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Radio Frequency Ablation for Primary Liver Cancer

An Evidence-Based Analysis

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series.*

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practicing medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

If you are aware of any current additional evidence to inform an existing evidence-based analysis, please contact the Medical Advisory Secretariat: MASInfo@moh.gov.on.ca. The public consultation process is also available to individuals wishing to comment on an analysis prior to publication. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

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Abbreviations

CI	Confidence interval
HCC	Hepatocellular carcinoma
ICER	Incremental cost-effectiveness ratio
LYG	Life-year gained
RFA	Radio frequency ablation
PEI	Percutaneous Ethanol Injection
TACE	Transcatheter arterial chemoembolization

Executive Summary

Objective

The Medical Advisory Secretariat undertook a review of the evidence on the safety, clinical effectiveness, and cost-effectiveness of radio frequency ablation (RFA) compared with other treatments for unresectable hepatocellular carcinoma (HCC) in Ontario.

Background

Liver cancer is the fifth most common type of cancer globally, although it is most prevalent in Asia and Africa. The incidence of liver cancer has been increasing in the Western world, primarily because of an increased prevalence of hepatitis B and C. Data from Cancer Care Ontario from 1998 to 2002 suggest that the age-adjusted incidence of liver cancer in men rose slightly from 4.5 cases to 5.4 cases per 100,000 men. For women, the rates declined slightly, from 1.8 cases to 1.4 cases per 100,000 women during the same period. Most people who present with symptoms of liver cancer have a progressive form of the disease. The rates of survival in untreated patients in the early stage of the disease range from 50% to 82% at 1 year and 26% to 32% at 2 years. Patients with more advanced stages have survival rates ranging from 0% to 36% at 3 years. Surgical resection and transplantation are the procedures that have the best prognoses; however, only 15% to 20% of patients presenting with liver cancer are eligible for surgery. Resection is associated with a 50% survival rate at 5 years.

The Technology: Radio Frequency Ablation

RFA is a relatively new technique for the treatment of small liver cancers that cannot be treated with surgery. This technique applies alternating high-frequency electrical currents to the cancerous tissue. The intense heat leads to thermal coagulation that can kill the tumour. RFA is done under general or local anesthesia and can be done percutaneously (through the skin with a small needle), laparoscopically (microinvasively, using a small video camera), or intraoperatively. Percutaneous RFA is usually a day procedure.

Methods

The leading international organizations for health technology assessments, including the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) and the International Network of Agencies for Health Technology Assessment (INAHTA), were scanned for previous systematic reviews on RFA. The Cochrane Library Database was also scanned. The most recent systematic review examined the literature up to October 2003. Five previous health technology assessments were found.

To update the international systematic reviews, the Medical Advisory Secretariat systematically reviewed the literature from January 1, 2003 to the third week of April 2004. Peer-reviewed literature from EMBASE, MEDLINE (including in-process and other nonindexed citations) and the Cochrane Library Database were searched for the following search terms:

- Catheter ablation
- Radiofrequency or radio-frequency or radio frequency or RFA or RFTA
- Liver neoplasms or liver cancer or hepatocellular or hepatocellular or hepatic
- Cancer

The inclusion criteria were as follows:

- Population: patients with primary hepatocellular carcinoma
- Procedure: RFA used as the only treatment (not as an adjunct)
- Language: publication in English
- Published health technology assessments, guidelines, and peer-reviewed literature (abstracts and in-progress manuscripts)
- Outcomes: therapeutic response (% complete ablation), mortality, survival, and tumour recurrence

Grey literature, where relevant, was also reviewed.

Summary of Findings

The Medical Advisory Secretariat included 5 previous health technology assessments from 2002 to 2004 and 9 peer-reviewed studies from January 2003 to April 2004 in its review. The health technology assessments suggested that RFA is as safe and effective for treating up to 3 or 4 small (< 4 to 5 cm), unresectable liver tumours in the short term (2 years). One small randomized controlled trial (RCT) that compared RFA with percutaneous ethanol injection (PEI), another ablative technique, suggested that RFA is at least as safe and effective for small unresectable primary liver tumours compared to PEI. However, the patient populations and comparison technologies in the peer-reviewed literature and the previous health technology assessments were heterogeneous; therefore, meta-analyses could not be performed.

RFA has also been used to treat colorectal and neuroendocrine liver metastases and kidney, lung, breast, and bone cancer. Although this report did not focus on these indications because of a paucity of published evidence of effectiveness, some individual patients with the above indications may benefit from RFA; therefore, RFA may quickly diffuse into these areas. Various clinical trials focussing on these indications are underway.

Conclusions

- Level 2 evidence suggests RFA is as safe and perhaps more effective than percutaneous ethanol injection to treat HCC.
- RFA and percutaneous ethanol injection are more effective and more cost-effective than transcatheter arterial chemoembolization.
- RFA is marginally more expensive, yet more cost-effective than percutaneous ethanol injection.
- Complications are few, but experienced interventional radiologists should do RFA.
- RFA may benefit some patients with liver metastases or other primary cancers, although published evidence of effectiveness has not yet been established.

Objective

To conduct an evidence-based analysis on the effectiveness and cost-effectiveness of radio frequency ablation (RFA) for hepatocellular carcinoma (HCC), or primary liver cancer. A systematic review of the literature was supplemented with health care system information to allow recommendations for the provision of this technology in Ontario to be made. Although RFA has been proposed for liver metastases and other disease sites, this report focuses on RFA for primary liver cancer. The safety and effectiveness of RFA for other indications will be reviewed later, when more evidence is available.

Liver cancer is the fifth most common type of cancer globally. (1;2) Although liver cancer is most prevalent in Asia and Africa, its incidence is increasing in more industrialized countries, primarily due to an increase in the prevalence of hepatitis B and C. (3;4) About 1.5% of incident cancers in Ontario in 2000 were of the liver. (5) Most people who present with symptoms of liver cancer have a progressive form of the disease. Survival in untreated patients in the early disease stage ranges from 50% to 82% at 1 year and 26% to 32% at 2 years. (1;6) Patients with more advanced stages of the disease have rates of survival ranging from 0% to 36% at 3 years. (1;6)

RFA is a relatively new technique for the treatment of small HCC that cannot be treated with surgery. This technique applies alternating high-frequency electrical currents to the cancerous tissue. The intense heat leads to thermal coagulation that can kill the tumour. (3;4) RFA is performed under general or local anesthesia and can be done percutaneously (through the skin with a small needle), laparoscopically (microinvasively, using a small video camera), or intraoperatively. Percutaneous RFA is usually a day procedure.

