabine has shown equivalent progression-free and overall survival rates. The main advantages of capecitabine over 5-FU/LV in these trials are the convenience of oral dosing and lower toxicity, although hand-foot syndrome and hyperbilirubinemia were more common with capecitabine(98;99).

Perhaps the most promising new agent is irinotecan. Irinotecan was first investigated for second-line treatment metastatic colorectal cancer after failure of 5-FU-based regimens. Irinotecan was shown to improve survival and quality of life when compared to supportive care(100) and when compared to 5-FU(101). Because of this promise shown in second-line treatment of liver metastases findings, two recent

randomized trials have compared 5-FU/LV plus irinotecan to 5-FU/LV as first-line treatment (11;12). Both have shown statistically significant improvements in overall survival. Median survival was 17.4 months versus 14.1 months in one study(12) and 14.8 months versus 12.6 months in the other(11) (see Table 3). While side effects were more frequent when irinotecan was added to 5-FU/LV, quality of life scores appeared to remain stable or were improved. Even more recently, the addition of bevacizumab, a monoclonal antibody to vascular endothelial growth factor, to this combination has resulted in median survival as high as 20 months(13).

Despite the chemotherapeutic agents used, a universal concern among patients and physicians is the side effects of the drugs. Side effects of chemotherapy can impair quality of life and lead to reductions in the doses given or even cessation of treatment. Almost every patient experiences some adverse effects, although the severity is variable. Some of the more common severe or life-threatening adverse effects of 5-FU/LV include neutropenia, diarrhea, mucositis, and vomiting(11;12). In a randomized trial comparing 5-FU/LV alone and with irinotecan, the side effects were severe enough to discontinue treatment in 6.4% of the 5-FU/LV group and in 7.6% of the 5-FU/LV and irinotecan group(11).

Table 3. Overall Survival with 5-Fluorouracil, Leucovorin, With and Without Irinotecan

Authors	Median Survival (months)		
	5-FU/LV and Irinotecan	5-FU/LV	p Value
Saltz(11)	14.8	12.6	0.04
Douillard(12)	17.4	14.1	0.03

In summary, the outcomes after chemotherapy treatments have continued to improve over the years. The widely accepted standard of care is 5-FU/LV. Newer agents such as capecitabine may offer some advantages over this regimen in terms of convenience and safety profile. However, one of the most promising regimens at present is the combination of irinotecan, 5-FU, and LV. This combination has been shown to provide a survival advantage over 5-FU/LV alone while maintaining quality of life. Median overall survivals of 14.1 to 17.4 months have been achieved. Questions remain concerning what the optimal dosing schedule is to maximize survival benefits and quality of life of patients while minimizing toxicity. Of course, research continues into the development of new agents.

C. Ablative Treatments Including Radiofrequency Ablation

Unfortunately, only a minority of patients with liver metastases are candidates for surgical resection(1;7;8). Even in patients with normal preoperative hepatic function, curative resection of multiple lesions can lead to inadequate hepatic reserve. Patients with primary hepatocellular carcinoma are often poor surgical candidates because of limited hepatic reserve due to coexisting cirrhosis of the liver. They may also be excluded from the possibility of hepatic resection because of severe medical comorbidities. Patients with multiple lesions may not be surgical candidates because proximity of lesions to critical vascular or biliary structures can make resection technically impossible. Other treatments have been explored for such patients(14).

Ablative treatments have been designed to destroy tumour cells while limiting damage to uninvolved hepatic parenchyma. One of the first such alternative procedures studied was percutaneous ethanol injection. PEI has been shown to be an effective treatment for nodular-type HCC. Long-term outcomes in patients with small HCC lesions were almost equivalent to surgical resection(102;103). There are limitations to this procedure, however. It is not effective in larger HCC lesions or in septated HCC lesions because ethanol diffusion within the tumour is not complete and viable tumour cells remain after the procedure(104;105). PEI has also been ineffective in the treatment of metastatic disease, with the exception of metastases from neuroendocrine tumours(106). Complications of the procedure include biliary reflux with secondary sclerosing cholangitis(107).

Cryoablation is another ablative techniques that has been used. It involves placing a probe that can be cooled with liquid nitrogen into the centre of a liver tumour(108). The liquid nitrogen acts to freeze an area of liver tissue encompassing the tumour. The tumour cells are destroyed by the formation of ice crystals which disrupt the normal cell structures(14). The complications associated with this procedure are substantial, and include cracking of the frozen liver, signifcant haemorrhage, cold injury to adjacent organs, biliary fistulae, coagulopathy, thrombocytopenia, myoglobinuria and renal failure, hepatic abscess, and pleural effusions(14;108).

Newer interventions for malignant liver tumours have been developed to overcome these drawbacks of PEI and cryoablation. Radiofrequency ablation is one such technique, and holds promise as an effective treatment. Radiofrequency energy is used to generate a high frequency alternating current that moves from the tip of a needle-shaped electrode into the surrounding tissue. This alternating current causes the acceleration of ions in the tissue, which results in the generation of heat. A typical RFA treatment can result in local tissue temperatures over 100°C, which causes coagulation necrosis of the tumour and a small area of surrounding hepatic parenchyma(14). The delivered current is inversely proportional to the square of the distance from the electrode, so the temperature falls rapidly as the distance from the electrode increases.

In the past, a major limitation of RFA was the small area of necrosis that could be achieved. This increased the number of electrode deployments that were necessary to treat all but the smallest lesions. Two modifications of the simple electrodes were designed to overcome this problem and to allow treatment of larger lesions(104). Radionics™ manufactures a cooled-tip electrode that uses chilled saline to cool the

needle tip in order to limit charring at the tip of the electrode. The charring restricts propagation of the radiofrequency waves. Therefore, the cooled-tip electrode is able to ablate a larger zone of tissue. Another modification used by some manufacturers (Boston Scientific© and RITA Medical Systems, Inc.) is an expandable needle with tines that are deployed radially from the tip. These multiple tines dramatically increase the active surface of the electrode and increase the amount of tissue coagulated. Larger RFA catheters capable of ablating larger tissue volumes are also being evaluated(109).

At present RFA is generally used to treat HCC and metastatic liver tumours in patients who have disease confined to liver, yet do not meet the criteria for surgical resectability. Radiofrequency ablation may expand the population of patients who may be treated with aggressive liver-directed therapy to attempt to increase survival and/or quality of life(14). Some patients who would not be candidates for surgical resection because of bilobar disease may be treated with a combination of RFA and resection. Patients with liver tumours that are unresectable because of proximity to vital structures may still be candidates for RFA. The flowing blood in major hepatic vessels acts as a heat sink and protects the vessel wall from thermal injury, while allowing ablation of the neighbouring tumour. The protection offered to the vessel endothelium by the heat dissipation of the blood flow may, however, also increase the risk of leaving viable tumour cells behind(104). In contrast to the 'heat sink' effect of blood vessels, the treatment of HCC in a cirrhotic liver may benefit from an 'oven effect'(110). The densely fibrotic, poorly vascularized cirrhotic liver may act as a barrier to heat dissipation from the target lesion and the tumour nodule may then receive a greater proportion of the heat generated. Treatment of lesions in the area of the hepatic hilum where the portal vein and

hepatic arteries enter the liver, however, risks thermal injury to the biliary tract and can lead to biliary strictures or fistulae. RFA cannot be used to treat lesions in this area(14;104).

Another problem encountered with RFA is that it relies on real-time imaging to guide proper probe placement. Currently, most authors use real-time ultrasound to guide RFA probe placement. The problem is that RFA produces hyperechoic microbubbles as tissue is heated, which obscures deeper portions of the lesions and make proper positioning difficult(111-115). Newer imaging methods are being investigated to overcome this problem, and may reduce the local recurrence rates(114;115).

There have been several recent studies evaluating the effectiveness of RFA as a treatment modality for both primary and secondary malignancies of the liver. The first studies looked at the ability of RFA to achieve complete necrosis of the tumour, while later studies began to report longer-term efficacy (see Table 4).

1. Studies Evaluating Degree of Tumour Necrosis

Livraghi et al compared RFA to percutaneous ethanol injection with regards to the degree of tumour necrosis achieved and complications(110). Eighty-six patients with HCC and cirrhosis or chronic infection with the Hepatitis C virus (HCV) received either PEI (44 patients with 60 tumours) or percutaneous RFA (42 patients with 52 tumours). All tumours were no greater than 3 cm in diameter. They used the distance that the patients lived from hospital to determine the treatment received. The group that received PEI had complete necrosis, as judged by computed tomography (CT) scan criteria, in 48

of 60 tumours (80%). Most patients experienced moderate pain, but there were no other complications. The group that received RFA had a higher rate of complete tumour necrosis, with 47 of 52 tumours (90%) being completely treated, but also had a higher rate of complications. In addition to most patients experiencing moderate pain, there was one hemothorax, one intraperitoneal haemorrhage, one pleural effusion, and one case of mild cholecystitis.

Livraghi et al then evaluated the efficacy of ultrasound-guided percutaneous RFA in the treatment of medium (3.1 – 5.0 cm diameter) and large (5.1 – 9.5 cm diameter) HCC's(111). One hundred fourteen patients with 80 medium and 46 large HCC's were treated. Most patients experienced mild or moderate pain, and 2 patients (1.8%) suffered moderate to large pleural effusions that were treated conservatively. Overall, complete necrosis was achieved in only 60 of the 126 lesions (48%). Smaller tumours and non-infiltrating tumours had higher rates of complete necrosis, suggesting that RFA may have limited efficacy in larger lesions.

Because most studies that have evaluated the degree of tumour necrosis achieved with RFA did so using CT or magnetic resonance (MR) imaging and small deposits of viable tumour may remain undetected, Scudamore et al assessed the degree of tumour necrosis by pathologic examination(107). Ten patients, who had a total of 12 lesions, were scheduled to have surgical resection of their tumours. The histological type of tumours was colorectal in 7 patients, leiomyosarcoma in 2 patients, and carcinoid in 1 patient. No patient had more than 2 lesions, and no lesion was greater than 4 cm in diameter. These patients underwent percutaneous RFA up to 6 weeks prior to resection. Nine of the 12 ablations were resected and sent for pathologic examination to assess the

degree of necrosis. There were no operative deaths and no complications in the series. Of the 9 resected lesions, only one lesion showed residual viable tumour cells. These viable cells were adjacent to a large blood vessel, indicating that perhaps the heat sink effect of the vessel had protected the tumour cells.

Because major blood vessels may afford protection to adjacent tumour cells, Rossi et al(116) investigated whether the efficacy of percutaneous RFA could be improved with occlusion of the tumour's blood supply. Sixty-two patients with cirrhosis and a solitary HCC who were not considered to be operative candidates had the blood supply to their tumours occluded by either a balloon catheter or with gelatin sponge particles. They then underwent percutaneous RFA. The patients' mean age was 68.1 years and the mean diameter of the lesions was 4.7 cm (range 3.5 cm to 8.5 cm). No fatal or major treatment-related complications occurred. Most patients experienced fever. Two patients developed acalculous cholecystitis and one patient had intimal dissection of the hepatic artery without clinical sequelae. A complete response was achieved in 56 of 62 patients (90%). Two patients then underwent hepatic resection. The remaining 60 patients were followed for a mean of 12.1 months. Twenty-nine patients (48%) had recurrent disease and 31 (52%) had no signs of recurrence. Three patients died of advanced disease and 3 died of other causes. The estimated 1-year survival was 87%.

2. Studies With Clinical Follow-Up

Studies investigating RFA have included patients with a wide range of tumour types. Many of theses studies have investigated the effectiveness of RFA in patients with

HCC's. Others have included a mixed population of patients with primary and secondary tumours, while others have focused on metastatic disease with a major focus on colorectal metastases.

i. Studies of Patients with Hepatocellular Carcinomas

Curley et al used a combination of open, laparoscopic, and percutaneous ultrasound-guided RFA to treat 110 patients with HCC and cirrhosis (Child class A, 50 patients; B, 31 patients; C, 29 patients) (117). All patients were considered to have unresectable disease based on multifocality of lesions, proximity of lesions to vital structures, or poor hepatic reserve. Patients with small lesions that were easily visualized with transabdominal ultrasound were treated percutaneously, especially if they were at a high surgical risk (76 patients). All other patients were treated using open (31 patients) or laparoscopic (3 patients) approaches. Most patients had solitary lesions (77.3%) and no patient had more than 4 lesions. Mean tumour size was 2.8 ± 0.8 cm in the percutaneous group versus 4.6 ± 1.7 cm in the open and laparoscopic groups. Patients were followed for at least 12 months with a median follow-up of 19 months. Of 34 patients who underwent open or laparoscopic RFA, no patient had evidence of residual disease based on postoperative CT or MRI imaging. Six of the 76 patients who underwent percutaneous RFA showed evidence of residual disease and, consequently, underwent another treatment of percutaneous RFA. There were no deaths within 90 days of treatment, however, treatment-related complications developed in 14 patients. After a median follow-up time of 19 months a total of 54 patients (49%) had recurrences of HCC. Only 4

patients (3.6%) had a recurrence in a lesion that was treated with RFA. At the time of publication, 28 patients (26%) had died of recurrent disease, 3 patients (2.7%) had died of other causes, 26 patients (24%) were alive but had developed recurrent disease, and 53 patients (48%) were alive with no radiological evidence of recurrent disease. Fourteen patients with solitary recurrences underwent a second procedure and 12 of these patients remained disease-free at the time of publication. Therefore, a total of 65 (59%) of the 110 patients were alive without evidence of recurrence after a median follow-up time of 19 months.

Poggi et al described their experience with percutaneous ultrasound-guided RFA in 15 patients with unresectable HCC(118). The patients were considered to have unresectable disease due to advanced age, advanced cirrhosis, bilobar disease, or refusal of surgery. The mean age of the sample was 70 years. Thirteen patients had solitary lesions and no patient had more than 3 lesions. The median diameter of the lesions was 33 mm with a range of 15 mm to 62 mm. The 15 patients had a total of 18 lesions. One patient required surgery to remove the HCC lesion after developing a large intraperitoneal haemorrhage. Another patient developed a pleural effusion and two others developed peri-hepatic fluid collections. All three resolved spontaneously. Complete necrosis, as judged by CT scanning was achieved in 15 of the 17 remaining lesions. The two lesions that were not completely ablated were treated with percutaneous ethanol injection. After a mean follow-up period of 9.2 months (range 3-24 months), 11 of 14 patients (79%) showed no evidence of local or distant recurrence, 2 patients (14%) did not have a complete response to RFA, and 1 patient (7%) developed a new lesion.

Llovet et al treated 32 patients with single hepatocellular carcinomas less than 5 centimetres in diameter with ultrasound-guided percutaneous RFA(119). All patients were considered not to be operative candidates and the mean age was 67.4 ± 1 year. There were no procedure-related mortalities, but treatment-related morbidity was seen in 8 patients (25%). They did note a high rate of tumour seeding along the track of the RFA needle. This was seen in 4 of the 32 patients (13%). Complete tumour ablation, as measured by CT scan one month after the procedure, was found in 21 patients (65%). The median follow-up was 10 months with a range of 2 to 23 months. The mean survival was 20.2 months and the actuarial 1-year survival was 85%.

ii. Studies Including Patients with Primary and Secondary Tumours

Jiao et al treated 35 patients with primary and secondary malignant liver tumours(120). The mean age of the sample was 54 years (range 19 to 83). Eight patients had primary HCC's, 17 had colorectal metastases, and 10 had metastases from other primaries. The patients were considered to have unresectable disease on the basis of poor hepatic reserve or the number and location of lesions. Five patients had percutaneous RFA, 17 had open RFA alone, and 13 had open RFA in conjunction with surgical resection. There were two deaths within 1 month of treatment in the group of patients who underwent RFA and hepatic resection. One was due to a severe chest infection and renal failure and the other was due to recurrence of disease. Serious complications developed in 4 patients. Of the patients with hepatocellular carcinoma, 7 of 8 patients remained alive with stable disease at a mean follow-up of 10.4 months. Ten of 17 patients

with colorectal metastases had no progression of disease at a mean follow-up of 7.6 months. Four had died and 3 had progression of disease. When all patients were taken as a group, 24 (69%) had no progression of disease at a mean follow-up time of 10.1 months. Seven (20%) had died with a mean survival of 3.7 months, and 4 (11%) were alive but had progressive disease at a mean follow-up of 5.3 months.

Curley et al treated 123 patients who had a total of 169 unresectable primary and metastatic liver tumours with ultrasound-guided radiofrequency ablation(121). The majority of patients had either metastatic colorectal carcinoma (50% of patients) or hepatocellular carcinoma (39% of patients). All patients had no evidence of extra-hepatic disease. Patients with 1 or 2 small (> 3.0 cm diameter) peripheral lesions were considered for percutaneous RFA (31 patients), while the others were treated with an open technique. The median age of the patients was 57 years (range 24 to 80 years) and the median tumour diameter was 3.4 cm (range 0.5 to 12 cm). Eighteen patients underwent hepatic resection in conjunction with RFA. The median follow-up was 15 months. Two patients who underwent RFA plus resection developed peri-hepatic abscesses that required percutaneous drainage. One patient who received RFA alone suffered haemorrhage 5 days after the treatment, requiring transfusion and embolization of the right hepatic artery. Tumour recurred locally in only 3 of 169 treated lesions, however, new hepatic or extra-hepatic disease occurred in 34 of the patients (28%).

Bowles et al studied 76 patients with unresectable primary and metastatic liver tumours(122). The etiologies of the liver tumours were hepatocellular carcinoma in 25 patients, colorectal metastases in 39 patients, and other metastases in 12 patients. Mean tumour size was 3.0 ± 2.4 cm (range 0.4-18.0 cm) and the mean number of tumours was

3.3 ± 2.7 (range 1-14). Patients with more than 50% of the liver replaced by tumour were excluded, while those with hepatic dysfunction or cirrhosis were not. All together there were 99 procedures performed to treat 328 tumours. Fifty-seven were percutaneous, 8 were laparoscopic, and 34 were open. Ultrasound was used to guide the RFA probe. In general, percutaneous procedures were used when the goal was palliation, while laparoscopic procedures were more often performed for curative intent and open procedures were used for deeper lesions and when RFA was performed in conjunction other surgical resections. Five liver and 3 lung resections were performed at the time of open RFA. One patient (1.3%) died of liver failure due to lack of functional reserve after a large ablation, while 7 major and 17 minor complications occurred in the 99 procedures. Mean follow-up was 15 months with a range of 1 to 39 months. Twenty-two of the 76 patients (29%) had local recurrences. The mean survival rates in the series were 24 months for patients with HCC and 25 months for patients with colorectal metastases. Most patients with liver metastases were treated with systemic chemotherapy postoperatively, and selected patients with HCC received regional chemotherapy. The authors noted that survival in this population of patients with unresectable tumours was much better than in similar populations receiving either no treatment or receiving chemotherapy, and that the survival curve was comparable to other reported survival curves of patients with resectable tumours who underwent surgery(123;124).

iii. Studies of Patients with Metastatic Tumours

Solbiati et al performed ultrasound-guided percutaneous radiofrequency ablation in 16 patients with metastatic liver tumours who had either not been considered surgical candidates or who had refused surgery(113). There were a total of 31 metastases, which were colorectal in 9 patients, gastric in 3 patients, leiomyosarcoma in 2 patients, pancreatic in 1, and peri-ampullary in 1. Five patients had synchronous metastases resected at the time that the primaries were resected and 4 had prior liver lesions resected. Lesions ranged in size from 1.2 to 7.5 cm in diameter, but 87% were less than 3 cm. Only one complication was reported. One patient who had ablation of a peripheral leiomyosarcoma suffered an intraperitoneal haemorrhage that was managed nonoperatively and without transfusion. Based on CT or MR imaging, 50% of patients had a complete response and 18 of 31 tumours (58%) showed a complete response. Twelve of the patients were followed for at least one year. By 12 months, all 12 patients of these patients were living, but 2 had died by 13 months and 1 had died by 16 months. At a mean follow-up time of 16.6 months, disease-free survival was achieved in 8 of 12 patients.

Solbiati et al treated 29 patients who had a total of 44 metastatic liver tumours with a percutaneous cooled-tip RFA probe using ultrasound guidance(125). Twenty-two patients had metastatic colorectal cancer, while the others had gastric (5 patients), breast (1 patient), or pancreatic cancers (1 patient). Twenty patients had solitary lesions and the others had between 2 and 4. The lesions ranged in size from 1.3 to 5.1 cm in diameter, with 62% being less than 3 cm in diameter. There were no deaths, but one patient had an

intraperitoneal haemorrhage that was treated conservatively and did not require a blood transfusion. Complete necrosis of 66% of the tumours, as assessed by CT or MR imaging 7 to 14 days later, was achieved. Fifteen (34%) of the 44 lesions showed evidence of local recurrence at 6 months. Smaller tumours were more likely to have complete necrosis. Of 21 patients followed for 6 months, 16 (76%) remained disease-free at 6 months. Eighteen patients were followed for 12 months, and 50% were disease-free at that time. Three of 9 patients who were followed for 18 months remained disease-free. Overall survival was 100% at six months, 94% at 12 months, and 89% at 18 months.

Sixty-eight patients with 121 metastatic liver tumours were treated with radiofrequency ablation by de Baere et al(126). The metastases were mainly colorectal in origin. No patient had more than 5 tumours (mean 1.8 tumours) and no lesion was larger than 45 mm in diameter. Twenty-one patients underwent RFA with concurrent hepatic resection. The other 47 patients were considered unresectable and underwent percutaneous RFA. Thirty-eight of these had undergone prior partial hepatectomy. Fifty-four of the patients (with 100 metastases) had been followed for at least 4 months (mean follow-up of 13.7 months) and were included in the study. The remaining patients had been followed for less than 4 months and were not included. There were no treatment-related deaths, but two patients required percutaneous drainage of hepatic abscesses and one patient suffered a bile leak. After a mean follow-up of 13.7 months 8 patients (15%) had died. Thirty-seven patients (69%) had recurrent disease, either in the liver or at distant sites. Nine of these patients had local recurrences. Seventeen patients (31%) remained disease-free.

Livraghi et al recently investigated the efficacy of RFA in 24 patients with liver metastases from breast cancer(112). They treated 24 patients with 64 liver metastases from breast cancer, which ranged in size from 1.0 to 6.6 cm in diameter (mean 1.7 cm), with percutaneous ultrasound-guided RFA. The mean age was 51.5 years. These patients either had no evidence extra-hepatic metastases (16 patients) or were considered to have stable extra-hepatic metastases (8 patients). Six of the patients with disease confined to the liver had previously received systemic chemotherapy. Two patients had previously undergone liver resection followed by chemotherapy via hepatic arterial infusion. No treatment-related mortality or major morbidity was reported. One patient developed an asymptomatic perirenal hematoma and one patient had pain likely related to diaphragmatic irritation. Based on CT findings, there was complete necrosis in 59 of 64 lesions (92%). Follow-up ranged from 4 to 44 months with a mean of 10 and a median of 19. Fourteen of the 24 patients (58%) developed new metastases during the follow-up period. Four of these patients had local recurrences. The remaining 10 patients continued to be free of any signs of metastatic disease at the time of publication. Twenty-three of the 24 patients were still alive at a mean follow-up of 10 months.

Solbiati et al reported one of the largest series of patients with colorectal liver metastases with the longest follow-up periods to date(127). They treated 117 patients who had a total of 179 hepatic metastases with follow-up ranging from 6 to 52 months. The patients all had metachronous lesions and were considered to have unresectable disease due to general health considerations, technical reasons, or refusal of surgery. Percutaneous RFA was performed with real-time ultrasound guidance. The mean age of the sample was 65 years. The number of lesions treated ranged from 1 to 4 (mean 1.5)

and the mean diameter was3.2 cm. No treatment-related deaths occurred. One patient suffered a perforation of the right colon adjacent to an exophytic metastasis, but recovered completely after colon resection, and one patient suffered a self-limited intraperitoneal haemorrhage. Complete ablation based on CT findings was achieved in 176 of 179 (98%) of tumours. Local recurrences occurred in 70 (39.1%) lesions, however. Local recurrences were more common in larger (>3 cm lesions), and all local recurrences occurred within 18 months of treatment. New metastases developed in 67 of the 117 patients (57%) at a median time of 12 months. Median survival was estimated to be 36 months, and 1-, 2-, and 3-year survival rates were 93%, 69% and 46%, respectively.

Iannitti et al reported a series of 123 patients with a mixture of primary and secondary liver tumours that had 3-year follow-up(128). Sixty-nine males and 54 females underwent 168 RFA procedures (a combination of percutaneous and open approaches). All patients were considered to have unresectable disease on the basis of poor liver reserve, medical co-morbidities, or anatomic reasons. Fifty-two patients had colorectal metastases, 30 had HCC's, and 41 had a variety of other primary and secondary malignancies. One patient died within 30 days of the procedure due to a stroke and 12 patients suffered complications, including hepatic abscess (4 patients), transient liver dysfunction (3 patients), segmental liver infarctions (2 patients), arterio-venous fistula (1 patient), diaphragmatic paralysis (1 patient), and systemic haemolysis (1 patient). Several of the patients who experienced recurrences (43 patients) underwent repeat RFA procedures. For the 52 patients with CRC metastases, overall survival was 87% at 1 year,

77% at 2 years, and 50% at 3 years. For the 30 with HCC, overall survival was 92% at 1 year, 75% at 2 years, and 60% at 3 years.

Oshowo et al published another series reporting 3-year survival(129). They report a series of 45 consecutive patients presenting to their centre with solitary colorectal liver metastases. Twenty of these patients were candidates for liver resection and underwent the procedure. The other 25 were not candidates for resection because of proximity to major vascular structures (9 patients), medical co-morbidity (9 patients), and extra-hepatic disease (7 patients). These 25 patients underwent percutaneous RFA. They had a mean age of 57 years and the median size of lesion was 3 cm (range 1 to 10 cm). There were no mortalities, but 1 patient developed a pleural effusion requiring treatment. The 20 patients who underwent resection had a mean age of 63. Most (16 patients) had metachronous lesions. One patient died postoperatively and 1 patient developed pneumonia. The 3-year survival for the patients who underwent RFA was 52.6% and the 3-year survival for the patients who underwent hepatic resection was 55.4%, suggesting that RFA could offer similar survival to hepatic resection even though the patients were not considered candidates for resection.

RFA has a low rate of complications and mortality. Livraghi et al report a mortality rate of 0.3% and a major complication rate of 2.2% in a series of 2,320 patients undergoing RFA (130). Another series of 312 patients by de Baere et al reports a mortality rate of 1.4% with a major complication rate of 5.7%(131). It would appear that RFA is a safe procedure with a low complication rate. Further study is needed to determine whether the survival benefits may be comparable to those of hepatic resection.

Table 4. Summary of Results of Above RFA Papers

Author	Year	No. Patients (n)	Tumour Type	Complete Necrosis* (%)	Patient Follow-Up
Livraghi(110)	1999	42	HCC (< 3 cm diameter)	90	--
Livraghi(111)	2000	114	HCC (medium and large lesions)	48	--
Scudamore(107)	1999	9	Metastases (mainly colorectal)	89	--
Rossi(116)	2000	62	HCC (solitary, mean 4.7 cm)	90	87% 1-year survival
Curley(117)	2000	110	HCC and cirrhosis	95	59% disease-free at median F/U of 19 mos.
Poggi(118)	2001	15	HCC (median 3.3 cm diameter)	88	79% with no sign of recurrence at mean of 9.2 mos.
Llovet(119)	2001	32	HCC (solitary, < 5 cm diameter	65	20.2 mo. mean survival
Iannitti(128)	2002	30	HCC		60% 3-year survival
Jiao(120)	1999	35	HCC and metastases (mainly colorectal)	69	69% with no progression of disease at mean F/U of10.1 mos.
Curley(121)	1999	123	HCC and metastases (mainly colorectal)	98	72% with no progression of disease at median F/U of 15 mos.
Bowles(122)	2001	76	HCC and metastases (mainly colorectal)	71	25 mo. mean survival
Solbiati(113)	1997	16	Metastases (mainly colorectal)	50	DFS in 8 of 12 at mean F/U of 16.6 mos.
Solbiati(125)	1997	29	Metastases (mainly colorectal)	66	89% 18-month survival
De Baere(126)	2000	54	Metastases (mainly colorectal)	83	31% disease-free at mean F/U of 13.7 mos.
Livraghi(112)	2001	24	Breast cancer metastases	92	42% disease-free at mean F/U of 10 mos.
Solbiati(127)	2001	117	Colorectal metastases	98	46% 3-year survival
Iannitti(128)	2002	52	Colorectal metastases		50% 3-year survival
Oshowo(129)	2003	25	Colorectal metastases		55.4% 3-year survival

* Complete Necrosis was judged by radiological criteria in most cases.

D. Natural History of Untreated Colorectal Liver Metastases

When evaluating any medical treatment, the benefits of the treatment must be compared to the benefits of its alternatives. Especially in cases where these treatments have significant morbidity and mortality, it is always an alternative not to treat the disease at all. For metastatic colorectal cancer where the treatments may cause severe side effects or even death, it is important to keep the natural history of the disease in perspective when examining the available treatments. Unfortunately, there are not many recent publications reporting the natural history of colorectal liver metastases, and the existing studies often had heterogeneous patient populations in terms of extent of disease. Regardless, a summary of the existing literature is given below.

In 1981, Bengtsson et al(132) reported a retrospective series that included 155 patients with synchronous metastases diagnosed at laparotomy and 5 with metachronous lesions. None of them received treatment, either medical or surgical, for the metastatic disease. Overall, the median survival from the time of diagnosis for patients with synchronous lesions was 4.5 months (mean 5.6). When 30-day operative mortality for the exploratory laparotomy was eliminated, the median survival became 6.1 months (mean 7.5). These patients were an unselected group and had varying degrees of liver involvement and extra-hepatic disease. For the 5 patients with metachronous disease, the median survival was 5 months (mean 7.5) from the time of diagnosis.

Wagner et al(133) in 1984 reported a retrospective series of 466 patients who had liver metastases diagnosed at the time of laparotomy for the primary lesion. Of these patients, 252 had no extra-hepatic disease. Seventy of these 252 patients had unilateral

disease that was considered resectable, but for unspecified reasons was not resected. The median survival from diagnosis for these 70 patients with resectable disease was 21 months for those with solitary metastases (n=39) and 15 months for those with multiple metastases (n= 31). More than 20% of those with solitary metastases lived at least 3 years. The remaining 182 patients with no extra-hepatic disease, but with widespread, unresectable hepatic disease, had a median survival of less than a year. Of note, about half of the patients received chemotherapy for metastatic disease.

Arnaud et al(134) in 1984 reported a retrospective series of 65 patients with liver metastases from colorectal cancer found at laparotomy for the primary lesion. Nine of these died within 30 days postoperatively. None of the 56 remaining patients received adjuvant therapy of any sort. The overall median survival was 7 months, with a 1-year survival of 28% and a 2-year survival of 7%. Of 5 patients with solitary lesions, the mean survival was 27 months, while those with unilobar disease survived a mean of 17 months and those with bilobar disease survived a mean of 8 months.

Scheele et al(135) in 1990 reported the largest series of patients with colorectal liver metastases. Patients were initially seen between 1960 and 1987. Most (80%) had the diagnosis made at laparotomy, while the rest had their diagnoses made with CT or ultrasound. One group of 902 patients with unresectable disease and 19 patients whose disease could not be accurately staged had a median survival of 6.9 months. Another group was made up of 62 patients with disease that appeared to be resectable in retrospect, but who did not undergo resection because of past differences in treatment strategy. This group had a median survival of 14.2 months. The natural history was

altered in some patients, since 113 patients in the first group and 8 patients in the second group received chemotherapy via hepatic artery infusion.

Stangl et al(136) in 1994 reported a retrospective study of 1099 patients with colorectal liver metastases, including 340 patients who underwent resection of metastases, 123 who received regional chemotherapy, and 70 who received systemic chemotherapy. This left 566 patients who received no intervention for their metastatic disease. Forty-eight were excluded due to a second primary malignancy, and 34 were excluded because they died within 30 days of laparotomy for the primary lesion. The median survival of the remaining group was 7.5 months, with 1-, 2-, 3-, and 5- year survival rates of 31.3%, 7.9%, 2.6%, and 0.9% respectively. Those with solitary lesions had a median survival of 10.8 months, while those with unilateral and bilateral lesions had median survivals of 11.8 and 6.8 months, respectively. Overall, patients without extra-hepatic disease survived a median of 9.6 months compared to a median of 6.4 months for patients with extra-hepatic disease. It should be noted that since treatment allocation was not randomized, those with better prognoses might have selectively received adjuvant therapy. It is possible that many of the patients in this series were also included in the above series by Scheele at al.

Görög et al(137) in 1997 reported a series of 57 patients who underwent laparotomy for rectal cancer and were found to have liver metastases. Four were excluded on the basis of operative mortality, and 6 were excluded because they received adjuvant treatment. Of the remaining 47 patients, 8 had extra-hepatic disease. Overall median survival was 8.5 months, while median survival times for those with solitary metastases and with multiple metastases were 11 months and 7.5 months, respectively.

Lastly, Luna-Perez et al(138) in 1998 reported on 77 patients with unresectable colorectal liver metastases, of whom 45 received no chemotherapy because of physician indications or patient choice. Overall, median survival was 13 months. Of those with less than 25% liver involvement by tumour, median survival was 20 months compared to 6 months for those with more than 25% liver involvement.

It should be reiterated that some of the patients included in these case series did receive chemotherapy. For these patients, the true natural history was altered. Among these patients, administration of chemotherapy was not random and those with better prognoses may have been selectively offered chemotherapy. While the range of reported survival figures was quite broad, patients with limited disease (solitary metastases) had expected survivals ranging from 11 to 27 months (see Table 5).

Table 5. Natural history of colorectal liver metastases

Author	Median Survival (months)*				
	Overall	Hepatic Disease			Extra-hepatic Disease
		Solitary Met	Unilateral	Bilateral	
Bengtsson(132)	6.1				
Wagner**(133)		21	15	<12	
Arnaud(134)	7	27 (mean)	17 (mean)	8 (mean)	
Scheele[†](135)	14.2				
Scheele[††](135)	6.9				
Stangl(136)	7.5	10.8	11.8	6.5	6.4
Görög(137)	8.5	11			

Author	Overall	Hepatic Disease		Extra-hepatic Disease
		< 25 % Involved	> 25% Involved	
Luna-Perez(138)	13	20	6	

* Metastases were untreated unless specified

** About half of subjects received chemotherapy (selectively)

† This figure refers to 62 patients with resectable disease (8 received regional chemotherapy)

†† This figure refers to 902 patients with unresectable disease and 19 patients whose disease could not be accurately staged

Chapter 3. Existing Cost-Effectiveness Analyses for the Treatment of Malignant Liver Tumours

Information regarding the costs and the cost-effectiveness of medical and surgical treatments are becoming more and more important today, in large part due to the increasing costs and the budgetary constraints of the healthcare system. However, there are few reports concerning the cost-effectiveness of treatments for malignant liver tumours, especially concerning surgical treatment (see Table 6). No publication in the context of the Canadian Healthcare System could be identified.

Gazelle has recently published two cost-utility studies for the treatment of colorectal liver metastases, one comparing surgical resection to no treatment(139) and one comparing percutaneous radiofrequency ablation to hepatic resection(140). In the former paper, Gazelle et al created a decision model to predict survival, quality of life, and cost of surgically resecting colorectal liver metastases(139). The model was quite complex, involving the presence, number, size, location, growth, detection, and removal of up to 15 individual metastases per patient. The parameter estimates for the model were taken from published literature. The model seemed reasonably accurate, as it predicted a 5-year survival of just over 30%, but did predict slightly higher survival for patients with up to 5 lesions than for patients with single lesions. Costs were taken from a societal perspective using Medicare reimbursement rates in the United States in 1998 U.S. dollars. These rates may not be a completely accurate measure of true costs(141). Time costs for patients receiving treatment were included using average daily wage rates. Travel costs and costs borne by family and other caretakers were not included, however. Utility scores were assumed to be equivalent to the scores of the general population

except in the first month following surgery and in the last month of life. These assumptions may not be strictly accurate as QOL may begin to deteriorate sooner than the last month of life. Ramsey at al found quality of life deteriorated in the last year of life for colorectal cancer patients, but were not more explicit in their description(142). The marginal cost-effectiveness of resection over no treatment varied with the frequency of follow-up imaging. A strategy allowing resection of up to 6 lesions with one repeat resection and CT scan imaging every 6 months cost $53,200, but offered a marginal gain of 2.63 QALY's at a cost of $18,100 per QALY. A limitation of the study is that surgical resection was compared to a "no treatment" strategy that provided a median survival between 6.3 and 11.5 months depending of the tumour burden. In practice, most patients that do not undergo surgery would receive chemotherapy and expect significantly longer survivals. The marginal cost-utility ratios reported in the study may have been more clinically relevant if chemotherapy had also been considered as an alternative treatment.

The second study by Gazelle at al compared percutaneous RFA to hepatic resection(140). The previous decision model(139) was modified to include a treatment strategy with percutaneous RFA. Using a base case strategy of ablation of up to 5 lesions and follow-up CT scanning every 4 months, RFA yielded a gain over no treatment of 0.65 QALY's at a cost of $2,400 per QALY (in 1998 U.S. Dollars). A strategy of resecting up to 4 lesions, allowing one repeat resection, and follow-up imaging every 6 months yielded a gain of 0.76 QALY's at a cost of $24,300 per QALY compared to the base case RFA treatment. The authors concluded that surgical resection was more effective than RFA. The cost-utility varied with the frequency of follow-up imaging, but

consistently yielded marginal cost-utility ratios less than $35,000 per QALY compared to RFA.

A cost-effectiveness study from the United Kingdom by Beard et al, dealt with hepatic resection for colorectal liver metastases(143). Resection was compared to palliative chemotherapy with 5-fluorouracil (5-FU) and leucovorin (LV). This study used decision analysis and took the viewpoint of their healthcare system, excluding costs borne by the patients and their families and productivity costs. The analysis did take into account the costs accumulated when patients underwent laparotomy but curative resection was not possible. Such patients with inoperable disease then received palliative chemotherapy, as did patients experiencing a recurrence when re-resection was not feasible. Survival data for patients undergoing resection were taken from a previously published case series of liver resection(68), but survival data for patients receiving palliative chemotherapy was taken from a study reporting the natural history of untreated colorectal liver metastases among patients without signs of extra-hepatic disease(133). This did allow comparison to patients who were similar in terms of extents of disease and major co-morbidities, but the survival benefits of chemotherapy may not have been taken into account with this control group. About half of these patients did receive chemotherapy on a selective basis, and the survival benefits of chemotherapy have likely changed significantly since this paper was published in 1984. Costs of resection were estimated from a retrospective review of 100 hepatic resections performed in their centre. Costs of palliative chemotherapy were taken from previously published reports modified with data form their centre. The average cost of resection was $10,787 (US in 1999) and the average cost of palliative chemotherapy with 6 months of 5-FU/LV was $10,670.

Using a timeframe of 5 years, hepatic resection was estimated to provide a marginal survival benefit from 1.6 years (undiscounted survival benefits) to 1.8 years (when discounted at 6%) with a cost-effectiveness ratio of $8,378 (undiscounted) to $9,576 (discounted at 6%) per life-year gained (LYG).

Another recent study by Shetty et al looked at the cost-effectiveness of percutaneous radiofrequency ablation for hepatocellular carcinoma and colorectal metastases of the liver compared to palliative care (no chemotherapy)(144). The authors included costs from the perspective of the American healthcare system, including costs of treating complications and excluding costs borne by patients and their families as well as productivity costs. Productivity costs refer to the loss of economic productivity as the result associated with illness or disability(141;145-147). The costs were derived from 2000 Medicare reimbursement fees, which as the authors discuss may not be truly representative of the actual costs of the interventions. The baseline analysis assumed that percutaneous RFA was done as an outpatient procedure requiring 4 hours of observation after the procedure and that patients required an average of 1.6 procedures to ablate their lesions. Survival for patients receiving palliative care was estimated to be 10 months for patients with HCC or CRC metastases. Since the survival benefit of RFA has not been firmly established, the authors chose to calculate cost-effective ratios over a range of possible survival benefits rather than using a specific figure for survival with RFA. The cost to the healthcare system of an outpatient RFA was estimated to be $4,322 (in 2000 U.S. dollars) and the cost of an inpatient procedure was $7,182. The marginal cost-effectiveness ratios of percutaneous RFA done as an outpatient compared to palliative care, based on marginal survival benefits of 6 months, 1 year, 2 years, and 3 years, were

$20,424, $11,407, $6,731, and $5,034 per LYG respectively. These results were sensitive to number of treatments, hours of observation, frequency of follow-up, cost of computed tomography, and whether the procedure was done on an inpatient or outpatient basis.

In 1993, Smith et al published a cost-utility study from Australia which dealt with adjuvant chemotherapy for Dukes' C colon cancer(148). While this paper did not deal directly with patients with liver metastases, it did deal with patients undergoing 5-FU-based chemotherapy. The authors performed a cost-utility study based on the survival results of a paper published in 1990 by Moertel et al that compared 5-FU and Levamisole to observation in patients with resected Dukes' B or C colon cancer(149). This paper by Moertel et al was an important paper that prompted the National Institutes of Health in the U.S. to adopt adjuvant 5-FU/Levamisole as standard treatment for colon carcinoma. Smith et al determined utility scores for different scenarios, including having surgery alone and having surgery plus chemotherapy with three different degrees of side effects (good, medium, and bad scenarios). They used a time trade-off method in a rather small sample of 8 chemotherapy patients and 8 non-patients adjusted for age and marital status. The utility for having surgery alone was 1.00 while utilities for receiving chemotherapy were 0.93, 0.88, and 0.80 for the good, medium, and bad scenarios, respectively. Costs were taken from the hospital viewpoint, including overhead and capital costs, in 1990/91 Australian dollars. The authors concluded that a 52-week course of adjuvant chemotherapy cost an average of $7000. Adjuvant 5-FU/Levamisole offered an average survival benefit of 2.4 years, but only 0.4 QALY's. This resulted in a cost-utility ratio of $17,500/QALY. This ratio was very sensitive to the probabilities used and the assumptions made. One weaknesses of the paper was the small sample size on which the

utility scores are based. The time trade-off method used assumed that life after surgery is valued at a utility of 1.00, which almost certainly is an overestimate since it did not take into account disutility from having surgery (which may result in a colostomy) and that the utility for the general population should be less than 1.0 because of other disease conditions which may affect QOL. Thus, the utility values may not be accurate. Also, there may be significant error in the overall survival calculations. Smith et al assumed a life expectancy of 20 years for patients who did not suffer recurrence. They also assumed that patients with recurrence died at exactly 5 years. These two assumptions may have influenced the number of QALY's considerably, since the conclusions were very sensitive to the probabilities and assumptions used.

Two papers have addressed the cost-effectiveness of irinotecan compared to 5-fluoruracil-based therapy as second-line treatments for metastatic colorectal cancer(150;151). Both papers used the results of a previously published randomized trial by Rougier et al(101) as the source of survival data. This trial by Rougier et al compared irinotecan to 5-FU-based chemotherapy as second-line treatment of colorectal metastases. For patients randomized to the 5-FU arm, investigators were allowed to choose between 3 different 5-FU regimens. Resource consumption data that was recorded prospectively in Rougier's study was used to estimate costs from a U.K. perspective (Iveson et al(150)) and from a French perspective (Levy-Piedbois et al(151)). Median survival from the time of randomization was 10.8 months in the irinotecan group and 8.5 months in the 5-FU group. Both cost-effectiveness studies assumed the viewpoint of their respective healthcare systems, excluding productivity losses and costs borne by patients and families. Both studies reached similar conclusions. Drug acquisition costs were higher in

the irinotecan group, but this was offset by lower costs of administration and lower costs of treating complications due to fewer days spent in hospital. Average total hospital costs for the irinotecan group were £8,253 (in 1998 £ Sterling) in the U.K.(150) and $14,135 (in 1999 US dollars) in France(151). The costs for the various 5-FU regimens ranged from £5,9863 to £9,981 (in 1998 £ Sterling) in the U.K.(150) and from $12,192 to $12,344 (in 1999 US dollars) in France(151). Depending on the specific 5-FU based regimen used, the cost-effectiveness of the irinotecan regimen ranged from being the dominant strategy to costing £11,947 (in 1998 £ Sterling) per LYG in the U.K.(150) and from $9,344 to $10,137 per LYG (in 1999 US dollars) in France(151).

Vaiani et al have published two letters reporting results of two cost-effectiveness analyses comparing the addition of irinotecan to 5-FU/LV to 5-FU/LV alone as first-line treatment for metastatic colorectal cancer(152;153). One was based a randomized, controlled trial by Douillard et al(12) and one was based on a randomized, controlled trial by Saltz et al(11). They used the cost of irinotecan in Italy for the economic evaluation. Their results have only been published in letters so the full details are not available, but in both cases the cost-effectiveness ratios were quite high at €49,290 (in 2000 Euros)(153) and €49,066 per LYG (in 2001 Euros)(152).

Glimelius et al(154) studied the cost-effectiveness of palliative chemotherapy in advanced gastrointestinal cancer. Sixty-one patients with surgically incurable gastric, pancreatic, biliary, or colorectal cancer were randomized to receive either primary chemotherapy or supportive care. Average costs were taken from the perspective of the health care system in Sweden. Quality of life was scored in a fashion where a utility score of 1 was assigned to all times where quality of life remained stable with no symptoms or

was improved. All other disease states received a value of 0. Based on this approach, palliative chemotherapy was about 50% more expensive, but offered about a 50% increase in overall survival and about a 100% increase in quality-adjusted survival. The incremental cost per LYG was $21,333 and the incremental cost per QALY was $20,154 (in 1992 US dollars). When only patients with advanced colorectal carcinoma were considered, the cost per LYG and per QALY for palliative chemotherapy was $10,897 and $9,897, respectively.

Studies have examined the cost-effectiveness of hepatic artery infusion (HAI) chemotherapy compared to systemic chemotherapy for the treatment of hepatic metastases from colorectal cancer. Durand-Zaleski et al(155) compared the cost-effectiveness of hepatic arterial infusion chemotherapy using floxuridine (FUDR) to systemic chemotherapy using 5-flavouracil and leucovorin and to palliative care. Costs were determined from the societal perspective and included productivity costs calculated using the traditional human capital method as well as costs borne by patients and their families. However, the productivity losses of part-time employees were calculated using a wage rate for half-time work and the productivity losses of those who were unemployed were omitted. Disability payments were included in these societal costs, although many would consider these to be transfer payments and not societal costs(141;145-147). HAI chemotherapy was the most costly treatment, but also provided a longer duration of survival with normal quality of life (as measured by the Rotterdam Symptom Checklist (RSC)(156), the Sickness Impact Profile (SIP)(157), and the Hospital Anxiety and Depression Scale (HAD)(158) taken monthly). The cost-effectiveness of HAI compared to systemic chemotherapy was approximately $35,295 (in 1995 US dollars) per LYG

with normal quality of life. Since the calculation of productivity costs did not account for time of people who were not working and the number of people who had retired was higher in the systemic chemotherapy group, the societal costs were likely underestimated to a greater degree in that group.

Another paper by Durand-Zaleski et al(159) used the results of a meta-analysis on the efficacy of HAI chemotherapy(91) to form the basis of a cost-effectiveness analysis. Seven trials included a total of 654 patients with unresectable liver metastases from colorectal carcinoma. The trials included in the meta-analysis compared HAI with FUDR to various systemic chemotherapy regimens. The mean survival (discounted) in the HAI group was 16.3 months compared to 13.1 months in the systemic regimens. Costs from the perspective of the health care system, including costs of treating complications, were estimated from costs of treating similar patients at a hospital in Paris, France and at a hospital in Palo Alto, U.S.A. The cost-effectiveness of HAI compared to the control groups (in 1995 US dollars) was $73,635 per LYG in Paris and $72,300 per LYG in Palo Alto respectively.

The cost-effectiveness of treating hepatocellular carcinoma is also an important issue. Studies have compared liver transplantation to liver resection for HCC, and have found that transplant is more cost-effective provided the waiting time is not too long. As the wait for transplant increases, long-term survival decreases because disease progression results in patients being removed from the waiting list and resection becomes the preferred treatment(15;160). Also, living donor transplantation may become more cost-effective than cadaveric transplantation as the waiting time for cadaveric transplantation increases(161).

Table 6. Summary of existing cost-effectiveness publications regarding the treatment of malignant liver tumours

Author	Year	Perspective	Treatments Being Compared	Cost-Effectiveness Ratio ($US)
Gazelle(139)	2003	Society	Hepatic resection vs. no treatment for CRC liver mets	$18,100 per QALY (1998 US dollars)
Gazelle(140)	2004	Society	Hepatic resection vs. percutaneous RFA for CRC liver mets	$24,300 per QALY (in 1998 US dollars)
Beard(143)	2000	Health Care System	Hepatic resection vs. palliative chemotherapy for CRC liver mets	$9,576 per LYG (1999 US dollars)
Shetty(144)	2001	Health Care System	Percutaneous RFA vs. palliative care for CRC mets or HCC	$5,034 to $20,424 per LYG (2000 US dollars)
Smith(148)	1993	Health Care System	Adjuvant 5-Fu based chemotherapy vs. observation for Dukes' C colon cancer	$17,500 per QALY (1990/91 Australian dollars)
Iveson(150)	1999	Health Care System	Irinotecan vs. 5-FU based chemo for 2nd-line treatment of CRC mets	Dominant to £11,947 to per LYG (1998 £ Sterling)
Levy-Piedbois(151)	1999	Health Care System	Irinotecan vs. 5-FU based chemo for 2nd-line treatment of CRC mets	$9,344 to $10,137 per LYG (1999 US dollars)
Vaiani(152;153)	2000, 2001	Health Care System	Irinotecan plus 5-FU/LV vs. 5-FU/LV for 1st-line treatment of CRC mets	€49,290 and €49,066 per LYG (2000, 2001 Euros)
Glimelius(154)	1995	Health Care System	Palliative chemotherapy vs. supportive care for advanced GI cancer	$9,897 per QALY (1992 US dollars)
Durand-Zaleski(155)	1998	Society	HAI vs. systemic chemotherapy for CRC mets	$35,295 per year of normal QOL (1995 US dollars)
Durand-Zaleski(159)l	1997	Health Care System	HAI vs. systemic chemotherapy or symptom control for CRC mets	$72,300 to $73,635 per LYG (1995 US dollars)
Sarasin(160)	1998	Health Care System	OLT vs. hepatic resection for HCC	$84,410 per LYG (1995 US dollars)
Majno(15)	2000	Health Care System	Resection with salvage transplant vs. primary transplant for HCC	$27,932 per LYG (1998 US dollars)
Sarasin(161)	2001	Health Care System	Living donor vs. cadaveric transplant for HCC	$36,400 per QALY (1998 US dollars)

The choice of treatment for malignant liver tumours is often dictated by both the potential survival offered and by the potential morbidity of the treatment. Quality of life after treatment is an important factor, and can be influenced by both the course of the disease itself and the side effects of its treatments. Unfortunately, quality of life after treatments for liver tumours is often not well described in clinical studies and patients must often rely mainly on anecdotal information.

In addition to a scarcity of published reports, another problem in describing quality of life among cancer patients is a lack of a common scoring system among studies. No single scoring system to describe health-related quality of life has been uniformly accepted among investigators and the few studies that exist used different scoring systems. As a result, it is difficult to make comparisons between different treatments and draw broad conclusions about these treatments' effect on patients' quality of life. Another drawback of such scoring systems is that it is often unknown what magnitude of change in score reflects a clinically significant change in QOL(17).

There are, however, a few of studies dealing with QOL as the primary outcome measure. Ramsey et al(142) sampled a cancer registry in Washington State to identify 173 colon cancer survivors who were at least 1 year from their diagnosis. The sample included patients with all TNM stages except Stage 0. Patients were then given two separate quality of life instruments, the Functional Assessment of Cancer Therapy Scales for colorectal cancer (FACT-C) and the Health Utilities Index Mark III (HUI3). The FATC-C is a disease-specific instrument that covers cancer-related issues and colorectal carcinoma-specific issues. It measures the attributes of physical, emotional, functional,

and social well-being plus satisfaction with the patient-physician relationship(162). The HUI3 is a generic multi-attribute scoring system and is described in detail below (see Methodology). Response rates to the surveys were quite poor, ranging from a 16.4% completion rate to 50.8% depending on the time period. It should also be noted that by including only patients who had survived at least a year from the diagnosis, the authors may have selected patients with more favourable prognoses, resulting in artificially high QOL scores. The study found that those who obtain long-term remissions have a relatively high and sustained quality of life. The scores in the first 3 years after diagnosis were lower and more variable than scores for later years, possibly due to disease recurrence or side effects of treatment. For all stages except Stage IV, FACT-C scores appeared to stabilize at a relatively high level after 36 months. HUI scores were not significantly different between stages at diagnosis. The scores increased over time since diagnosis (see Table 7). Pain, functional well-being, and social well-being were the health attributes most affected. Only emotional well-being scores improved over time. In a retrospective analysis, patients who died within 12 months of the survey had significantly lower HUI3 scores (0.65 vs. 0.85 for the whole population), indicating a deterioration of quality of life in the last year of life. This was presumably due to the effects of disease recurrence. They also noted that patients who had recent surgery (within 1 month of the survey) had significantly lower QOL (HUI3 scores were 0.58 for those who underwent recent surgery compared to 0.85 for the others; p<0.001). The nature of the surgery was not specified. There was a trend towards lower QOL among patients who had chemotherapy or radiation therapy within 1 month that was not significant. The study was not powered to detect these differences. This would suggest

that these treatments impact negatively on QOL, but only temporarily. Interestingly, they also found that patients with colostomies did not have significantly different QOL from those without colostomies.

Table 7. Change in Quality of Life Scores Over Time Since Diagnosis (Taken from Ramsey et al(142))

QOL Instrument	Time Since Diagnosis (months)				
	13-24	25-36	37-60	>60	Overall
HUI3 Score (mean*)	0.80 (0.20)	0.88 (0.12)	0.84 (0.14)	0.90 (0.09)	0.85 (0.15)
FACT-C Score (mean*)	108.5 (20.5)	110.8 (14.6)	112.4 (13.6)	114.5 (12.9)	111.3 (16.0)

* Numbers in parentheses represent standard deviations

While there have been few, if any, studies dealing primarily with quality of life after surgical treatment of liver metastases, there have been a few studies on palliative chemotherapy for liver metastases whose primary outcome measures have been quality of life. Earlam et al(163) investigated differences in quality of life among patients with colorectal liver metastases who underwent symptom control, systemic chemotherapy, or regional chemotherapy. Quality of life information for 51 patients who received chemotherapy through hepatic arterial infusion and 49 patients who received symptom control alone was taken from a previous trial(164), while information for 35 patients receiving systemic chemotherapy was prospectively obtained. All patients completed the Rotterdam Symptom Checklist (RSC)(156), the Sickness Impact Profile (SIP)(157), and the Hospital Anxiety and Depression Scale (HAD)(158) monthly. They found that HAI

chemotherapy was associated with similar overall survival to systemic chemotherapy, but offered a statistically significantly greater proportion of that survival with normal quality of life scores. Patients receiving symptom control only had significantly higher anxiety scores at 1 month after initiation of treatment compared to chemotherapy patients, but this difference disappeared after 2 months. This may have been in part due to patients' perceptions that treatment is better than no treatment. Patients receiving systemic chemotherapy reported increased RSC physical scores and increased scores for sore mouth and tingling hands and feet compared to symptom control patients.

Poon et al(165) reported serial measurements of quality of life in a group of 66 patients who underwent surgical treatment of hepatocellular carcinoma in Hong Kong. QOL was measured with a Chinese translation of the Functional Assessment of Cancer Therapy-General (FACT-G) before surgery and at 3, 6, 9, 12, 18, and 24 months after surgery. They found that surgical resection of HCC was associated with a statistically significant increase in QOL scores. Three months after surgery the average FACT-G scores were higher in all domains (physical, social, emotional, and functional well-being, and relationship with physician). The total average score, out of a possible 116 points, was 83.5 preoperatively and 94.1 postoperatively. The average scores for the entire group gradually declined towards preoperative values from 6 to 24 months after surgery, as some of the group experienced recurrences. Those who experienced recurrences suffered declining QOL after the initial increase. In those patients without recurrence, there was no significant drop in the average QOL score. In contrast, a group of patients with unresectable disease who were offered transarterial chemoembolization (TACE) showed

no improvement in FACT-G scores from baseline, and showed a gradual worsening of scores beginning at 6 months.

Although few studies presently exist that report quality of life in patients with liver malignancies, there is a growing trend to include such measures in ongoing research. Historically, formal evaluations of QOL were very rare during the evaluation of chemotherapy regimens for advanced colorectal cancer. Presently, however, all the ongoing trials evaluating new drug regimens include an evaluation of QOL(166). For instance, two recent trials investigating the addition of irinotecan to 5-FU/LV(11;12) both included the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer. The addition of irinotecan to 5-FU/LV did not comprise and possibly improved quality of life. The increase in survival with irinotecan was statistically significant.

Chapter 5. Objectives

The present study was a pilot project to compare different available treatments for colorectal liver metastases. The goal was to generate hypothesis data regarding the cost-utility of these various treatments. Because colorectal cancer is responsible for most liver malignancies in North America, hepatic colorectal metastases were the primary focus of the study. Although the initial results of RFA appear promising, the technique is still relatively new and long-term survival has not yet been reported. Currently, the treatment of choice for metastatic liver disease is surgical resection when feasible(4-6). It is hoped that RFA will be able to offer similar survival with less morbidity and mortality. If longer-term follow-up suggests this may be true then randomized controlled trials would be indicated. The present study was designed to generate hypothesis data as to whether the cost-utility of RFA and hepatic resection are similar enough to justify such a trial. Systemic chemotherapy and symptom control alone (i.e. palliative treatment) were included in the study because the costs and quality of life after all treatments for liver metastases are poorly described and the cost-utility of all treatment options should be within an acceptable range(19) if physicians are to continue to recommend them.

Presently there are only a few studies evaluating the cost-utility treatments for liver malignancies, none of which have been preformed within the context of the Canadian healthcare system. Other limitations of these studies have been discussed in previous chapters. The present study was designed to overcome these limitations and report the cost and quality of life associated with treatments for colorectal liver metastases. It was realized that the sample size of this study would not allow firm

conclusions to be drawn, but instead generate hypothesis data to explore whether the cost-utilities of RFA and hepatic resection are close enough to consider randomized trials in the future (should the long-term results of RFA prove promising). One purpose of the study was to uncover pitfalls in the implementation of a cost-utility analysis for these treatments. The pitfalls could then be corrected when implementing a possible randomized trial in the future.

The objectives of this study are:

1. To perform a cost-utility analysis evaluating the following available treatments for colorectal liver metastases: surgical resection, radiofrequency ablation, systemic chemotherapy, and symptom control alone.

2. To describe and compare the quality of life after receiving these various treatments for hepatic malignancies

3. To generate a hypothesis concerning the cost-utility of various treatments for hepatic malignancies that may be further tested with a randomized, controlled trial in the future.

Chapter 6. Methods

A. Study Design

      This study was a cost-utility analysis comparing various interventions for the treatment of malignant liver tumours. The study was purely descriptive and did not influence the treatment received by the patients in any way. The study received approval from the University of Manitoba's Health Research Ethics Board. The treatment interventions under evaluation were:

     1) Surgical resection

     2) Radiofrequency ablation

     3) Systemic chemotherapy

     4) Expectant management

Subjects were followed prospectively to measure quality of life and the costs of treatment from a societal perspective. Survival data observed in the study was supplemented by data extracted from existing published literature. A decision analysis model was created and a cost-utility analysis was performed.

B. Patient Selection

      The primary focus of the study was patients with liver metastases from colorectal carcinoma (CRC), however patients with any liver malignancy were considered eligible. This was done to increase accrual into the study. Also, it was estimated that within the

two-year timeframe of the study the outcomes would be roughly equivalent. Initially, all new patients referred to medical oncologists at CancerCare Manitoba at the St. Boniface General Hospital site or to a hepatobiliary surgeon at St. Boniface General Hospital between June 2001 and July 2002 were eligible for the study. The accrual period was extended to December 2002 because the patient numbers were lower than expected. Patients were then followed for up to 2 years or until September 2003, which ever came first.

Following consultation with their physicians, patients determined which treatments they wished to pursue. Eligible patients were then approached regarding participation in the study. Informed consent was obtained from all participating subjects (see Appendix 1 for a copy of the informed consent form). It was initially anticipated that approximately 100 patients would be recruited in to the study over that time frame. This was a sample of convenience. Formal power calculations were not performed, since this study was not designed to reach firm conclusions, but to generate hypothesis data.

C. Treatment and Follow-up

This study did not influence patient treatment in any way, and the patients' physicians made treatment recommendations based upon their best clinical judgement. Patients were followed up to 2 years after enrolment in the study.

Patients receiving either surgical resection or RFA of their liver lesions were treated at the St. Boniface General Hospital. In all cases, RFA was done during an open, formal laparotomy. Their postoperative follow-up included periodic CT scans or MR

imaging at intervals determined by their treating physician or surgeon. Patients who received surgical treatment (hepatic resection or RFA) were also considered for adjuvant chemotherapy at the discretion of the medical oncologists. Patients with recurrent liver disease post-operatively were evaluated for possible repeat resection or RFA.

Medical oncologists at CancerCare Manitoba, an outpatient facility located at St. Boniface General Hospital, followed patients receiving systemic chemotherapy or palliative care. Patients undergoing chemotherapy were assigned to receive 1 of 5 chemotherapeutic regimens at the discretion of the treating oncologist:

1. Single agent irinotecan given in 3-week cycles at 350 mg/m^2 delivered intravenously over 90 minutes.

2. Irinotecan plus 5-fluorouracil (5-FU) and leucovorin (LV) based on the Saltz regimen(11). Treatment was given in 6-week cycles consisting of irinotecan at a dose of 125 mg/m^2 infused over 90 minutes, leucovorin at a dose of 20 mg/m^2 as an IV bolus, and 5-fluorouracil at a dose of 500 mg/m^2 as an IV bolus were given every week for 4 weeks, followed by a 2-week break.

3. Capecitabine given in 3-week cycles consisting of a daily dose of 2,500 mg/m^2 every day for 2 weeks followed by a 1-week rest period.

4. 5-Fluorouracil and leucovorin according to the Mayo Clinic regimen. This consisted of bolus 5-FU at a dose of 425 mg/m^2 and low-dose LV at 20 mg/m^2 per day for 5 days, given in a 28-day cycle.

5. 5-Fluorouracil and leucovorin according to the Roswell Park regimen. A dose of 500 mg/m^2 of leucovorin was given intravenously over 2 hours with 600 mg/m^2 of 5-fluorouracil given as an IV bolus 1 hour into the leucovorin

infusion. This regimen is given weekly for 6 weeks, followed by a 2-week rest period.

Patients received chemotherapy until disease progression or side effects occurred and it was decided by the patient and physician to discontinue treatment. Patients initially receiving palliative care were offered chemotherapy when symptoms of their disease appeared. Patients with complications due to their treatment or progression of disease were admitted to hospital as required.

The study participants were followed after entry into the study to measure their quality of life. The Health Utilities Index questionnaire (the HUI231E.40Q) was administered to the participants at entry into the study and then at 2 weeks, 3 months, 6 months, 9 months, 12 months, and 18 months after commencing treatment. They were also followed for a period of up to 2 years to measure ongoing costs and complications of treatment including repeat hospitalizations and mortality. Patients who were enrolled later in the study period were followed for less, since the study closed prior to completion of 2-year follow-up.

D. Cost Analysis

The costs of providing the various interventions for hepatic colorectal metastases were taken from the perspective of society as a whole, and measured in 2001 Canadian dollars. The following costs were taken into account:

    1) The medical resources consumed

    2) The non-medical resources consumed

3) The loss of productivity associated with illness or disability (The term *productivity costs* has been suggested to refer to these costs(141;145-147))

In all cases, attempts were made to measure the *opportunity costs* of the interventions under consideration. Opportunity cost is defined as the amount that a resource could earn in its highest valued alternative use(18), and represents the value of the alternative that must be foregone when resources are consumed to provide an intervention. This notion is especially important in medicine where limited resources dictate that the provision of one treatment often means foregoing the provision of another. In practice, however, it can be difficult to measure the theoretical opportunity cost, and measures which were thought to provide the best approximation were used in this study.

The costs of providing medical care have traditionally been described as being either *direct* or *indirect costs*(18;141;145). The use of these terms has created some confusion(141). In the medical literature, the term *direct cost* has typically been used to denote resources consumed by the intervention in question. These include costs borne by the healthcare system, families, and others in providing or obtaining treatment. The term *indirect cost* has typically been used to refer to the lost time of patients and their families. In the economic literature, the term *indirect cost* has been used to refer to overhead cost. This study avoided using the terms *direct and indirect cost,* as is recommended by Drummond et al(141). The separate components of each cost were described specifically to avoid confusion associated with this terminology.

Because costs were incurred over time, the analysis adjusted for inflation as well as a *discount rate*. There is a preference to receive benefits earlier and incur costs later that is independent of the effects of inflation and bank interest(18;141;147). To account for this time preference, future costs were discounted. As recommended by the U.S. Panel on Cost-Effectiveness in Health and Medicine, a discount rate of 3% was used for the baseline analysis, and a sensitivity analysis was performed using discount rates ranging form 0% to 10%(147). The future costs were also adjusted for the effects of inflation and converted to 2001 Canadian dollars using the Health and Personal Care Component of the Consumer Price Index for the year 2001, which was 1.96% per year(167).

1) Medical Resources Consumed

a) Hospital Costs – There are several methods that have been described for calculating the costs of inpatient hospital care. The Canadian Coordinating Office for Health Technology describes five such methods(146), which are explained below in order of increasing accuracy. *Generic per diem* and *specialty per diem* methods of calculating costs have the advantage of being simpler, but are less accurate(146). These methods are not able to identify small differences in cost between treatment alternatives. The method of using c*ost per weighted* case is more accurate, and usually classifies patients into *case-mix groups*(141). A case-mix group divides patients into clinically similar categories that are expected to use similar amounts of resources. Categories of patients that consume

more resources can be assigned a higher weight when calculating costs (less accurate than micro-costing, but more accurate than per diem costing). *Patient-specific costing* is based on data collected by tracking individual patients(146), and is useful for uncovering "subtle" differences in the cost of providing services to patients of the same case-mix group. The most precise and the most time consuming method is *micro-costing*(141;146). This involves tracking the actual amount of each resource consumed by each patient through time and motion studies. The method used by the St. Boniface General Hospital's (SBGH) cost-accounting system is a patient-specific costing method(168). This method was thought to provide a good balance between the necessary precision and amount of time and effort expended.

St. Boniface General Hospital (SBGH) has in place a detailed patient-specific cost-accounting system(168) for tracking all the *variable* costs relating to inpatient stays. Variable Costs are the costs of the goods, services, and inputs that change because of the intervention in question (e.g. the cost of laboratory tests changes as the number of tests performed changes) (145). The costs of each patient's hospital stay are individually measured, as the accounting system keeps detailed information on each patient. In designing this system, the cost of a particular service was calculated by measuring the number of workload units required to supply a defined quantity of that service. The number of workload units allocated to a defined quantity of any service was based on the proportion of the total resources consumed in providing that quantity of service. For instance, a service that required more labour or supplies than another would have been allocated more workload units. The total annual cost of that service in the hospital was then divided by the total number of workload units consumed during the provision of that

service to provide a cost per workload unit. By knowing the number of workload units required to provide a given amount of a service to each patient, the cost of providing that service to each patient can be calculated. The hospital's cost-accounting system has calculated the variable cost for each type of service available in the hospital. By tracking the amount of each service that is provided to each patient, the cost of providing each service to each patient can be calculated.

The costs tracked by the hospital cost analysts only include variable costs, so *fixed* costs such as overhead are not included in their data. Fixed Costs are the costs of those resources which, in a short time span, do not change according to the intensity or frequency of an intervention(145) (e.g. the cost of overhead may not change as the number of hospital visits changes). These costs are generally costs that are shared by many departments and include administration, medical records, heating and utilities, housekeeping, laundry, and food services. The methods used to account for these overhead costs are described below.

b) Nursing Costs – The cost of nursing care for each patient was calculated from individual patient data in the hospital's cost-accounting system. This system was in place prior to this study. The amount of nursing resources consumed during each nursing shift by each patient was recorded. Each nurse filled out a short form for each patient under his or her care at the end of each shift. These forms collected information regarding the amount and intensity of nursing care used by each patient, in order to measure nursing workload units consumed by each patient (See Figure 1 for a copy of this form). These forms do not contain sufficient detail to be considered equivalent to time and motion studies, but can identify differences in the amount of resources consumed among

different patients. It was expected that this level of accuracy would be sufficient to discover meaningful differences between patients undergoing the various treatments under consideration.

The cost allocated to caring for a patient was then calculated by taking the total annual nursing care budget for a particular ward, and dividing by that patient's portion of the total annual workload units. This allowed costs based on each patient's level of care to be calculated separately for each patient on each ward, including the intensive care units.

Figure 1. Copy of Form Used by Nursing Staff to Evaluate Intensity of Nursing Care

Patient Condition Indicators - Surgery

13069

		(Patient #1)	(Patient #2)	(Patient #3)	(Patient #4)	(Patient #5)	(Patient #6)
Admission / Transfer In		○ 1	○ 1	○ 1	○ 1	○ 1	○ 1
Discharge / Transfer Out		○ 2	○ 2	○ 2	○ 2	○ 2	○ 2
Transfer Within		○ 3	○ 3	○ 3	○ 3	○ 3	○ 3
Confused / Disoriented / Mentally Incapacitated		○ 4	○ 4	○ 4	○ 4	○ 4	○ 4
Sensory Deficits		○ 5	○ 5	○ 5	○ 5	○ 5	○ 5
Protective Needs		○ 6	○ 6	○ 6	○ 6	○ 6	○ 6
MOBILITY LIMITATIONS OR DEFICITS	Moderate	○ 7	○ 7	○ 7	○ 7	○ 7	○ 7
	Heavy	○ 8	○ 8	○ 8	○ 8	○ 8	○ 8
BATH	Self	○ 9	○ 9	○ 9	○ 9	○ 9	○ 9
	Partial	○ 10	○ 10	○ 10	○ 10	○ 10	○ 10
	Total	○ 11	○ 11	○ 11	○ 11	○ 11	○ 11
FEEDING ORAL / TUBE	Assist	○ 12	○ 12	○ 12	○ 12	○ 12	○ 12
	Total	○ 13	○ 13	○ 13	○ 13	○ 13	○ 13
Intake and Output		○ 14	○ 14	○ 14	○ 14	○ 14	○ 14
Incontinent / Impaction		○ 15	○ 15	○ 15	○ 15	○ 15	○ 15
Intravenous / Irrigation		○ 16	○ 16	○ 16	○ 16	○ 16	○ 16
Peritoneal Dialysis		○ 17	○ 17	○ 17	○ 17	○ 17	○ 17
Total Parenteral Nutrition / CVL / PIC		○ 18	○ 18	○ 18	○ 18	○ 18	○ 18
Specimen Collection		○ 19	○ 19	○ 19	○ 19	○ 19	○ 19
Tube Care		○ 20	○ 20	○ 20	○ 20	○ 20	○ 20
WOUND INCISION OR SKIN CARE	Simple	○ 21	○ 21	○ 21	○ 21	○ 21	○ 21
	Complex	○ 22	○ 22	○ 22	○ 22	○ 22	○ 22
Preparation for Surgery / Procedure		○ 23	○ 23	○ 23	○ 23	○ 23	○ 23
Oxygen Therapy		○ 24	○ 24	○ 24	○ 24	○ 24	○ 24
Physical Therapies		○ 25	○ 25	○ 25	○ 25	○ 25	○ 25
MONITOR	Q1H - Q4H	○ 26	○ 26	○ 26	○ 26	○ 26	○ 26
	Q1H or more	○ 27	○ 27	○ 27	○ 27	○ 27	○ 27
TEACHING NEEDS	Basic	○ 28	○ 28	○ 28	○ 28	○ 28	○ 28
	Special	○ 29	○ 29	○ 29	○ 29	○ 29	○ 29
Special Emotional Needs		○ 30	○ 30	○ 30	○ 30	○ 30	○ 30
Isolation		○ 31	○ 31	○ 31	○ 31	○ 31	○ 31
Out on Pass		○ 32	○ 32	○ 32	○ 32	○ 32	○ 32

Date:

☐☐ / ☐☐
Month   Day

Unit:

○ 6140 A6 West   ○ 6146 CVT

○ 6141 A7 West   ○ 6146s CVT Stepdown

○ 6143 A7 South ○ 6147 A4 South

○ 6145 B4 Ortho

Encounter ID (Patient #1)
Surname (Patient #1)
Encounter ID (Patient #2)
Surname (Patient #2)

Encounter ID (Patient #3)
Surname (Patient #3)
Encounter ID (Patient #4)
Surname (Patient #4)

Encounter ID (Patient #5)
Surname (Patient #5)
Encounter ID (Patient #6)
Surname (Patient #6)

	(Patient #1)	(Patient #2)	(Patient #3)	(Patient #4)	(Patient #5)	(Patient #6)
ADMISSION	○ 35	○ 35	○ 35	○ 35	○ 35	○ 35
MORNING CARE	○ 36	○ 36	○ 36	○ 36	○ 36	○ 36
TREATMENTS	○ 37	○ 37	○ 37	○ 37	○ 37	○ 37
POST PROCEDURE CARE	○ 38	○ 38	○ 38	○ 38	○ 38	○ 38
MEDICATIONS	○ 39	○ 39	○ 39	○ 39	○ 39	○

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c) Physician Costs – The remuneration provided for physicians' services was not included in the SBGH cost-accounting data. The costs for the various services provided were taken from the Manitoba Health Services Insurance Plan Physician's Manual, which is available from Manitoba Health (Manitoba Government) and lists the tariffs paid to physicians by the Manitoba Government for all services. These tariffs were considered to be the best approximation of the societal cost of physician services.

The cost of providing salaries to housestaff (residents, interns, and medical students) were estimated by multiplying the daily wages of the housestaff by the average number of housestaff on a particular ward, and then dividing this by the average number of patients on that ward. The annual salaries of the housestaff vary according to the number of years of post-graduate education, and were taken from the website of the Canadian Residency Matching Service (http://www.carms.ca/overview/manitoba.htm). This provided only a rough per diem cost of housestaff costs for each patient, but the amount of error in this calculation was expected to have a negligible effect on the final results.

d) Physiotherapy, Respiratory Therapy, and Occupational Therapy Costs – These costs were also included in the detailed cost-accounting system of SBGH. The costs for each type of patient encounter (e.g. screening, initial assessment, therapy session, case conferences, etc.) were measured based on workload management systems similar to those described above.

e) Diagnostic Imaging – These costs were captured by the hospital accounting system. This data is based on patient-specific data, and is available for each type of investigation. Costs captured by the hospital accounting system included all variable labour, benefits, and supplies used to deliver the service, but did not capture fees paid to radiologists for the interpretation of these tests. These fees were taken from the schedule of tariffs paid by the Manitoba Government.

f) Pathology – The costs incurred by the pathologic examination of specimens were also captured by the hospital cost-accounting system using a workload measurement system similar to that described above, based on the number and types of specimens received.

g) Laboratory Investigations – These costs were also obtained from the SBGH cost-accounting system. They are based on measuring workload units for each type of test. These costs included staffing and benefits, supplies consumed, as well as staff costs for performing phlebotomies.

h) Medication Costs – The hospital tracked the cost of each medication on formulary, including the cost of the drug plus the staff costs in the pharmacy (pharmacists, pharmacy technicians, etc.) The cost-accounting system tracked each medication given to each patient. These costs did not include the salary associated with a clinical pharmacist, which was added to the cost of the hospital stay of any patient admitted to a ward that employs a clinical pharmacist. This was estimated according to the daily salary of the pharmacist divided by the average number of patients on that ward.