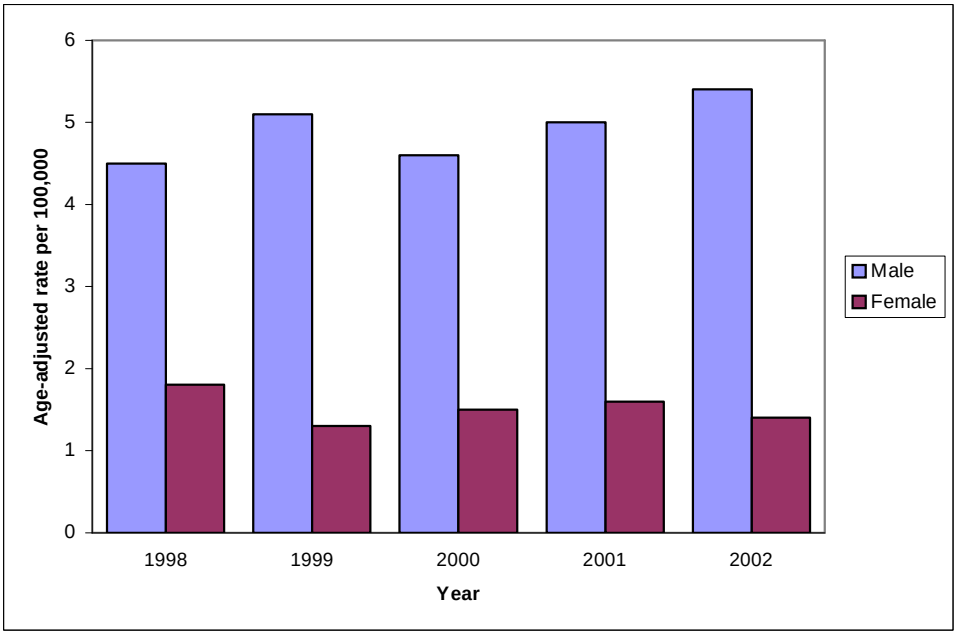
Background

Clinical Need: Target Population and Condition

Figure 1 shows the age-standardized incidence of liver cancer per 100,000 people in Ontario from 1998 to 2002 (Ontario Cancer Registry Data, Cancer Care Ontario; accessed 2004). The incidence of liver cancer has risen slightly among men during this period from 4.5 cases to 5.4 cases (per 100,000 men). The incidence has fallen slightly for women, from 1.8 cases to 1.4 cases (per 100,000 women). About 1.5% of incident cancers in Ontario in 2000 were of the liver. (5)

The natural history of untreated liver cancer is difficult to ascertain. Liver function, degree of cirrhosis, and other clinical factors are associated with survival. (1;6) Survival in untreated patients in the early disease stage ranges from 50% to 82% at 1 year and 26% to 32% at 2 years. The rate of survival for patients with more advanced stages of the disease ranges from 0% to 36% at 3 years. (1;6)

Figure 1: Age-adjusted Incidence* of Primary Liver Cancer by Sex in Ontario, 1998 to 2002



*per 100,000 people

Data courtesy of the Cancer Registry, Cancer Care Ontario, May 2004

Prognosis and the severity of liver disease is estimated through a classification system that is widely used by clinicians. The Child-Turcotte-Pugh classification system (7) combines hepatic features, such as albumin and bilirubin levels, with clinical indications such as prolongation of prothrombin time, evidence of ascites (abnormal buildup of fluid in the abdomen), and encephalopathy (brain dysfunction). Table 1 lists the clinical features on which the system is based. The points are added to gain an understanding of the degree of liver dysfunction. Class A (0 to 1 point) is associated with a good prognosis, Class B (2 to 4 points) is associated with moderate prognosis, and Class C (≥ 5 points) is associated with a poor prognosis.

Existing Treatments for Primary Liver Cancer

The choice of treatment for patients with primary liver cancer depends on the size and number of tumours, the presence and extent of cirrhosis, and the presence of vascular invasion. (3;6) The only potentially curative treatments are transplantation and surgical resection.

Table 1: Point System to Determine Liver Function, Child-Turcotte-Pugh Class*

	Number of Points		
	0	**1**	**2**
Albumin, g/dL	> 3.5	2.8–3.5	< 2.8
Bilirubin, mg/dL	< 2	2–3 mg	> 3
Prolongation of Prothrombin time, seconds	< 4	4–6	> 6
Ascites	0	Controlled with routine medical therapy	Refractory to medical therapy
Encephalopathy	0	Controlled with routine medical therapy	Refractory to medical therapy

*Once points are added: Class A: 0 to 1 point, good prognosis; Class B: 2 to 4 points, moderate prognosis; Class C: 5 or more points, poor prognosis

Data from www.aafp.org/afp/990415ap/223.html and

Pugh RN, Murray-Lyon et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60:646-649.

Survival rates for resection range from 40% to 70% at 5 years for small tumours. (1;3;6) Survival rates for transplantation at 5 years are about 80% for stage I cancer, 65% for stage II, 40% to 60% for stage III, and 10% to 15% for stage IV. (6) However, only 15% to 20% of patients with liver cancer are eligible for resection. (3;6) About 5% of patients with HCC in Ontario may receive a transplant in a given year. (Personal communication, Medical Consultant, 2004) Factors associated with eligibility for resection or transplantation are patient-specific pathology, anatomical distribution of the disease, size and number of tumours, and existence of comorbid conditions.

If surgical resection and transplantation are not feasible, other possible treatments include chemoembolization, immunotherapy, and ablative techniques that kill the tumour cells directly, such as percutaneous ethanol injection (PEI), or cryotherapy. (3;6) Systemic and regional chemotherapy are not indicated for HCC, because their effectiveness is limited. (6;8) A description of some of these treatments is in the paragraphs that follow.

Transcatheter arterial embolization and transcatheter arterial chemoembolization (TACE): *During transcatheter arterial embolization, an embolizing agent, a solution of tiny particles injected to create a small blockage, is administered through a catheter that is placed directly in the hepatic artery that carries blood to the tumour in the liver. Embolization alone can result in the localized destruction of the tumour. Combined localized chemotherapy and embolization (i.e., TACE) is achieved through the same mechanism as transcatheter arterial embolization. Higher doses of chemotherapy may be used than with systemic chemotherapy, because the delivery directly into the hepatic artery can reduce the potential of serious systemic side effects. (6;9;10)*

In a meta-analysis of TACE for unresectable HCC, (11) investigators found a lower overall 2-year mortality rate (odds ratio [OR] 0.54 [95% CI, 0.33–0.89], P=.015) compared with conservative treatment. Reports of mortality differences between TACE and transcatheter arterial embolization are mixed, indicating that adding chemotherapy may or may not improve outcomes. Adequate hepatic artery

function is necessary for this treatment.

Ablative techniques: *These techniques collectively involve the injection of an agent or the targeted application of generated heat, freezing, sound waves, or microwaves that kill the tumour. Some of these techniques are still experimental and have limited data to support their routine use. RFA and PEI are the ablative techniques that have been used most frequently. Ablation is usually offered to patients ineligible for transplantation. (3)*

Percutaneous ethanol injection (PEI): *Developed in 1983, (12) absolute ethanol (i.e., alcohol, 99.5% or 95%) is injected into the deepest part of the tumour. As the needle is withdrawn, the alcohol diffuses into the cells of the tumour, triggering their dehydration, which subsequently kills them. The amount of alcohol needed depends on the pathology of the tumour. The number of treatments necessary for complete ablation is about twice the diameter of the tumour (cm). (3;13) Based on case series and retrospective studies, the 1-year survival rates for patients with lesions 5 cm or less range from 83% to 100%. The 5-year rates of survival can be as high as 70% in carefully selected patients. (3;6)*

Cryoablation: *In this "cold" procedure, liquid nitrogen is delivered to the liver tumour, guided by ultrasound using a specially designed probe. Ice crystal formation during the rapid freezing process kills the tumour. (10) This procedure is not done routinely in Ontario now, due to the observation of major complications to the liver (Personal communication, Medical Consultant, 2004).*

Microwave coagulation therapy: *This technique relies on heat-energy conversion to destroy cancerous tissue using a high-frequency electromagnetic wave. Coagulation and tumour death is achieved by polarizing water molecules that are heated by alternating microwaves. Microwave coagulation therapy is applied with an electrode that is placed in the tumour. (10) This technique is not used routinely in Ontario. (Personal communication, Medical Consultant, 2004)*

New Technology Being Reviewed: Radio Frequency Ablation

RFA is a relatively new technique to treat patients with small unresectable HCCs. It uses high-frequency alternating currents to heat tumours of 3 to 5 cm up to 60°C, which leads to thermal coagulation and ultimately kills the tumours. A generator operating at 50 to 200 watts of power sends electrical impulses to a 15- to 21-gauge radio frequency probe with a 2 to 3 cm tip that is inserted into the hepatic lesion. Different types of electrode needles may be required for different tumour sizes and shapes. For example, elliptical tumours, or those beside a blood vessel, can be treated with expandable electrodes or by multiple or sequential insertions of a single electrode. A ground electrode is also attached to the patient. (3;14)

Patients eligible for RFA are usually ineligible for surgery because of their age, certain characteristics of their tumours, and because they have other (comorbid) conditions. (3;14) These patients typically have 4 or fewer lesions less than 5 cm in diameter in the liver (excluding those patients with tumours in the perihilar region). RFA has been used with surgery when tumours are less than 1 cm in diameter. However, these patients are different from those with unresectable lesions and are usually considered separately.