Nurses, in all but extremely rare instances, administered the medications. The costs of administering medications were, therefore, included in the nursing costs associated with each patient.

i) Costs of Blood Products – The number of transfusions and the number of units per transfusion received by each patient were measured through a review of the patients' charts (both from St. Boniface General Hospital and from CancerCare Manitoba). Tretiak et al(169) measured the costs of inpatient and outpatient allogenic transfusion of packed red blood cells (RBC's) in the Canadian Health Care system, based on the average costs at 8 hospitals in 4 provinces (see Table 8). Costs were taken from the societal perspective and included the costs of collection, production, distribution, and administration. They included the costs of patient time, the cost of wastage, and the costs of acquired HIV and Hepatitis C infections. The costs, in 1993 Canadian dollars, are:

Table 8. Costs of Inpatient and Outpatient Allogenic RBC Transfusions in Canada (in 1993 Dollars)(Taken from Tretiak et al(169))

	Inpatient Transfusion	Outpatient Transfusion
1 Unit of RBC's*	$210	$280
2 Units of RBC's*	$392	

* RBC's refers to Red Blood Cells.

These costs were used in this study, after adjusting to 2001 dollars using inflation rates provided by Statistics Canada(170). In 2001 dollars, the cost of 1 unit of RBC's as an inpatient was $240 and the cost as an outpatient was $320. The cost of transfusing 2 units was $448.

j) Costs Associated with Surgery – Costs from the operating room were not captured in the hospital's cost-accounting system. These costs were acquired by prospectively tracking the resources consumed in the operating room (OR) during each case. Costs associated with surgical procedures in this study were made up of several components, including the surgeon and anaesthetist fees, nursing time, time of other support staff, materials and supplies consumed during the procedure, medications administered, and the costs of overhead.

Fees for the surgeons and the anaesthetists were taken from the Manitoba Health Services Insurance Plan Physician's Manual. The nursing resources consumed during each case were determined by multiplying the number of nurses assigned to a particular case by their hourly wages and by the length of the case. For most cases, three nurses were assigned. The amount of resources provided by other support staff, such as orderlies, were calculated in a similar way. The amounts of all surgical supplies and equipment consumed in each case were prospectively tracked by one of the nurses in the operating room. This included all products consumed, such as suture material, sponges, and other non-reusable items. The medications provided by the anaesthetists were also tracked in a similar fashion. The costs of providing care to a patient in the recovery room were calculated based on the amount of time spent in the recovery room.

The overhead costs associated with the operating rooms and the recovery room were calculated as described below.

k) Hospital Overhead – All of the above costs measured by the SBGH cost-accounting system or measured in other ways are variable costs only. They include all variable labour, benefits, and supplies consumed to provide a service. They exclude overhead.

Some authors would argue that overhead costs should not be included in cost-effective analyses, since these costs are not altered by methods of care and are relatively stable over time(171). This may be true in some circumstances where a practice change will not affect the amount of overhead costs consumed, for instance a choice between two surgical procedures which would each consume the same amount of overhead. However, in situations where a program that might avert some hospitalization is being assessed, it is relevant to estimate the value of the freed central resources that could be used for other purposes(141). In this study where comparison was made among different surgical procedures that might have different lengths of hospital stay and among outpatient chemotherapy, the amount of central services consumed was not expected to be equal between all programs. For this reason, overhead was included among the costs in this study.

There are four commonly described methods for allocating overhead, which are the direct method, the step-down method, the multiple allocation method, and the simultaneous equation method(141;172). The direct method is simple and easy to use, however, it does not take into account the interaction of services among cost centres. The simultaneous equation method accounts for interactions between each cost centre, as do the other two methods, but with less work. A computer algorithm can be used to solve the multiple equations. A recent study of costs in the Canadian healthcare system found no significant difference in the costs produced by the various allocation methods(172).

Because the process of determining overhead costs would have been an extremely complex and time-consuming process, these costs were taken from a recent Manitoba study that calculated the components of the average cost per weighted case in all hospitals in Manitoba for the fiscal year 1997/98(173). The components labelled by Finlayson et al as administrative services and support services for SBGH were used to calculate overhead in this study (see Table 9). For SBGH, administration services and support services accounted for 16.5% of the cost per weighted case (taken from Figure 26 of their report). Therefore, to calculate overhead in this study, the total of all inpatient medical costs for patients at St. Boniface General Hospital was multiplied by 16.5%.

Because the outpatient facility at CancerCare Manitoba is located within St. Boniface General Hospital, the same overhead figure of 16.5% of costs were used for the determination of the overhead portion of costs for outpatients treated at CancerCare (see below). It is possible that individual patients could use different amounts of overhead, particularly for inpatients and outpatients, but the above figures were expected to yield a reasonable estimation. The amount of error in this estimation was considered very unlikely to influence the overall results of the cost analysis.

Table 9. Components of Hospital Overhead

Administrative Services	Administration
	Finance
	Human Resources
	Systems Support
	Communications
	Materiel Management
	Registration
	Health Records
Support Services	Volunteer Services
	Housekeeping
	Laundry and Linen
	Plant Administration
	Plant Operation
	Plant Security
	Plant Maintenance
	Bio-Medical Engineering
	Case Management Coordination
	Patient/Client Transport
	Patient Food Services

l) Outpatient Costs Associated with Treatment at CancerCare Manitoba – CancerCare Manitoba is a specialized medical facility designed to offer state-of-the-art medical care for patients with cancers of many types. A broad range of specialists and treatments are available for such patients at a centralized facility. Patients receiving chemotherapy or

palliative care were treated as outpatients by medical oncologists through the facilities of CancerCare Manitoba. When patients required admission to hospital, the relevant costs were captured by the SBGH cost-accounting system as described above.

CCMB does not have a detailed cost-accounting system in place to capture the costs of treating patients in their facility. These costs were calculated using a *case-mix group* approach. Patients receiving chemotherapy for their liver tumours were assigned to receive one of several chemotherapeutic regimens according to their medical oncologists best clinical judgement. Patients entered into the same chemotherapy regimen were assigned to the same case-mix group. The medication costs for each case-mix group were calculated separately for each dose, and a cost for each patient was based on the number of doses received. The amounts of all other relevant resources consumed by a patient in a particular case-mix group, including the nursing resources and other staff resources, were estimated. This provided a cost per treatment associated with each case mix-group (see Appendix 2 for resources used by each case-mix group). The costs of treatment in each case-mix group were calculated for 1 cycle of chemotherapy. The total cost was then calculated for the number of cycles of chemotherapy received by a patient. Details of the duration of and number of treatments received were extracted from the patients' charts. It should be noted that the cost of 5-FU and LV according to the Roswell Park regimen were calculated by the staff at CCMB. The costs of 5-FU and LV according to the Mayo Clinic regimen were assumed to be equivalent to the costs of the Roswell Park regimen in the cost-utility analysis. The costs of each regimen are shown in Table 10.

Table 10. Cost per Cycle of Chemotherapy for Each Case-Mix Group

Regimen	Cost per Cycle
Irinotecan	$2,663.61
Irinotecan, 5-FU, and LV	$1,096.78
Oral Capecitabine	$1,033.34
5-FU and LV	$254.00

The physician costs associated with each outpatient clinic visit to the medical oncologists at CCMB were obtained from the Manitoba Health Services Insurance Plan Physicians Manual. These tariffs are the closest approximation of the societal opportunity costs and represent the gross income collected by physicians for outpatient visits. From this gross income, payments for overhead of the office and support staff are made, leaving a net amount for physician remuneration. Therefore, overhead for physician appointments was included in the tariff.

Most visits to CancerCare Manitoba were for the purposes of receiving chemotherapy. The portion of overhead expenses for these visits was calculated at a rate of 16.5%, as explained above. Again, this may not be completely accurate, but was considered to be a reasonable approximation.

m) Outpatient Office Visits at Other Facilities– As noted above, the societal cost of outpatient visits is largely reflected in the tariffs provided to the physicians by the Manitoba Government. These tariffs will cover physician remuneration as well as staffing, supply, and overhead costs of running an office. The tariff paid to a surgeon for

performing an operation in Manitoba includes the cost of the first 6 months of outpatient follow-up, as the tariff collected for the operation is also used by the surgeon to cover the costs of outpatient follow-up and to cover the costs associated with the office. The costs of longer-term follow-up was obtained from the fee schedule paid by the Manitoba Government.

n) Investigations and Tests for Outpatients – The outpatient offices of the surgeon involved with this study and the oncologists involved with this study are affiliated with St. Boniface General Hospital. Thus, most outpatient laboratory and radiological investigations were performed at facilities associated with St. Boniface General Hospital. As such, they were captured by the hospital's cost-accounting system. By using the relevant patients' hospital chart numbers, these costs were tracked.

The costs of outpatient investigations done at other facilities could not be captured by the cost-accounting system of St. Boniface General Hospital. The number of and types of investigations performed were determined by a review of the patients' charts. It was then assumed that the costs of tests performed at other facilities were equivalent to those performed at SBGH. This may not have been exactly true, as overhead costs may have differed, but the error in this assumption was not expected to significantly influence the results.

o) Costs of Providing Home Care – The cost per visit of providing homecare was taken form the Cost List for Manitoba Health Services(174). Information regarding the use of Home Care was obtained in patients' charts and the cost calculated by multiplying the

number of days where Home Care was used by the cost per visit rate ($28.74 per visit by Registered Nurse).

p) Prescription Drug Costs – These costs were recorded by patients in the personal diary of costs. These diaries consisted of forms where patients recorded all costs paid out of their own pockets. The costs recorded by the patients were the total amount charged by the outpatient pharmacies, and included the cost of the medication and the dispensing fee charged by the pharmacy (which will cover pharmacy overhead and staffing costs). If patients were reimbursed for such costs (e.g. from a prescription drug plan) the costs of the medications were still captured in the diary of costs. The reimbursement would have been considered a transfer payment, which is neither a cost or a gain to society(141) and were not included in the analysis.

2) Non-Medical Resources Consumed

a) Costs Incurred by Individual Patients – Each patient enrolled in this study was given a form to record all costs that they paid on their own. These forms included a personal diary of costs to record all out-of-pocket expenses including the time spent by the patients pursuing medical treatment. These costs included prescription medications (see above), non-prescription medications, travel costs and the time spent receiving treatment.

b) Non-prescription Drug Costs – These costs were also recorded by the patients, and included the costs of all non-prescription medications and supplies related to the treatment in question.

c) Travel Costs – It was anticipated that several study participants would live a great distance outside of Winnipeg, as the hospital has a considerable catchment area. For this reason, it was necessary to include travel costs as they might make up a substantial portion of the societal cost of treatment. The distances travelled by patients were recorded in the cost diaries, as were expenses such as bus fare, cab fare, and airfare. Expenses for car travel by out-of-own patients was calculated by estimating the distance travelled by the patient from their address. The cost estimate was then based on an average fuel price of 70¢ per Litre (observed in September, 2001(175)) and an average fuel economy of 7.7 L per 100 KM for 2001 full size cars(176). Patients travelling long distances recorded the costs of room and board in their diary of costs when applicable.

3) Patient Time and Loss of Productivity

a) Patient Time – The time that a patient spends seeking care or undergoing treatment is a significant resource used by the patient and by society. There is a great deal of controversy regarding the valuation of lost time during treatment, and the associated loss of economic production associated with the disease and its treatment(18;141;145;146;177;178). One of the major areas of controversy is how

investigators should count the lost economic productivity associated with the morbidity of a disease or with its treatment in the economic analysis. There is considerable debate about whether to count this as a cost and include it in the numerator, or whether to measure its effect on the number of quality adjusted life years (QALY's) gained and include it in the denominator.

It is generally agreed that the time that a patient spends seeking and undergoing care should be included as a cost in the numerator of the analysis(18;141;145;147;178-180). The debate arises when discussing whether the effects of morbidity and mortality on the economic productivity should be included as a cost in the numerator, or as an effect of treatment in the denominator of the cost-utility ratio.

There are three commonly described approaches to account for these productivity costs in the economic analysis. The traditional approach to measuring the societal cost of having a person out of the work force due to morbidity from a disease or from its treatment is termed the *human capital approach*(180;181). The cost to society is estimated by taking the amount of time that the individual is out of the workforce and multiplying this by that individual's wage rate. This is the approach favoured by some investigators(181), who argue that the opportunity cost of the morbidity time is measured by the dollar amount that one would have to compensate that individual for time spent on that intervention.

Some argue that the human capital approach may actually overestimate the cost to society when an individual is removed from the work force due to illness(141;178-180). For short-term absences, the loss of production could be made up by the individual upon return to work, or by co-workers who could perform the individual's duties while absent.

For long-term absences the company could hire another individual, possibly a formerly unemployed person. Thus, in both instances, the costs to society may be less than the costs calculated by the human capital approach. For this reason, Koopmanschap and Rutten describe a second method to calculate productivity costs, termed the *friction cost method*(180). Friction costs encompass the transient costs of replacing a worker, including short-term productivity losses during a vacancy period, decreases in productivity during a learning period for a new worker, as well as recruitment and training costs(182). According to this method, from a societal perspective the loss of income that one worker suffers due to a disease or its treatment will be offset by the gain of income achieved by a replacement worker(183). Only the costs of absenteeism and replacing the worker are important. Thus the net cost to society is lower than predicted by the human capital approach.

Weinstein et al(184) disagree with this approach. They suggest that the previously unemployed replacement worker gains the benefit of employment at the expense of lost leisure time. This represents no net benefit or cost to society when this individual's time is valued at its opportunity cost. Therefore, the friction cost method would tend to underestimate the true cost to society since it does not capture the loss of leisure time for the previously unemployed individual. This approach may also underestimate the full cost to society because other important costs such as those accrued by family and friends for taking care of the individual may not be included(181).

The above two methods for capturing productivity costs place a monetary value on the productivity losses and include this as a cost in the numerator of the economic analysis. By convention, the denominator is used to account for the improvement in

health and QALY's associated with an intervention(147). When the effects of an intervention on the length and quality of life are included in the denominator, but monetary values for lost life-years and lost productivity from morbidity and mortality are also included in the numerator, there is a risk of *double counting*(147;184). Using the above two approaches, there is a danger that the effects of a disease and its treatment may be counted both as a cost and as an effect on quality of life.

Weinstein et al(147) suggest that approaches which include productivity costs in the numerator are valid only if the instrument used to measure quality of life expressly excludes the impact of lost productivity on quality of life. When instruments are silent concerning the consideration of lost income, it is assumed that the financial effects have been considered by the patient and are included in the denominator(147;182). Therefore, these effects may be double counted if productivity costs are included in the numerator.

Because of this danger, a third approach to accounting for productivity costs has been described by the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine(147). This approach involves capturing the productivity costs associated with morbidity in the denominator. Proponents of this approach(145;147;184) recommend using preference-weighted measures of health-related quality of life to value morbidity changes. They recommend that the cost of the time spent seeking and receiving treatment be counted as costs of providing a treatment and placed in the numerator, whereas the productivity losses and morbidity encountered after receiving an intervention should be included as effects of treatment and included in the denominator.

This does require a distinction between treatment time and non-treatment time that may be somewhat arbitrary(145), and in some cases may be very difficult(178). The

time spent seeking or undergoing treatment (i.e. treatment time) is a component of the intervention and should be valued in monetary terms and included in the numerator(147). Time spent sick or recuperating is fully captured in the measurement of QALY's in the denominator(145;147). Similarly, mortality from a disease or from its treatment is fully captured by the measure of QALY's in the denominator, and should not be included in the numerator(145;184).

A criticism of this approach is that it only captures the productivity losses of the individual patients, as only the individual patients' utilities for health outcomes are measured and included in the denominator. By only measuring the effects to the individual, the societal cost may not be reflected(181;183). The U.S. Panel acknowledges this, and recommends that the costs to the rest of society be calculated separately, in monetary terms(184). These other costs include costs to family, friends and other caregivers as well as transient friction costs to employers.

There is certainly much debate concerning the most appropriate way to account for productivity costs, and consensus has not been reached. Several approaches have been put forward, and there are arguments in support of each of them. While the various viewpoints have been kept in mind and the controversies considered, this study followed the guidelines set forth by the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine(147) for the reasons stated above and to maintain consistency between different studies and allow comparison.

The time patients spend seeking treatment and undergoing treatment was incorporated into the analysis by estimating the monetary value and counting it as a cost in the numerator. All time spent visiting health care providers before and after treatment,

including the necessary travel times as well as the time spent receiving treatment were converted to a monetary equivalent and included in the numerator. Patients recorded these times in their personal diary of expenses. The time spent in convalescence or recuperating from the various treatments was considered an effect of the treatment. Accordingly, this was fully captured in the denominator of the cost utility ratio and was not included in the numerator. Morbidity from the disease process itself was captured in the denominator. Correspondingly, mortality from a disease or from its treatment was fully captured by the measurement of QALY's and the economic loss was not included in the numerator of the cost analysis.

The average hourly wage of full-time earners of the same gender was used to account for patients' treatment time costs in the analysis(185). The argument for using the wage rate to value lost production is based on the viewpoint that wage rates are the equivalent of the value of marginal productivity(183). The wage figures obtained from Statistics Canada were categorized according to full-time or part-time status and gender, but not according to age(185). Therefore, the wage rates were gender-specific, but not age-specific. Although, some may argue against adjusting the wage rates on the basis of gender, the use of a targeted wage rate to age and gender approximates the opportunity cost of time to society(145;184). By not using figures specific for age as well as gender, there may have been some error in terms of opportunity cost, but the magnitude of this error was considered to be unlikely to influence the final results to any significant degree. Occupation-specific rates were not used because we wanted the results to be applicable to patients across the country. The use of occupation-specific wages might limit the generalizability of the results because the occupations of patients seen in a single urban

hospital in Manitoba may not be the same occupations of patients in other institutions across the country.

The hourly wage rates used in the cost analysis were $24.63 for males and $17.63 for females. These figures were adopted from Statistics Canada(185) by adjusting to 2001 dollars according to inflation(170).

There is also disagreement about how to value the time costs of people who are not currently employed. It has been argued that the opportunity cost of a person who works in the home would actually be higher than the wage of someone of the same age and gender because loss of time from such things as working in the home and taking care of children also has a loss of utility(178). In this study, a wage rate for full-time earners of the same gender was used to estimate time costs of people not in the labour force(185). Any loss of utility was captured in the denominator of the analysis. It should be noted that according to economic theory, this wage rate may have been slightly lower than the opportunity cost of time for people who are not employed(145). In theory, an individual will work at a given wage only if the wage rate is higher than the value of the individual's time being otherwise spent. Someone who chooses not to work may value his or her time at a higher-than -average rate. The wage rate would be a lower estimate of the value of his or her time. Therefore, there may be a slight underestimation using this approach, but the targeted wage rate should be close enough to the real opportunity cost and is the method recommended by several authors(145;147).

The valuation of lost time for retired persons is also problematic(145;178). The same wage rates were again used to estimate the opportunity cost. This may be biased

due to economic factors(145), however, the amount of error will probably not influence the results significantly.

The valuation of leisure time is another contentious issue. People have argued to value lost leisure time at a value anywhere from zero, to average wages, to average overtime earnings. Brouwer et al suggest that the loss of leisure time should be captured in the denominator of the analysis as an effect on quality of life(178;183). Others argue to use an overtime rate (time and a half or double time) as it is the price that an employer must pay, at the margin to buy some of the worker's leisure time(141). Weinstein et al(147;184) recommend valuing the lost leisure time while seeking and undergoing treatment at the same value as the average wage rate. In this study, an average wage rate targeted to age and gender was used to account for lost leisure time taken up by pursuing or receiving care, as recommended by Weinstein et al. The same wage rates, therefore, was used for time off work and for lost leisure time. As in the case of people who are not employed, this approach may be a lower bound on the opportunity cost(145). This degree of error was not expected to influence the findings of the study. It would also have been very difficult to separate leisure time from work time, and the valuation of leisure time would have been very subjective and varied from person to person. This dilemma was avoided by using the same rate for work and for leisure.

b) Caregiver Time – As noted above, caregiver time must be included as it is a relevant societal cost. Patients also recorded time spent by caregivers as a result of disability from their disease or treatment. The cost of paid caregivers was recorded as the amount paid.

The time spent by unpaid caregivers such as family members was valued at an hourly rate equal to full-time earners of the same gender.

4) Costs Incurred Beyond Time Frame of Study

As the follow-up period of this study is at most 2 years, there will be costs incurred by patients surviving beyond that time that will not be captured. Such costs will likely include the costs of ongoing follow-up and costs associated with medical care at the end of life. Assumptions were necessary to deal with these costs. Costs of future follow-up were assumed to be the same as the costs of follow-up measured within the study period. Costs of health care towards the end of life for patients surviving beyond 2 years were assumed to be the same as those costs incurred by patients who died within the time frame of the study. These assumptions were expected to be reasonable and were not expected to result in significant error in the results. Also, any future costs not captured, for instance care in the final stages of life, and were expected to be similar between all treatment groups and not to influence the difference in cost between treatments.

E. Measurement of Quality of Life

The Health Utilities Index (HUI), designed by Torrance and colleagues at McMaster University, was used to measure QOL in this study. The instrument is

protected by copyright and a licensing fee was paid for a training session and for permission to use the HUI in this study. The HUI is a generic instrument that provides a comprehensive framework to measure health status and to calculate utility scores for different health states(186). There are two complementary components of the HUI. The first is a multi-attribute classification system that is used to describe health status. The second is a preference-based, multi-attribute utility function that is used to assign corresponding utility scores to a particular health status.

There are three HUI measurement systems, the HUI Mark I (HUI1), the HUI Mark II (HUI2), and the HUI Mark III (HUI3). The first system developed was the HUI1. Its function was to assess the health status of survivors of neonatal intensive care, but was further extended for paediatric application by Cadman et al(187). This work formed the basis for the HUI2. Although it was developed to assess outcomes of treatments for childhood cancer, the HUI2 is quite general and has since been adapted for use in adult settings such as general population health surveys(186;188;189). The most recent system, the HUI3, was designed for application in a broader age range and to overcome the HUI2's modest limitations, which include a lack of structural independence between some attributes (see Appendix 3 for HUI2 attributes) identified in the HUI2 system(186). The HUI3 contains 8 independent attributes with 5 or 6 levels per attribute, thus specifying 972, 000 unique health states (see Appendix 4 for HUI3 attributes).

Each version of the Health Utilities Index assigns a score to each health attribute and also a multi-attribute score representing overall health status based on the individual's responses to a questionnaire. A score of 1 is the highest score and represents perfect health and a score of 0 represents death, or its equivalent. The preferences used

for calculating utility scores in the HUI3 come from a random sample of 504 adults from Hamilton, Ontario(186). The latest version (HUI3) allows some health states to receive a score below 0, as the general population considered some health states to be worse than death.

The use of HUI questionnaires has been found to be acceptable to members of the general population, physicians, nurses, patients, parents of paediatric patients, and survey methodologists at Statistics Canada(190). It has been shown to be a reliable, responsive, and valid measure of quality of life in a variety of studies(191). Despite evidence of the validity of the HUI3, some may argue that the HUI3 has not been thoroughly peer reviewed. Therefore, while this study primarily used the HUI3, scores from the HUI2 were also reported.

Reliability of the HUI3 among adult populations has been demonstrated with data from the 1991 Canadian General Social Survey(190). By interviewing 506 randomly selected individuals at 1-month intervals, an overall test-retest reliability of 0.767 was demonstrated. Mathias et al(192) found excellent to good inter-rater agreement (intraclass correlation coefficient (ICC) 0.65 to 0.85) for each of the HUI3 attributes when used with stroke patients and their caregivers.

Face validity of the HUI3 is supported by the observation that although there are many levels on each attribute, all levels of each attribute have appeared at least once in population health surveys(186). Evidence supports the predictive validity of the utility scores generated from the multi-attribute HUI3 function(193). Based on data from 73 health states and interview subjects not used for fitting the utility function, they observed

high agreement (ICC = 0.88) between directly measured scores and scores predicted by the HUI3. The mean difference per health state was small (0.008).

Much of the clinical experience using the HUI and much of the evidence of its construct validity comes from the HUI2 in paediatric populations. Saigal et al found that the HUI2 was able to distinguish between the health status of children with extremely low birth weight children (mean overall HUI2 score = 0.82) and among control children (mean overall HUI2 score = 0.95) at the age of 8 years(194). Fourteen percent of children with extremely low birth weight had no functional limitations versus 50% of children in the control group with no functional limitations(195).

The construct validity of the HUI3 for adult populations is now well established(191). Grootendorst et al examined on the construct validity of the HUI3 by comparing the global utility scores of patients with stroke, arthritis, or both to the scores of patients with neither condition. As expected, patients suffering from stroke (mean utility score = 0.54) and from arthritis (mean utility score = 0.77) had utility scores significantly lower than those who did not (mean utility score = 0.93)(196). Mittmann et al studied the utility scores obtained with the HUI3 for Canadians with various chronic conditions living in the community(197). The HUI3 was able to discriminate differences in utility for various conditions. These previously measured scores serve to illustrate the abilities of the HUI3 as well as serve as clinical reference points for comparing other conditions and for future studies (see Table 11).

Table 11. HUI3 Multi-Attribute Utility Scores for Various Chronic Conditions Among

Canadians Living in the Community*

Health Condition†	Mean ± SD HUI3 Score
No Chronic Condition	0.93 ± 0.08
Alzheimer's Disease	0.58 ± 0.26
Arthritis	0.78 ± 0.20
Arthritis‡	0.77
Back Problems	0.81 ± 0.19
Bronchitis/Emphysema	0.79 ± 0.21
Cancer	0.82 ± 0.18
Cataracts	0.77 ± 0.20
Diabetes	0.79 ± 0.21
Heart Disease	0.77 ± 0.21
Hypertension	0.82± 0.18
Migraine	0.83 ± 0.18
Stroke	0.68 ± 0.23
Stroke‡	0.54
Peptic Ulcer	0.80 ± 0.20
Urinary Incontinence	0.70± 0.23

* Diseases are not mutually exclusive
† All scores from Mittmann et al(197) unless otherwise specified
‡ From Grootendorst et al(196)

The HUI2 and HUI3 have been shown to be valid and responsive systems for quantifying the burden of morbidity during the treatment of cancer in childhood(198). In a population of children with acute lymphoblastic leukemia receiving maintenance chemotherapy, the HUI2 and HUI3 were found to be sensitive to the changing adverse event profile during each cycle of chemotherapy. The attributes of pain, emotion, and ambulation were most affected. Since the HUI3 was sensitive to the rapidly changing

levels of morbidity among these patients receiving chemotherapy (although a paediatric population), it can be expected that the HUI3 will be similarly responsive among the present population of cancer patients receiving various interventions for liver tumours that will likely have significant side effects.

The HUI has not been used in patients undergoing liver resection, but the HUI2 has been used in a survey of children who were long-term survivors after undergoing liver transplantation(199). The instrument was found to be sensitive to changes in QOL in this population. The mean global utility score was 0.86 ± 0.13, which was significantly less than a reference group of healthy 8-year-old children who had a mean score of 0.95 ± 0.07. The attribute of emotional well-being and pain were the most severely affected.

Although, the HUI3 has not been used specifically among patients with liver metastases, it has been used by Ramsey at al in a group who had survived at least 1 year after the diagnosis of colorectal cancer(142). They found the quality of life measured by the HUI3 in these patients was generally very good, and that the HUI3 scores correlated with the quality of life scores obtained with the Functional Assessment of Cancer Therapy Scales for Colorectal carcinoma (FACT-C)(162). The HUI3 was sensitive to deteriorations in quality of life that occurred in patients who were in their last year of life and died of their disease and to changes that occur soon after surgery.

A HUI questionnaire, the HUI231E.40Q, was used to assess the health status of patients enrolled in this study. This instrument is able to measure single-attribute and multi-attribute utility scores for both the HUI Mark II and Mark III. A nurse administered the questionnaire to eligible patients at the time of enrolment in the study, prior to any treatment intervention. This first questionnaire was given in the form of a person-to-

person interview. Subsequently, after treatment was initiated, the same questionnaire was administered after 2 weeks, 3 months, 6months, 9 months, 12 months and 18 months. Up to 7 questionnaires were completed, provided patient survival and follow-up time both allowed for this. These serial multi-attribute utility scores tracked changes in the health-related quality of life of the patients, and were used to calculate the number of quality-adjusted life years (QALY's) associated with each treatment modality (see section on decision analysis). When patients were unable to complete the HUI questionnaire, a close friend or family member was asked to complete the questionnaire on their behalf.

F. Cost-Utility Analysis

A decision tree was constructed using a Markov model to represent the different treatment pathways for colorectal liver metastases and their associated outcomes. The decision analysis was performed using the computer software Data 3.5 © (Treeage Software, Inc., 1999). A 1-month cycle length was chosen since clinically relevant changes in health status are possible within that time frame, especially for treatments such as chemotherapy and palliative care (see Figure 2 for representation of decision model in the format used by Data 3.5 ©).

In this model patients were categorized into one of two discrete health states, "alive" or "dead". Patients receiving any treatment were initially in the "alive" state and at the end of each 1-month cycle they either remained in the "alive" state and entered the next cycle, or died from disease progression or from complications of treatment (Figures 3 and 4 show the possible transitions between health states in the form of Markov-state diagrams). The decision analytical model then calculated the expected survival associated

with each treatment and adjusted these survival times by the quality of life scores

obtained with the HUI. This permitted a cost-utility analysis to be performed using the

costs and the quality-adjusted survival associated with each intervention.

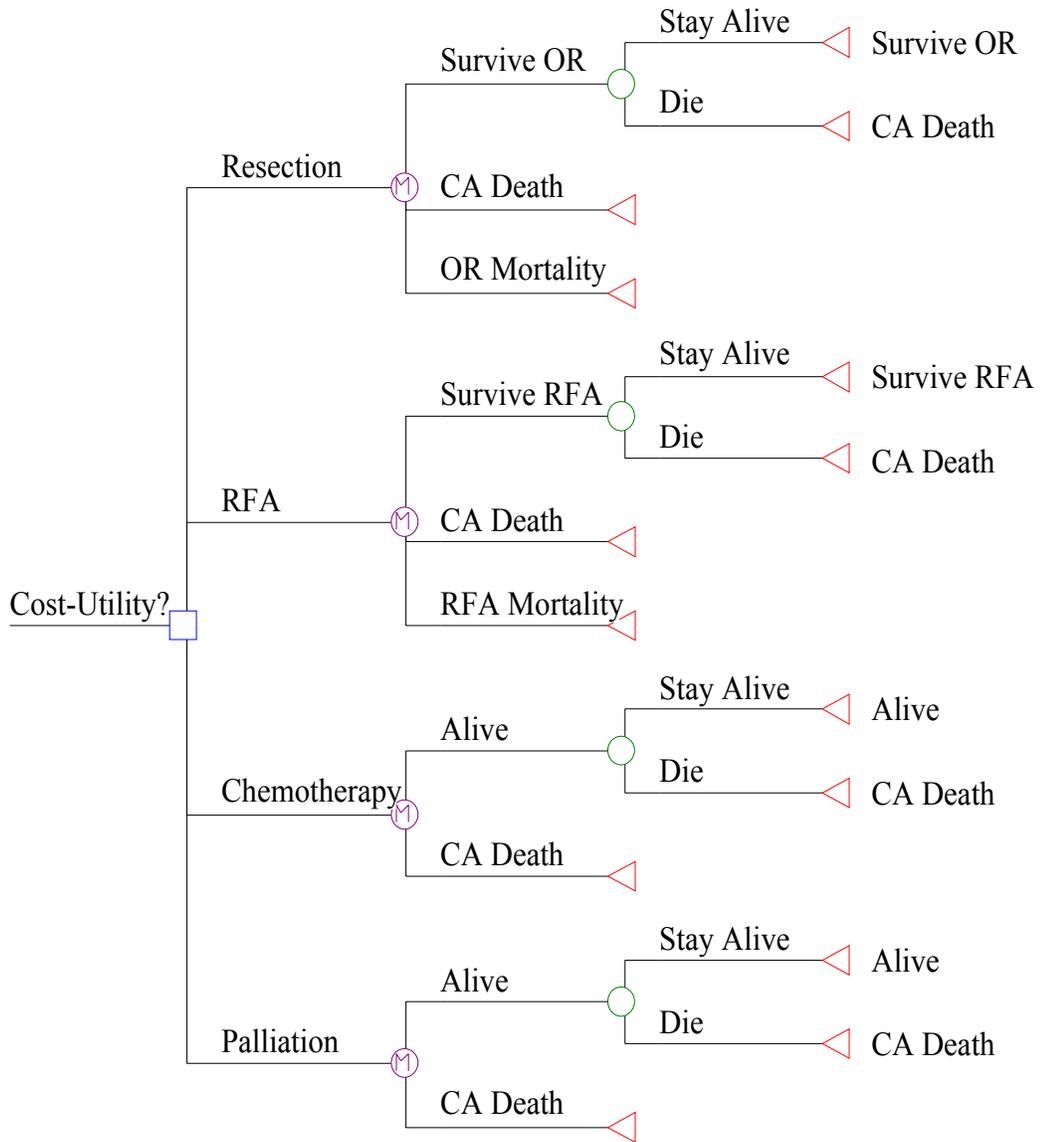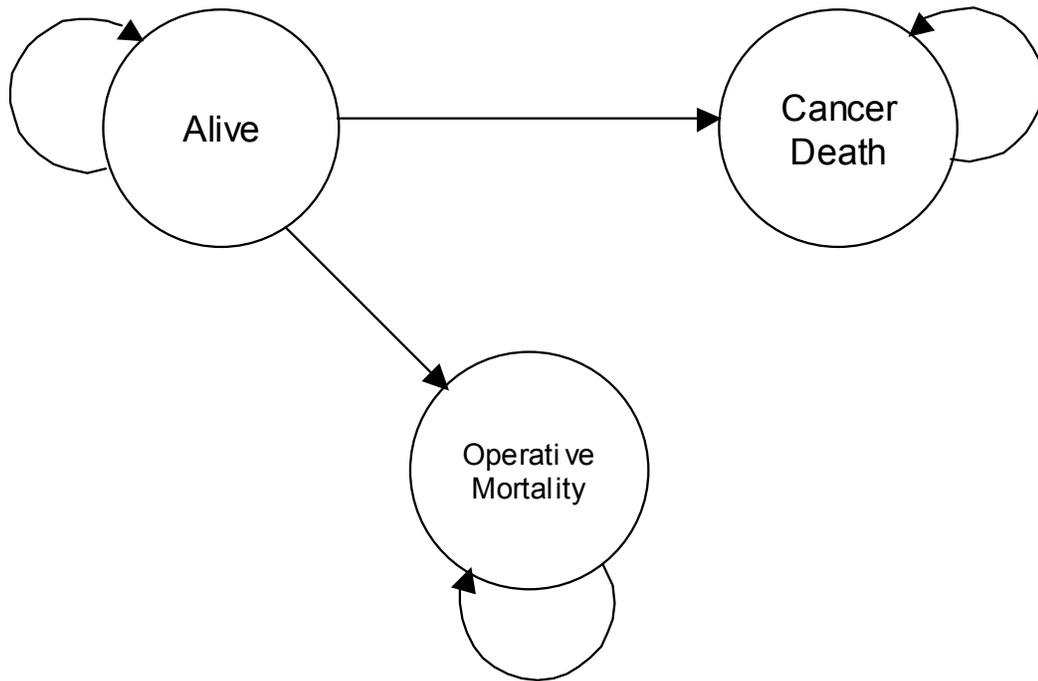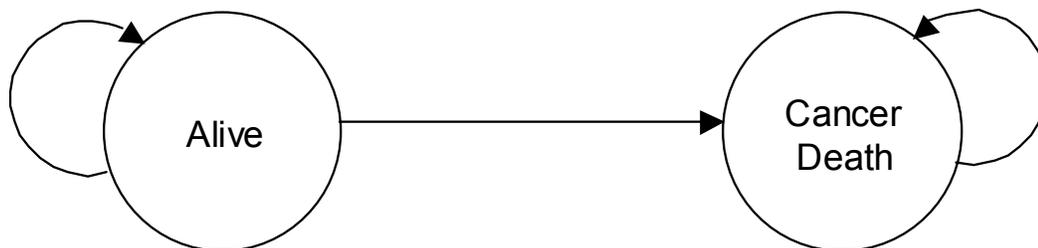Figure 2. Representation of Markov Decision Model in the Format Used by Data 3.5 ©

Figure 3. Markov-State Diagram for Surgical Resection and Radiofrequency Ablation

Each circle represents a Markov state, and arrows indicate transitions

Figure 4. Markov-State Diagram for Chemotherapy and Palliative Care

Each circle represents a Markov state, and arrows indicate transitions.

Because the current study was a pilot project conducted over a period of two years, the limited number of participants necessitated that survival data be supplemented with survival data from other published reports. The recent literature (since 1997) was searched using PubMed. The best available outcome data for hepatic resection and for RFA came published case series. Operative mortality was defined as any death occurring within 30 days of surgical resection or RFA. Outcome data for chemotherapy was taken from randomized controlled trials. For palliative care outcomes, the literature search was not limited to the past 5 years because of the limited number of studies (see Chapter 2).

The group of patients in the "alive" state at any given time consisted of patients suffering complications of the treatment or of progressive disease as well as those who may have been cured. Thus, the reported utility scores included patients suffering complications as well as patients who may have been cured. In this manner, the QOL for patients both with and without disease or complications was directly measured and incorporated into the analysis. This avoided the degree of error that would have been introduced if the effects of disease progression or complications was modeled rather than measured.

Several assumptions were made when constructing the Markov model:

1. Patients suffering operative mortality (death within 30 days of surgical resection or RFA) incur the cost of the treatment costs, but receive no utility (i.e. a utility score of 0).

2. Since utility scores were measured only at specific time intervals, QALY's were calculated assuming that the utility scores between measurements changed in a linear fashion from one score to another.

3. Since the last measured utility score was 18 months after beginning a treatment intervention, utility for those patients who survived beyond the follow-up period was assumed to remain constant at the level measured at 18 months. The QOL of patients with and without disease was measured up to 18 months, so the future utility in the model also accounted for this.

4. For patients who died before the end of the 2-year follow-up period, utility between the last measured score and their death was calculated by assuming that utility decreased in a linear fashion from the last measured score to zero at the time of death.

After calculating the cost-utility associated with each treatment modality uncertainty in the model was accounted for by performing sensitivity analyses.

J. Statistical Analysis

As mentioned previously, the projected sample size of 100 patients was a sample of convenience. Formal power calculations were not performed because this study was not designed to draw firm conclusions, but to generate hypothesis data. Continuous variables were analyzed with the Mann-Whitney U test. A non-parametric test was chosen since the samples were so small and data was unlikely to be normally distributed. For categorical variables, the Fisher's Exact Test was used. When testing for differences in quality of life over time, repeated measures ANOVA was used when appropriate.

Statistical significance was defined using a p = 0.05. The statistical analysis was performed using SPSS® Base 14.0 for Windows®.