RFA may be done percutaneously, laparoscopically, or intraoperatively, but there are no trials that compare these modes of delivery. The use of these approaches may influence outcomes. Open or laparoscopic RFA may allow the detection of small tumours not seen with prior imaging. Most often, ultrasound is used to guide needle placement and to monitor the ablation. More recently, computer tomography (CT) or electrodes guided by magnetic resonance (MR) imaging have been developed. (14) (Personal communication, Medical Consultant, 2004)

Treatment sessions are usually from 1.5 to 4 hours (Personal communication, Medical Consultant, 2004).

Complete ablation may occur in 1 session, but the number of sessions varies according to the size of the lesion and the type of electrode delivery system. (14) During and after treatment, an elliptical lesion with ill-defined margins can be seen. This persists up to several months after treatment. Follow-up with CT or MR imaging often cannot distinguish between an ablated tumour and residual disease. This may be seen as a major disadvantage of RFA. (14)

RFA has also been proposed for metastatic liver cancer, particularly for colorectal disease. In Canada, 13.9% of new cancers in men and 12.4% of new cancers in women were colorectal, making this the third most common type of incident cancer, according to Canadian Cancer Society statistics published in 2004. (2) At diagnosis, about 25% of patients with primary colorectal cancer will have liver involvement and 25% more will have metastatic liver disease as their cancer progresses. (3) Few studies have examined RFA for colorectal or cancers metastasized to the liver, and, at this time, systematic reviews have not found evidence for its effectiveness. (9;10;15)

Tumours in the bone, kidney, lung, and breast have also been treated with RFA, with very little documentation of clear effectiveness. Many clinical trials are underway that may help to elucidate the effectiveness of RFA for these indications.

Regulatory Status

Health Canada has licensed 2 types of systems for coagulation necrosis of soft-tissue lesions. Boston Scientific Corporation (San Jose, CA), formerly Radiotherapeutics, has the following systems indicated for the induction of coagulation necrosis of soft tissue:

- MRI LeVeen Electrode (licence 61842, Class 2)
- RF 2000 Radiofrequency Generator with a 3.5cm LeVeen needle electrode (licence 9161, Class 3)
- RF 3000 Radiofrequency Generator with 4.0 cm LeVeen needle electrode (licence 25512, Class 3)

The generating systems rely on the monitoring of impedance level to determine how long to ablate a tumour.

Rita Medical Systems Inc (Mountain View, CA; distributed by Sigmacon Health Systems Corporation in Toronto, ON) have the following systems licensed for use in percutaneous, laparoscopic, or intraoperative electrosurgical procedures in the coagulation and ablation of soft tissue.

- Rita Electrosurgical RF Generator (licence 15546; Class 3)
- Electrosurgical RF Generator (licence 18482; Class 3)
- Rita Electrosurgical Array Device (licence 10144; Class 2). This licence includes the following devices that deliver energy generated from an RF generator in percutaneous, laparoscopic, or intraoperative coagulation and ablation of soft tissue:
  - Rita Electrosurgical Array Device
  - Rita Starburst XL Electrosurgical Device
  - Rita Starburst Electrosurgical Device
  - Rita Starburst XLI Electrosurgical Device
  - Rita Starburst FLEX Electrosurgical Device
  - Rita Starburst MRI Electrosurgical Device
  - Rita Starburst SDE Electrosurgical Device

These systems rely on a temperature gauge to determine the length of ablative treatment.

Literature Review on Effectiveness

Objective

To summarize the evidence on the safety, clinical effectiveness, and cost-effectiveness of RFA compared with other treatments for unresectable HCC in Ontario.

Methods

The leading international organizations for health technology assessment were scanned for previous systematic reviews about RFA. These were the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) and the International Network of Agencies for Health Technology Assessment (INAHTA). The Cochrane Library Database was also scanned. The most recent systematic review examined the literature up to October 2003.

To update these international systematic reviews, the Medical Advisory Secretariat systematically reviewed the peer-reviewed literature from January 1, 2003 to the third week of April 2004. Peer-reviewed literature from EMBASE, MEDLINE (including in-process and other nonindexed citations), and the Cochrane Library Database were searched for the following search terms:

- Catheter ablation
- Radiofrequency or radio-frequency or radio frequency or RFA or RFTA
- Liver neoplasms or liver cancer or hepato-cellular or hepatocellular or hepatic
- Cancer

The inclusion criteria were as follows:

- Population: patients with primary hepatocellular carcinoma
- Procedure: RFA used as the only treatment (not as an adjunct)
- Language: publication in English
- Published health technology assessments, guidelines, and peer-reviewed literature (abstracts and in-progress manuscripts)
- Outcomes: therapeutic response (% complete ablation), mortality, survival, and tumour recurrence

Grey literature, where relevant, was also reviewed.

Results of Literature Review

Summary of Existing International Health Technology Assessments

According to the Medical Advisory Secretariat's review process, previous international systematic reviews and health technology assessments on RFA were identified and critically appraised. Five systematic reviews were found. Detailed descriptions of these reviews are in Appendix 1. Brief descriptions and conclusions are in Table 2.

The systematic reviews were published from 2002 to 2004. They relied on similar literature with few new

comparative studies reported. For example, the earlier health technology assessments relied on abstracts that were later published and subsequently included in the most recent assessments.

The most recent Cochrane review (16) included 1 RCT (17) comparing RFA with PEI, and 1 older RCT comparing RFA with microwave ablation therapy, though the latter did not include survival outcomes. (18) Only the Blue Cross Blue Shields (14) review attempted to limit patient heterogeneity by comparing studies where either RFA or PEI was the sole treatment for patients with small HCC. According to the authors of the Blue Cross Blue Shields study, these 2 procedures are indicated for similar patient populations. Despite the attempt at homogeneity, a meta-analysis still was not possible, because there was only 1 well-designed head-to-head trial (the same RCT as in the Cochrane review). (17)

The major complication rates from RFA across the health technology assessments, ranged from 3% to 8%, although complications were defined differently among the reviews. (4;9;10) About one quarter of patients were noted to feel pain resulting from the RFA procedure. (16;10) The potential for needle track seeding (diffusing cancerous cells as the needle is retracted) was of concern; however, the rate of occurrence of this was small. (14) The complete ablation rate was better for RFA (>85%) compared with PEI (70%–96%) in the Blue Cross Blue Shields report, (14) although this difference was not significant. RFA was associated with a slightly increased benefit (16) (relative risk [RR] 1.14 [95% CI, 1.02–1.19]) with fewer treatment sessions necessary for complete ablation compared with PEI. Tumour recurrence across varying time frames ranged from 12% to 14% for RFA (9;10;16) and was higher for other comparative techniques (24% for microwave therapy (9;16); 3.5%–26% for PEI). (4;14)

The rate of overall survival for RFA treatment at 2 years was 63% to 98% compared with 62% to 92% for PEI treatment, and 45% to 62% using RFA compared with 43% to 84% for PEI at 3 years, suggesting equivalent outcomes of the 2 procedures. (14) Local recurrence-free survival and event-free survival also favoured RFA at 2 years (RR 0.17 [95% CI, 0.06–0.5], P=.002; RR 0.48 [95% CI, 0.27–0.85], P=.012). (4;9;14;16)

The review by the Medical Services Advisory Committee in Australia included an economic analysis that supported the use of RFA over PEI. This will be discussed in detail further in this report.