A Cost-Utility Analysis of Liver Resection for Malignant Tumours: a Pilot Project

By

Michael Andrew McKay

VOULUME 2 of 2

A Thesis Submitted to the Faculty of Graduate Studies
In Partial Fulfillment of the Requirements for the Degree of

MASTER OF SCIENCE

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Chapter 7. Results

A. Patient Characteristics

Forty patients were recruited into the study (See Table 12 for the baseline characteristics of all patients). There were 29 males and 11 females, with a mean age of 64.4 years. Seven patients underwent hepatic resection, seven patients underwent RFA (sometimes in combination with resection), 20 patients received systemic chemotherapy, and 6 patients received symptom control alone. The majority of patients had colorectal primaries, but there were tumours of other histology also. Two patients had gastrointestinal stromal tumours (GISTs), three had hepatocellular carcinomas (HCC's), two had cholangiocarcinomas, and one patient had a testicular germ cell tumour. There was a fairly even split between synchronous and metachronous lesions, and most patients (81%) did not have documented extra-hepatic disease at the time of enrolment.

Table 12. Characteristics of Overall Study Population

Category		Overall	Resection	RFA	Chemo	Palliative
N		40	7	7	20	6
Age	Mean	64.4	66.6	57.9	63.4	73.2
	SD	11.1	10.8	12.1	11.3	4.7
M:F	M	29 (73%)	6 (86%)	5 (71%)	12 (60%)	6 (100%)
	F	11 (28%)	1 (14%)	2 (29%)	8 (40%)	0 (0%)
No. Lesions*	<=3	19 (50%)	7 (100%)	3 (43%)	4 (22%)	5 (83%)
	>3	19 (50%)	0 (0%)	4 (57%)	14 (88%)	1 (17%)
Tumour Type*	Colorectal	32 (80%)	5 (71%)	6 (86%)	17 (85%)	4 (67%)
	Other	8 (20%)	2 (29%)	1 (14%)	3 (15%)	2 (33%)
Time of Metastases*	Synchronous	17 (49%)	3 (43%)	4 (66%)	7 (41%)	3 (60%)
	Metachronous	18 (51%)	4 (57%)	2 (33%)	10 (59%)	2 (40%)
Extra-hepatic Disease*	Y	7 (19%)	0 (0%)	1 (14%)	4 (22%)	2 (40%)
	N	30 (81%)	7 (100%)	6 (86%)	14 (78%)	3 (60%)
ASA Score*	Mean	2.61	2.71	2.43	2.70	3.00
	n	28	7	7	10	2
	SD	0.49	0.49	0.55	0.48	0.00

*For some categories, information was not available for all patients

The characteristics of the individual patients according to the primary treatment received are listed below in Tables 13 to 16.

Table 13. Characteristics of Patients Undergoing Hepatic Resection

Gender	Age	Tumour Type	No. Liver Lesions	Timing of Lesion	Location	Extra-hepatic Disease	Type of Resection	Chemo	Co-Morbid Disease*	ASA Score
M	61	Rectal	1	Metachronous	R Lobe (Segment 6)	No	Wedge	No	COPD, Gout, Osteoporosis	3
M	72	GIST	1	Metachronous	R Lobe (Segment 8)	No	Wedge	Yes	DM II	2
M	61	Colon	1	Synchronous	L Lobe (Segment 2)	No	Wedge	Yes	COPD, Obesity, Hypothyroid	3
M	48	Testicular	1	Synchronous	R Lobe	No	R Lobe	Yes	HTN	3
M	74	Colon	1	Synchronous	R Lobe	No	Wedge	No	HTN	3
M	69	Rectal	1	Metachronous	R Lobe	No	Wedge	No	HTN, DM II, Hypothyroid	2
F	81	Colon	1	Metachronous	L Lobe	No	Wedge	No	Nil	3

* COPD (chronic obstructive pulmonary disease), DM II (type II diabetes mellitus), HTN (hypertension)

Table 14. Characteristics of Patients Undergoing Radiofrequency Ablation

Gender	Age	Tumour Type	No. Liver Lesions	Timing of Lesion	Location	Extra-hepatic Disease	Treatment	Chemo	Co-Morbid Disease*	ASA Score
F	42	Rectal	4	Synchronous	R Lobe	Yes	RFA	No	0	2
F	77	Rectal	2	Metachronous	L + R Lobes	No	Resection & RFA	No	DM II, PE, HTN, Breast CA	3
M	63	Colon	2	Synchronous	L + R Lobes	No	Resection & RFA	Yes	HTN	2
M	64	Rectal	4	Synchronous	L + R Lobes	No	Resection & RFA	Yes	DM II	2
M	50	HCC	1	NA	R Lobe	No	RFA	No	HCV, HTN, DMII, OA, Gout	3
M	60	Rectal	4	Metachronous	L + R Lobes	No	Resection & RFA	No	Nil	3
M	49	Colon	4	Synchronous	R Lobe	No	RFA	Yes	Nil	2

* DM II (type II diabetes mellitus), PE (pulmonary embolism), HTN (hypertension), HCV (Hepatitis C virus), OA (osteoarthritis)

Table 15. Characteristics of Patients Receiving Systemic Chemotherapy*

Gender	Age	Tumour Type	No. Liver Lesions	Timing of Lesion	Location	Extra-hepatic Disease	Chemo Regimen	Co-Morbid Disease†	ASA Score
M	77	Rectal	6	Synchronous	L + R Lobes	No	Irinotecan, 5-FU, LV	0	2
F	51	Colon	Multiple	Synchronous	L + R Lobes	No	Oxaliplatin, 5-FU, LV	PUD	
F	79	Colon	Multiple	Synchronous	L + R Lobes	Yes	Xeloda	HTN, Hypothyroid, Osteomyelitis	3
M	59	Colon	Multiple	Metachronous	L + R Lobes	Yes	Irinotecan, 5-FU, LV	Arthritis, BPH	
F	59	Colon	5	Metachronous	L + R Lobes	No	Irinotecan, 5-FU, LV	Obesity, DM II	3
M	69	Cholangio CA	Multiple	Synchronous	L + R Lobes	No	5-FU, LV	Afib, IHD, Melanoma	
M	72	HCC	1	N/A					
M	72	Colon							
M	60	Colon	1	Metachronous	L Lobe	No	Irinotecan, 5-FU, LV	DM II, HTN	
M	57	Colon	3	Synchronous	R Lobe	No	Irinotecan, 5-FU, LV	0	2
F	79	GIST	Multiple	Metachronous	L + R Lobes	No	Gleevec	Arrhythmia, Valve Disease, HTN, OA	3
F	70	Colon	3		L + R Lobes	No	Irinotecan, 5-FU, LV		
M	76	Rectal	2	Metachronous	L Lobe	No	Xeloda	COPD	3
M	63	Colon	Multiple	Metachronous	L + R Lobes	No	Irinotecan, 5-FU, LV	Obesity, DM II	3
M	61	Rectal	Multiple	Synchronous	L + R Lobes	No	Irinotecan, 5-FU, LV	Cardiac Transplant, DM II, HTN, Obesity, Gout	3
F	51	Rectal	Multiple	Metachronous	L + R Lobes	Yes	Irinotecan, 5-FU, LV	HTN	3
F	47	Colon	4	Metachronous	L + R Lobes	No	Irinotecan, 5-FU, LV	Nil	
F	42	Colon	Multiple	Synchronous		Yes			
M	52	Colon	Multiple	Metachronous	L + R Lobes	No		Cholelithiasis	2
M	71	Colon	4	Metachronous	L + R Lobes	No	Irinotecan, 5-FU, LV	IHD, MI, HTN	

* Not all information was available for every participant from available charts
† PUD (peptic ulcer disease), HTN (hypertension), BPH (benign prostatic hypertrophy), DM II (type II diabetes mellitus), Afib (atrial fibrillation), IHD (ischemic heart disease), OA (osteoarthritis), COPD (chronic obstructive pulmonary disease), MI (myocardial infarction)

Table 16. Characteristics of Patients Receiving Symptom Control Alone*

Gender	Age	Tumour Type	No. Liver Lesions	Timing of Lesions	Location	Extra-hepatic Disease	Chemo	Co-Morbid Disease	ASA Score
M	78	Colon	3	Synchronous		Yes	Yes	DM II, COPD, HTN, Prostate CA	
M	76	HCC	1	NA	L Lobe	No	Yes	DM II, COPD, IHD, TIA, Pacemaker	
M	76	Rectal	3	Metachronous	L + R Lobes		No	Glaucoma	
M	73	Cholangio CA	1	Synchronous	L Lobe	No	No	HTN	
M	65	Colon	1	Metachronous	L Lobe	Yes	No	Nil	3
M	71	Rectal	Multiple	Synchronous	L + R Lobes	No	No	HTN, Arthritis	3

* Not all information was available for every participant from available charts
† DM II (type II diabetes mellitus), COPD (chronic obstructive pulmonary disease), HTN (hypertension), IHD (ischemic heart disease), TIA (transient ischemic attack)

The patient characteristics were generally similar between groups in terms of age, gender, and types of tumours, presence of synchronous or metachronous tumours, and ASA scores. Patients undergoing RFA tended to be younger than other patients, including patients undergoing hepatic resection. The age difference between those who had resection and those who had RFA was not statistically significant (p=0.22; Mann-Whitney U test). Among patients who were not treated surgically, patients who elected to receive symptom control alone tended to be older than patients who received chemotherapy, but this difference was not statistically significant (p = 0.055; Mann-Whitney U test). Compared with patients who underwent hepatic resection, the patients who underwent RFA had a greater number of liver lesions (mean of 1.0 versus 3.0; p < 0.01; Mann-Whitney U test). Patients who received chemotherapy as the primary treatment had more lesions than patients receiving other treatments (p < 0.05; Mann-Whitney U test).

B. Treatment and Follow-Up

Study recruitment began in June of 2001, and concluded in December of 2002. Patient follow-up was performed until September of 2003. Individual patients were followed until the final Health Utilities Index telephone interview (which took place 18 months after treatment began), until they died of disease, until they withdrew from the study, or until the study period ended, whichever came first.

Unfortunately, there were several patients who either withdrew from the study or were lost to follow-up. One patient in the group who underwent resection (1 of 7) withdrew form the study and one patient in the group who received RFA (1 of 7) was lost to follow-up. Three patients in the group who received chemotherapy as their primary treatment (3 of 20) were lost to follow-up. Of the patients who elected to receive symptom control alone, 2 were lost to follow-up and 1 withdrew from the study (for a total of 3 of 6). The loss to follow-up occurred at various times during the study period, so there were varying amounts of information available for these patients depending on how early in the follow-up period they were lost or withdrew. Patients with whom we lost contact were telephoned several times, but we were unable to contact them again. Their charts were reviewed to check if it had been documented that they had died, but there was no documentation. It is possible that they had died or moved residences. There were no statistically significant differences in any baseline characteristic between those who were lost to follow-up and those who were not.

The study participants were grouped according to the primary treatment modality that they underwent. Some patients underwent more than one treatment. Patients who

underwent hepatic resection or RFA and experienced tumour recurrence were evaluated for possible repeat resection or RFA and for systemic chemotherapy or palliative care. No patient underwent a repeat hepatic resection or RFA. Four of seven patients who underwent RFA did so in conjunction with hepatic resection because their burden of disease was not amenable to resection alone. Three patients in the group who underwent hepatic resection and three patients in the group who underwent RFA also received systemic chemotherapy. Two patients in the group who initially decided to receive symptom control alone ultimately chose to receive chemotherapy during the time course of the study. Three patients in the group receiving chemotherapy as the primary treatment had an initial exploratory laparotomy with the intent to perform hepatic resection or RFA. After finding extensive disease, the surgical procedure was terminated and these patients received chemotherapy.

C. Survival Data

1) Hepatic Resection

There was no operative or peri-operative mortality. As of August, 2003, 4 of the 7 patients who underwent hepatic resection were still alive, while 3 had died of disease (see Table 17). Two of the 4 living patients were free of disease after 368 and 794 days and 2 were alive with disease 304 and 773 days after surgery (DFS was 141 and 264 days, respectively). The 3 patients who died had survived 347, 359, and 526 days. Thus, the actual 1-year and 2-year survival rates were 67% and 40%, respectively. It should be noted that 3 of these patients received chemotherapy in addition to surgery. The patient

with a GIST tumour received Gleevec while one patient with metastatic colorectal cancer received irinotecan, 5-FU, and leucovorin and the patient with a germ cell primary received cisplatin and etoposide.

Table 17. Observed Survival for Patients Undergoing Hepatic Resection

Treatment Date (dd/mm/yy)	Treatment	Type of Resection	Primary Cancer	Date of Recurrence (dd/mm/yy)	Date of Death (dd/mm/yy)	Disease-Free Survival	Overall Survival (toAug31/03)
28/06/01	Resection	Wedge	Rectal			794	794
19/07/01	Resection	Wedge	GIST	3/27/02		264	773
6/2/02	Resection	Wedge	Colon	6/6/02	17/07/03	120	526
21/02/02	Resection	R Lobe	Testicular	6/6/02	15/02/03	105	359
23/07/02	Resection	Wedge	Colon	3/3/03	27/03/03	323	347
27/08/02	Resection	Wedge	Rectal			368	368
31/10/02	Resection	Wedge	Colon	3/21/03		141	304

Because the patient numbers were small in this sample, the survival data was taken from recent published literature(20-26;28-57;70). The simple average of the reported survival rates was chosen for the baseline analysis. The mean of the operative mortality rates reported in these case series was 2.9% and the mean of the reported values for 5-year survival was 32.9% (see Tables 1 and 2 in Chapter 2). These figures were used in the decision analysis. The resulting survival curve is shown in Figure 5 below.

Figure 5. Average of Survival Rates Reported in Literature for Patients Undergoing
Hepatic Resection
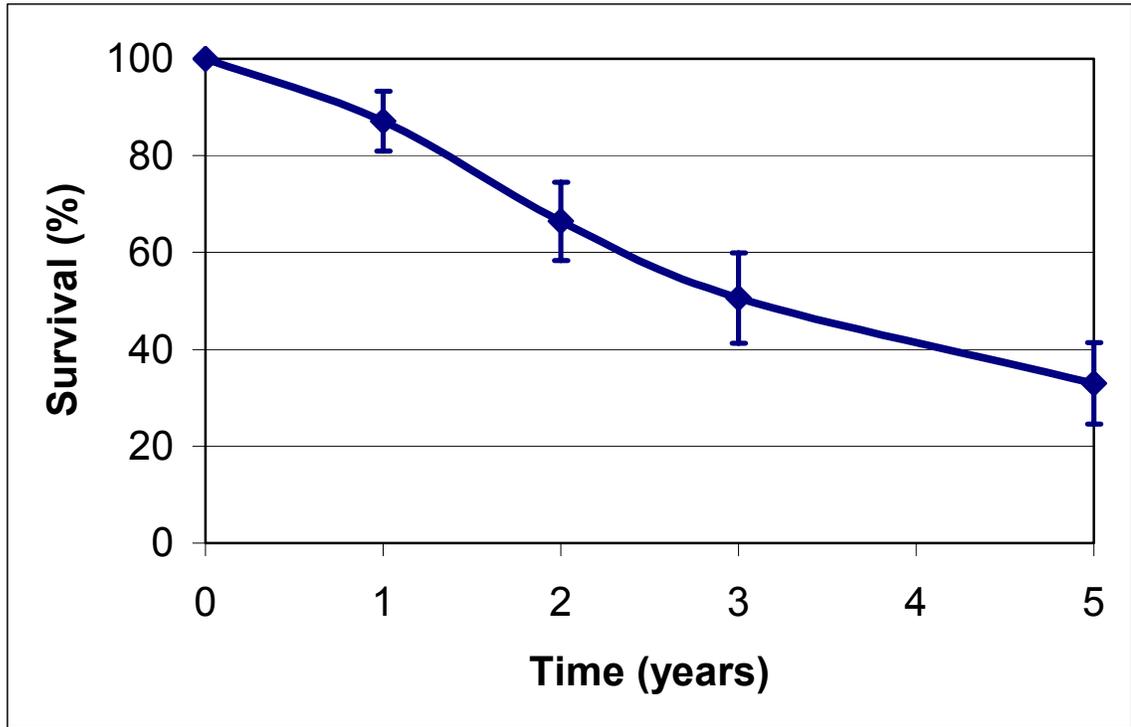
The error bars on the graph represent standard deviations.

2) Radiofrequency Ablation

There were no operative or peri-operative deaths. Survival could be calculated for
6 of the 7 patients who received radiofrequency ablation (see Table 18), as there was no
available survival information for one patient who withdrew from the study. Of the
remaining six participants, one had died of recurrent disease after 249 days. Two were
alive with disease after 482 and 484 days, and three patients were alive without signs of
disease after 262, 734 and 812 days. Thus, the actual 1-year and 2-year survival rates
were 80% and 67%, respectively. It should be noted that 3 of these patients with

colorectal cancer metastases received chemotherapy in addition to RFA. The
chemotherapy consisted of irinotecan, 5-FU, and leucovrin.

Table 18. Observed Survival for Patients Undergoing Radiofrequency Ablation

Treatment Date (dd/mm/yy)	Treatment	Type of Resection	No. Lesions Ablated	Primary Cancer	Date of Recurrence (dd/mm/yy)	Date of Death (dd/mm/yy)	Disease-Free Survival	Overall Survival (toAug31/03)
10/6/01	RFA	N/A	4	Rectal			NA	812
30/8/01	Resection & RFA	L Lateral Lobe	1	Rectal			734	734
5/10/01	Resection & RFA	L Lateral Lobe	1	Colon	8/3/02	7/12/02	154	249
6/12/01	Resection & RFA	L Lateral Lobe	3	Rectal	6/5/02		151	482
4/4/02	RFA	N/A	1	Hepatocellular	6/7/03		428	484
11/14/02	Resection & RFA	Wedge	2	Rectal			NA	NA
12/12/02	RFA	N/A	4	Colon			262	262

Again, no conclusions about survival can be made from such short follow-up and
low patient numbers, so this data was supplemented with data form the recent literature.
There are no existing studies reporting long-term follow-up of patients who have received
RFA. To date, the longest reported follow-up is 3 years(127-129). The averages of the 1-,
2-, and 3-year survival figures in these series are 89.4%, 69.3% and 49.5%, respectively.
Assuming that the death rate stays constant after 3 years, the 5-year survival was modeled
to be 28.6% using a natural logarithmic survival function. The survival reported in these
recent studies may rival the 3-year survival data for patients undergoing hepatic
resection, even though these patients were considered to have unresectable disease(129).
Further study and longer-term survival data are needed to see if this is indeed the case.
The survival curve from these studies, which was used in the analysis, is represented in

Figure 6. The mean of reported mortality rates from two larges series was 0.8%(130;131). This figure was used for the cost-utility analysis.

Figure 6. Average of Survival Rates Reported in Literature for Patients Undergoing Radiofrequency Ablation
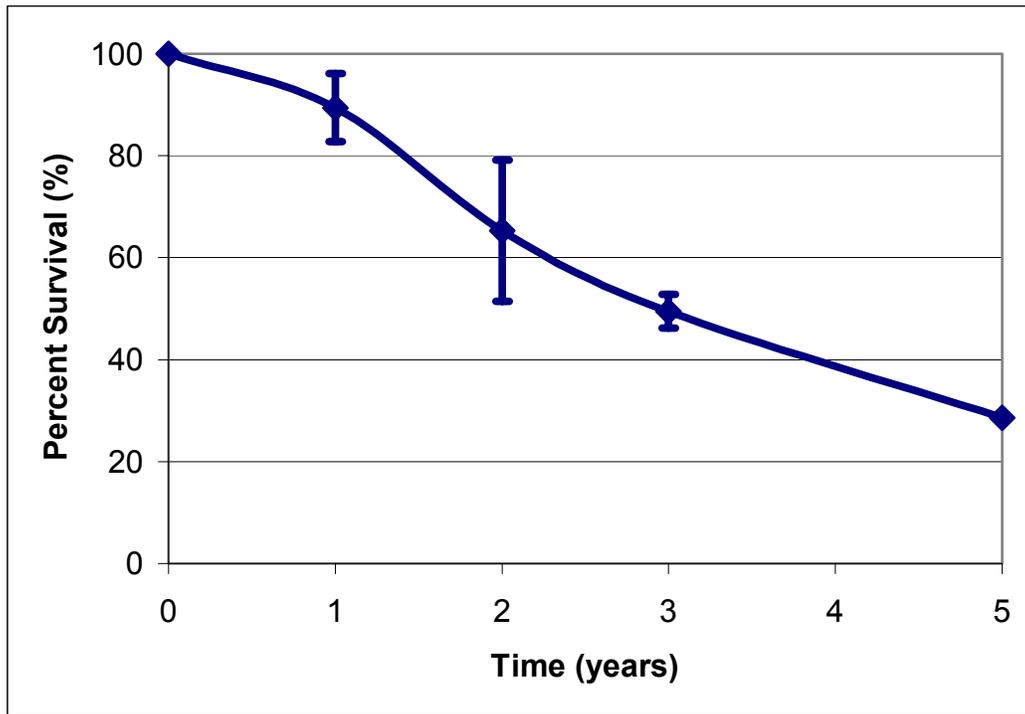
Note that the survival beyond 3 years has been modeled assuming a logarithmic survival curve. The error bars shown in the graph represent standard deviations.

3) Systemic Chemotherapy

Survival data could be calculated for 17 of 20 patients who received chemotherapy as their primary treatment modality. Survival could not be measured for the other 3 patients because information could not be found in the available charts. These patients received their treatment in other institutions where we did not have approval from the Ethics Boards to access the information. Eight of these 17 patients were still alive at the completion of the study. The mean and median survival for this group were

both 373 days. The actual 1-year survival rate was 60%. Two-year survival could not be calculated because none of the 8 patients who were still alive at the end of the study period had been followed up for 2 years. The survival data for these 17 patients for whom there was adequate information to calculate survival is listed below in Table 19.

Table 19. Observed Survival for Patients Receiving Systemic Chemotherapy

Agents	Tumour	No. Lesions	Timing of Lesions	Extra-hepatic Disease	Treatment Start 1Date (dd/mm/yy)	Date of Death (dd/mm/yy)	Overall Survival (toAug31/03)
Irinotecan, 5-FU, LV	Rectal	6	Synchronous	No	6/9/01	22/12/02	472
Xeloda	Colon	Multiple	Synchronous	Yes	27/08/01	14/05/02	134
Irinotecan, 5-FU, LV	Colon	Multiple	N/A	Yes	17/09/01		713
Irinotecan, 5-FU, LV	Colon	5	Metachronous	No	22/11/01		647
5-FU, LV	Cholangio CA	Multiple	Synchronous	No	19/11/01	5/31/03	568
	HCC	1	N/A		3/12/01	30/01/02	58
	Colon				7/1/02	11/4/02	93
Irinotecan, 5-FU, LV	Colon	1	Metachronous	No	29/01/02		579
Irinotecan, 5-FU, LV	Colon	3	Synchronous	No	8/4/02		510
Irinotecan, 5-FU, LV	Colon	3		No	6/2/02	14/02/03	373
Irinotecan, 5-FU, LV	Colon	Multiple	Metachronous	No	4/4/02		514
Irinotecan, 5-FU, LV	Rectal	Multiple	Synchronous	No	4/25/02	1/2/03	282
Irinotecan, 5-FU, LV	Rectal	Multiple	Metachronous	Yes	09/0702	12/9/02	65
Irinotecan, 5-FU, LV	Colon	4	Metachronous	No	10/9/02		355
	Colon	Multiple	Synchronous	Yes	25/03/02	26/12/02	276
	Colon	Multiple	Metachronous	No	10/7/02		416
Irinotecan, 5-FU, LV	Colon	4	Metachronous	No	14/11/02		290

There are blank entries because some information was missing in the charts that were available.

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The survival data used in the decision analysis was taken from recent published randomized controlled trials of systemic chemotherapy for metastatic colorectal cancer(11;12). Median survival in the two recent RCT's involving irinotecan, 5-FU, and leucovorin was 14.8 months(11) and 17.4 months(12). This survival data was used in the decision analysis. The survival curve based on these figures is shown below in Figure 7. The survival beyond 1 year was modeled, using a logarithmic survival curve assuming that the death rate remained constant.

Figure 7. Average of Survival Rates Reported in Literature for Patients Receiving Systemic Chemotherapy
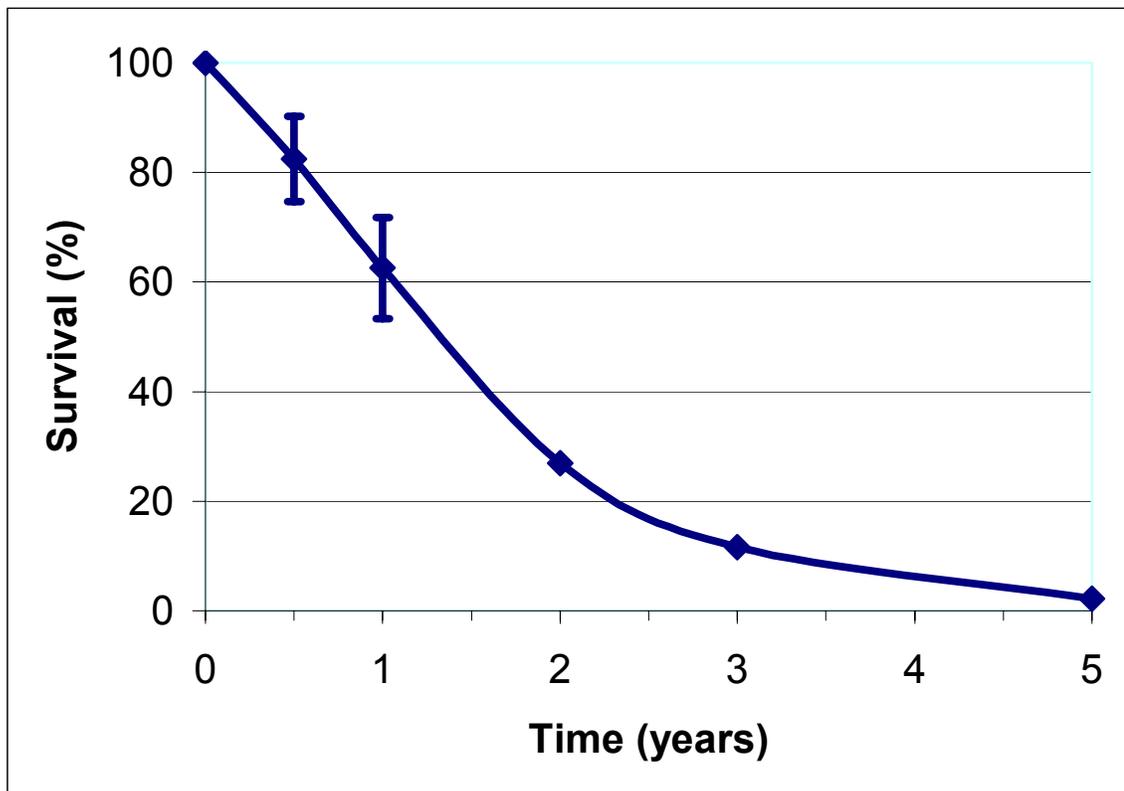
Note that the survival beyond 1 year has been modeled assuming a logarithmic survival curve. The error bars shown in the graph represent standard deviations.

4) Symptom Control Alone

Of the 6 patients who elected to receive treatment for symptoms only, survival figures could only be measured for the 3 who were not lost to follow-up. Of these three remaining patients, two died after 84 and 343 days, while one was alive at the conclusion of the study after 262 days. The survival data for this group of patients came from previously published studies(132-138). The survival curve is shown in Figure 8 below. Averages of the reported survival rates at 1, 2, 3,and 5 years are 31%, 10%, 3% and 1%, respectively. These figures are for the entire patient population reported in these studies. Subgroup survival rates were not used.

Figure 8. Survival Curve for Patients Receiving Symptom Control Alone From Literature
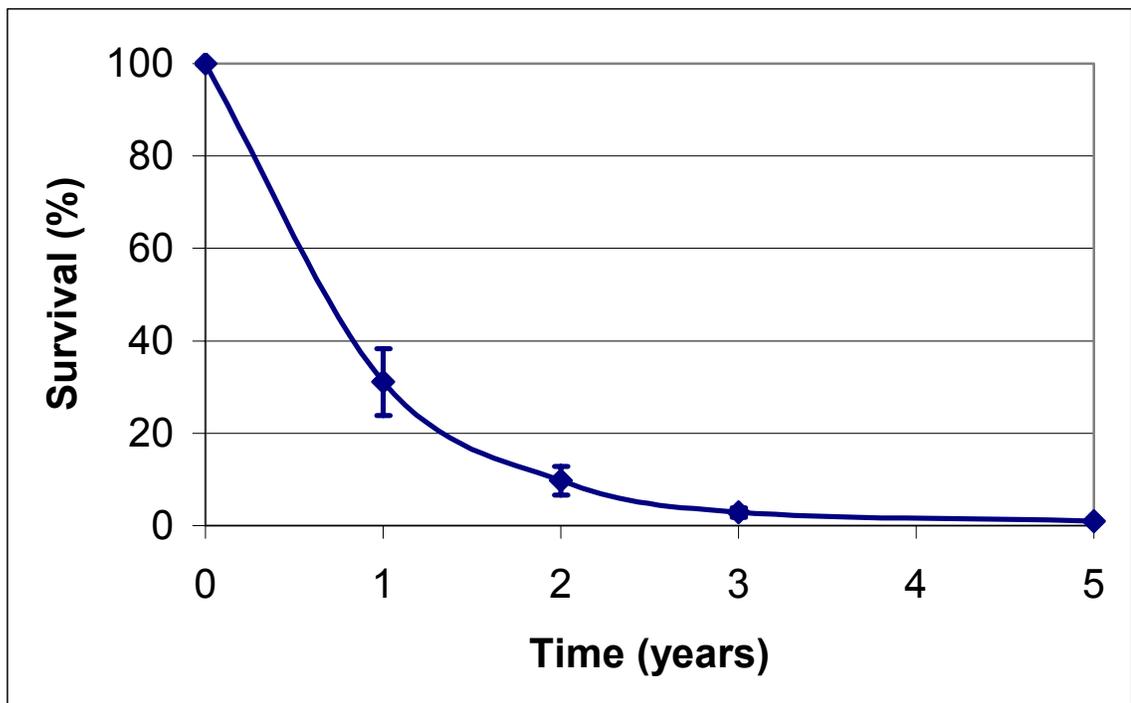
The error bars shown in the graph represent standard deviations.

D. Quality of Life

1) Hepatic Resection

The mean baseline overall utility score (prior to resection) was 0.86 when using HUI3 data and 0.77 when using HUI2 data. Table 20 shows the mean overall HUI3 and HUI2 scores measured at 2-weeks, 3-, 6-, 9-, 12-, and 18-months. Mean overall utility scores for each month were then calculated by linear interpolation of the measured values (as shown in Figure 9). The HUI2 and HUI3 scores appeared consistent, and as such, the HUI3 scores were used primarily. A sensitivity analysis was performed using the HUI2 scores in the cost-utility analysis to evaluate whether the choice of HUI instrument affected the conclusions (see below).

The mean utility scores dropped after surgery and remained below baseline for approximately 3 months before returning to baseline values or higher. The measured long-term utility appears excellent, however, this is based on only a few patients. Utility scores are not available to 18 months for all patients because one patient withdrew from the study before the 3-month HUI3 questionnaire could be administered, because 2 patients died before the 18-month questionnaire, and because the time frame of the study did not allow 18month follow-up for 2 patients who were entered later in the study period.

Table 20. Measured Health Utilities Index Scores Over Time Since Hepatic Resection

Time	n	HUI Mark III*	HUI Mark II*
Baseline	7	0.86 (0.14)	0.77 (0.18)
2 Weeks	7	0.75 (0.24)	0.76 (0.20)
3 Months	5	0.85 (0.13)	0.85 (0.10)
6 Months	4	0.96 (0.27)	0.94 (0.02)
9 Months	4	0.77 (0.42)	0.83 (0.27)
12 Months	2	0.99 (0.02)	0.97 (0.04)
18 Months	2	0.99 (0.02)	0.97 (0.04)

* Standard deviations in brackets

Figure 9. Health Utilities Index Mark II and III Scores Since Hepatic Resection
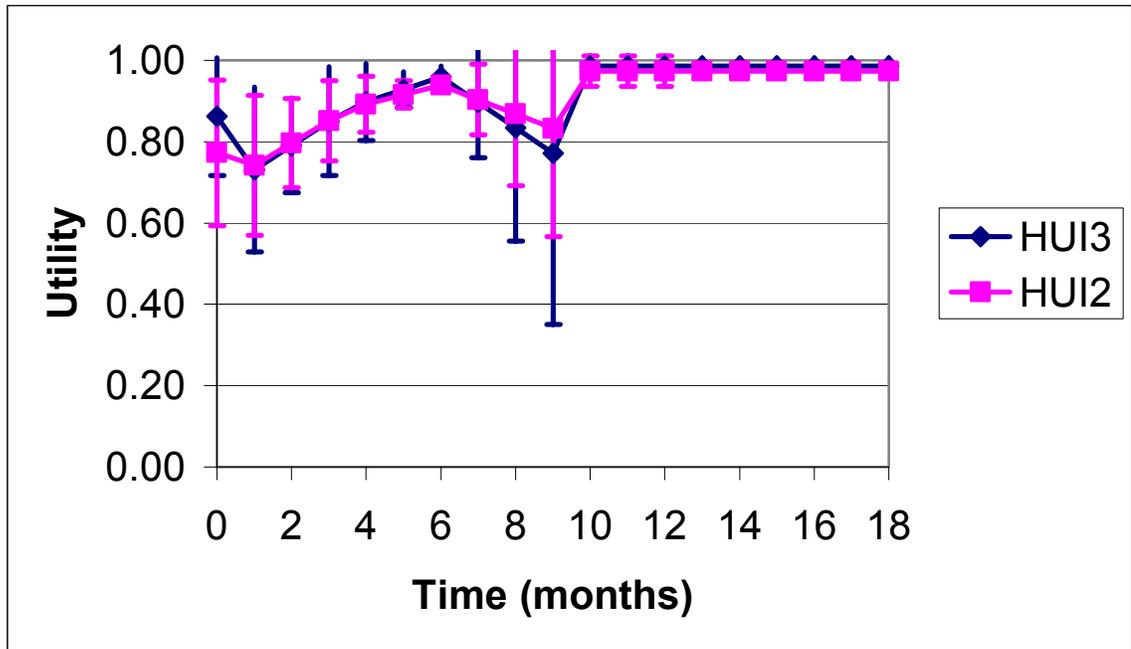
The error bars shown in the graph represent standard deviations.

B) Radiofrequency Ablation

The mean baseline overall utility score (prior to RFA) was 0.95 when using HUI3 values and 0.91 when using HUI2 values. Table 21 shows the mean overall HUI3 and HUI2 scores measured at 2-weeks, 3-, 6-, 9-, 12-, and 18-months. Again, the HUI2 and HUI3 scores appeared consistent. The mean utility scores dropped after the RFA procedure (which required a laparotomy) and remained below baseline for approximately 3 months. Figure 10 shows the scores over time since undergoing RFA. Again, not every patient had utility scores measured until 18 months post treatment because one patient was lost to follow-up shortly after undergoing RFA, one patient died before the 9-month questionnaire could be administered, and the time frame of the study did not allow it in two patients who were enrolled later in the study period.

Table 21. Measured Health Utilities Index Scores Over Time Since RFA

Time	n	HUI Mark III*	HUI Mark II*
Baseline	7	0.95 (0.06)	0.91 (0.08)
2 Weeks	6	0.65 (0.32)	0.64 (0.25)
3 Months	6	0.88 (0.17)	0.91 (0.07)
6 Months	6	0.75 (0.28)	0.81 (0.15)
9 Months	5	0.84 (0.16)	0.88 (0.09)
12 Months	4	0.87 (0.15)	0.88 (0.08)
18 Months	3	0.71 (0.25)	0.79 (0.16)

* Standard deviations in brackets

Figure 10. Health Utilities Index Mark II and III Scores Since RFA
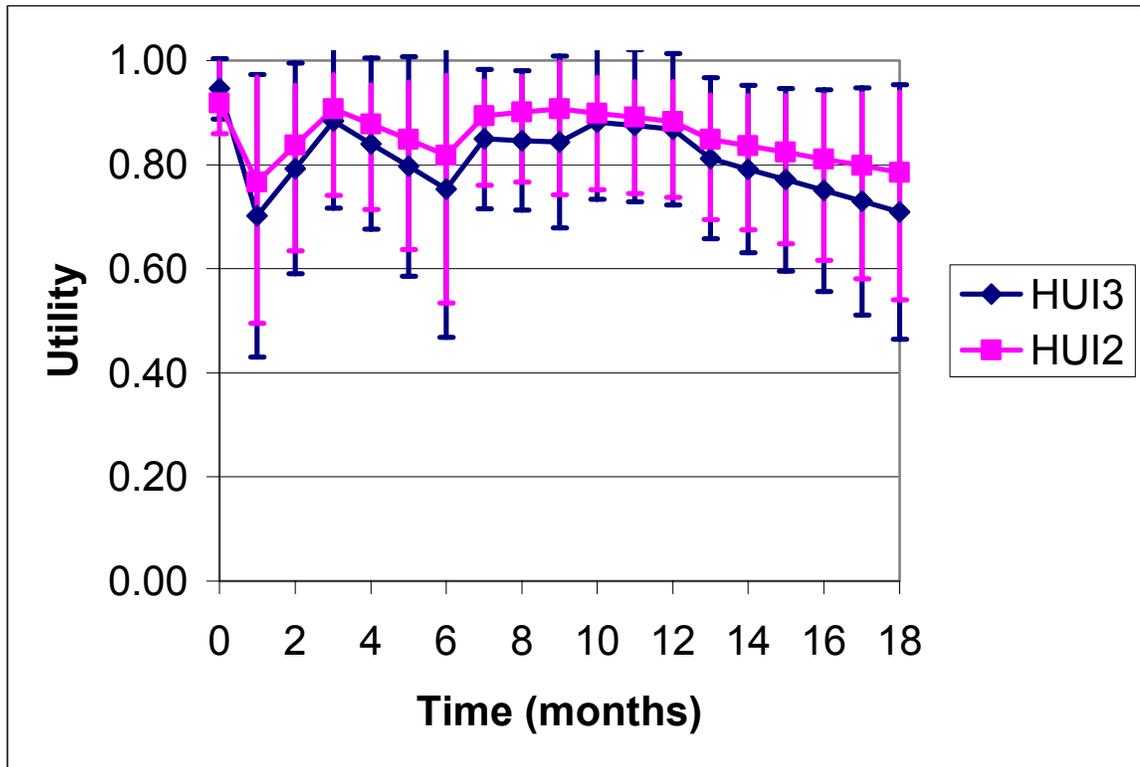
The error bars shown in the graph represent standard deviations.

C) Systemic Chemotherapy

The mean baseline overall utility score (prior to treatment) was 0.81 when using HUI3 data and 0.83 when using HUI2 data. Table 22 shows the mean overall HUI3 and HUI2 scores measured at 2-weeks, 3-, 6-, 9-, 12-, and 18-months. Again, the HUI2 and HUI3 scores appeared consistent. The utility scores did not appear to be quite as high in the patients who received chemotherapy as the primary treatment modality as in the patients who underwent hepatic resection or radiofrequency ablation. The mean utility scores dropped towards the end of the follow-up period, possibly as a result of disease progression. Figure 11 shows the scores over time since beginning chemotherapy. Again, not every patient had utility scores measured up to 18 months post treatment because

three patients were lost to follow-up (after 6 months for two patients and after 1 month for one patient), there were 9 deaths in the study period, and the time frame of the study may not have allowed it in some cases.

Table 22. Measured Health Utilities Index Scores Over Time Since Starting Chemotherapy

Time	n	HUI Mark III*	HUI Mark II*
Baseline	20	0.81 (0.24)	0.83 (0.16)
2 Weeks	19	0.78 (0.25)	0.81 (0.18)
3 Months	14	0.85 (0.17)	0.88 (0.09)
6 Months	12	0.89 (0.15)	0.91 (0.08)
9 Months	7	0.83 (0.17)	0.87 (0.08)
12 Months	6	0.89 (0.14)	0.91 (0.06)
18 Months	2	0.66 (0.36)	0.79 (0.14)

* Standard deviations in brackets

Figure 11. Health Utilities Index Mark II and III Scores Since Starting Chemotherapy
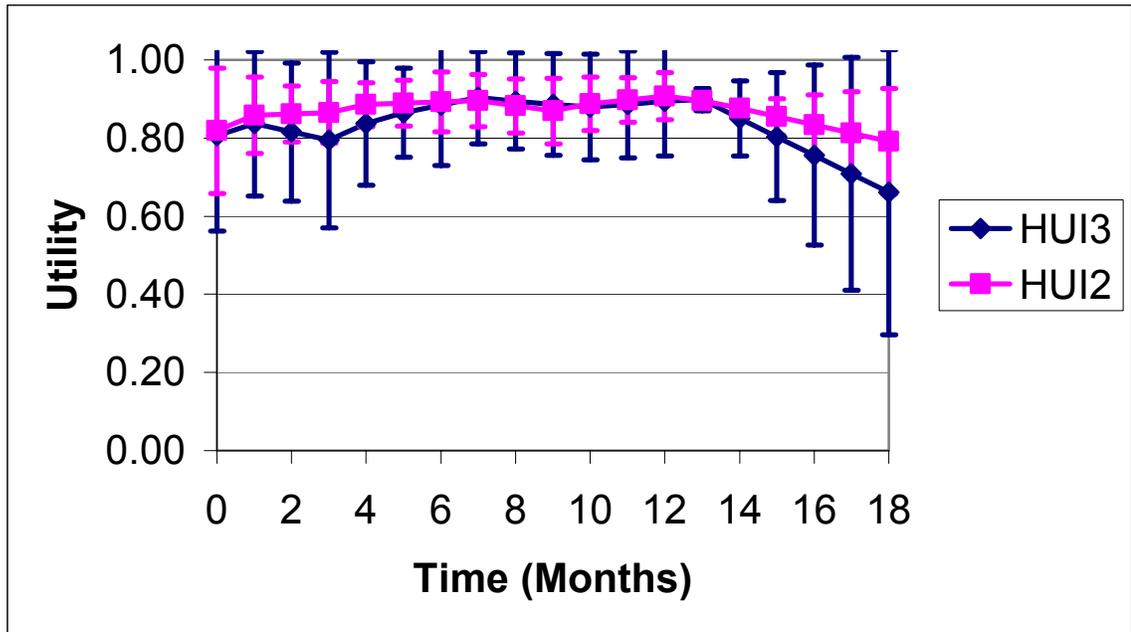
The error bars shown in the graph represent standard deviations.

D) Symptom Control Alone

The mean baseline overall utility score (upon enrolment into the study) was 0.80 when using HUI3 scores and 0.88 when using HUI2 scores. Table 23 shows the mean overall HUI3 and HUI2 scores measured at 2-weeks, 3-, and 6-months. Again, the HUI2 and HUI3 scores appeared consistent. The utility scores appeared to be quite high, although patient numbers were low. The longest follow-up in this group was 6 months. This is because one patient withdrew from the study before the 6-month questionnaire could be administered, two patients were lost to follow-up (one at 6 months and one at 1

month), two patients died during the study period, and one patient could only be followed

to the 6-month questionnaire because of the time frame of the study period.

Table 23.   Measured Health Utilities Index Scores Since Enrolment in Symptom Control
Arm

Time	n	HUI Mark III*	HUI Mark II*
Baseline	6	0.80 (0.20)	0.88 (0.10)
2 Weeks	5	0.93 (0.07)	0.94 (0.05)
3 Months	4	0.97(0.03)	0.96 (0.03)
6 Months	3	0.98 (0.02)	0.97 (0.03)

 * Standard deviations in brackets

Figure 12. Health Utilities Index Mark II and III Scores Since Enrolment in Symptom
Control Arm
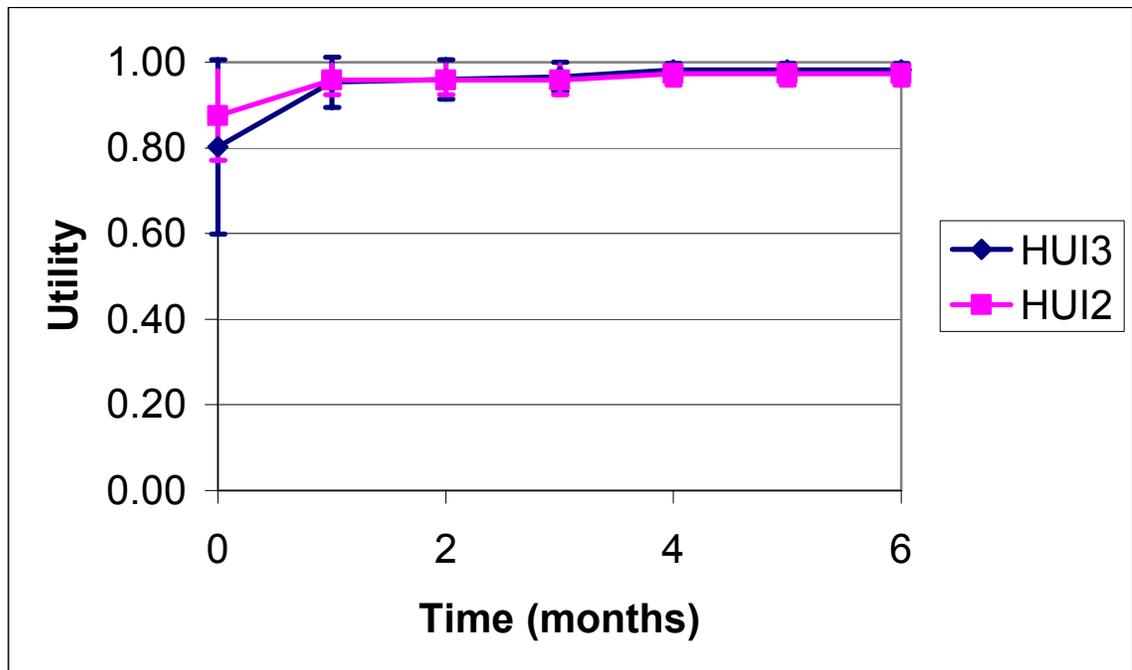
The error bars shown in the graph represent standard deviations.

5) Health Utilities Index Mark III Scores According to Treatment Received

Figure 13 shows the HUI3 scores for all treatments. Hepatic Resection seems to offer the highest long-term utility of the available treatments for liver metastases, however, this should be interpreted with caution. The number of patients involved is very low, and firm conclusions cannot be drawn.

Figure 13. Health Utilities Mark III Scores for All Treatments
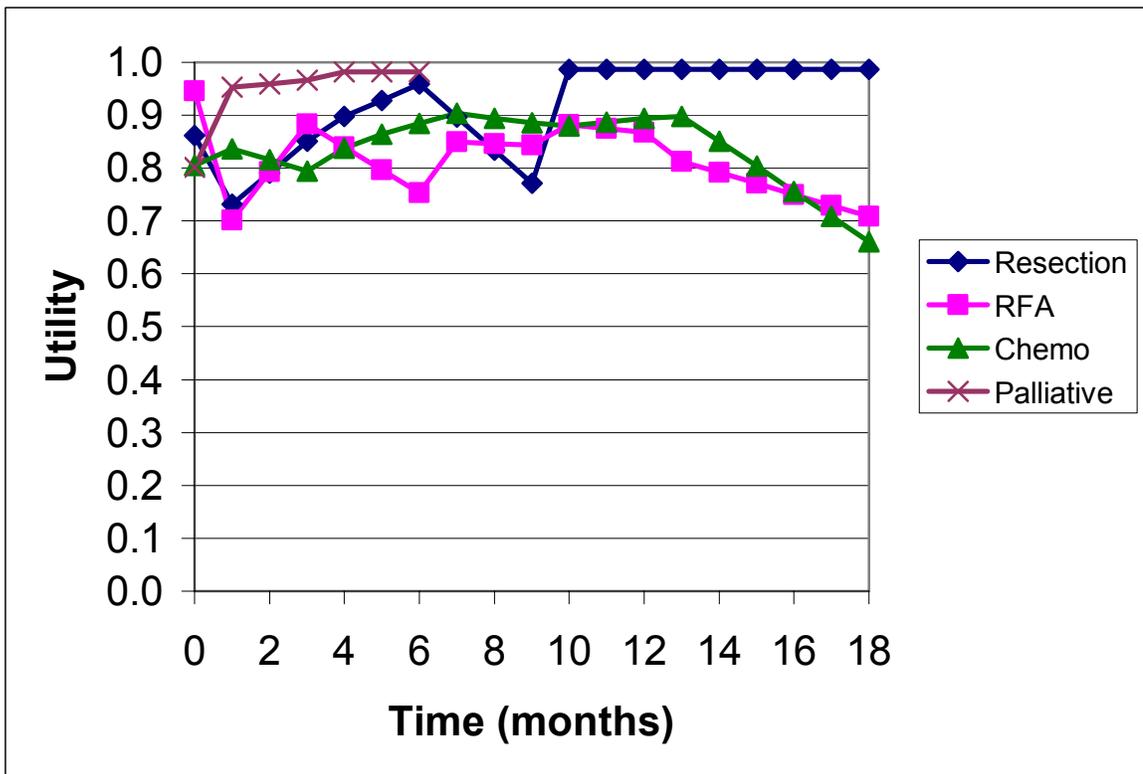
6) Health Utilities Index Mark III Single Attribute Scores

The Health Utilities Index is a multi-attribute scoring function. This tool can be used to calculate a global utility score that describes the overall health status of a patient. It also measures the status of 8 different health attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. To determine how the different treatments influenced each of these health attributes individually, the HUI3 single attribute utility scores were calculated for each patient and tracked over time. These results are shown graphically in Figures 14 to 21.

Figure 14. HUI3 Single-Attribute Utility Scores for Vision
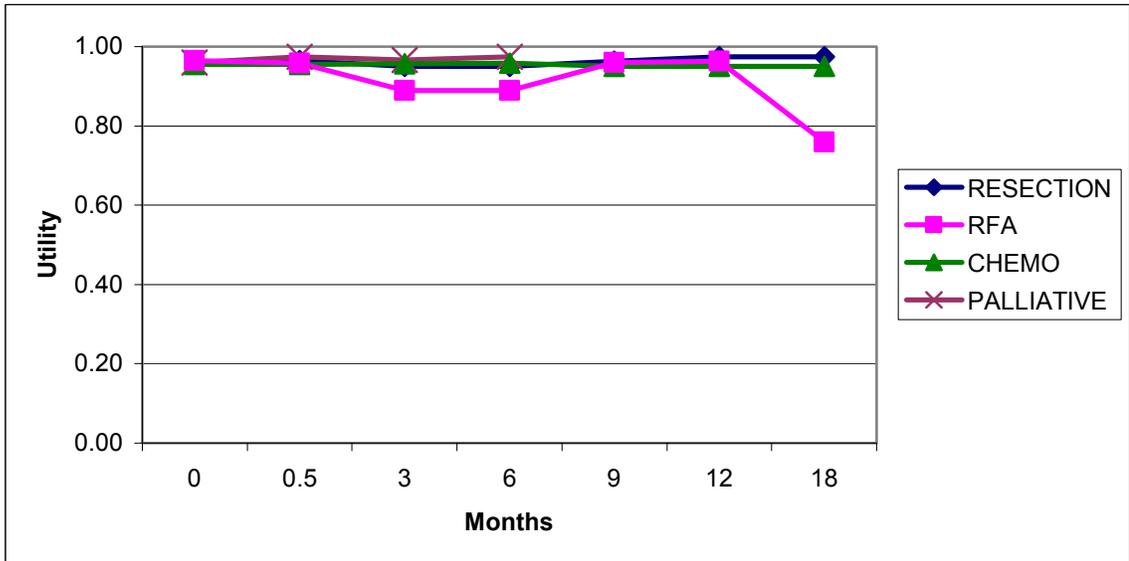
Figure 15. HUI3 Single-Attribute Utility Scores for Hearing
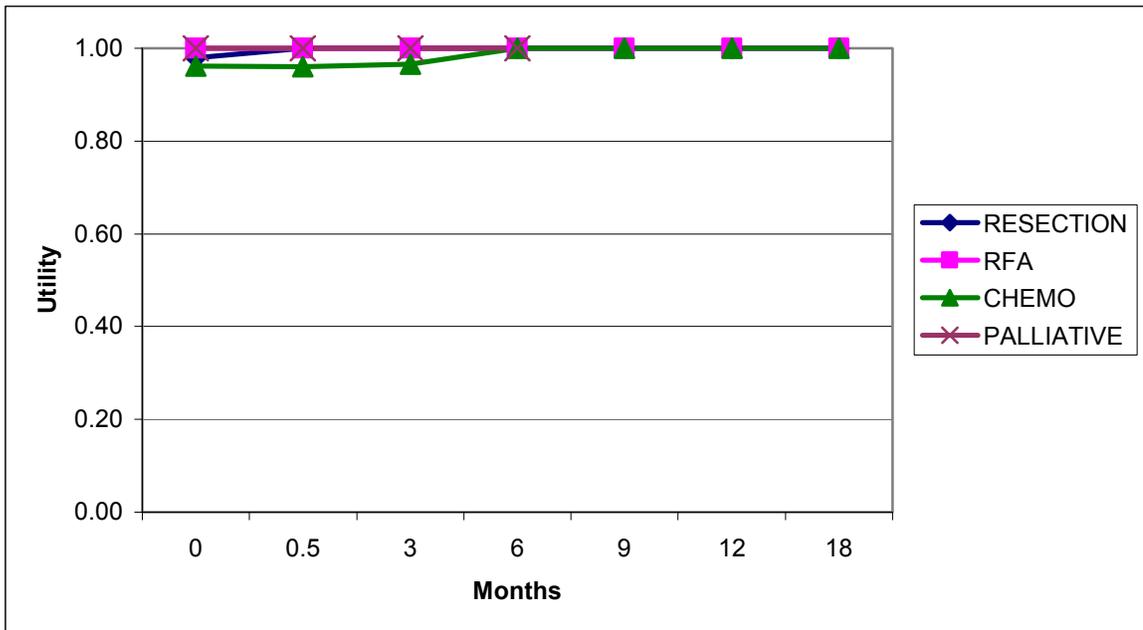
Figure 16. HUI3 Single-Attribute Utility Scores for Speech
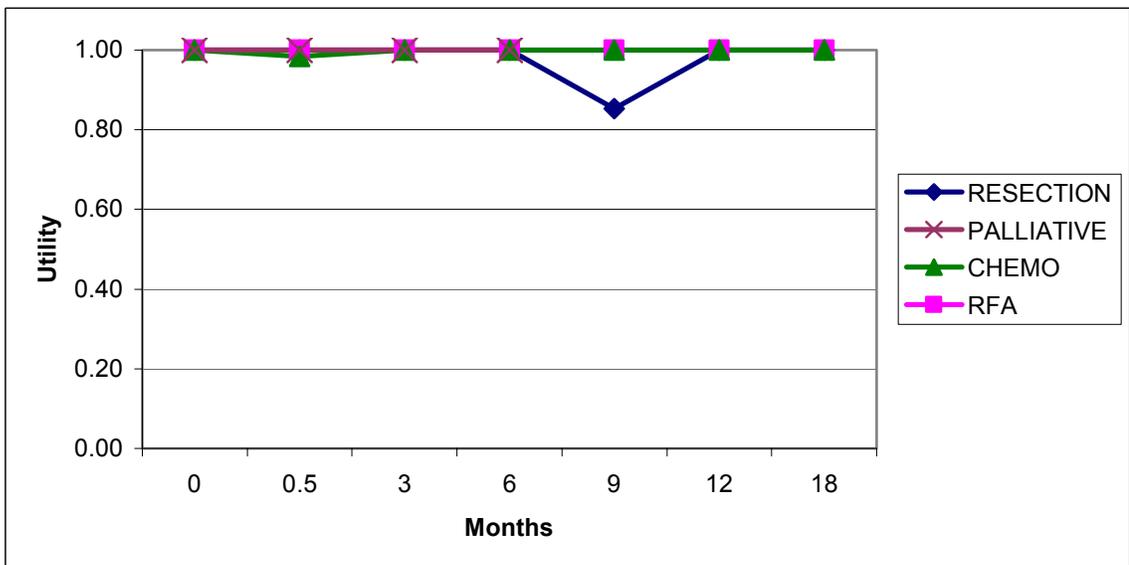
Figure 17. HUI3 Single-Attribute Utility Scores for Ambulation
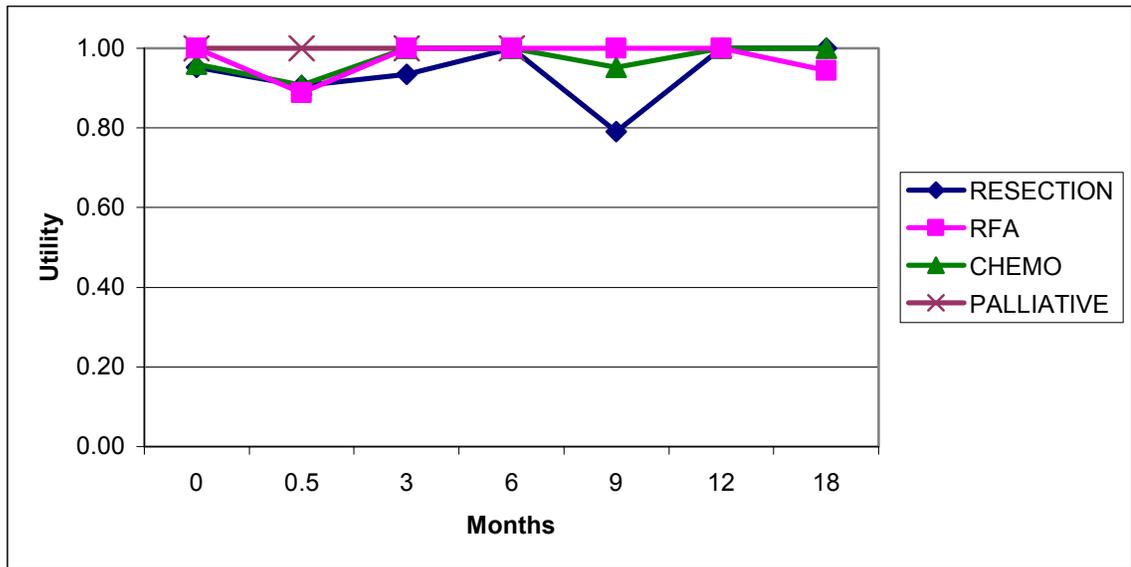
Figure 18. HUI3 Single-Attribute Utility Scores for Dexterity
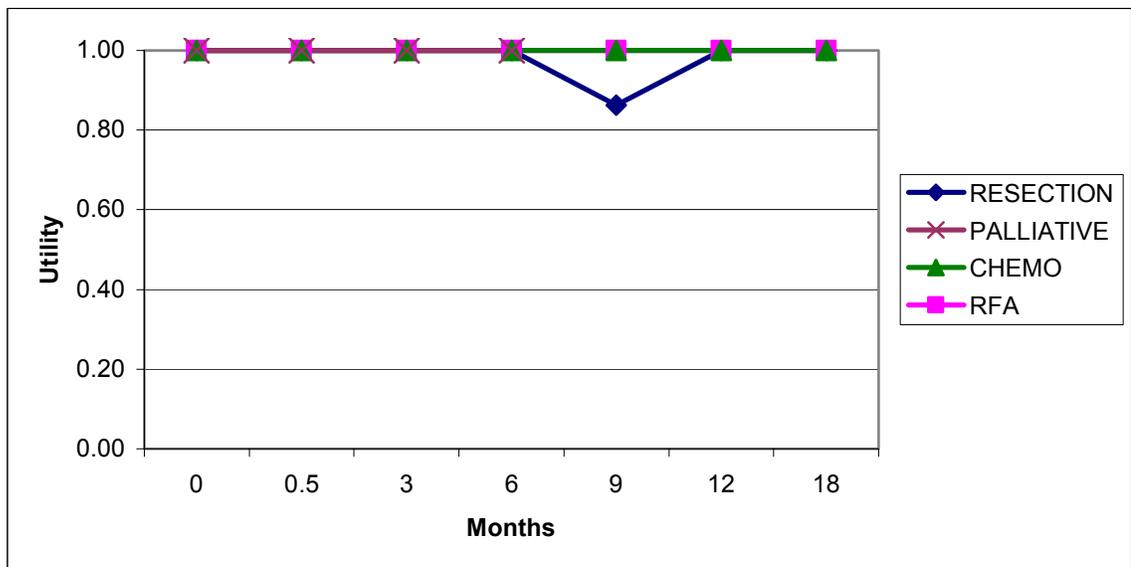
Figure 19. HUI3 Single-Attribute Utility Scores for Emotion
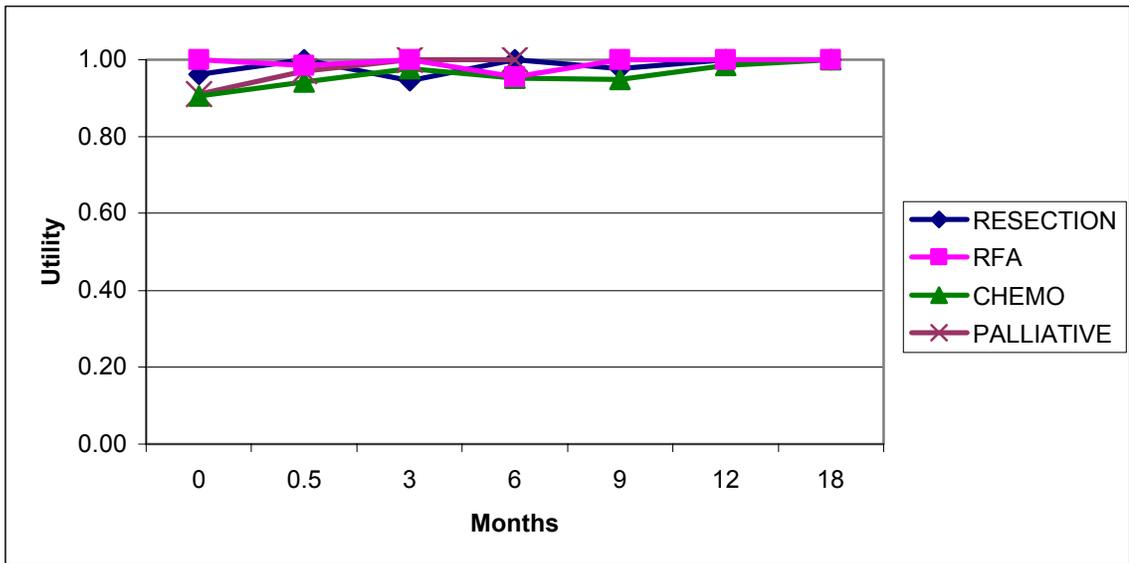
Figure 20. HUI3 Single-Attribute Utility Scores for Cognition
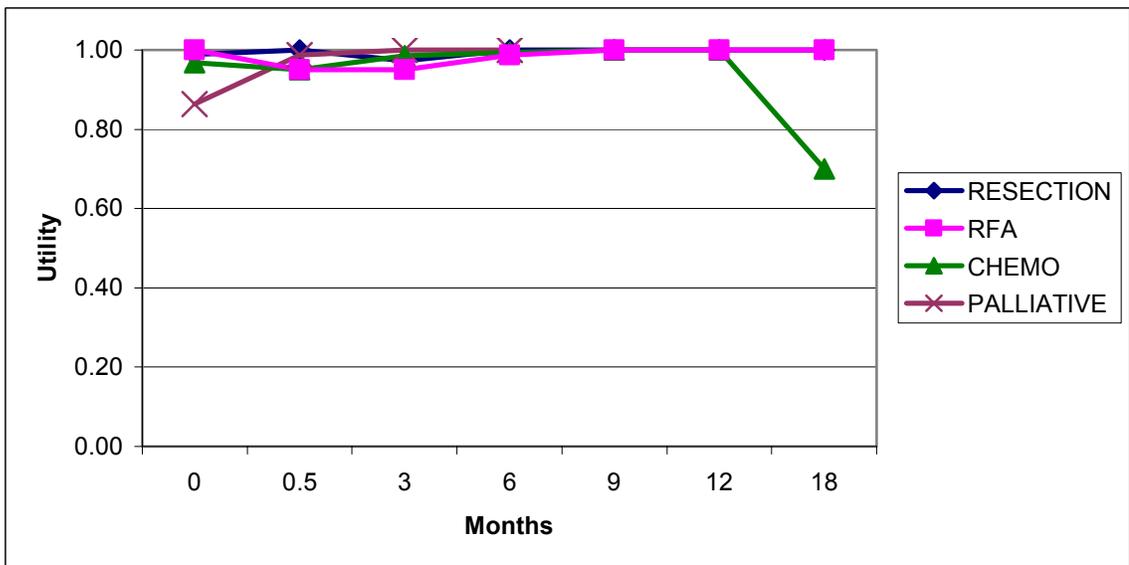
Figure 21. HUI3 Single-Attribute Utility Scores for Pain
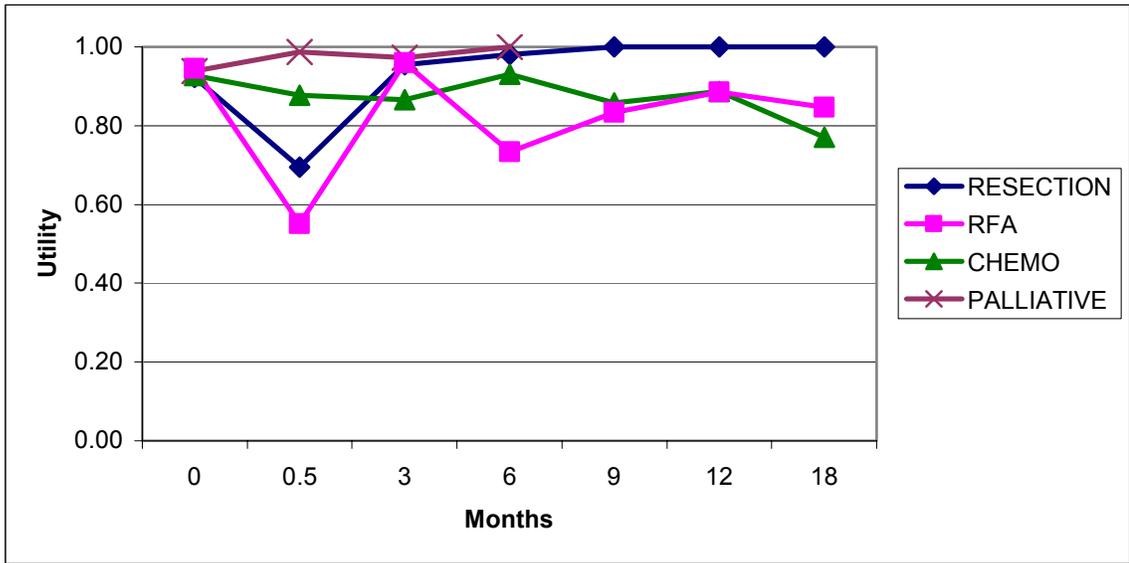
Most of the individual health attributes were quite constant over time. The attribute of pain, however, was an exception. For patients who underwent liver resection or radiofrequency ablation, pain was significant in the postoperative period. At the 2-week interview, pain scores were notably decreased. The pain scores then improved over time to near baseline, presumably as people recovered from their operations. It is this postoperative pain that seems to explain the drop in overall utility. As noted in Figures 9 and 10, the utility associated with liver resection and with RFA recovered to around baseline levels after a few months, and remained relatively high thereafter.

7) Utility Scores According to Disease Recurrence

We wanted to examine whether the presence of recurrent disease in the patients who underwent hepatic resection or RFA influenced their quality of life. Figure 22 shows that although patients with disease recurrence tended to have slightly lower utility scores after about 7 months from treatment, the difference was not significant ($p = 0.90$; repeated measures ANOVA). This is likely because the sample size was small and the variability in the scores was quite high. It would be expected that with a larger sample such differences would become apparent.

Figure 22. Health Utilities Mark III Scores Between Patients With and Without Disease Recurrence
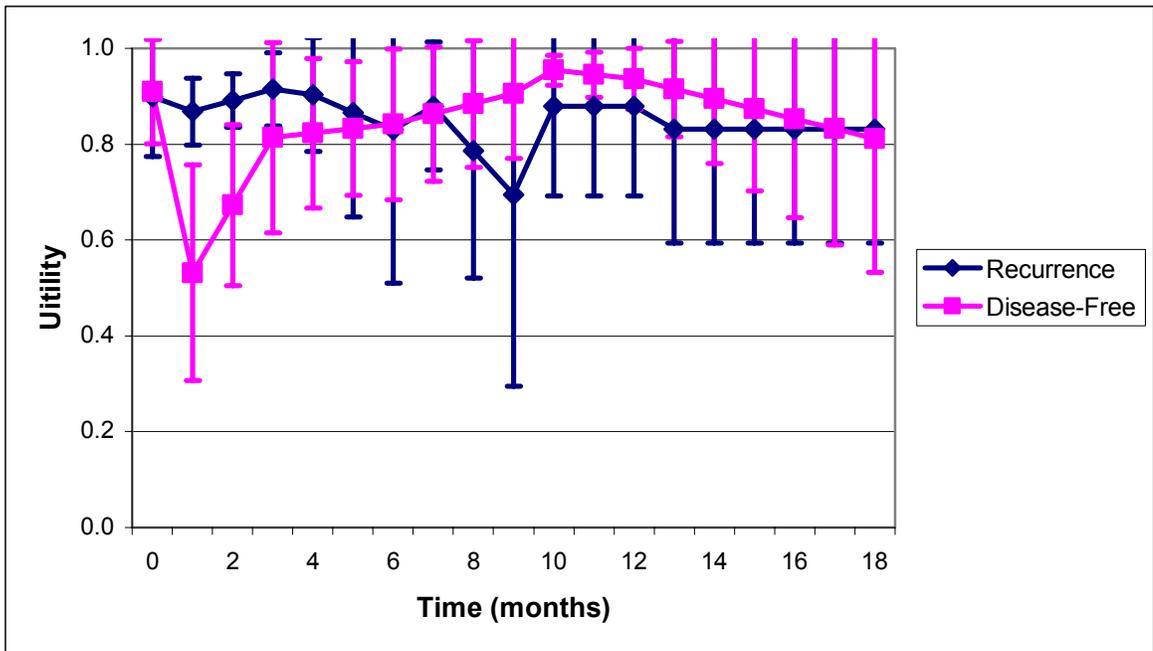
The error bars shown in the graph represent standard deviations.

8) Utility Scores for Surgical Patients According to Addition of Chemotherapy

We also wanted to examine whether the addition of chemotherapy would influence the QOL of patients who had surgery for their liver tumours. Figure 23 shows that there was no significant difference in QOL between patients undergoing hepatic resection or RFA who did or did not have chemotherapy ($p = 0.90$; repeated measures ANOVA). Again, it must be kept in mind that the sample size was small and the variability in the scores was quite high.

Figure 23. Utility Scores for Surgical Patients According to Addition of Chemotherapy
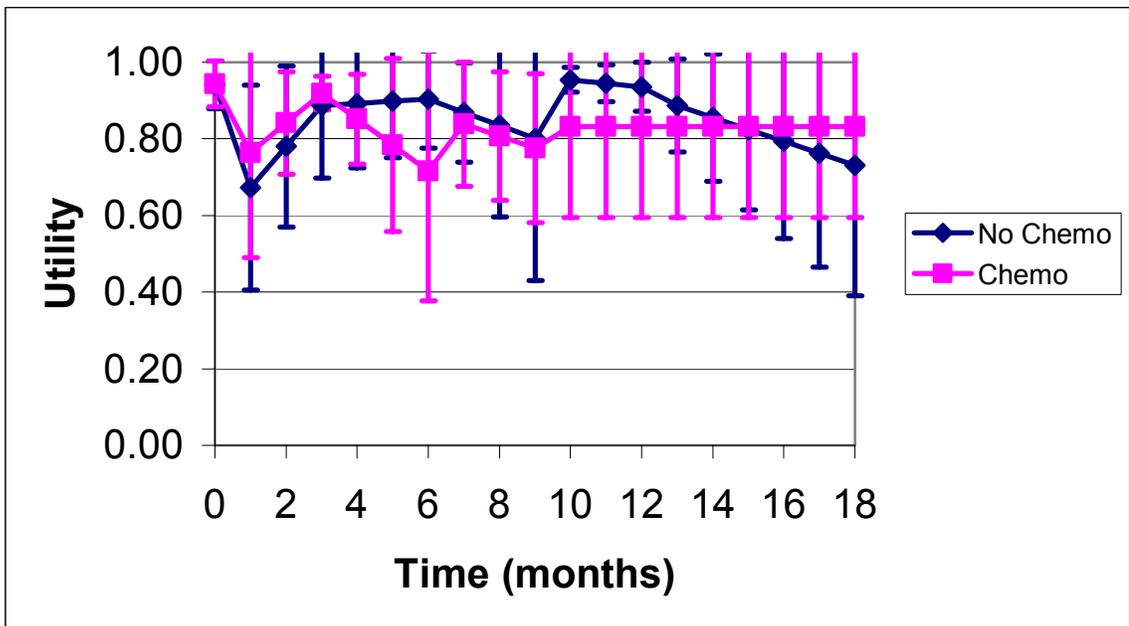
E. Economic Data

1) Initial Medical Costs of Treatment

The costs incurred at the start of a patient's treatment included the cost of the initial diagnostic work-up and for patients who underwent liver resection or radiofrequency ablation, the costs of the treatments themselves. Thus, patients who had liver resections or RFA had significant medical costs at the outset of their treatments because of the costs of their surgeries. Patients who received systemic chemotherapy or symptom control alone had much lower initial medical costs.

For patients undergoing liver resection or RFA, these initial costs are summarized in Table 24 and Figure 24. All patients who underwent RFA (those who underwent RFA with and without hepatic resection) were grouped together. The costs of the initial diagnostic work-up (mainly radiological investigations) and the hospitalization for the surgery are included as "initial costs". The surgeon's fees and the anaesthesiologists' fees were included in the OR costs, while the radiologists' fees were included in the costs of the diagnostic imaging.

Table 24. Initial Hospital Costs of Treatment for Patients Undergoing Liver Resection and RFA

Category	Resection		RFA		p Value*
	Average	SD	Average	SD	
LOS[†]	7.3	2.0	6.4	1.7	0.60
Nursing	$1,860.86	$676.50	$1,608.77	$456.52	0.66
Lab Fees	$171.83	$36.61	$128.30	$72.26	0.23
Imaging	$324.37	$49.46	$485.81	$134.99	0.09
Medications	$115.71	$69.57	$86.48	$67.65	0.34
Other	$267.28	$118.07	$156.76	$81.43	< 0.05
OR Costs	$2,907.72	$517.52	$3,131.98	$907.65	0.66
Overhead	$424.74	$134.12	$370.56	$110.91	0.66
Total	**$6,064.61**	**$1,220.75**	**$5,971.23**	**$1,142.73**	**0.66**

* Measured with Mann-Whitney U test
† Length of Stay in hospital (measured in days)

Figure 24. Initial Hospital Costs of Treatment for Patients Undergoing Liver Resection and RFA
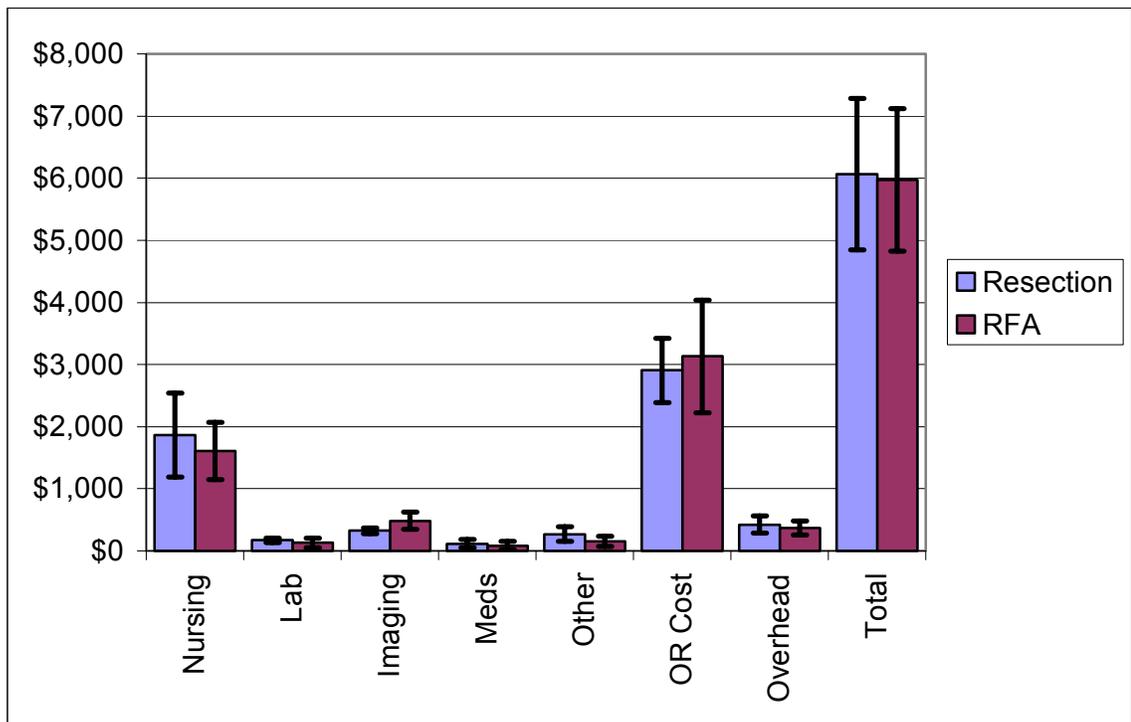
The error bars shown in the graph represent standard deviations.