With the exception of the earliest systematic review, (10) the collective conclusion based on the limited available evidence was that percutaneous RFA was effective in treating patients with small, unresectable HCC, but not patients with colorectal or other liver metastases. RFA was determined to be as safe as other current treatments.

Table 2: Summary of Existing Health Technology Assessments, 2002 to 2004*

	Cochrane, United Kingdom 2004 (16)	Blue Cross Blue Shields, United States 2003 (14)	NICE, United Kingdom 2003 (4;20)	Medical Services Advisory Committee, Australia 2003 (9)	ASERNIP-S, Australia 2002 (10)
Literature Included	2 RCTs: RFA vs. PEI, 2003 RFA vs. Microwave, 2001	1 RCT: RFA vs. PEI, 2003 -2 comparison -12 case series PEI: -3 comparison -11 case series	ASERNIP-S report 4 comparison	To January 2003 1 small RCT 3 RCT abstracts 3 non-RCTs	Systematic review to May 2002 4 RCTs, 1 quasi-randomized trial and 7 retrospective non-RCTs
Population/ Comparators	HCC	Inoperable liver cancer (small tumours) RFA vs. PEI only	RFA vs. any other treatment for primary HCC or metastatic disease	RFA vs. surgical or ablative treatment of primary or secondary liver cancer	RFA vs. surgery and ablative treatments for primary and secondary liver cancer
Complications	Pain: 29% RFA 25% PEI	Hospitalization: 2%–3% for RFA and PEI	3%–5% based on patient selection and surgical expertise	2% major 8% minor	Pain: RFA > PEI (RR=3.13; 95% CI, 1.90–5.14)
Mortality				2% RFA vs. 12% PEI at 2 years 0% RFA vs. 30% TACE	
2- year overall survival	98% RFA 88% PEI (NS)	63%–98% RFA 63%–92% PEI (40%–64% medical management*)			
2- year local recurrence- free survival **2-year event-free survival**	64% RFA 43% PEI (P=.01)	RR=0.17; 95% CI, 0.06–0.5; P=.002 RR=0.48; 95% CI, 0.27–-0.85, P=.012		96% RFA 62% PEI (P<.01)	96% RFA 62% PEI (P<.01)

3-YEAR OVERALL SURVIVAL		45-62% RFA 43%–84%PEI (13%–28% medical management*) *medical not empirically evaluated			
Recommendations	Need RCTs with homogeneous patients and standardized outcomes	RFA is as safe and effective as PEI for small, unresectable HCCs with no extrahepatic disease	Patient selection, monitoring, and surgical expertise important for positive outcomes Patients should be aware of risks & benefits and short follow-up of studies	Public funding should support percutaneous RFA for treatment of non-resectable hepatocellular carcinoma	No trial assessed RFA adequately. RFA is safe compared with other treatments. Need further research, including a registry

*RFA represents radio frequency ablation; PEI, percutaneous ethanol injection; TACE, transcatheter arterial chemoembolization; HCC, hepatocellular carcinoma; RCT, randomized controlled trial; NS, not significant

The reviews collectively stated that the quality of research on RFA to date poses methodological difficulties. Only a few small comparative trials have been done, with or without randomization. Study sample sizes have been relatively small, ranging from about 30 to just over 100 patients. Many of the studies also have included heterogeneous patient populations and a mix of outcome measures and modes of RFA, so that data across studies could not be pooled and effectiveness could not be stated definitively. For these reasons, no meta-analyses have been performed.

Summary of Medical Advisory Secretariat Literature Review

To augment the previous international health technology assessments, 100 articles were retrieved through a keyword search of the peer-reviewed literature from January 2003 to the third week in April 2004. Of these, 91 were excluded due to the following reasons:

- 20 studies – the focus was on imaging techniques used with RFA.
- 18 studies had mixed patient populations (eligible/ineligible for resection); HCC and metastases were aggregated in the analysis.
- 12 studies did not study patients with liver cancer.
- 11 studies had fewer than 20 patients.
- 13 studies combined therapies.
- 6 studies were review articles.
- 2 studies were discussion papers.
- 6 studies did not focus on RFA.
- 3 studies were cited in the most recent health technology assessment (Blue Cross Blue Shields report).

Table 3 lists the 9 studies included in this review according to the Medical Advisory Secretariat's criteria for quality of evidence.

Table 3: Levels of Quality of Evidence

Study Design	Level of Evidence	Number of Eligible Studies
Large RCT unpublished but reported to an international scientific meeting	1(g)*	
Small RCT	2	1
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	1
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	1
Case series (single site)	4c	5
Retrospective review, modeling	4d	1
Case series presented at international conference	4(g)	

*g=grey literature

Small Randomized Controlled Trial

One small RCT (17) (Level 2 evidence) was found through the systematic review. This study was included in the Cochrane (16) and Blue Cross Blue Shields reports (14), and its abstract (19) was included in the NICE (4) and the Australian reports (9;10). Because it is the only well-conducted randomized trial reported, its detailed analysis is warranted here.
Inclusion criteria for this RCT were as follows:

- Adult patients with liver cirrhosis and a single nodule ≤ 5 cm or 3 nodules ≤ 3 cm
- Nodules located at least 1 cm from the hepatic hilum or gallbladder
- No evidence of vascular involvement or extrahepatic metastases
- Hepatic cirrhosis classified by Child-Turcotte-Pugh Class A or B
- Prothrombin time ratio (normal time/patient's time > 50%)
- Platelet count > 50,000 mm^3
- No previous treatment for HCC
- Ineligible for liver transplant or surgery

Ultrasound and CT were used to determine the number and size of HCCs and to establish no vascular involvement. After retrospectively excluding 2 patients, 102 patients were randomized blindly to receive either percutaneous RFA (n=52 patients with 71 tumours) or PEI (n=50 patients with 73 tumours).

RFA was performed using a 50-watt generator and an expandable 15-gauge electrode with 4 lateral curved electrodes on the tip and 1 larger electrode. Local anesthetic was used, and the needle was inserted according to the location of the HCC. The electrodes emitted temperatures of 95°C within 2 to 3 minutes. A single 8-minute procedure was performed for nodules 3 cm or smaller. For nodules measuring 3.1 to 5 cm, the pullback technique was used, during which as many as 6 overlapping ablations were performed in 1 to 3 needle insertions.

A treatment schedule was developed for patients randomized to receive PEI. It consisted of 4 to 8 sessions once or twice weekly, depending on the clinical characteristics of the patient. Either a 22-gauge non-cutting tip or a 21-gauge closed conical tip with multiple terminal side holes was used for the injections. At each session, 1 to 2 injections of 2 to 10 ml of sterile 95% ethanol were administered into each nodule.

The study outcomes were as follows:

- Overall survival time (from treatment to last follow-up or death)
- Local recurrence-free survival time (from treatment to local recurrence or death)
- Event-free survival time (from treatment to local recurrence, extrahepatic metastases, new HCCs, or death)
- Therapeutic effectiveness (% nodules completely ablated) after 1 week
- Multivariate analysis of treatment techniques and baseline characteristics (Cox proportional hazards)

The mean follow-up was 22.9 months (SD, 9.4) for the RFA group and 22.4 months (SD, 8.6) for the PEI group. At 3-month intervals, patients were assessed by ultrasound and alpha-fetoprotein levels. At 6 months, they were assessed by CT. If new nodules were found, patients were treated with the same regimen as at study enrollment, presuming that they still met the study criteria. Multicentric primary liver cancer was treated with TACE or another medical treatment. These patients remained in the study, and their outcomes were analyzed with everyone else's.

The authors noted that demographic and clinical characteristics were similar at baseline between groups. Seventy per cent of patients in the PEI group and 87% of patients in the RFA group were classified as Child-Turcotte-Pugh Class A. However, 30% of patients in the PEI arm were classified as Child-Turcotte-Pugh Class B, compared with 13% of patients in the RFA arm. Therefore, the patients in the RFA group may have had fewer symptoms than those in the PEI group. No patients were in Class C.