The costs of treatment for both hepatic resection and for RFA were similar with no significant differences found, with the exception of the costs grouped as "other". These costs consisted mainly of costs associated with physiotherapy, occupational therapy, and the pre-operative anaesthesia clinics. The major portion of the cost for both procedures resulted from the operative procedure. The costs of the hospital stay and the diagnostic work-up made up a smaller proportion of the costs, and again were similar between treatment groups. The lengths of hospital stay associated with each treatment were also similar at 7.3 days and 6.4 days for hepatic resection and RFA, respectively. The difference was not statistically significant. The costs associated with surgery for these two groups of patients are shown below in Table 25 and Figure 25. There were no significant differences in terms of length of operation and cost.

Table 25. Cost of Surgery for Patients Undergoing Hepatic Resection and RFA

Category	Resection		RFA		p Value*
	Average	SD	Average	SD	
OR Time (min)	291	77	279	61	0.70
OR Staffing	$477.68	$126.26	$457.54	$99.90	0.70
Supply Costs	$549.98	$181.89	$1,107.10	$833.15	0.14
PARR Costs[†]	$58.96	$21.91	$53.30	$15.49	0.75
Overhead	$179.29	$40.62	$304.25	$235.96	0.28
MD Fees[‡]	$1,641.81	$324.23	$1,553.80	$211.71	0.48
Total	$2,907.72	$517.52	$3,131.98	$907.75	0.85

* measured with Mann-Whitney U test
† Post Anaesthesia Recovery Room Costs
‡ MD Fees include the fees paid to the surgeons and to the anaesthetists

Figure 25. Cost of Surgery for Patients Undergoing Hepatic Resection and RFA
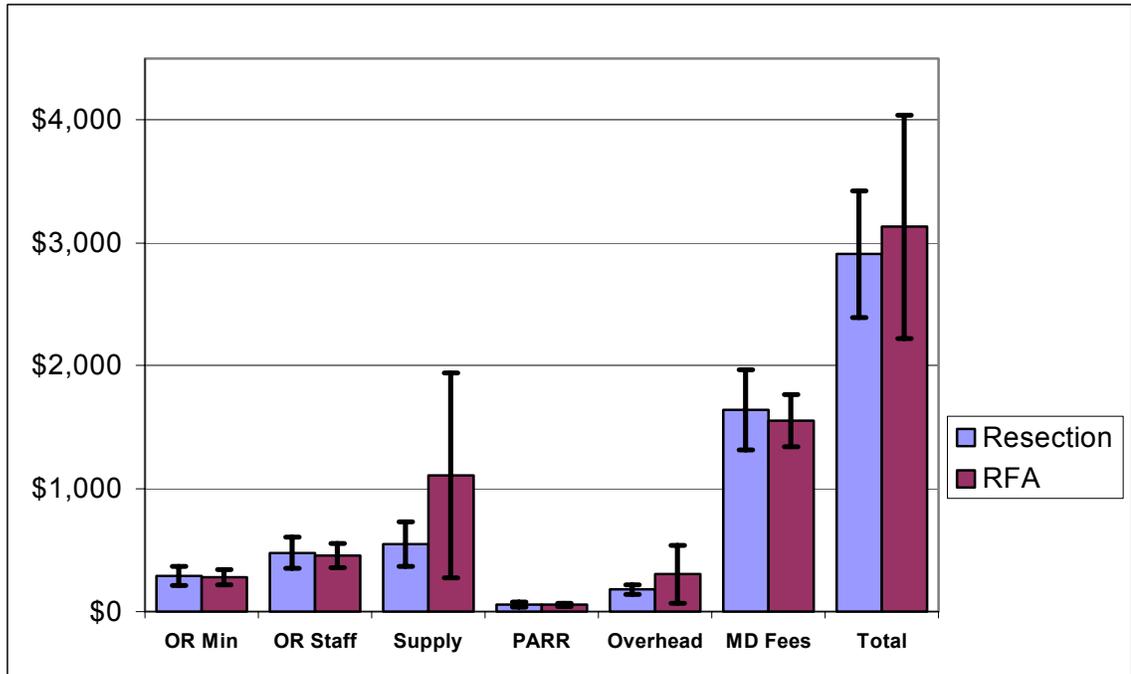
The error bars shown in the graph represent standard deviations.

The average initial treatment costs for patients receiving systemic chemotherapy and for patients receiving symptom control alone were $439.08 and $499.77, respectively. These costs included the costs involved in establishing the diagnosis plus the cost associated with exploratory laparotomy in those patients who underwent exploration only to have the procedure abandoned because of the intra-operative findings. There were three patients who went on to receive systemic chemotherapy as the primary modality who had an initial exploratory laparotomy, but none in the group who received symptom control alone.

2) Outpatient Medical Costs

Patients who received chemotherapy or supportive care were treated primarily in the outpatient setting. There were 15 patients of the 20 who received systemic chemotherapy as the primary treatment modality for whom the costs of outpatient treatment could be calculated. For the remaining 5 patients there was not enough information in the available charts, as they received their treatment at other facilities where we did not have approval from ethics to access the charts. Some patients did switch chemotherapeutic regimens throughout the study period and this was accounted for in the cost analysis (although not shown in Table 26 to prevent the table from becoming too cluttered).

Table 26. Chemotherapy Costs for Patients Receiving Chemotherapy as the Primary Treatment

Initial Regimen	Cost/Cycle	No. Cycles	Chemo Cost	No. Visits	Physician Costs	Overhead	Total Cost	No. Months	Cost/ Month
Oxaliplatin, 5-FU/LV	$1,096.78	18	25225.94	34	$1,499.35	$4,409.67	$31,134.96	12	2594.58
Capecitabine	$1,033.34	5	5166.7	16	$760.45	$977.98	$6,905.13	5	1381.03
Irinotecan, 5-FU/LV	$1,096.78	15	16451.7	20	$924.65	$2,867.10	$20,243.45	18	1124.64
5-FU/LV	$254.00	5	3270	25	$1,129.90	$725.98	$5,125.88	13	394.30
Irinotecan, 5-FU/LV	$1,096.78	$10.00	23032.38	20	$924.65	$3,952.91	$27,909.94	18	1550.55
Irinotecan, 5-FU/LV	$1,096.78	10	25225.94	25	$1,129.90	$4,348.71	$30,704.55	17	1806.15
Gleevec	$3,264.00	14	45696	11	$555.20	$7,631.45	$53,882.65	14	3848.76
Capecitabine	$1,033.34	11	11366.74	17	$801.50	$2,007.76	$14,176.00	9	1575.11
Irinotecan, 5-FU/LV	$1,096.78	18	26322.72	29	$1,190.45	$4,539.67	$32,052.84	16	2003.30
Irinotecan, 5-FU/LV	$1,096.78	10	10967.8	4	$164.20	$1,836.78	$12,968.78	7	1852.68
Irinotecan, 5-FU/LV	$1,096.78	8	8774.24	11	$555.20	$1,539.36	$10,868.80	4	2717.20
Irinotecan, 5-FU/LV	$1,096.78	14	15354.92	18	$842.55	$2,672.58	$18,870.05	10	1887.01
Irinotecan, 5-FU/LV	$1,096.78	8	8774.24	6	$349.95	$1,505.49	$10,629.68	5	2125.97
Irinotecan, 5-FU/LV	$1,096.78	14	21935.6	15	$719.40	$3,738.08	$26,393.08	11	2399.37
Irinotecan, 5-FU/LV	$1,096.78	16	17548.48	27	$1,212.00	$3,095.48	$21,855.96	9	2428.44
Average	**$1,176.62**	**11.7**	**$17674.23**	**18.5**	**$850.62**	**$3,056.60**	**$21,581.45**	**11.2**	**$1979.27**
SD	**$616.42**	**4.2**	**$10806.52**	**8.5**	**$354.37**	**$1,795.43**	**$12,676.86**	**4.8**	**$793.75**

There were patients in the other treatment groups who also received chemotherapy at the discretion of their treating physicians. Some patients may have visited the medical oncologists, but not received chemotherapy. The costs of these visits were captured in the cost data as well. A summary of the costs attributed to chemotherapy for patients receiving hepatic resection, RFA, and symptom control is presented in Table 27 below.

The cost of receiving chemotherapy for all patients was entered into the cost-utility model as a function of time. For instance, patients who underwent hepatic resection and also received chemotherapy tended to do so several months after undergoing surgery. The costs were represented in the model according to the time at which they were observed to occur in the patient sample of the study.

Table 27. Costs for Chemotherapy in Patients Undergoing Other Primary Treatment Modalities

Treatment	No. Receiving Chemo	Months Until Start	Months until Stop	Average Total Cost	No. Months	Cost per Month*
Resection	3 of 7	9.7	5.0	$6,008.19	5.0	$1,003.72
RFA	3 of 7	3.7	9.3	$17,842.87	9.3	$830.89
Chemo	20 of 20	0.5	11.2	$21,581.45	11.2	$1,979.27
Palliative	2 of 6	4.0	5.3	$1,020.97	5.3	$478.22

*Cost per month refers to the cost per month for those months when chemotherapy was given. These costs were inputted into the cost-utility model only for the average period of time when patients received their chemotherapy.

3) Medical Costs Associated with Patient Follow-Up

These costs included follow-up diagnostic imaging, outpatient office visits with physicians, and costs of subsequent hospitalizations for complications of treatment or disease recurrence. Unfortunately, these costs were not measured completely. The length of study follow-up was not sufficient to capture the costs of treating disease recurrences. The available charts from St. Boniface General Hospital and CancerCare Manitoba were searched for repeat hospitalizations, and none were identified in the study period. Charts from other facilities were not available. It is possible that such hospitalizations occurred,

perhaps at other hospitals or after the study period. For patients who underwent liver resection or RFA cost data for radiological investigations were captured, but for other patients there was scant data. Noting these limitations, the average follow-up costs measured for patients who had liver resections was $59.15 per month. For patients who had RFA, the average monthly cost was $21.35. Because these costs were thought to be inaccurate and underestimates of the true follow-up costs, the costs were estimated to be $75 for the baseline analysis for all treatments. This assumption was tested in a sensitivity analysis (see below).

4) Costs Borne by Patients and Their families

Patients were given diaries to record this information, however, there were few patients for whom this information was captured and often when this information was captured, it was incomplete. The costs included costs of medications and other supplies needed by the patients, as well as costs associated with the time spent by patients and their caregivers while pursuing treatment (see Table 28). Unfortunately, these costs were not captured accurately in this study. The reasons for this are outlined in the discussion. Two of the patients who underwent hepatic resection had such costs collected for 4 months and 8 months of the total study period. Based on the limited data, their own monthly personal expenditures averaged $64.52. Three patients who underwent RFA had data available for 5 months, 11 months, and 12 months of the study period. Based on this limited information, their average monthly out-of-pocket expenses were $94.55. Six of the patients receiving systemic chemotherapy as the primary treatment had available

information, and the average monthly cost for this category was $214.68. One patient

who elected to receive symptom control alone had available cost data for this category.

The average cost was $202.15. These figures were used in the baseline analysis, but the

uncertainty in these values was explored via sensitivity analysis.

Table 28. Patient and Caregiver Expenses Associated with Each Treatment Modality

Treatment	Time Spent (hrs)	Time Cost	Medication Costs	Travel	Time Period*	Cost per Month	Average
Resection			$208.29		4	$52.07	$64.52
	25	615.75			8	$76.97	
RFA	6.75	$119.00	$40.61		5	$31.92	$94.55
	14	$246.82			11	$22.44	
	83.5	$2,056.61	$20.00	$675.00	12	$229.30	
Chemo	53.5	$1,317.71	$689.93		12	$167.30	$214.68
	42	$1,034.46	$1,086.11		4	$530.14	
	6.5	$114.60	$59.00		8	$21.70	
	44.5	$1,096.04			5	$219.21	
	42	$1,034.46	$74.00		18	$61.58	
	117	$2,881.71			10	$288.17	
Palliative	3	$73.89	$965.85	$1,212.88	6	$202.15	$202.15

* Refers to the number of months for which this cost data is available

F. Cost-Utility Analysis

Using the survival data from the literature as shown above, the utility scores

associated with each treatment, and the cost data listed above, the decision analysis

model was used to perform a cost-utility analysis comparing the available therapies for

malignant liver tumours. Costs that may have occurred beyond the timeframe of the study

were modeled. They were assumed to be the same as the costs of follow-up observed in

the study. The effects of this assumption were explored in a sensitivity analysis (below).

The inflation rate in the baseline analysis was the Health and Personal Care Component of the Consumer Price Index for the year 2001, which was 1.96% per year(167). The discount rate used in the baseline analysis was 3%(141;147). As seen in figure 26, hepatic resection was the most expensive treatment at $20,122. It also appeared to be the most effective treatment, yielding 2.51 QALY's for a cost-utility ratio of $8,027 per QALY. Radiofrequency ablation appeared to be slightly less effective, yielding 1.99 QALY's. However, RFA also appeared to be less costly, resulting in a cost-utility ratio of $7,965 per QALY. Thus, the cost-utilities of liver resection and of radiofrequency ablation appeared similar. Systemic chemotherapy yielded the highest cost-utility ratio at $12,751 per QALY. Symptom Control alone had the best cost-utility ratio at $4,788 per QALY, but was the least effective treatment with an average gain of 0.82 QALY's.

Figure 26. Cost-Utility Ratios of Treatments for Malignant Liver Tumours Using HUI3 Data

	Total Cost	Effect	C/E Ratio
Resection	$20,121.60	2.5066 QALY's	8,027.44 $/QALY
RFA	$15,844.50	1.9893 QALY's	7,964.73 $/QALY
Chemotherapy	$15,069.32	1.1818 QALY's	12,750.98 $/QALY
Palliation	$3,899.18	0.8160 QALY's	4,778.24 $/QALY

When comparing the cost-utility of various treatments, it is important to know the overall cost-utility and also the marginal cost-utility between treatments. If the treatments

are similar in effectiveness, the marginal difference in cost-effectiveness can become a very important when deciding which treatment to offer. The marginal cost-utility ratios of the various treatments are shown in Figures 27 and 28.

Compared to symptom control alone, systemic chemotherapy yielded an additional 0.37 QALY's at a marginal cost of $11,170 for a marginal cost-utility ratio of $30,537. The next most effective treatment appeared to be RFA, with a marginal yield of 0.81 QALY's compared to chemotherapy. The marginal cost over chemotherapy was $775 resulting in a marginal cost-utility ratio of $960 per QALY. Hepatic resection had a marginal cost of $4,277 and marginal utility 0.52 QALY's compared to RFA. The marginal cost-utility ratio of hepatic resection compared to RFA was, therefore, $8,269 per QALY. When compared to systemic chemotherapy, hepatic resection yielded1.32 QALY's at an additional cost of $5,052 for a marginal cost-utility ratio of $3,814 per QALY.

The marginal cost-utilities of both hepatic resection and RFA compared to no treatment (symptom control alone) were also calculated. Compared to symptom control, hepatic resection yielded 1.69 QALY's at a marginal cost of $16,222 for a marginal cost-utility ratio of $9,596 per QALY. Compared to symptom comtrol, RFA yielded 1.17 QALY's at a marginal cost of $11, 945 for a marginal cost-utility ratio of $10,182 per QALY.

Figure 27. Marginal Cost-Utility Ratios of Treatments for Malignant Liver Tumours Using HUI3 Data

	Marginal Cost	Marginal Effect	Marginal C/E
Resection	$4,277.10	0.5173 QALY's	8,268.61 $/QALY
RFA	$775.18	0.8075 QALY's	959.95 $/QALY
Chemotherapy	$11,170.15	0.3658 QALY's	30,537.10 $/QALY
Palliation			
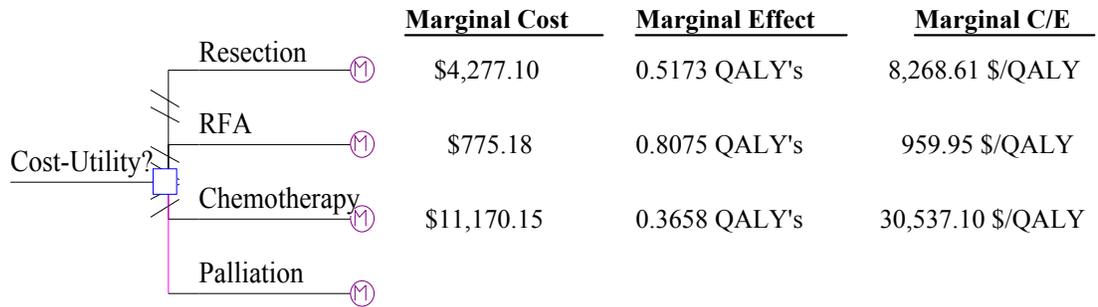
Cost-Utility?

Figure 28. Marginal Cost-Utility Ratios of Treatments for Malignant Liver Tumours Using HUI3 Data

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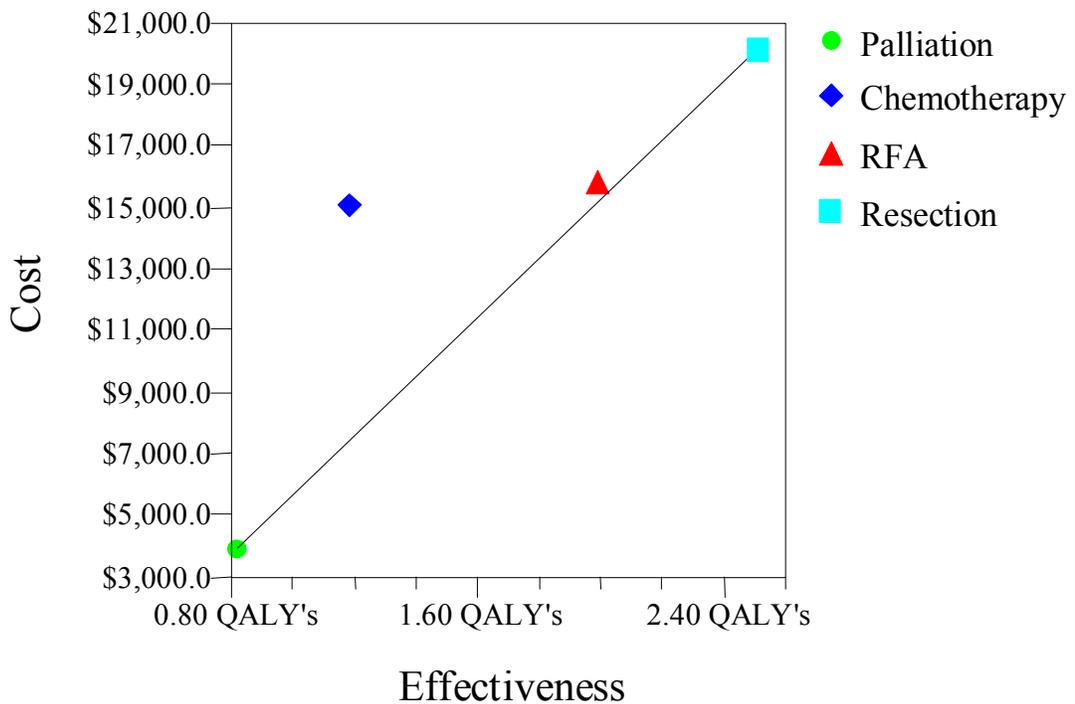
G. Sensitivity Analysis

1) Use of Health Utilities Index Mark II Scores

The utility scores obtained form the Health Utilities Index Mark III were used in the baseline analysis. The analysis was run using the Health Utilities Index Mark II scores to evaluate whether the choice of HUI instrument altered the conclusions. As shown in Figure 29, the overall results were similar. The costs remained the same and the utility scores were similar, but the utility associated with RFA was slightly greater in this case. The cost-utilities for liver resection and for RFA were close ($7,903 per QALY compared to and $7,226 per QALY, respectively).

Figure 29. Cost-Utility Ratios of Treatments for Malignant Liver Tumours Using HUI2 Data

		Total Cost	**Effect**	**C/E Ratio**
Resection	Ⓜ	$20,121.60	2.5462 QALY's	7,902.60 $/QALY
RFA	Ⓜ	$15,844.50	2.1928 QALY's	7,225.56 $/QALY
Chemotherapy	Ⓜ	$15,069.32	1.1392 QALY's	13,228.09 $/QALY
Palliation	Ⓜ	$3,899.18	0.8101 QALY's	4,812.91 $/QALY

Cost-Utility?

2) Using Unadjusted Survival Data

The analysis was also performed using survival data alone (i.e. not quality-adjusted). The results of the cost-effectiveness analysis are shown in Figure 30. Because the survival data used in the baseline analysis for RFA was similar to that of hepatic resection, the number of life-years gained was almost identical between resection and RFA. The cost-effectiveness ratio for RFA ($5,881 per LYG) was lower than that of hepatic resection ($7,507 per LYG).

Figure 30. Cost-Effectiveness Ratios of Treatments for Malignant Liver Tumours

	Total Cost	Effect	C/E Ratio
Resection	$20,121.60	2.6803 LYG	7,507.09 $/LYG
RFA	$15,844.50	2.6944 LYG	5,880.57 $/LYG
Chemotherapy	$15,069.32	1.5911 LYG	9,471.09 $/LYG
Palliation	$3,899.18	0.8346 LYG	4,671.72 $/LYG

Cost-Utility?

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3) Changes in Utility Scores

The sample size in this pilot study was small, and there were few patients on which to base the utility scores. Consequently, there may have been a significant margin of error in the results. The longer-term utility scores for hepatic resection were quite high over the last several months of the follow-up period, and they were based only on two patients who had utility scores at 18 months. The longer-term utility of RFA dropped towards the end of the study period, based on three patients who had utility scores at 18 months. Given larger numbers of patients and longer follow-up, this observed difference in long-term utility between hepatic resection and RFA may or may not have been validated. One-way sensitivity analyses were performed to explore whether uncertainty in the utility score measurements would effect the cost-utility analysis. The utilities associated with hepatic resection and with RFA were varied between a score of 0.5 and a perfect score of 1.0 for each monthly stage of the cost-utility analysis. As seen in Figures 31 and 32, the cost-utilities of the treatments were very sensitive to changes in the utility scores. When the utility associated with hepatic resection ranged from 0.5 to 1.0, the cost-utility of hepatic resection ranged from $14,199 to $7,071 per QALY. When the utility associated with RFA ranged from 0.5 to 1.0 cost-utility of RFA ranged from $11,140 to $5,548 per QALY. Hepatic resection appeared more cost-effective than RFA only when the utility was greater than approximately 0.9. On the other hand, RFA remained more cost-effective than hepatic resection until the utility for RFA dropped below approximately 0.69.

Figure 31. Cost-Utility as Utility for Hepatic Resection Changes
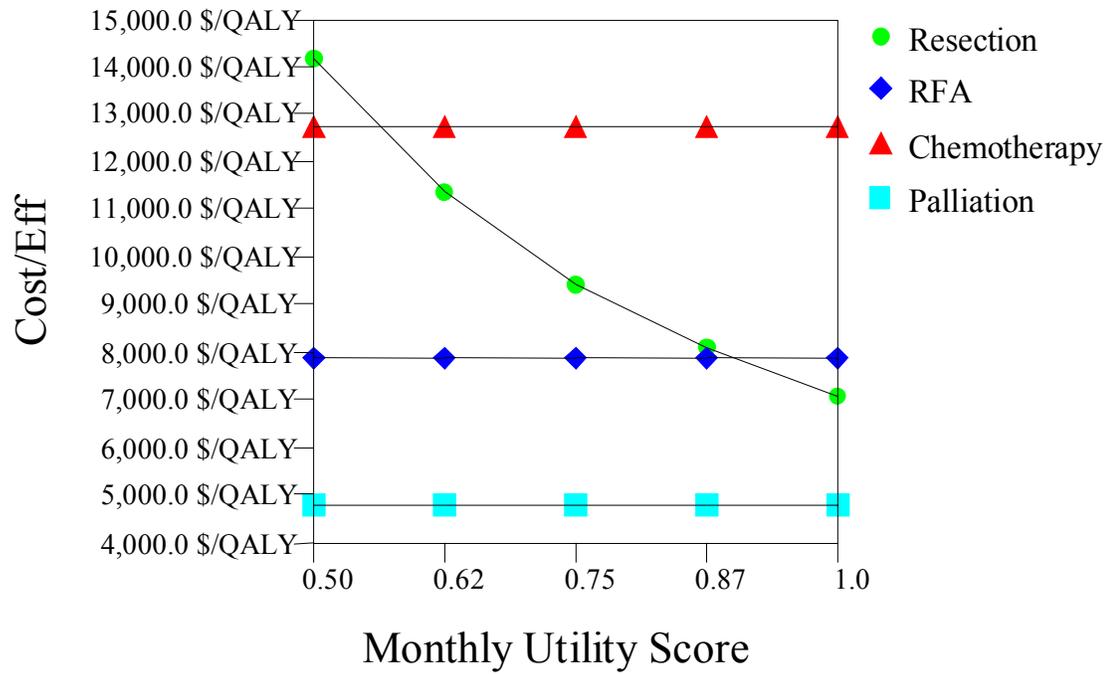
Figure 32. Cost-Utility as Utility for RFA Changes
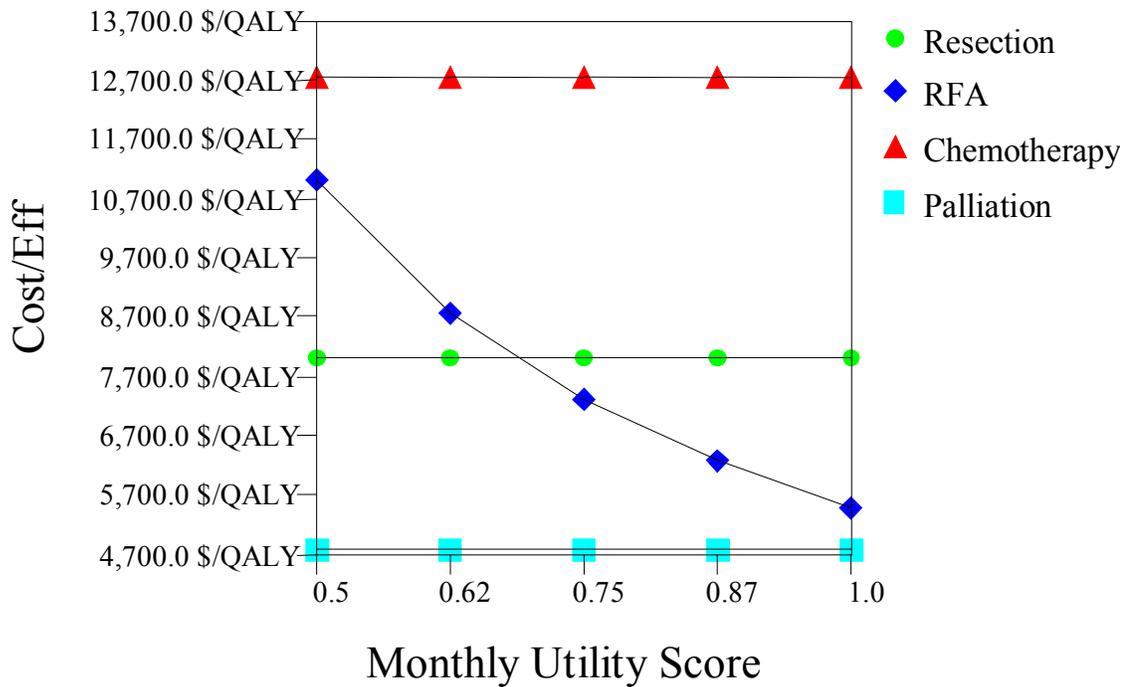
4) Changes in Survival Associated with Hepatic Resection

One of the major contributors to the cost-utility of the various treatments was the survival benefit of the particular therapy. As demonstrated above, the survival figures used in the baseline analysis assumed that the survival benefit of RFA was almost the same as that of hepatic resection. The 5-year survival figure used for patients undergoing hepatic resection in the model was 32.9%. Some recent trials have reported much higher survival benefits with better patient selection(9). Therefore, a sensitivity analysis was done to explore the effects of increased survival with hepatic resection. In the sensitivity analysis, the 5-year survival associated with hepatic resection ranged from as high as 60% to as low as 15%. When the 5-year survival with hepatic resection dropped to 17.4%, the expected utility of hepatic resection became equal to the expected utility of

RFA (with 5-year survival of 28.6%). With a range of 5-year survival after resection from 15% to 60%, the expected utility after resection ranged from a low of 1.88 QALY's to a high of 3.31 QALY's (see Figure 33).

Figure 33. Expected Utility as Survival with Resection Changes
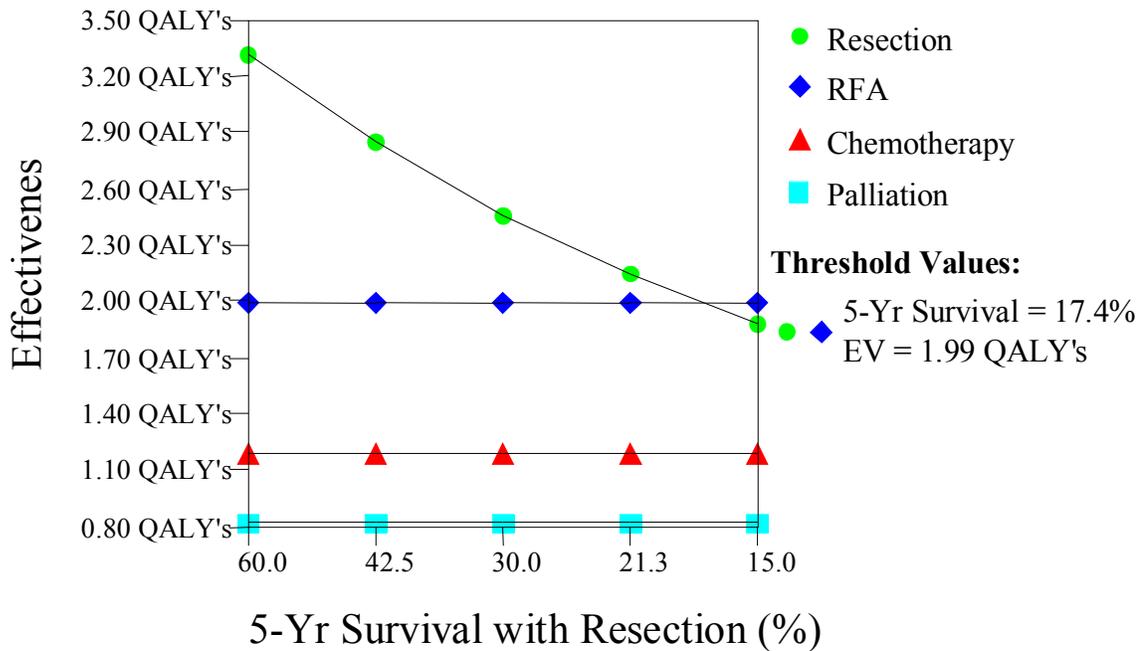
Note that the scale for survival is ordered from higher survival to lower survival. The software used for the cost-utility analysis would not allow the scale to be in increasing order because the calculation was performed based on the rate of dying from disease as the variable. Thus, the death rate is ordered from low to high, but not the survival.

As shown in Figure 34, the cost per QALY associated with hepatic resection is lower than the cost per QALY associated with RFA when the 5-year survival after hepatic resection increased is above 33%.

Figure 34. Cost-Utility as Survival with Resection Changes
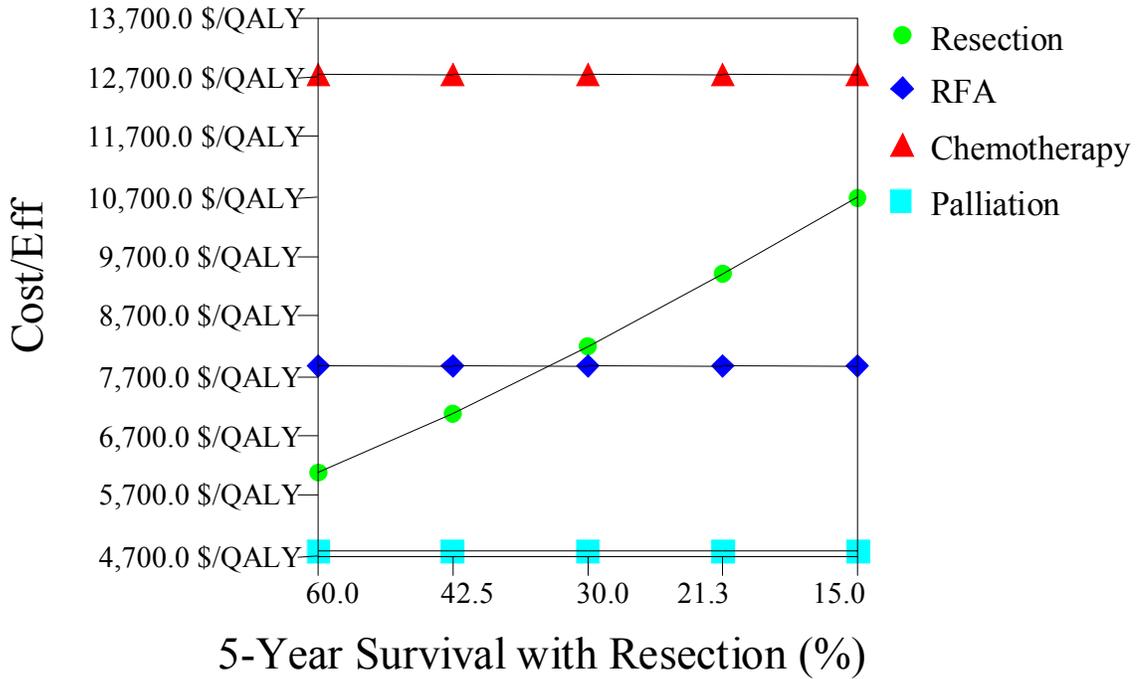
Note that the scale for survival is ordered from higher survival to lower survival. The software used for the cost-utility analysis would not allow the scale to be in increasing order because the calculation was performed based on the rate of dying from disease as the variable. Thus, the death rate is ordered from low to high, but not the survival.

5) Survival Associated with Chemotherapy

The survival benefits associated with systemic chemotherapy have significantly increased with newer regimens. As such, the effects of further increased survival were examined with a sensitivity analysis. In the baseline analysis, the survival data for chemotherapy was taken from two randomized trials studying 5-FU, leucovorin, and irinotecan with median survivals of 14.8 months and 17.4 months (11;12). The range of median survivals used in the sensitivity analysis was 12 to 30 months. As seen in Figure 35, the cost-utility of chemotherapy was sensitive to the survival benefit. However, the

cost-utility never matched that of hepatic resection or RFA even when the median survival was almost doubled to 30 months.

Figure 35. Cost-Utility as Survival with Chemotherapy Changes
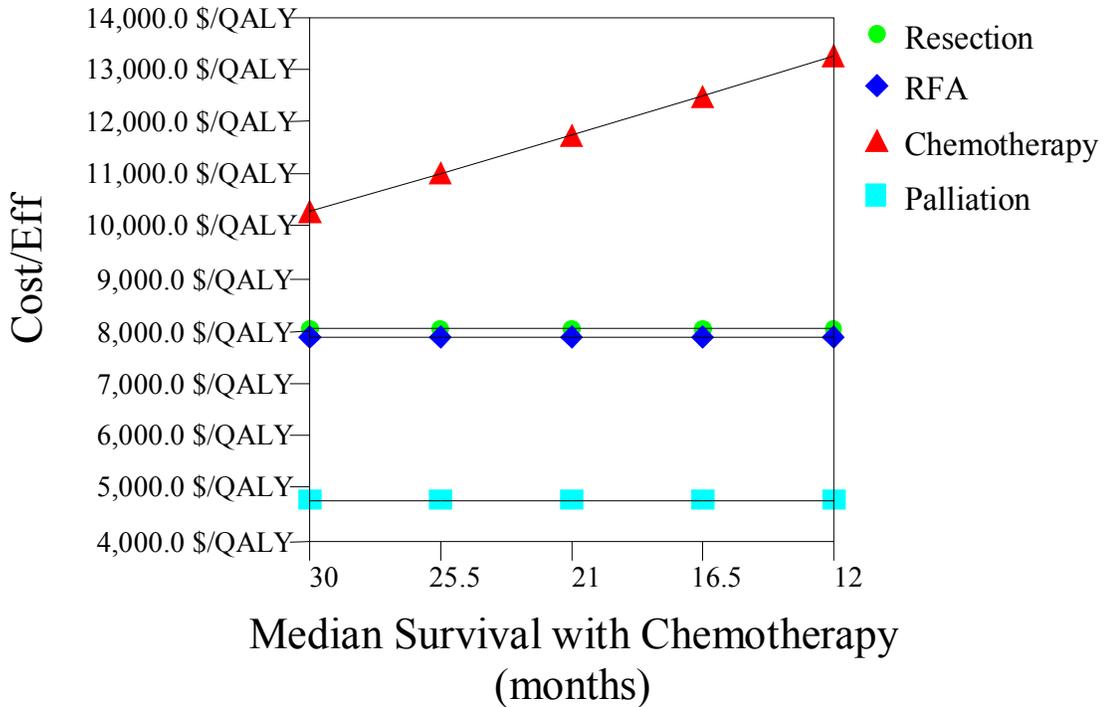
Note that the scale for survival is ordered from higher survival to lower survival. The software used for the cost-utility analysis would not allow the scale to be in increasing order because the calculation was performed based on the rate of dying from disease as the variable. Thus, the death rate is ordered from low to high, but not the survival.