Table 4 shows the main findings from this study. At 2 years, rates of local and event-free recurrence-free survival were significantly higher in RFA-treated patients compared with PEI-treated patients (RR 0.17 [95% CI, 0.06–0.51], P=.002; and RR 0.48 [95% CI, 0.27–0.85], P=.12, respectively).

Table 4: Results of Randomized Controlled Trial Comparing Radio Frequency Ablation with Percutaneous Ethanol Injection, 2003 (17)

	Radio Frequency Ablation	*Percutaneous Ethanol Injection*
Complete ablation, n (%)	63/69 HCCs (91) in 1.1 sessions	60/73 HCCs (82) in 5.4 sessions
Mild to moderate pain requiring analgesics, n (%)	15/52 (29)	13/50 (26)
Fever (>38.5°C), n (%)	10/52 (19)	5/50 (10)
Hemorrhage, infection, needle-track seeding or hepatic failure, n	0	0
Deaths during follow up, n (%)	1 renal failure	***5/50 (10)*** 2 due to tumour progression 1 advanced cirrhosis 1 continuous alcohol abuse 1 variceal bleeding after portal venous infiltration
1-year survival rates, % (95% CI)	100	96 (90–100)
2-year survival rates, % (95% CI)	98 (93–100)	88 (78–98)
Local recurrence, n	3	13
1-year local recurrence-free survival, % (95% CI)	98 (94–100)	83 (73–94)
2-year local recurrence-free survival, % (95% CI)	***96 (90–100)*** RR=0.17 (95% CI, 0.06–0.51; P=.002)	***62 (46–77)***
New tumours, n	13	11
1-year event-free survival, % (95% CI)	86 (77-96)	77 (65–89)
2-year event-free survival, % (95% CI)	64 (49–79)	43 (27–60)
	RR=0.48 (95% CI, 0.27–0.85), P=.012)	

From Radiology 2003, Vol. 228; Lencioni RA, Allgaier HP, Cioni D, et al; Small heptocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol infection

The probability of local recurrence-free survival after RFA was significantly greater than after PEI (P=.002), as measured by Kaplan-Meier survival curves at follow-up at 6, 12, 18, 24, and 30 months. The survival benefit, however, appeared to take place after 6 months. Similarly, the probability of event-free survival significantly favoured RFA (P=.012).

As Table 5 suggests, RFA was independently protective for recurrence-free survival (adjusted RR 0.20 [95% CI, 0.05–0.73], P=.015), but not for event-free survival. Tumour size greater than

3 cm was independently associated with significantly higher rates of local recurrence-free survival (adjusted RR 8.67 [95% CI, 1.90–39.66], P=.005]) and event-free survival (adjusted RR 7.21 [95% CI, 2.26–22.97], P<.001]). The confidence intervals surrounding these estimates were quite wide, indicating that there was a high degree of variability in the true estimate, likely due to small sample size.

Table 5: Significant Factors Associated With Overall Survival, Local Recurrence-Free Survival, and Event-Free Survival from a Randomized Controlled Trial Comparing RFA with PEI, 2003*

Significant Independent Risk Factors	*Overall Survival*	*Adjusted Local Recurrence-Free Survival*	*Adjusted Event-Free Survival*
RFA treatment	***No significant risk factors***	RR=0.20 (95% CI, 0.05–0.73, P=.015)	
Tumour > 3 cm		RR=8.67 (95% CI, 1.90–39.66; P=.005)	RR=7.21 (95% CI, 2.26–22.97, P<.001)
Bilirubin > 34.2 µmol/L			RR=2.35 (95% CI, 1.02–5.43, P=.46)

** Adapted from Radiology 2003, Vol. 228; Lencioni RA, Allgaier HP, Cioni D, et al; Small heptocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanolinfection, with permission from Radiological Society of North America and the author.*

The authors of this study concluded the following:

- RFA is more effective than PEI for treating small HCCs.
- RFA should be considered the ablative treatment of choice for patients who are ineligible for resection or transplantation.
- More research is necessary to determine the effectiveness of RFA in patients with more advanced stages of the disease.
- RFA did not provide any advantage over PEI in preventing new modules from developing.
- Newer ablative devices and new techniques may increase the effectiveness of RFA over other techniques.

Medical Advisory Secretariat Commentary on This Study

Although the authors explained their method of randomization in this small RCT, they did not provide a sample size calculation. It is unclear why the clinical presentation of patients in the RFA group appeared to be less severe than those in the PEI group, as classified by the Child-Turcotte-Pugh score. There was no significant overall survival benefit, perhaps due to the small sample size and few deaths in each treatment arm. Further, after ablative treatment failure was observed, patients who required chemoembolization or another treatment regimen remained in the study. Finally, the authors did not fully comment on the higher complication rate associated with RFA compared with PEI.

Non-Randomized Comparative Trial (Level 3a Evidence)

One comparative study (21) attempted to compare 100 patients who had decompensated liver cirrhosis with unresectable HCC (Child-Turcotte-Pugh Class B or C) and who were treated with either repeated

TACE, laparoscopic RFA, or conservative treatment. Table 6 shows how they assigned patients to treatment.

Table 6: Treatment Assigned to Patients with Unresectable Primary Liver Cancer in a Comparative Study, 2004 (21)

	TACE* (n=20)	Laparoscopic RFA* (n=40)	Conservative Treatment (n=40)
Tumour > 5 cm	√		√
Fewer than 3 tumours < 5 cm	√	√	√
More than 3 tumours	√		√
Serum total bilirubin > 2mg/dL		√	√

*TACE represents transcatheter arterial chemoembolization; RFA, radio frequency ablation

From Hsieh C-B, Chang H-M, Chen T-W et al. Comparison of treascatheter arterial chemoembolization, laparoscopic radio frequency ablation for decompensated cirrhotic patients with hepatocellular carcinoma. World J Gastrenterol 2004; 10(4):505-508

As Table 6 shows, only patients with fewer than 3 tumours smaller than 5 cm were assigned to each of the 3 treatments and specifically to laparoscopic RFA. According to the authors, the mean tumour diameter of patients receiving laparoscopic RFA was significantly smaller (P<.05) than in the TACE group.

Mean follow-up was at 12.5 months (range, 3–30 months), 11.3 months (range, 2.5–29 months), and 10.5 months (range, 3.1–30 months) for the laparoscopic RFA, TACE, and conservative treatment groups, respectively. Table 7 shows the major outcomes in this study. The patients in the TACE group had significantly more major complications than did the patients in the laparoscopic RFA group.

Kaplan-Meier survival and recurrence curves were done to 30 months for patients with stage II carcinomas only. Thirty-seven patients with stage II tumours in the laparoscopic RFA group, 9 in the TACE group, and 14 in the control group had tumours of 3.4 cm (SD, 0.8), 3.7 cm (SD, 1.0), and 3.6 cm (SD, 0.9), respectively. According to the authors, mean tumour size was not significantly different across treatments in this patient subgroup. The survival rate for patients in the laparoscopic RFA stage II subgroup was better than in the TACE or conservative treatment group (P<.003). No significant difference in recurrence was observed when the laparoscopic RFA and TACE groups were compared. (Patients in the conservative treatment group were not included in the recurrence survival curve.) The authors concluded that patients treated with RFA had better clinical outcomes than those treated with TACE, especially those in Child-Turcotte-Pugh Class B or C, or patients with stage I or II primary liver cancer.

Table 7: Comparison of Outcomes for Laparoscopic RFA and TACE in a Comparison Study, 2004* (21)

	Laparoscopic RFA (n=40)	TACE (n=20)	P
1-month mortality, n (%)	1 (2.5)	1 (5)	
Major complications – total, (%)	7 (17.5)	9 (45)	<.05
Hepatic failure, n	3	3	
Pulmonary embolism, n			
Stroke, n	0	1	
UGI bleeding, n	0	1	
Pneumonia, n			
Refractory ascites, n	2	2	
	1	0	
	1	2	
Minor complications, total (%)	7 (17.5)	7 (35)	
Pneumothorax, n	3	0	
Wound infection, n	2	0	
Burns, n	2	0	
Post embolization syndrome, n	0	7	
Local 1-year recurrence rate, n	12	7	
Local 2-year recurrence rate, n	19	11	

*RFA represents radio frequency ablation; TACE, transcatheter arterial chemoembolization

From Hsieh C-B, Chang H-M, Chen T-W et al. Comparison of treascatheter arterial chemoembolization, laparoscopic radio frequency ablation for decompensated cirrhotic patients with hepatocellular carcinoma. World J Gastrenterol 2004; 10(4):505-508

The Medical Advisory Secretariat's Commentary on This Comparison Trial

Internal bias may have been inherent in the treatment comparisons in this study. The authors noted that RCTs are difficult to do in this patient population, because each indication is specific to a treatment modality; however, it was clear that there were clinical differences favouring RFA among patients in the treatment arms. The number of patients in each arm was also skewed, with more patients in the RFA arm. The authors attempted to level the patient population through a subanalysis of only patients with stage II HCC in the survival and recurrence analyses. Despite the finding of no significance between groups, there were still more patients with smaller tumours in the stage II primary liver cancer laparoscopic RFA group. These issues could have affected the results that led to the conclusion that laparoscopic RFA had better outcomes than the other treatments. Recurrence was not assessed for conservative treatment. The reason for this is unknown.

Case series

Appendices 2, 3, and 4 detail the prospective and retrospective case series included in this review. Overall, the studies were not comparable, because they had different patient populations and outcome measures.

The case series studies were as follows: 1 multisite study (n=56); (22) 5 single-site case series with samples of 56, 69, 86, 87, and 158; (23;24;25;26;27) and 1 small retrospective case series. (28) Across studies, the median follow-up was 16 months to 20 months, ranging from 6 months to 38 months overall. In 3 studies, 50% to 60% of patients were in Child-Turcotte-Pugh Class A. (22;24;26) In the other 2 studies, the proportions were 80% and 100% (23;25). Where reported, over 80% of patients had 1 tumour smaller than 3 cm. (25;22;24;27) One study looked at the outcome of RFA for patients with small tumours (< 3 cm) and larger tumours (3.8 cm). (25)

Results showed the rates of complete ablation were over 80% for tumours smaller than 3 cm. (25-27) For larger tumours, these rates were 27%, 57%, and 83%. (27;26;25) Recurrence-free survival at 1 year in the multisite study was 92% for tumours smaller than 2 cm, 51% for tumours larger than 2 cm, and 35% for subcapsular tumours. (22) Event-free survival in 1 study was 82% at 1 year, 74% at 2 years, and 70% at 3 years. (23)

Two studies examined overall survival. One reported a rate of 94% at 3 years. (23) The other reported survival rates at 18 months of 90% for patients with tumours less than 3 cm, 83% with tumours 3.1 to 5 cm, and 80% with tumours 5.1 to 8 cm. (25) Multivariate analyses found that significant risk factors for recurrence were larger tumour size (> 2–3 cm), (22;24) subcapsular location, (22;24) location near main portal, (26) and elevated alpha fetoprotein. (26)

Although these studies could not be aggregated because of heterogeneous patient characteristics and outcome measures, the general conclusion was that there was a survival benefit of 70% to 94% at 3 years for patients with nonsubcapsular tumours smaller than 3 cm.

The Medical Advisory Secretariat's Commentary on the Systematic Literature Reviews of Radio Frequency Ablation

This literature review included studies with RFA as the only treatment for patients with unresectable HCC, so that the procedure could be assessed in a relatively homogenous population. Nonetheless, many of the studies included patients of varying disease advancement and severity. However, clinical

homogeneity in this patient population is difficult because HCC is a very complex condition with patients presenting for treatment at various disease stages and with multiple comorbidities. Finally, in some of these studies, patients for whom RFA was unsuccessful and who needed more treatment were sometimes kept in the study. This could have biased the results.
Despite these shortcomings, the small body of literature has indicated that RFA safely and effectively treats primary liver cancer in the short term (up to 2 years), mostly for patients with few tumours (< 3 nodules) that are small (< 3 cm) and nonsubcapsular. Further, RFA appears to have some survival benefit when compared with similar technologies. There is not enough evidence, however, to determine which mode of RFA (open, laparoscopic, or percutaneous) achieves the best outcomes.
RFA has been used for patients with liver metastases, such as colorectal (9;14;15) or neuroendocrine, (9) and for patients with tumours in the kidney,(29) lung,(30) and bone (e.g., osteoid and osteoma), (31;32), but there is not enough published evidence to suggest that RFA is effective for these patients. RCTs are underway that will potentially elucidate the effectiveness of RFA for these patients.

Existing Guidelines for the Treatment of Primary Liver Cancer

The Medical Advisory Secretariat found 1 recent set of guidelines based on systematic reviews for the various treatment options for primary liver cancer. (8) Commissioned by the British Society of Gastroenterology, this report was developed because of the increase in the incidence in HCC in developed countries. Further, surgical treatment is only appropriate for less than one-quarter of diagnosed patients. The guideline focused on 3 issues:

- To determine which patients are at high risk for HCC and which should be actively followed
- To determine which investigations are required to diagnose HCC definitively
- To determine the most appropriate treatment modality based on the patient's clinical condition

Table 8 shows the treatments, evidence, and recommendation grades for the surgical and nonsurgical management of HCC. As stated earlier in this report, the management and treatment of HCC depends on each patient's clinical condition. Chemotherapy and hormone therapy are not indicated for primary liver cancer.

Table 8: Guidelines for the Management of Primary Liver Cancer in Adults, 2003(8)

	Indication	Evidence Grade*	Recommendation Grade†
Surgical			
Liver transplant	Patients with cirrhosis and small HCC (≤ 5 cm single nodule or up to 3 lesions of ≤ 3 cm) Patients with replicating hepatitis B with small HCC as defined above should be given antiviral therapy and considered for transplantation	2a	B
Hepatic resection	Primary therapy for patients with HCC and a noncirrhotic liver	2a	B

	In patients with hepatic cirrhosis and good hepatic functioning (Child-Turcotte-Pugh A), and where liver transplant is not appropriate, only units with a high degree of expertise in this surgery and management of liver failure should perform this procedure.		
Non-surgical Percutaneous ethanol injection	Best suited for peripheral, small (< 3 cm) nodules	2b	B
Radio frequency ablation	Good alternative, but data are limited	2b	
Chemoembolization	May increase survival in highly selected patients with good liver reserve (lipiodol is effective for pain or bleeding from HCC)	2a	B
Systemic chemotherapy	Associated with poor response and should be used only for research with new agents	1	A
Tamoxifen	No survival benefit in controlled trials and is therefore not recommended	1	A

*Evidence: 1a: Meta-analysis of randomized controlled trials (RCT); 1b: At least 1 RCT; 2a: At least 1 well-designed controlled study without randomization; 2b: At least 1 other type of well-designed quasi experimental study; 3: Well-designed nonexperimental descriptive study; 4: Expert committee reports or opinions

†Recommendation: A: Requires at least 1 good RCT; B: Requires clinical studies without randomization; C: Requires evidence from category 4 above in absence of directly applicable clinical studies

From: Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut 2003; 52(Suppl III):iii1-iii8.

Economic Analysis

The Medical Advisory Secretariat systematically reviewed the literature on the economics of RFA. Any economic study on just RFA or comparing RFA with another therapeutic method was included, regardless of the presence of primary or metastatic disease.

Results of Literature Review on Economics

Two reports were extracted. The Australian Medical Services Advisory Committee (MSAC), as part of their systematic review (9) in 2003, compared the incremental cost-effectiveness of RFA with PEI per 1-year local recurrence-free survival rate. From the United States, Shetty in 2001 (33) compared the cost-effectiveness of RFA with palliative care. Tables 9, 10, and 11 summarize the results from these 2 studies.