6) Changes in Operative Mortality Associated with Hepatic Resection

The operative mortality for hepatic resection used in the baseline analysis was 2.9%. In some centres, the rate may be higher or lower. Therefore, a sensitivity analysis was done using a range from 0% to 10% to explore the influence of operative mortality

on the cost-utility. As seen in Figure 36, the operative mortality of hepatic resection had little influence (within a clinically reasonable range of values).

Figure 36. Cost-Utility as Operative Mortality of Hepatic Resection Changed
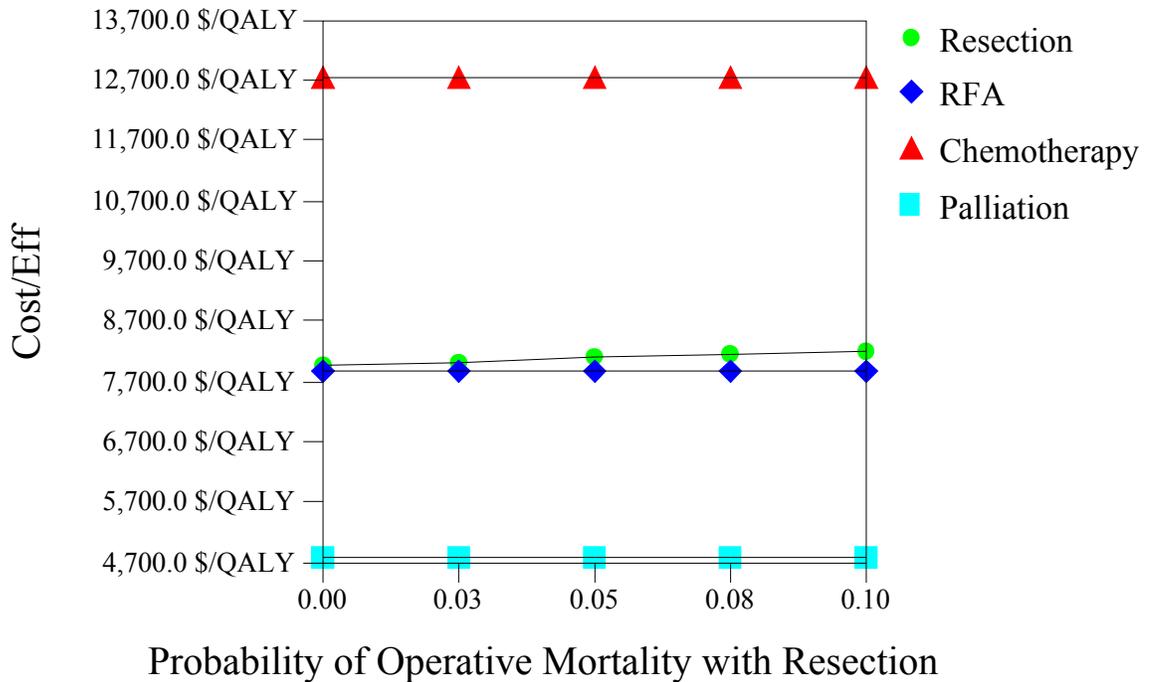
7) Excluding Chemotherapy Costs for Patients Having Surgery or Symptom Control

One of the major contributors to the overall cost was the cost of providing chemotherapy. For patients who underwent hepatic resection or RFA and also received chemotherapy, a substantial proportion of the cost of treatment came from the chemotherapy. If the costs of chemotherapy were excluded from the analysis for patients who had surgery or who chose to have symptom control alone, the costs of hepatic

resection, RFA, and symptom control were substantially lower (as seen in Figure 37). The cost-utility ratios for hepatic resection and RFA were still quite similar, however, at $5,526 and $5,758 per QALY, respectively.

Figure 37. Cost-Utility Excluding Chemotherapy Costs From Patients Undergoing Surgery or Symptom Control Alone

		Total Cost	Effect	C/E Ratio
Resection	Ⓜ	$13,852.08	2.5066 QALY's	5,526.24 $/QALY
RFA	Ⓜ	$11,455.18	1.9893 QALY's	5,758.30 $/QALY
Chemotherapy	Ⓜ	$15,069.32	1.1818 QALY's	12,750.98 $/QALY
Palliation	Ⓜ	$2,760.16	0.8160 QALY's	3,382.43 $/QALY

Cost-Utility?

8) Changes in Initial Costs of Hepatic Resection and Radiofrequency Ablation

A significant portion of the costs associated with hepatic resection and RFA was related to the initial costs of the procedures. Many centres perform RFA as a percutaneous procedure in an outpatient setting. While this is most common for the treatment of HCC, it has also been reported for the treatment of metastatic disease(113;125-127). Thus, the costs of RFA in those centres may be much less. A sensitivity analysis was performed to explore how uncertainty in these initial costs influenced the analysis. The range of costs associated with RFA considered in the sensitivity analysis was $2,000 to $10,000. Similarly, variation in the initial costs of hepatic resection was examined with a range from $4,000 to $12,000. It was thought that

hepatic resection may be more costly in some cases, particularly if there were serious peri-operative complications requiring extended hospital stays. As shown in Figures 38 and 39, the cost-utilities of these two treatments appear to be quite sensitive to the costs of the initial treatments. Radiofrequency ablation had a cost-utility between $5,968 and $9,990 per QALY when the initial cost of providing RFA was between $2,000 and $10,000 (see Figure 29). Hepatic Resection had a cost-utility ranging from $7,203 to $10,395 per QALY when the initial cost of offering hepatic resection ranged from $4,000 to $12,000. A two-way sensitivity analysis was performed, allowing both the initial costs of hepatic resection and of RFA to change. As shown in Figure 40, RFA remains the preferred treatment in terms of cost-utility for most combinations of these costs. Only when the initial cost of resection is very low and the cost of RFA is very high, does the cost-utility of liver resection appear to be lower than that of RFA.

Figure 38. Cost-Utility as Initial Cost of RFA Changes
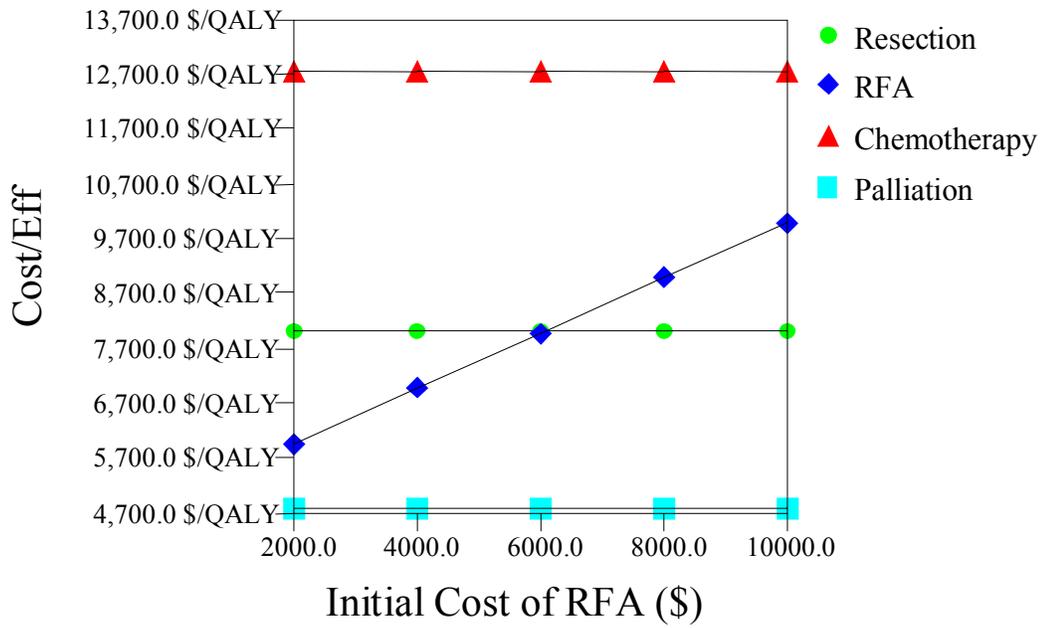
Figure 39. Cost-Utility as Initial Cost of Hepatic Resection Changes
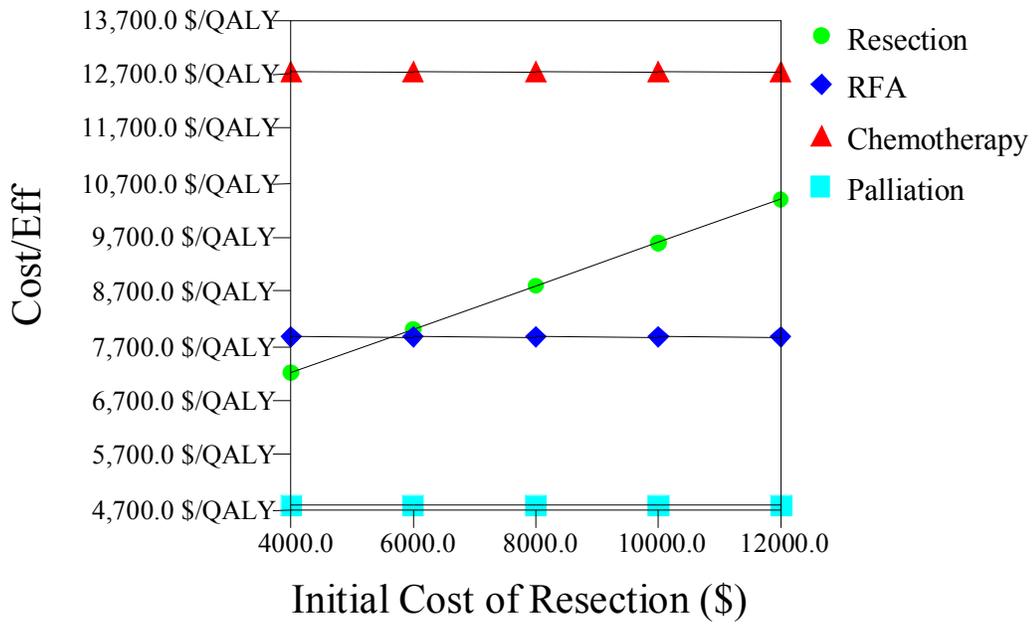
Figure 40. Preferred Treatment as Initial Costs for Hepatic Resection and RFA Change
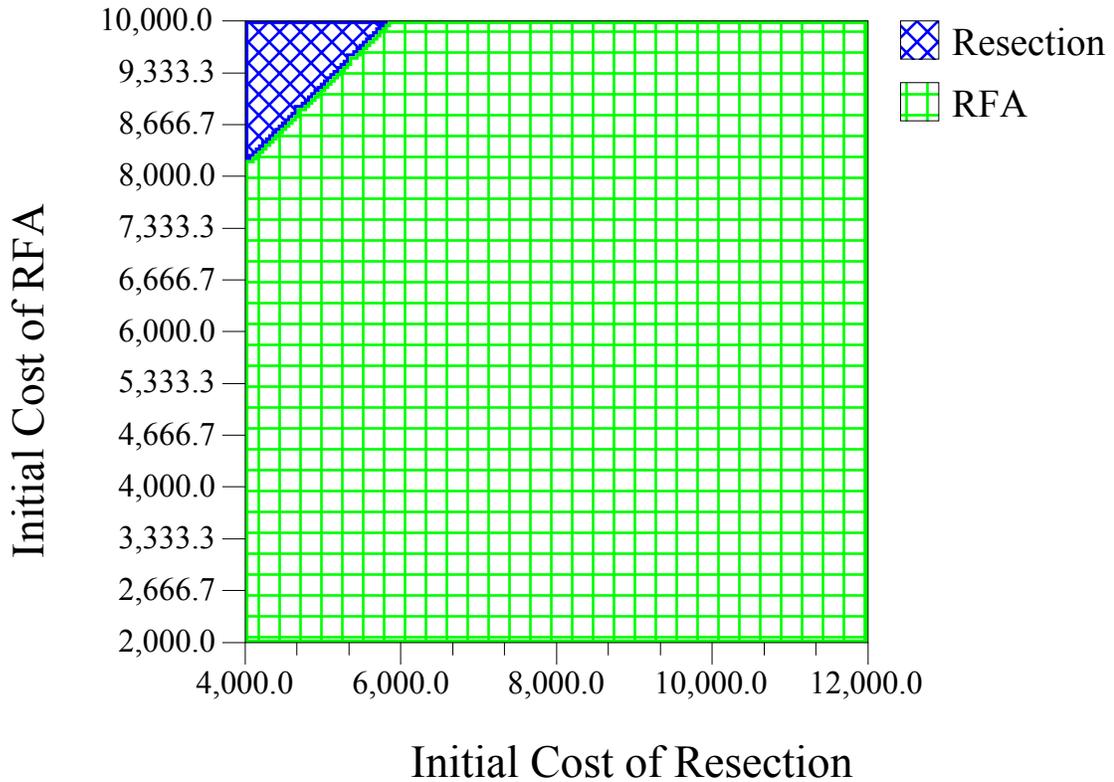
9) Change in Costs of Follow-Up and Costs Beyond the Timeframe of the Study

As noted above, there was limited data available to calculate the medical costs associated with patient follow-up. These included such costs as follow-up diagnostic imaging, outpatient office visits with physicians, and costs of subsequent hospitalizations for complications of treatment or disease recurrence. An assumption was made in the baseline analysis that these costs were approximately $75 per month. Figure 41 shows the results of a sensitivity analysis that explores the effect of this assumption on the results. This assumption was found not to influence the overall results of the analysis. The overall costs of the treatments did increase as the costs of follow-up ranged from $0 to $500 (a

value much higher than likely to be seen in practice) per month, but the relative rankings of the different treatments in terms of overall cost-utility did not change. This is provided that the follow-up costs remained the same for all treatments. It is possible that the follow-up costs for patients receiving chemotherapy would be higher than for other patients.

Figure 41. Cost-Utility as Medical Costs of Patient Follow-Up Changes
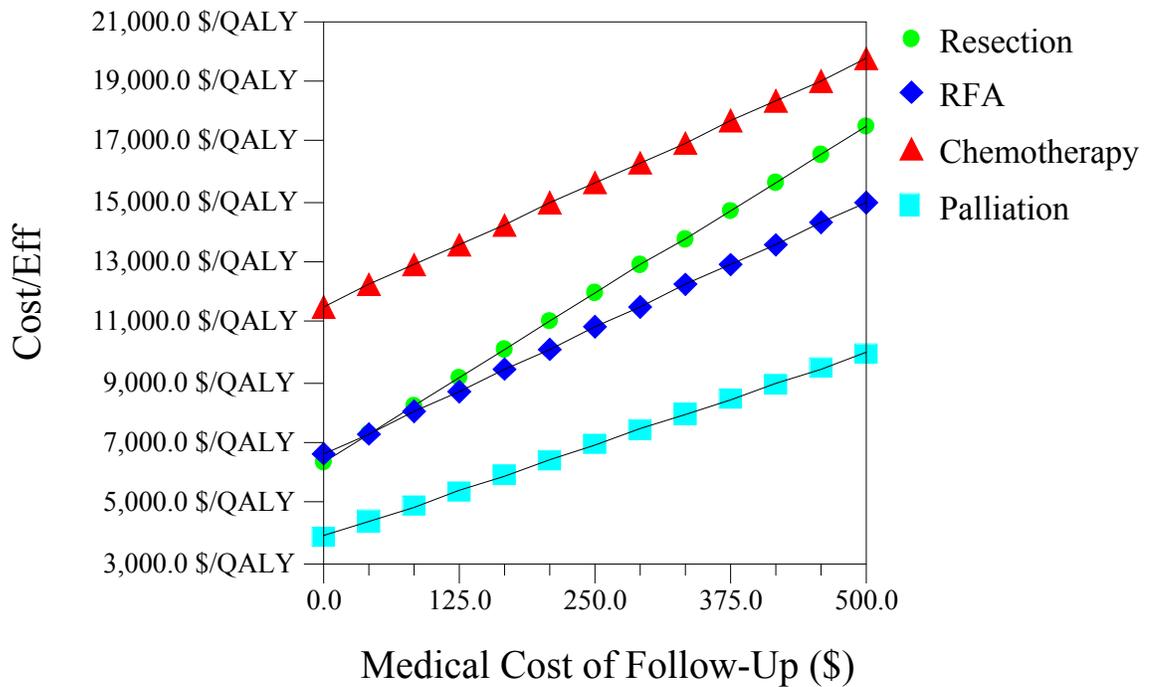
10) Change in Costs Borne by Patients and Caregivers

There was limited data available to measure the costs borne by individual patients and their families. Consequently, a two-way sensitivity analysis was performed to explore how changes to these amounts would influence the results of the analysis. The

costs borne by patients experiencing hepatic resection and RFA ranged from $0 to $500 per month. As seen in Figure 42, the results of the analysis only changed at the extreme ranges of these costs. The cost-utility of RFA was better than that of hepatic resection for most values of these expenses. Only when the patient-borne costs for resection were very low and the patient-borne costs for RFA were very high did the results of the analysis change in favour of hepatic resection.

Figure 42. Preferred Treatment as Costs Borne by Patients and Caregivers Change
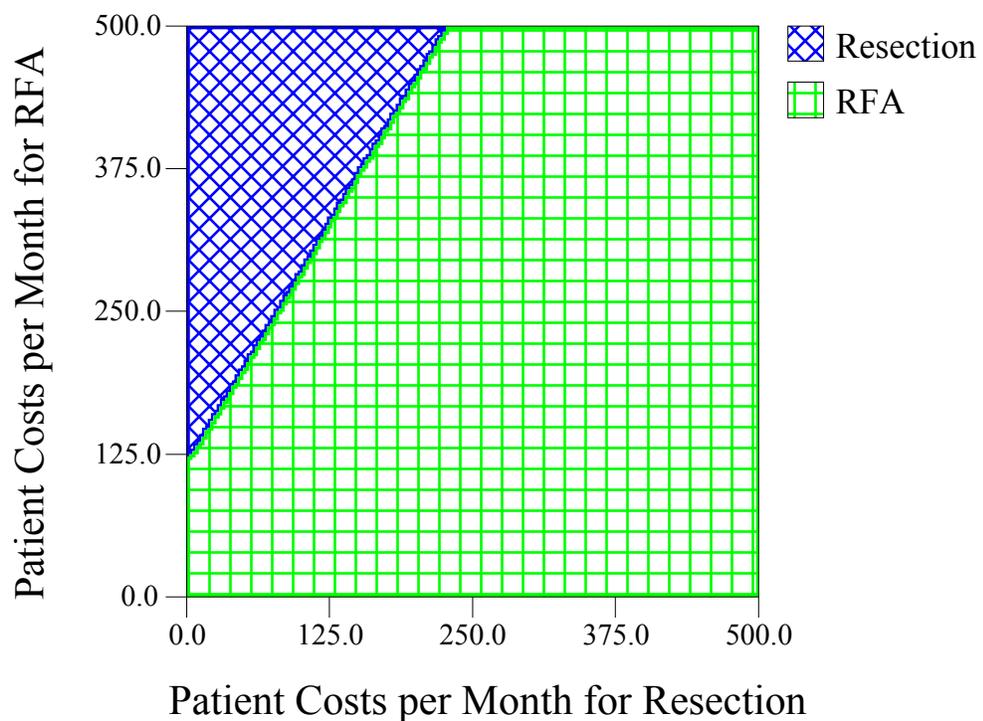
Because of the considerable controversy over the inclusion of productivity costs, a sensitivity analysis was done excluding the costs borne by patients and their caregivers

(which include productivity costs). Figure 43 shows the results. The overall results are similar. The ranking of cost-utility ratios was unchanged, but the magnitude of the ratios was lowered for all treatments.

Figure 43. Cost-Utility Excluding Costs Borne by Patients and Their Caregivers

	Total Cost	Effect	C/E Ratio
Resection	$16,520.34	2.5066 QALY's	6,590.73 $/QALY
RFA	$12,477.52	1.9893 QALY's	6,272.21 $/QALY
Chemotherapy	$10,921.45	1.1818 QALY's	9,241.23 $/QALY
Palliation	$1,885.95	0.8160 QALY's	2,311.14 $/QALY

11) Changes in the Discount Rate

The discount rate in the baseline analysis was 3% as recommended by the U.S. Panel on Cost-Effectiveness in Health and Medicine(147) and by Drummond et al(141). A sensitivity analysis was performed with a range of discount rates form 0 to 10%. As Figure 44 shows, the discount rate had little influence on the results.

Figure 44. Cost-Utility as the Discount Rate Changes
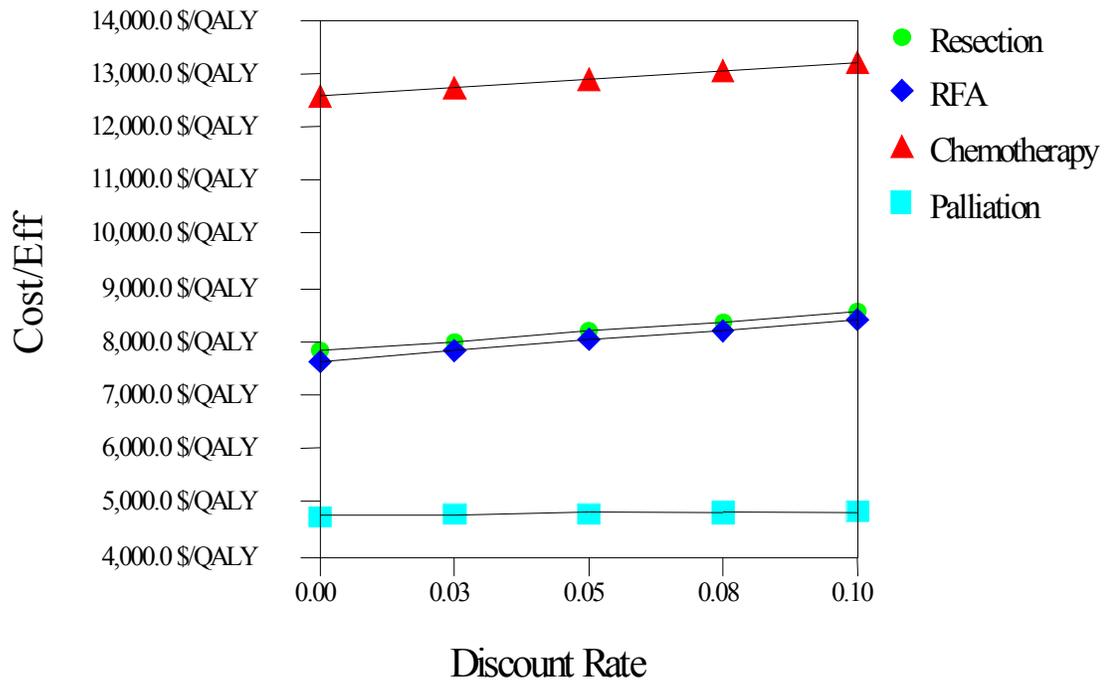
Chapter 8. Discussion

The patient characteristics were generally similar between groups in terms of age, gender, and types of tumours. Patients undergoing RFA tended to be younger than other patients, including patients undergoing hepatic resection. This may be due to a more aggressive approach to treating younger patients, even in the presence of unresectable disease. The age difference between those who had resection and those who had RFA did not reach statistical significance (p=0.17). Patients who elected to receive symptom control alone were older than patients who received chemotherapy (p = 0.049). This may represent a tendency to treat older patients less aggressively for fear of side effects, the inability to tolerate systemic chemotherapy, and the presence of other medical co-morbidities.

Differences were seen in the number of tumours and the presence of extra-hepatic disease. This can be explained by the design of the study. Patients entered into the study had different extents of disease. Patients who were candidates for hepatic resection were offered that treatment as it is considered to be the standard of care(4-6). These patients were selected on the basis of having disease amenable to curative resection. Therefore, they had less advanced disease and tended to be in better overall medical condition (or were at least considered to be capable of withstanding the physiologic stress of major surgery). All patients selected to undergo hepatic resection alone had only 1 liver lesion, and none had extra-hepatic disease documented at the time of entry into the study. This is in contrast to patients receiving other treatments. Patients receiving chemotherapy seemed to have the most advanced disease. Patients receiving RFA had significantly more lesions that did the patients undergoing hepatic resection and were considered not

to have disease amenable to resection alone. Four of the seven patients undergoing RFA had ablation in conjunction with resection of one or more lesion. Thus, RFA was sometimes used to extend the indications of surgical treatment. Patients who underwent a combination of RFA and liver resection were grouped with patients who underwent RFA alone since RFA was hypothesized to be less effective than hepatic resection and that the effectiveness of RFA would be the major determinant of survival.

The quality of life data generated by this study indicate that patients who underwent hepatic resection had quite good long-term quality of life. The average baseline HUI3 score for patients about to undergo hepatic resection was 0.86. In the period shortly after surgery, these scores dropped, but after 3 to 6 months, the scores returned to baseline or higher for most patients. The utility scores measured at two weeks reflect a temporary decline in quality of life after hepatic resection. The single-attribute utility scores shown in figures 14 to 21 show that this decline in quality of life is largely due to the pain experienced by these patients. The longer-term HUI3 scores are very high, at 0.99 at 12 months post surgery and beyond. To put these scores into a clinical perspective, the mean HUI3 utility scores for people considered to be in good health and without chronic medical conditions taken from a population-based sample of over 17,000 Canadians was 0.93(197). Table 11 describes HUI3 scores for individuals living in the community with various chronic medical conditions.

This indicates that long-term survivors after hepatic resection have excellent quality of life that does not appear to be influenced by prior disease or treatment. The effects of surgery appear to be short-lived.

It must be kept in mind, however, that this data is based on a small sample size. It was only possible to follow two patients who underwent hepatic resection to 18 months. This is because one patient withdrew from the study before the 3-month HUI3 questionnaire could be administered, because 2 patients died before the 18-month questionnaire, and because the time frame of the study did not allow 18month follow-up for 2 patients who were entered later in the study period. Therefore, this long-term quality of life data may not be truly representative. It is very likely that given more time and more patients, disease recurrence or other factors would be seen and the quality of life would drop to some degree (this possibility was explored in a sensitivity analysis – see below). One of the two patients followed to 18 months had recurrent disease, so it is likely that longer follow-up would detect effects of this disease recurrence on quality of life.

Radiofrequency ablation was associated with a similar trend in quality of life. The baseline HUI3 score was 0.95, and a drop in utility due to postoperative pain was seen at two weeks. The utility scores then generally rose to baseline values. There was more variability in the utility scores and the score did fall towards the end of the study period. This is likely a result of the effects of recurrent disease on the quality of life. There were three of seven patients followed to 18 months. One was documented to have recurrent disease and had an overall HUI3 score of 0.66 at 18 months. Of the two remaining patients, one had excellent quality of life with HUI3 score of 0.97, while the other had a poor score of 0.49. The latter patient did not have documented disease recurrence, but had poor scores largely due to pain. It is unclear whether this patient may have had undocumented disease responsible for the pain or whether it was secondary to the surgery

itself or secondary to an unrelated condition. The decline in HUI3 scores towards the end of the study period may be explained by disease recurrence alone, however. As seen in Figure 22, patients undergoing hepatic resection or RFA who remained disease-free tended to have greater quality of life scores than those with recurrences, but the difference was not significant. Again, the sample size was extremely small and firm conclusions cannot be made about the long-term quality of life associated with RFA, although in many cases it does appear to be good. With more patients, it is likely that the large variability in scores would decrease. A sensitivity analysis was performed to examine the effect of uncertainty in the utility scores on the cost-utility analysis (see discussion below).

Quality of life in patients treated with systemic chemotherapy appeared to remain reasonably high for the first several months of treatment, reaching as high as 0.89 on two occasions (6 and 12 months). This is close to the average scores of a healthy population(197). The HUI3 scores dropped after 12 months of treatment, however. Disease invariably progresses with systemic chemotherapy, and this is the likely explanation. The drop in HUI3 scores found to occur at two weeks post treatment might be partly explained by the fact that three of the 20 had initial exploratory laparotomies and this may have impacted their quality of life because of postoperative pain. Again, the sample size is small, with only 6 patients having utility score measurements at 12 months and only two at 18 months.

Figure 23 demonstrates that the addition of chemotherapy to patients who underwent hepatic resection or RFA did not impair quality of life. Again, it should be noted that the sample size is quite low and there is a risk of type II error.

The patients who elected to receive symptom control alone had quite high utility scores, suggesting the absence of treatment-related side effects may be important, although a third of these patients did choose to receive chemotherapy during the course of their disease. It should be kept in mind that 3 of these 6 patients were lost to follow-up and that no patient had utility score measurements beyond 6 months after being entered into the study.

The initial costs of hepatic resection and RFA were found to be quite similar (see Table 24), at $6,065 and $5,971 respectively (measured in 2001 Canadian dollars). The difference was not statistically significant. These costs include the costs of the preoperative work-up (mainly radiological investigations), the operating room costs of providing the surgery, and the hospital costs for the admission. The OR costs were similar at $2,907 and $3,132 for hepatic resection and RFA, respectively. There was no significant difference in mean operating time between hepatic resection and RFA, at 291 and 279 minutes, respectively. The mean hospital stay was 1 day less for RFA (7.3 versus 6.4 days), but the difference was not statistically significant. The operating room costs accounted for roughly half the total costs of hepatic resection and RFA, followed closely by the costs of providing nursing care. The largest component of the operating room costs was the fees paid to the physicians (the surgeons and the anaesthetists). The cost of supplies used in the operating room was the next highest portion of the OR costs, followed closely by the other staffing costs (nurses, orderlies, etc.).

The cost data supplied by the cost-accounting system at the St. Boniface General Hospital appeared to be quite accurate. It used a patient-specific approach. While not as accurate as micro-costing methods, a comparison to the Cost List for Manitoba Health

Services(174) revealed that the cost data was accurate. The average cost per case for the refined diagnostic related group 2030 (malignancy of the hepatobiliary system or pancreas) was $3,562. This cost excludes physician fees and overhead. The average cost for liver resection in this study was $6,065, but excluding physician costs and overhead it becomes $3,819. Considering that the $3,819 cost includes preoperative imaging, the costs from this study are very close to the figure of $3,562 reported by Jacobs et al(174). This provides support for the findings of this paper.

In this study, RFA was done as an open procedure using intra-operative ultrasound guidance. Thus, the procedure required a significant hospital stay while patients recuperated from a laparotomy, as well as a substantial amount of time in the operating room and all the included expenses. Many centres perform RFA with a percutaneous technique that can be performed in an outpatient setting. Often this is done for cases of hepatocellular carcinoma(110;111;116;118), but percutaneous RFA has been performed for colorectal metastases as well(113;125-127). The costs of percutaneous RFA would be likely be much lower. There are several reasons why a percutaneous approach was not used in the current study. There were four patients who underwent RFA in conjunction with hepatic resection in order to expand the capabilities of surgery to include patients who would not otherwise be candidates. These patients needed laparotomy regardless. Another reason is that the sensitivity of intra-operative ultrasound is higher than that of other preoperative imaging modalities to detect hepatic lesions. IOUS has been shown to alter decision-making in the operating room in 18% to 73% of cases(200-203). Elias et al found unsuspected metastases in 41% of patients who underwent hepatectomy for CRC liver metastases that would not have been treated with

percutaneous techniques(204). These lesions were found with a combination of intra-operative palpation and IOUS at laparotomy, but went undiagnosed with preoperative imaging with at least two of computed tomography scanning (CT), magnetic resonance imaging (MRI), or transabdominal ultrasound (US). As technology improves and preoperative imaging becomes more sensitive the value of IOUS may eventually decrease. However, currently it is considered the "gold standard" and patients treated percutaneously may receive less than optimal treatment if some metastases are missed. Another advantage of an open surgical approach is the ability to include hepatic inflow occlusion to prevent dissipation of heat and increase the likelihood of complete tumour necrosis(14). Tumours abutting the diaphragm or other organs are not always amenable to a percutaneous approach because it is necessary to protect these other organs from thermal injury(14). If patients were to undergo RFA in the outpatient setting, we would anticipate a significant difference between the cost of resection and RFA, although it is possible that the effectiveness would suffer. A sensitivity analysis was performed to explore the effect of decreased cost with RFA (see discussion below).

For patients who decided to receive systemic chemotherapy or symptom control alone, the initial medical costs of treatment were much less. There was no operative procedure and no required hospital admission at the outset of treatment, except for 3 patients who underwent an initial exploratory laparotomy and then chemotherapy (the cost of the exploratory laparotomy was included in the initial costs). Therefore, the initial costs of providing chemotherapy and symptom control are much lower, at $439 and $500, respectively. The majority of these costs were accumulated during the initial diagnostic work-up, which consisted mainly of radiological investigations.

The medical costs associated with outpatient treatment were highest for patients who chose to receive chemotherapy primarily. As seen above in Table 26, the medical costs of chemotherapy were considerable. These costs were accumulated over time, as patients received several courses of chemotherapy over several months. The average monthly cost was $1,979.

Patients receiving other treatments as the primary modality were not excluded from also receiving chemotherapy. As seen in Table 27 these costs were also significant. The timing and duration of the chemotherapy for these other patients differed between groups. This difference in timing was reflected in the cost-utility analysis model. For instance, 3 of 7 patients who underwent hepatic resection also had chemotherapy. The chemotherapy was given for an average duration of 5 months, and on average began 5 months after surgery (see Table 27). The timing of these costs was factored into the decision model.

Because treatment of cancer involves a multi-disciplinary approach with specialists from different backgrounds, it was felt that the costs of providing chemotherapy to patients undergoing surgery or symptom control should be included in the analysis as this approximates what is done in clinical practice. Certainly, if the benefits of adjuvant treatment are included, the costs should be as well. A sensitivity analysis was performed where the costs of chemotherapy for subjects undergoing surgery or symptom control were excluded from the analysis to test if this had any effect on the results (see discussion below).

It was anticipated at the outset of the study that there would be a considerable amount of other medical costs associated with follow-up. These costs were expected to

include costs of subsequent hospitalizations for complications of treatment and complications of disease recurrence. It was expected that a significant proportion of patients who succumbed to cancer would need to be admitted to hospital for treatment prior to their deaths. The charts available at St. Boniface General Hospital and at CancerCare Manitoba were examined on several occasions to capture such hospitalizations. None were found during the study period. Many patents lived in other cities or closer to other hospitals within Winnipeg, so it is possible that these hospitalizations did occur without being measured in the present study. It is also possible that many hospitalizations did occur at St. Boniface General Hospital after the study period ended. For instance patients who began treatment close to the end of the study period may have had complications that occurred later. Another possible factor is that the cost-accounting department at the hospital was several years behind in its data analysis. The department made a special effort to gather all data for patients who underwent hepatic resection and RFA. For patients receiving chemotherapy, there may have been data for hospitalizations that was not available because it was not yet analyzed. Patients receiving chemotherapy had hospital cost data up to only December 2001 in many cases. As discussed in the results section above, an average cost of $75 per month of follow-up was used in the baseline analysis for each treatment modality. A sensitivity analysis was performed to examine the effect of the uncertainty in these figures (see discussion below).

The non-medical costs were also incompletely captured in this study. The study patients were provided with diaries to record their own out-of-pocket expenses and time commitments. Unfortunately, very few of these forms were properly filled out and

returned to the study researchers. The main reason for this is that patients received their follow-up at a variety of centres. It was not possible for the researchers to meet the patients at each of these locations, as the research team had limited resources and numbers. The physicians involved in their care were often quite busy and were unaware which patients were participating in the study. As a result, study participants were not often reminded to return the diaries. Perhaps a greater study budget would have allowed a larger research team to able to provide a greater time commitment to follow-up and remind patients about these cost diaries. This would certainly be an area to improve upon in further studies. As seen in Table 28, costs borne by the patients and their caregivers were available for a minority of patients. Two of seven patients undergoing hepatic resection, 3 of 7 undergoing RFA, 6 of 20 patients receiving chemotherapy, and 1 of 6 patients receiving symptom control alone had data available for these non-medical costs. Even then, most of this data was available for only a small percentage of the follow-up period. A sensitivity analysis was done to explore uncertainty in these costs (see discussion below).

The baseline cost-utility analysis (see Figure 26) indicates that the cost-utility of hepatic resection and radiofrequency ablation are similar. Resection appeared to offer a greater quality-adjusted survival than RFA, but at a higher cost. Consequently, the cost-utility ratio of RFA was slightly lower than that of resection ($7,9650 per QALY for RFA compared to $8,027 per QALY for hepatic resection). In the baseline analysis, the cost of hepatic resection was higher than the other treatments with an expected value of $20,122 compared to $15,845, $15,069, and $3,899 for RFA, chemotherapy, and symptom control, respectively. It also appeared to be the most effective treatment with an expected

value of 2.51 QALY's, compared to 1.99, 1.18, and 0.82 QALY's for RFA, chemotherapy, and symptom control, respectively. The treatment associated with the lowest cost-utility ratio was symptom control alone with a ratio of $4,778 per QALY. Clearly, this was also the least effective treatment, and would not be the preferred treatment even though it may seem to be the most cost-effective. Systemic chemotherapy is associated with the highest cost-utility ratio at $12,751 per QALY.