As expected, the direct costs of any type of RFA (inpatient or outpatient) per treatment session were much higher than for either PEI or palliative care (Table 9). The cost in the report by MSAC did not include professional fees, whereas the report by Shetty included all hospital-based costs, including initial consultation, treatment workup, follow-up procedures (CT scan), and professional fees. The cost of palliative care included diagnostic workup (CT scan), professional fees, and symptom control. Inpatient palliative costs were not included in Shetty's estimate.

Complete tumour ablation is typically achieved in 1 RFA treatment session, whereas PEI requires multiple sessions. MSAC calculated the incremental cost-effectiveness ratio (ICER) per treatment session using only the cost differences between RFA and PEI. The ICER per local recurrence-free 1-year survival (LRFS) for various combinations of RFA and PEI treatment sessions are in Table 10. The authors assigned a 14% survival benefit to RFA based on the survival figures of the RCT abstract in their report (98% local recurrence-free survival for RFA – 84% for PEI for 1 session at 1 year).(30) Using a high (25% benefit for RFA) and a low (3% benefit for RFA) estimate of local recurrence-free survival, the ICER/LRFS were $6,000 to $10,000 and $50,000 to $83,333, respectively, for percutaneous RFA. The estimates for laparoscopic and open RFA were higher.

Table 9: Costs of RFA and Comparators from Analyses by the Medical Services Advisory Committee (9) and Shetty (33)*

	MSAC, Australia, 2003 (Population-Based Analysis)	Shetty, United States, 2001 (n=46)
Patient population and treatment	HCC*	HCC or metastatic liver disease 73 lesions 83 treatment sessions Mean lesion size: 3.1 cm ± 1.1
Comparator	Percutaneous, laparoscopic, and open RFA vs. PEI*	Percutaneous RFA vs. palliative care
Number of cases	Population-based: 200 incident cases/year	Single-centre hospital costs from 46 patients; retrospective analysis
Assumptions	14% risk difference between RFA and PEI (98% vs. 86%) (16)	Payer perspective (Medicare)
RFA costs per session†		
Disposable probes, $	1,496–2,376	
Hospital costs Percutaneous RFA Laparoscopic RFA Open RFA	 1,496–2,376 2,508–3,388 (1-day hospital stay) 5,852–6,732 (7-day hospital stay)	
Generator	35,200–57,200	
PEI costs Needle cost per session	176	
Total outpatient RFA procedure (Includes initial evaluation, RFA procedure, observation room time, lab fees, medication, repeat computed tomography at 1 month follow-up)		$5,185.20
Inpatient RFA (Includes above plus anesthetist fees, cost of hospital days stay, and cost of		$8,618.00

potential complications) **Palliative care** (computed tomography scan, outpatient office visit, lab tests, symptom control costs; no long-term inpatient hospital costs)		$602.51

*HCC represents hepatocellular carcinoma (primary liver cancer); RFA radio frequency ablation; PEI, percutaneous ethanol injection

†Converted to Canadian currency; Purchasing Power Parity for 2002 GDP, OECD 2003 (PPP=0.88 Cdn/Australian $)

Adapted from Medical Services Advisory Committee. Radiofrequency ablation of liver tumours. Canberra: Medical Services Advisory Committee (MSAC). 2003, Commonwealth of Australia; From Shetty SK, Rosen MP, Raptopoulos V, et al. Cost-effectiveness of percutaneous radiofrequency ablation for malignant hepatic neoplasms. J Vasc and Int Radiology 2001; 12(7);823-833

Table 10: Incremental Cost-Effectiveness Ratio per 1-year Local Recurrence-Free Survival of Radio Frequency Ablation Vs. Percutaneous Ethanol Injection (9) *

	Percutaneous RFA†	Laparoscopic RFA	Open RFA
ICER per LRFS, Cdn $†			
1 RFA session vs. 1 PEI session	9,428–15,714	16,657–22,942	40,542–48,828
1 RFA sessions vs. 3 PEI sessions	6,914–13,200	14,142–20,428	38,028–44,314
2 RFA sessions vs. 3 PEI sessions	17,600–30,172	32,057–44,628	NA
1 RFA session vs. 1 PEI session (3% benefit for RFA)	44,000–73,333	77,733–107,067	189,200–218,533
1 RFA session vs. 1 PEI session (25% benefit for RFA)	5,280–8,800	9,328–12,848	22,704–26,224

*Converted to Canadian currency; Purchasing Power Parity for 2002 GDP, OECD 2003 (PPP=0.88 Cdn$/Australian $)

†RFA represents radio frequency ablation; PEI, percutaneous ethanol injection; ICER, incremental cost-effectiveness ratio; LRFS, local recurrence-free survival

Adapted from Medical Services Advisory Committee. Radiofrequency ablation of liver tumours. Canberra: Medical Services Advisory Committee (MSAC). 2003, Commonwealth of Australia

Table 11: Cost-Effectiveness and Break-Even Analysis per Life Year Gained for Reimbursement Scenarios: RFA vs. Palliative Care (33)*

	Outpatient RFA (Current Reimbursement Compared With Palliative Care†	Inpatient RFA Compared With Palliative Care
Cost-effectiveness compared with palliative care/life-year gained, $		
6 months	24,508.80	35,421.60
		19,144.80
1 year	13,688.40	10,804.80
2 year	8077.20	7,860.00
3 year	6,040.80	5,282.40
4 year	4,190.40	
Break-even analysis, US$	**Months**	**Months**
$100,000/LYG	1.1	1.66
$50,000/LYG	2.26	3.41
$20,000/LYG	6.14	9.25

* Converted to Canadian currency; Purchasing Power Parity for 2002 GDP, OECD 2003 (PPP=1.20 Cdn$/United States $)

†RFA represents radio frequency ablation

From Shetty SK, Rosen MP, Raptopoulos V, et al. Cost-effectiveness of percutaneous radiofrequency ablation for malignant hepatic neoplasms. J Vasc and Int Radiology 2001; 12(7);823-833

As Table 11 suggests, outpatient RFA has a more favourable cost-effectiveness per life-year gained (LYG) compared with palliative care than does inpatient RFA, with a marginal median survival at 6 months, 1, 2, and 3 years when focusing on direct hospital costs. Further, Shetty found that to achieve thresholds of $20,000, $50,000, and $100,000 per LYG, outpatient RFA would have to achieve 6.14, 2.26, and 1.1 months of marginal median survival, while inpatient RFA would have to achieve 9.25, 3.41, and 1.66 months of marginal median survival.

Ontario-Based Budget Impact Analysis

Ontario Estimates

The age-adjusted incidence of liver cancer in Ontario in 2002 was 5.4 cases per 100,000 men and 1.4 cases per 100,000 women. The crude incidence was 5.8 cases per 100,000 men and 1.8 cases per 100,000 women. (Ontario Cancer Registry, Cancer Care Ontario; Accessed May 2004). These rates amount to about 450 new cases of liver cancer per year in Ontario, based on the 2001 Ontario population of 11.9 million.