In addition to overall cost-utility, the marginal cost-utility is important when deciding between alternative treatments. The marginal cost-utility refers to the expected costs and benefits when choosing one treatment over an alternative. In some cases, the ratio of the additional utility to the additional expense can be prohibitive even if the overall average cost-utility is not. In other words, there can be situations where choosing from the current treatment to the next most effective treatment can be prohibitive if the additional benefit is small in relation to the additional cost. Symptom control alone had the lowest cost-utility ratio, but because this appeared to be the least effective treatment it cannot be considered the optimal treatment. As seen in Figure 27, systemic chemotherapy had a marginal cost of $11,170 compared to symptom control alone. The marginal increase in quality-adjusted life was 0.37 QALY's yielding a marginal cost-utility ratio of $30,537 per QALY. This marginal cost-utility ratio is within the range of what is considered acceptable(19), and chemotherapy should be considered a cost-effective treatment for liver metastases from colorectal cancer. Radiofrequency ablation appeared to offer a greater number of QALY's than chemotherapy (a marginal benefit of 0.81 QALY's). The cost was higher, with a marginal cost of $775 yielding a marginal cost-utility of $960 per QALY. This would be considered to be a very good marginal cost-

utility ratio and RFA would be considered to be a valid treatment option for liver metastases when it is feasible to offer it based on these figures. Hepatic resection appeared to offer an additional benefit of 0.52 QALY's compared to RFA at a marginal cost of $4,277. This resulted in a marginal cost-utility ratio of $8,269 per QALY, again a value well within the accepted range(19). Comparing hepatic resection to systemic chemotherapy demonstrated that hepatic resection had a marginal cost increase of $5,052 and a marginal increase of 1.32 QALY's for a marginal cost-utility ratio of $3,814 per QALY.

As with any decision analysis technique and with cost-effectiveness studies in general, several assumptions must be made during the analysis. These assumptions may have significant influence on the results of the studies. Sensitivity analyses are a commonly used method to explore the influence of these assumptions on the results. Sensitivity analyses were done in this study to explore the influence of uncertainty in several variables. These variables included which version of the Health Utilities Index was used (HUI2 or HUI3), the effect of using unadjusted survival data, differences in the magnitude of the measured utility scores, changes in survival associated with different treatments, changes in operative mortality, changes in the costs of chemotherapy, changes in the initial costs of providing hepatic resection and RFA, changes in the medical costs of follow-up, changes in the costs borne by patients and their families, and changes in the discount rate used.

The utility scores obtained with the two versions of the Health Utilities Index were quite similar. This provides evidence of the validity of the Health Utilities Index Mark III. The cost-utilities of hepatic resection, RFA, chemotherapy, and symptom

control were \$8,027, \$7,965, \$12,751, and \$4,778 per QALY with the HUI3 and \$7,903, \$7,226, \$13,228, and \$4,813 per QALY with the HUI2, respectively. Thus, the choice to use HUI3 values had no influence on the results.

A sensitivity analysis was performed to examine the results obtained when unadjusted survival data was used. As seen above in Figure 30, the relative orders of the cost-utilities did not change. The values used for raw survival with hepatic resection and with RFA were similar in the baseline analysis. Therefore, when using unadjusted survival data, the benefits of hepatic resection and RFA were similar at 2.68 and 2.69 LYG's, respectively. The cost-effectiveness of hepatic resection and RFA were still quite close, although the discrepancy was slightly larger (\$7,507 per LYG and \$5,881 per LYG, respectively). The cost-effectiveness ratio of systemic chemotherapy was \$9,471 per LYG. Thus, the overall rankings were much the same.

As seen in Figures 31 and 32, the cost-utility ratios were sensitive to the utility scores. In this sensitivity analysis, the utility was varied from 0.5 to 1.0 and the effects were dramatic. It is unlikely, however, that utility scores would reach close to 0.5 in clinical practice. Ramsey at al showed excellent utility in long-term survivors of colorectal cancer, even in those with Stage IV disease(142). They sampled a cancer registry in Washington State to identify 173 colon cancer survivors who were at least 1 year from their diagnosis. The subjects completed questionnaires containing the Functional Assessment of Cancer Therapy Scales for Colorectal carcinoma (FACT-C) and the Health Utilities index Mark III. The average HUI3 score for the entire population was 0.85, which is similar to the scores observed in this study. They did note in a retrospective analysis that subjects in their last year of life (i.e. subjects who died within

12 months of the survey) had significantly lower HUI3 scores, with a mean of 0.65 (p = 0.002).

The utilities associated with both hepatic resection and RFA are likely to be fairly close in long-term survivors. Thus, any error in the utility scores observed in this study could influence the magnitude of the cost-utility ratios, but conclusions in terms of the relative rankings of cost-utility would likely be unchanged.

The quality-adjusted survival and the cost-utility of hepatic resection were found to be sensitive to changes in absolute survival with resection. This finding would certainly be important when considering the feasibility of a randomized trial comparing RFA to hepatic resection in the future. If improvements in surgical technique and peri-operative care continue to improve survival after hepatic resection, the survival benefits of RFA would need to be roughly equivalent to these newer figures in order to justify the trial. Again, however, it must be kept in mind that RFA is currently offered to patients who are not candidates for hepatic resection and selection bias is present. Survival associated with RFA in the setting of equivalent patients (i.e. candidates for resection) may be higher than the figures reported in studies where RFA was used to treat patients considered to have unresectable disease.

There have been significant improvements in the survival benefit with systemic chemotherapy over recent years(11;12). At present, however, surgery is the only treatment that offers the potential for long-term cure. As shown in Figure 35 it appears quite unlikely that even if the median survival achievable with chemotherapy doubled, could the cost-utility of chemotherapy match the cost-utility of surgical options. Doubling of survival with chemotherapy is unlikely to be achieved in the near future. Therefore,

even with significant improvements in chemotherapy, the preferred treatment modalities appear to be surgical treatments when they are possible. The cost-utility of chemotherapy appears to be within acceptable limits for patients who are not candidates for surgical intervention. This study gives strong economic support to the continued practice of providing palliative chemotherapy.

A sensitivity analysis was performed to evaluate the effects of changes in the operative mortality rates on the results of the analysis. Figure 36 demonstrates that the results are not sensitive to changes in the operative mortality rate, even when the rate was as high as 10%.

There may be wide practice variations across the country when it comes to the use of adjuvant or neoadjuvant chemotherapy for surgically resected liver metastases. Other centres may be more or less likely to offer chemotherapy to patients who undergo surgery. Therefore, a sensitivity analysis was done to examine whether eliminating the costs of chemotherapy would influence the overall results of the study. As seen in Figure 37, when the costs of providing chemotherapy to patients who had liver resection or RFA were omitted from the analysis, the cost-utilities of hepatic resection and RFA were lower, but still quite similar at $5,526 and $5,758 per QALY, respectively. Thus, the overall conclusion is not altered by the inclusion or exclusion of adjuvant chemotherapy for patients undergoing hepatic resection or RFA.

There is potential for the initial costs of hepatic resection and RFA to change significantly. For instance, if the complication rates for patients undergoing liver resection or RFA were higher and hospital stays increased, the costs would be considerably higher. Also, if RFA were to be performed as a percutaneous procedure, the

costs would be considerably lower. As discussed above, there are several reasons why this was not done in the present study. Figures 38 and 39 show that the cost-utilities of both hepatic resection and RFA were quite sensitive to the initial costs of the treatments. The overall results of the analysis, however, remained the same over much of the range of costs used in the sensitivity analysis. As seen in Figure 40, only when the cost of hepatic resection was much lower than the cost of RFA, was the cost-utility ratio of hepatic resection lower than that of RFA. This is a scenario that is unlikely to be seen in clinical practice. It is very likely that the costs of resection would be similar to or higher than the costs of RFA. In other words, the average cost-utilities were very sensitive to changes in the initial costs of providing these treatments, but the order of ranking of the different treatments remained the same.

Sensitivity analyses were done to evaluate the effect of uncertainty in the medical costs of patient follow-up, as well as the costs borne by patients and their caregivers. There was limited cost data available for these two variables, so assumptions were made in the baseline analysis. Figures 41 and 42 demonstrate that while the cost-utility ratios were sensitive to changes in these costs, these assumptions were unlikely to influence the overall results. Figure 43 shows that the results of the analysis were the same even when these costs were omitted all together. The magnitudes of the cost-utility ratios changed, but over most ranges of costs in the sensitivity analysis, the rankings of the treatments sis not change.

Changes in the discount rate did not have any appreciable effect on the results of the analysis (see Figure 44). Thus, although it is recommended to use a baseline discount rate of 3% rather than the traditional 5%(141;147), this is likely a minor point.

A. Limitations of this Study

One of the biggest difficulties in drawing firm conclusions from this data is the fact that it is purely a descriptive study with a small number of non-randomized patients. The study compared patients with different stages of disease. Currently, hepatic resection is considered to be the most effective treatment for hepatic metastases from colorectal cancer when it is feasible(4-6). Therefore, patients who were candidates for this operation were offered resection. Radiofrequency ablation was offered to patients who were not considered to be candidates to undergo liver resection. In some cases, this was because patients may not have been fit to undergo a more extensive procedure, but in most cases this was because the disease in the liver was not amenable to resection alone. Four of the seven patients undergoing RFA had hepatic resection plus RFA in an attempt to ablate disease that could not be completely resected using standard means because an adequate amount of functioning liver tissue could not be preserved with a formal resection. Patients who underwent chemotherapy as the primary treatment generally had advanced disease that could not be cured with resection because of extensive bilateral disease, distant metastases, or other medical co-morbidities that precluded major surgery. Similarly, patients who chose to receive symptom control alone had disease not amenable to surgical removal. Patients receiving symptom control alone were significantly older than patients who received chemotherapy. They may have had other co-morbidities that precluded chemotherapy as well. Thus, patients treated with different methods were not similar in terms of disease status.

The accrual rate was less than half of what was anticipated. The low sample size that resulted is a major limitation of the study. The cost data and especially the QOL data

were based on only a few patients. This must be kept in mind when interpreting the results. Part of the reason is that fewer patients were seen by the hepatobiliary surgeon during the study period than was expected. This may simply have been random variation. It is also likely that there were eligible patients seen by the medical oncologists that were not enrolled in the study. In a busy practice, it can be difficult for the physicians to remember to recruit patients to a study, particularly if there are several different studies taking place at the same time. The research team was limited in numbers and in resources, making it impossible to have a researcher present at many oncology clinics. When a researcher was present to remind the clinic staff, the accrual seemed to be higher. A researcher was only available to attend the medical oncology clinic less than half the time. In any future studies, it would be important to have a budget that would allow more research assistants. This would likely result in higher accrual rates.

For cost-effectiveness studies in general, there remain several methodological issues that are still unresolved. This paper has followed the recommendations of the US Panel on Cost-Effectiveness in Health and Medicine when measuring the costs of the treatments under evaluation for the reasons outlined above(147;147;205) (see the Methodology section). As discussed earlier, it should be noted that there are arguments both for and against this approach. Perhaps the largest criticism of the approach that was taken in this study is that productivity costs were included as effects of the disease and its treatment. Thus, these were included in the denominator of the cost-utility analysis. As discussed in detail previously (see Methods), the effects of morbidity were captured by the reduction in quality of life scores, thus avoiding the error of *double-counting*(147;184). This does offer the benefit of allowing comparisons to be made

across studies should authors adopt standard methods for cost analysis as suggested by the Panel(147;177;205). Of note, however, is that exclusion of costs for time spent receiving treatment did not alter the overall conclusions of the analysis. The cost-utility ratios were all lower when these costs were omitted, but the rankings did not change.

One minor limitation of this study is that there was no system used to measure the friction costs associated with time off work. While the US Panel on Cost-Effectiveness in Health and Medicine recommends that an individual's productivity losses be counted as an effect in the denominator, it also recommends that such costs borne by the rest of society, including friction costs, be included as a cost in the numerator(184) (the Panel does not discuss methods to do this, however). To measure such costs would have been extremely difficult and time consuming. Also, given the average age of the present patient population and the relatively high proportion of unemployed persons, these friction costs were unlikely to have a major effect on the conclusions of this paper. Even proponents of the friction cost method suggest that it is not always necessary to include such costs(182).

The instruments used to measure health-related quality of life were the Health Utilities Index Mark II and Mark III. The primary analysis used the utility scores generated from the HUI3. As previously discussed (see Methodology), this instrument has been validated and found to be responsive to differences associated with several chronic diseases(191;196;197). Furthermore, it has also been shown to be responsive to the acute changes experienced by cancer patients who are receiving chemotherapy(198), although this was a paediatric population. The HUI3 has been shown to be sensitive to changes in health-related quality of life among patients with colorectal cancer(142). The

instrument detected differences in QOL between a large sample of long-term survivors (who generally had very good quality of life) and a subgroup of patients who died of their disease within a year of the survey, indicating it is able to detect differences due to disease recurrence. This past experience with the HUI3 provided a rationale for use in this study. It was expected that the instrument would be sensitive enough to detect the acute and chronic changes experienced by patients with malignant hepatic tumours.

The results of this paper suggest that this was, in fact, the case. As expected, the utility in the early postoperative period for patients undergoing both resection and RFA decreased. As the initial symptoms, including pain, decreased appetite, limited mobility, anxiety, etc. abated the utility scores generally appeared to return to their baseline values (see Figures 14 to 21 above) The attribute most affected was that of pain. There was no significant difference between utility scores obtained form the Health Utilities Index Mark II and Mark III. This was seen in the graphs of utility over time for each of the treatment modalities (Figures 9 to 12 and Tables 20 to 23) as well as the sensitivity analysis comparing the results with both versions (Figure 29). The results of this study provide further evidence of the face validity of the Health Utilities Index Mark III. Suggestions that the HUI3 should not be used because it has not been as extensively validated as the HUI2 may not be justified.

For patients who received chemotherapy, the utility scores were consistent with expected results. The scores ranged between 0.89 and 0.66. As seen in Appendix 3, these scores are similar to the scores associated with other chronic medical conditions. As expected, there was a trend to decreased scores towards the end of the study period, suggesting that this may be due to the inevitable progression of disease. Again, this

provides evidence for the face validity of the Health Utilities Index Mark III and suggests that this instrument is sensitive to the changes in health status seen with patients with metastatic liver disease.

Another possible criticism of the choice to use the Health Utilities Index to calculate utility scores is that the instruments are generic. Some argue that "the best method to perform an accurate QOL evaluation in colorectal cancer is represented by the 'modular approach'"(166). The *modular approach* refers to the use of a combination of a generic instrument and a disease-specific measurement(166;206). The rationale for the modular approach is that the generic instrument may fail to detect specific quality of life changes that are unique to a particular disease process.

The responsiveness shown by the HUI3 and HUI2 in this study suggests that although these are generic instruments, the sensitivity to both acute and chronic changes in health status was adequate. One major disadvantage to the use of a disease-specific quality of life instrument for patients with malignant hepatic neoplasms is that, by definition, the utility scores generated would be specific to patients with malignant hepatic neoplasms. Thus, the comparisons of cost-utility ratios could not be made across different studies. Studies using different methodologies to calculate utility scores would not be comparable. To allow comparisons across studies was one of the main reasons to follow the recommendations of Weinstein et al form the US Panel on Cost-Effectiveness in Health and Medicine(147;177;205). By using the Health Utilities Index, which has been used by many other investigators and in many different diseases and health states, the utility scores of this study will be able to be compared to those of other disease states also obtained by the Health Utilities Index. In fact, the lack of standard methods in both

cost analysis and in the measurement of utility scores in the field of health economics creates problems in terms of both the quality and the generalizability of the existing literature. This study attempted to use well-established and standard methods for these reasons.

Another criticism of this analysis and possibly apply of all cost-utility analyses, which may be largely theoretical is that utility changes of other members of society were not considered. Although the perspective was that of society in general, only the utility of the person with the disease was measured. For instance, close family members and friends may also experience decreases in QOL due to anxiety and depression related to their loved one's condition. Changes in their utility were not measured. However, it is likely that utility scores for these other members of society are not relevant to the decision of resource allocation. For example, patients with large families that might worry more could not be given greater weight than patients with very small families. The inclusion of the additional utility values would likely only cloud the issues and introduce more uncertainty and error into the decision model. We are not aware of any author who has included these utility values in an analysis or who supports their inclusion.

This study relied on the technique of decision analysis, which is gaining increasing acceptance in health research. The greatest advantage of this technique is that it provides the ability to clarify difficult choices where the outcomes are not obvious. The issue of cost-utility is a difficult one in many cases. The cost-utility of the available treatments for hepatic malignancies depends on many complicated factors. The interaction of these various factors is complex and decision analysis allows people to sort through that complexity in a logical, systematic, and explicit manner. To do this,

however, certain assumptions are always necessary in the design of the decision model. These assumptions introduce error into the model, and this must be kept in mind when interpreting the results. In this study, the major assumptions involve the future costs and future effects of the treatments. Because patients were followed to a maximum of 2 years during the study, it is probable that future events were missed. For instance, the medical resources consumed in the final stages of disease were not captured if they occurred beyond 2 years. Costs associated with disease progression and subsequent hospitalizations were not observed, but it would be surprising if they did not occur. However, this would not be expected to introduce significant error into the overall results. While the end of life costs may be quite variable from individual to individual, these costs are likely to be similar between treatments as mortality would occur as the result of metastatic disease. When exploring the incremental cost-utility of these treatments, it is the difference in cost between treatments that is important. The amount of error would likely be similar for each treatment, and the incremental cost difference and the results of this study would not be significantly affected. The magnitude of the costs may have been influenced by this flaw and been falsely lowered to some extent, but the ranking of treatments in terms of cost-utility ratios would not likely have changed.

Another major assumption necessitated by the limited follow-up period was that the quality of life scores for patients surviving longer than 2 years were assumed to be stable after the last measurement at 18 months. The average HUI scores for each treatment were composed of scores from patients who were recurrence-free, patients experiencing recurrence, and patients experiencing side effects of the treatments. It would be expected that scores measured beyond 18 months would also be composed of patients

with and without recurrent disease or adverse effects. Thus, the previous scores would likely be appropriate and continue to be accurate. Caution is necessary, however, since the numbers of patients followed out to 18 months is low (2 patients undergoing hepatic resection, 3 patients who underwent RFA, and 2 patients who received chemotherapy as the primary treatment). With larger patient numbers, the value measured may have been different. Support for the decision to model future quality of life scores on the scores obtained at 18 months comes form a paper by Ramsey et al(142). Ramsey et al used the Health Utilities Index Mark III to measure long-term (> 60 months) quality of life in survivors of colorectal carcinoma, and found that those who achieved long-term remission had a relatively high and sustained QOL. Those with Stage IV disease did not have significantly lower HUI3 scores. Thus, the longer-term survival would likely have been associated with high quality of life scores as seen in this study.

The purpose of this study was not to draw firm conclusions comparing these treatment options for liver metastases form colorectal cancer. The design of the study precluded this possibility. It was non-randomized and the patient numbers were low. One of the purposes of the study was to develop hypothesis data to determine the feasibility of further comparisons of RFA to hepatic resection in the future. In other words, if this pilot study found supporting evidence that the cost-utilities of these two treatments were similar, then this would support the possibility of randomized trials in the future. Even with supporting evidence that the cost-utilities may be similar, further long-term survival data for RFA is needed before such a study could be done.

The long-term survival associated with RFA is still largely unknown, and would need to be evaluated before a randomized trial could ethically be carried out. While the

early reports of survival with RFA technology appear promising, it remains to be seen whether the longer-term data will meet the high expectations. Because RFA cannot be considered an equivalent treatment to liver resection at present, the existing trials have consisted of patients with unresectable disease(107;110-113;116-122;125-128;128;129). This may be on the basis of tumour size, number and location or on the basis of the patients' general health. In spite of unresectable lesions, the early follow-up data is promising and in some cases is comparable to that of surgical resection. Three-year follow-up has been reported in some studies and has been similar to that with hepatic resection(127-129).

This favourable 3-year survival data provides support for the technology. This survival data is impressive because the patients were not candidates for hepatic resection. Hopefully, this technology would demonstrate survival equivalent to or better than with hepatic resection in patients with resectable disease.

It should also be noted that the number of existing studies on RFA is low and these studies may suffer from a number of biases. Although these case series are comprised of patients with unresectable disease, they may still represent a highly selected group with favourable prognostic factors. There may be a considerable publication bias where only the series with favourable outcomes have been published. There may exist case series with less favourable survival data that have not been published. Therefore, despite several promising initial reports the technique of RFA must still be viewed with caution. Should these initial positive results translate into as promising long term results, a prospective randomized controlled trial would be needed prior to adopting RFA as standard treatment for patients in whom surgical resection would also be recommended.

Nonetheless, the present study, being a pilot project, is based on these early promising results of RFA. The probabilities of survival after receiving RFA that were used in the decision model were based on the early results of RFA. The model's time horizon is 5 years, and the 5-year survival probabilities for RFA used in the model were based on the 3-year observed survival data found in the literature and then extrapolated to 5 years assuming a logarithmic survival curve with mortality rates being constant after 3 years. If in the future, the survival curves for RFA are seen to drop more steeply after 3 years and the 5-year survival is not as good as the decision model assumes, the cost-utility ratio associated with RFA would be higher than seen in the present study.

However, should the longer-term survival benefit of RFA in a patient population of patients who are not considered to be candidates for hepatic resection (and, thus, would be expected to have a worse prognosis than patients who are considered candidates for resection) prove to be close to the long-term survival of patients undergoing hepatic resection, then this study helps provide rationale for a randomized controlled trial. The current study suggests that the cost-utility of the two treatments are likely to be similar. The quality-adjusted survival would likely be similar, and the cost-utility of the two treatments would be expected to fall within the range of what is currently accepted as appropriate. Therefore, a randomized trial would likely be justified should the survival benefit of RFA prove to be as promising as the early reports.

On the other hand, the survival data for the remaining treatments under evaluation is much better established. Hepatic resection is a well-established treatment for malignant liver tumours (both primary and secondary), and is considered the standard of care when feasible(4-6). There has been a trend over recent years towards increased survival with

hepatic resection. This may be due to improvements in peri-operative care, and intensive care and anaesthesia in particular. It may be due to improved surgical technique and technology to reduce blood loss in the operating room. It may also be due to improvements in preoperative imaging and, thus, patient selection(9). It is likely due to a combination of these factors. Of course, this trend towards improved survival must be taken into account prior to embarking on a randomized trial between hepatic resection and RFA. The long-term survival with RFA must be comparable to these recent and more promising survival figures associated with hepatic resection.

The survival benefits offered by chemotherapy are also more firmly established. This has been the area of intense research over the past several years, and proper randomized controlled trials are the norm. Thus, their conclusions are based on more solid evidence. New regimens are constantly being evaluated and improvements may be made over some of the most promising regimens that are available presently, such as irinotecan, 5-FU, and LV(11;12). Such newer regimens are likely to be more costly as well as more effective, so their potential cost-utility may vary. This study would suggest, however, that the cost-utility ratios of these newer agents would still likely be considerably higher than surgical treatments.

Chapter 9. Conclusions

The quality of life associated with hepatic resection and radiofrequency ablation appear to be quite good. The utility seems to drop in the immediate postoperative period because of pain experienced by the patients and then improves to equal to or better than baseline values. The quality-adjusted survival and the cost-utility of hepatic resection and RFA for colorectal liver metastases appear to be similar. The cost-utility ratio of systemic chemotherapy is higher, but still well within the range of what is considered to be medically and economically acceptable(19). The cost-utility ratio of symptom control alone appears to be low, but cannot be considered to be the preferred treatment as it also appears to be the least effective.

The analysis was sensitive to the magnitude of the utility scores, the survival associated with each treatment, and the costs of hepatic resection, RFA, and chemotherapy.

Should the long-term survival benefit of RFA prove to be close to that of hepatic resection, this pilot study offers support to the rationale for a randomized trial comparing the two treatments in the future.

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Appendix 1. Form Used to Obtain Informed Consent

A Cost Utility Analysis of Liver Resection for Malignant Tumors

Participant Information and Questionnaire Consent

<u>**Study Team**</u>

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You are being asked to participate in a research study. Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your family, friends or your doctor before making your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not understand.

<u>**Purpose of Study**</u>

This study is being conducted to identify the quality of life and cost effectiveness of treatments for malignant diseases of the liver. The purpose of the project is to provide information that will help patients and their doctors make decisions about their treatment and care.

A TOTAL OF 100 participants will participate in this study.

Study Procedures

If you take part in this study, we will ask you questions about your quality of life and costs that are associated with the treatment of your liver disease. You will be asked to complete an initial questionnaire with one of the study staff prior to starting your treatment. This questionnaire will be repeated with you on 6 occasions: 5-6 days after your first treatment, 3 months after treatment, 6 months after treatment, 9 months after treatment, 12 months after treatment, and again 18 months after treatment. Each questionnaire/interview should take no longer than 30 minutes. We will also ask you to keep a `Personal Expense Diary' to record your monthly expenses associated with your liver treatments. We will review this diary with you during the interview sessions.

We would like to assure you that all information you provide in the questionnaire and interview will be kept strictly confidential. Your name will be kept separate from the questionnaire data to ensure that you will not be identified in any way.

Participation in this study will not interfere in any way with the treatment and care of your liver disease.

The study will take place over a 2-year period.

Costs

The interviews and questionnaires are conducted at no cost to you. You will receive no payment or reimbursement for any expense related to taking part in this study.

Benefits

It is not expected that you will benefit from participation in this study. However, information from this study may benefit future patients with malignant liver tumors to help healthcare workers make timely, informed decisions about care and treatment.

Confidentiality

Medical records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. The research study staff will have access to your study records and medical chart at St. Boniface Hospital. Information gathered in this research study may be published or presented in public forums; however, your name will not be used or revealed. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Organizations, such as the University of Manitoba Health Research Ethics Board, may inspect and/or copy your research records for audit purposes. By signing the attached Informed Consent Form you consent to direct access to your medical records.

Voluntary Participation/Withdrawal from the   Study

Your participation in this study is strictly voluntary. You may refuse to participate or you may withdraw from the study at any time. Your decision not to participate or to withdraw from the study will not effect the health care you receive.

You are free to ask any questions that you may have about your rights as a research participant. If any questions come up during or after the study, contact the research team: _____ at (204) 237-2975.

For questions about your rights as a research participant, you may contact the University of Manitoba-Bannatyne Campus Research Ethics Board at (204)-789-3389.

Do not sign this consent unless you have had a chance to ask questions and have received satisfactory answers to all your questions.

Statement of Consent

I have read this consent form. I have had the opportunity to discuss this research with research staff. I have had my questions answered by them in a language I understand. The risks and benefits have been explained to me. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of my records that relate to this study by the University of Manitoba Research Ethics Board for quality assurance purposes.

By signing this consent form, I have not waived any legal rights that I have as a participant in a research study.

Participant Printed Name: _____   Date: _____ Participant Signature: _____

Research Staff

I, the undersigned, have fully explained the relevant details of this study to the participant named above and believed that the participant has understood and has knowingly given their consent.

Printed Name: _____   Date: _____

Signature: _____

Role in the study: _____

Appendix 2. Resources Used for Each Case-Mix Group at CancerCare Manitoba

Treatment Regime #1 - Irinotecan
Description:
Irinotecan q 3 weeks   350 mg/m^2 ≈ 5 cycles

a)   Initial Treatment Planning Visit – Clinic

RN* = 0.33 hrs
CC** = 0.25 hrs
LT ***= 0.16 hrs

* Initial patient education, explanation of requisitions, appointments, lab visits,
  Etc.
**Chart preparation
*** Peripheral blood draw

b)   Initial Treatment-Treatment Room
RN* = 2.0 hrs
CC = 0.16 hrs
PM= 0.50 hrs
PT= 0.33 hrs
* Actual hands on ≈ 1 hour, which would include pre-medication, chemotherapy
administration and 0.5 hr teaching/reinforcement

                             c)   Drugs and Supplies
Irinotecan 350 mg/m^2
Granisetron 1 mg P.O.   Pre Medication
Dexamethasone 12 mg P.O.   ' '
Atropine .25-1.0 mg IV push   ' '
IV Start Supplies:
N/S 250-500 ml
IV tubing
Jelco needle
Alcohol swab
Non-sterile 2x2 gauze
Tape
Bandage to D/C

d)   Symptom Management:
Loperamide P.O.

e)   Follow up/Case Management (± clinic visit)

         RN= 0.25 hrs
         CC= 0.16 hrs
         LT =0.16 hrs

Treatment Regimen #2   Saltz Regimen   (1 cycle = 6 weeks)
Description:
Irinotecan ≈ 125 mg/m^2 over 90-120 minutes ⎤   weekly x 4 weeks
FUFA ≈ 10 minutes   ⎦   then 2 weeks off

Cycles given → until disease progression on average 7-8 cycles maximum

a)   Initial Treatment Planning Visit – Clinic

        RN* = 0.33 hrs
        CC** = 0.25 hrs
        LT ***= 0.16 hrs
        * Initial patient education, explanation of requisitions, appointments, lab visits,
           Etc.
        **Chart preparation
        *** Peripheral blood draw

b)   Initial Treatment-Treatment Room
        RN* = 2.5 hrs
        CC = 0.16 hrs
        PM= 0.50 hrs
        PT= 0.33 hrs

        * Actual hands on ≈ 1 hour, which would include pre-medication, chemotherapy
        administration and 0.5 hr teaching/reinforcement

c)   Drugs and Supplies
        Irinotecan 350 mg/m^2
        FUFA
        Granisetron 1 mg P.O.   Pre Medication
        Dexamethasone 12 mg P.O.   ' '
        Atropine .25-1.0 mg IV push   ' '
        IV Start Supplies:
        N/S 250-500 ml
        IV tubing
        Jelco needle
         Alcohol swab
        Non-sterile 2x2 gauze
        Tape
        Bandage to D/C

        d)   Symptom Management:

1)   If crampy and/or diarrhea occurs within 24 hours – patient to return to clinic or ER for Atropine 0.25 – 1.0 mg IV push with RN = 1.0 hrs using supplies for IV start

2)   If cramping and/or diarrhea occurs after 24 hours of Treatment – patient takes Loperamide 4 mg at first symptom then 2 mg q2h until symptom free

e)   Follow Up / Case Management

RN = 0.25 hrs
CC = 0.16 hrs   } 1 Clinic Visit
Lab = 0.16 hrs

And   RN = 0.25 hrs
CC = 0.16 hrs   } 2 Phone Calls

Treatment Regime #3   Xeloda – Oral Chemotherapy
1 cycle = { 2 weeks on
            1 week off
# of cycles – 6 then progress to 2nd line therapy.

a)   Initial Treatment Planning Clinic Visit

        RN* = 0.33 hrs
        CC** = 0.16 hrs
        Lab*** = 0.16 hrs
        * Initial patient education, explanation of requisitions, appointments, lab visits,
          Etc.
        **Chart preparation
        *** Peripheral blood draw
Note: Oral chemotherapy therefore no treatment room visit

b)   Follow Up / Case Management

        RN = 0.25 hrs
        CC = 0.16 hrs   } 1 Clinic Visit
        LT = 0.16 hrs

        RN = 0.25 hrs   } 1-2 Phone Calls
        CC = 0.16 hrs

        Cycle # 2-6

a)   Pre-Treatment Clinic Visit
        RN = 0.08 hrs
        CC = 0.16 hrs
        Lab = 0.16 hrs

b)   Follow Up / Case Management
        RN = 0.25 hrs
        CC = 0.16 hrs   } 1 Clinic Visit
        LT = 0.16 hrs

        RN = 0.25 hrs   } 1-2 Phone Calls
        CC = 0.16 hrs

Treatment Regime #4   Roswell-Park Regime
*No Irinotecan involved in this regime at CCMB

1 cycle = q week x   6 weeks on Treatment   8-week cycle
                       2 weeks off
 # of cycles - 4 cycles
5 FU 500 mg/m^2 IV push midway through Leucovorin infusion - Leukovorin 500 mg/ m^2
– 2-hour infusion

a)   Initial Treatment Planning Clinic Visit

        RN* = 0.33 hrs
        CC**= 0.33 hrs
        Lab*** = 0.16 hrs
        * Initial patient education, explanation of requisitions, appointments, lab visits,
          Etc.
        **Chart preparation
        *** Peripheral blood draw

b)   Initial Treatment – Treatment Room Visit
        RN= 2.5 hrs
        CC = 0.16 hrs
        PM= 0.50 hrs
        PT= 0.67 hrs
        * Actual hands on ≈ 1 hour, which would include pre-medication, chemotherapy
        administration and 0.5 hr teaching/reinforcement

c)   Drugs and Supplies
        Drugs
        Granisetron 1 mg P.O.   Pre Medication
        Dexamethasone 12 mg P.O.   ' '
        Maxeran 20 mg P.O.   ' '
         5FU
        Leucovorin
        IV Start Supplies:
        N/S 250-500 ml
        IV tubing
        Jelco needle
         Alcohol swab
        Non-sterile 2x2 gauze
        Tape
        Bandage to D/C

d) Symptom Management:

RN= 1.0 hrs
Loperamide P.O.
Supportive IV therapy required for IV hydration and treatment of febrile neutropenia
IV Start Supplies:
N/S 250-500 ml
IV tubing
Jelco needle
Alcohol swab
Non-sterile 2x2 gauze
Tape
Bandage to D/C

e)   Follow Up / Case Management
RN = 0.25 hrs
CC = 0.16 hrs   x 1 Clinic Visit
LT = 0.16 hrs

RN = 0.25 hrs   x 1-2 Phone Calls
CC = 0.16 hrs

Appendix 3
Health Utilities Index Mark 2 (HUI2):
Multi-Attribute Health Status Classification System

Attribute	Level	Description
SENSATION	1	Able to see, hear, and speak normally for age.
	2	Requires equipment to see, hear, or speak.
	3	Sees, hears, or speaks with limitations even with equipment.
	4	Blind, deaf, or mute.
MOBILITY	1	Able to walk, bend, lift, jump, and run normally for age.
	2	Walks, bends, lifts, jumps, or runs with some limitations but does not require help.
	3	Requires mechanical equipment (such as canes, crutches, braces, or wheelchair) to walk or get around independently.
	4	Requires the help of another person to walk or get around and requires mechanical equipment as well.
	5	Unable to control or use arms and legs.
EMOTION	1	Generally happy and free from worry.
	2	Occasionally fretful, angry, irritable, anxious, depressed, or suffering night terrors.
	3	Often fretful, angry, irritable, anxious, depressed, or suffering night terrors.
	4	Almost always fretful, angry, irritable, anxious, depressed.
	5	Extremely fretful, angry, irritable, or depressed usually requiring hospitalization or psychiatric institutional care.
COGNITION	1	Learns and remembers schoolwork normally for age
	2	Learns and remembers schoolwork more slowly than classmates as judged by parents and/or teachers.
	3	Learns and remembers very slowly and usually requires special educational assistance.
	4	Unable to learn and remember.
SELF-CARE	1	Eats, bathes, dresses, and uses the toilet normally for age.
	2	Eats, bathes, dresses, or uses the toilet independently with difficulty.
	3	Requires mechanical equipment to eat, bathe, dress, or use the toilet independently.
	4	Requires the help of another person to eat, bathe, dress, or use the toilet.
PAIN	1	Free of pain and discomfort.
	2	Occasional pain; discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities.
	3	Frequent pain; discomfort relieved by oral medicines with occasional disruption of normal activities.
	4	Frequent pain, frequent disruption of normal activities; discomfort requires prescription narcotics for relief.
	5	Severe pain; pain not relieved by drugs and constantly disrupts normal activities.
FERTILITY	1	Ability to have children with a fertile spouse.
	2	Difficulty in having children with a fertile spouse.
	3	Unable to have children with a fertile spouse.
	3	Moderate pain that prevents a few activities.
	4	Moderate to severe pain that prevents some activities.
	5	Severe pain that prevents most activities.

Appendix 4
Health Utilities Index Mark 3 (HUI3):
Multi-Attribute Health Status Classification System

Attribute	Level	Description
VISION	1	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.
	2	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, but with glasses.
	3	Able to read ordinary newsprint with or without glasses but unable to recognize a friend on the other side of the street, even with glasses.
	4	Able to recognize a friend on the other side of the street with or without glasses but unable to read ordinary newsprint, even with glasses.
	5	Unable to read ordinary newsprint and unable to recognize a friend on the other side of the street, even with glasses.
	6	Unable to see at all.
HEARING	1	Able to hear what is said in a group with at least three other people, without a hearing aid.
	2	Able to hear what is said in a conversation with one other person in a quiet room without a hearing aid, but requires a hearing aid to hear what is said in a group conversation with at least three other people.
	3	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, and able to hear what is said in a group conversation with at least three other people, with a hearing aid.
	4	Able to hear what is said in a conversation with one other person in a quiet room, without a hearing aid, but unable to hearing what is said in a group conversation with at least three other people even with a hearing aid.
	5	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid.
	6	Unable to hear at all.
SPEECH	1	Able to be understood completely when speaking with strangers or friends.
	2	Able to be understood partially when speaking with strangers but able to be understood completely when speaking with people who know the respondent well.
	3	Able to be understood partially when speaking with strangers or people who know the respondent well.
	4	Unable to be understood when speaking with strangers but able to be understood partially by people who know the respondent well.
	5	Unable to be understood when speaking to other people (or unable to speak at all).
AMBULATION	1	Able to walk around the neighbourhood without difficulty, and without walking equipment.
	2	Able to walk around the neighbourhood with difficulty, but does not require walking equipment or the help of another person.
	3	Able to walk around the neighbourhood with walking equipment, but without the help of another person.
	4	Able to walk only short distances with walking equipment, and requires a wheelchair to get around the neighbourhood.
	5	Unable to walk alone, even with walking equipment; able to walk short distances with the help of another person, and requires a wheelchair to get around the neighbourhood.
	6	Cannot walk at all.

Health Utilities Index Mark 3 (HUI3):
Multi-Attribute Health Status Classification System (cont'd)

Attribute	Level	Description
DEXTERITY	1	Full use of two hands and ten fingers.
	2	Limitations in the use of hands or fingers, but does not require special tools or help of another person.
	3	Limitations in the use of hands or fingers, is independent with use of special tools (does not require the help of another person).
	4	Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with use of special tools).
	5	Limitations in use of hands or fingers, requires the help of another person for most tasks (not independent even with use of special tools).
	6	Limitations in use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools).
EMOTION	1	Happy and interested in life.
	2	Somewhat happy.
	3	Somewhat unhappy.
	4	Very unhappy.
	5	So unhappy that life is not worthwhile.
COGNITION	1	Able to remember most things, think clearly and solve day-to-day problems.
	2	Able to remember most things, but have a little difficulty when trying to think and solve day-to-day problems.
	3	Somewhat forgetful, but able to think clearly and solve day-to-day problems.
	4	Somewhat forgetful, and have a little difficulty when trying to think or solve day-to-day problems.
	5	Very forgetful, and have great difficulty when trying to think or solve day-to-day problems.
	6	Unable to remember anything at all, and unable to think or solve day-to-day problems.
PAIN	1	Free of pain and discomfort.
	2	Mild to moderate pain that prevents no activities
	3	Moderate pain that prevents a few activities.
	4	Moderate to severe pain that prevents some activities.
	5	Severe pain that prevents most activities.