Liver resection is the first line of treatment for primary liver tumours according to practice guidelines. (6;8) Eligibility for resection is based on the size and number of tumours in a patient's liver and other patient clinical characteristics, such as degree of cirrhosis. However, only 15% to 30% of patients presenting with HCC are eligible for resection. This accounts for an estimated 68 to 135 patients in

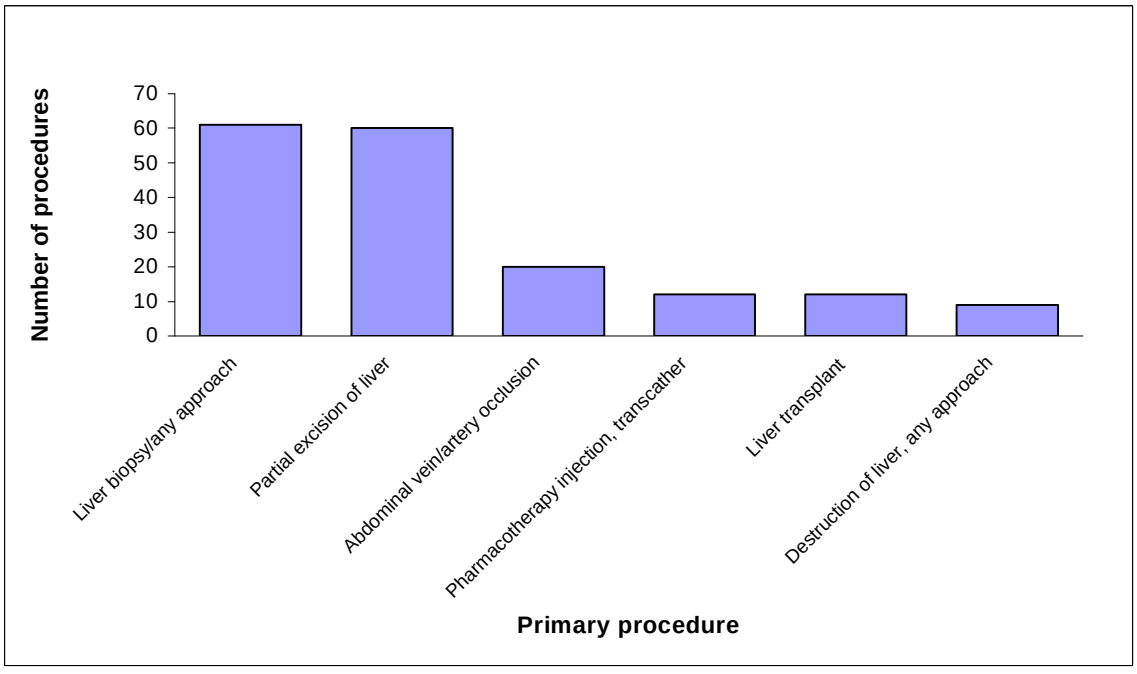
Ontario. According to hospital discharge data, there were about 60 partial liver resections in Ontario in fiscal year 2002 (about 13% of a possible 450 patients with primary liver cancer).

Transplantation is also used to treat liver cancer; however, patient characteristics, donor issues, and wait times make this a secondary choice. In 2002, about 12 liver transplants (3% of 450 patients with liver tumours) were performed (Ontario hospital discharge abstract data 2002). **[**

The utilization of treatments used for patients with unresectable liver tumours, such as RFA and its alternatives and adjuncts, is difficult to ascertain. Currently, administrative data are not sensitive enough to provide this information. In Ontario, there is no physician claims fee code or unique hospital discharge procedure code for RFA.

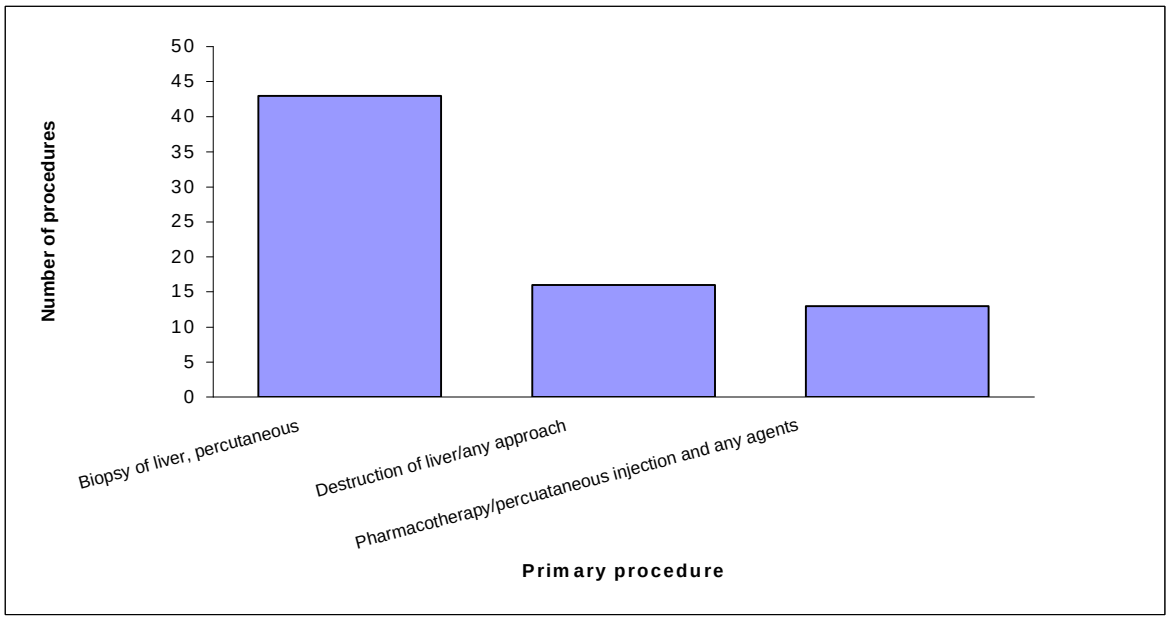
Using population-based hospital data, Figures 3 and 4 illustrate the most commonly coded primary inpatient and outpatient hospital procedures for patients with a primary diagnosis of liver cancer (ICD-9=155.0) in 2002/2003 in Ontario. About 400 hospital based inpatient records were found for approximately 300 primary inpatient procedures. These records were for 332 liver cancer patients in 2002/203. There were also 89 outpatient visits and 130 procedures performed for 72 unique patients. Aside from excision and transplantation, ablative procedures and TACE cannot be identified from these codes.

Figure 3: Number of Hospital Inpatient Primary Procedures for Patients with Liver Cancer (Diagnosis: ICD-9=155.0) in Ontario, 2002/2003



Data courtesy of Ontario hospital discharge abstract data, 2002/2003

Figure 4: Number of Hospital Outpatient Primary Procedures for Patients with Liver Cancer (Diagnosis: ICD-9=155.0) in Ontario, 2002/2003



Data courtesy of Ontario hospital discharge abstract data 2002/2003

In one Ontario practice, RFA is currently performed in 20% to 30% of liver tumour cases, based on patient presentation (Personal communication, Medical Consultant, 2004). Applying that percentage to the estimate of 450 patients with HCC in Ontario, 90 to 135 patients may receive RFA in Ontario per year.

It is estimated that about 140 RFA procedures have been performed in at least 9 teaching hospitals in Ontario. Most of the procedures have been done in Toronto and in the Greater Toronto Area (Personal communication, Consultant, 2004). Some of these 9 hospitals are thought to have done fewer than 5 procedures in the past year.

The cost of a radio frequency generator ranges from $20,000 to $30,000 (Cdn), depending on the make and model. Probes and needles for the ablation are disposable and typically cost from $600 to $1,000. Costs for other pads and electrodes necessary for this procedure are inexpensive. The annual cost of electrodes in Ontario is estimated at $84,000 to $140,000, based on about 140 RFA procedures. Alternatively, the total cost of PEI includes the cost of a needle (usually $25 to $100) and liquid ethanol.

Percutaneous RFA is performed as day surgery, usually as 1 session of 1.5 to 3 hours. It is guided most often by ultrasound, but CT guidance is also used. A CT scan is usually performed right after ablation to make sure that the complete tumour has been ablated. Follow-up by CT scan is usually done 2 to 3 weeks after the procedure and then every 6 months thereafter. PEI is also performed as day surgery and may take 3 or more 20-minute sessions for complete ablation. TACE requires 2 to 4 days in the hospital as an inpatient (Personal communication, Medical Consultant, 2004).

Interventional radiologists typically perform RFA in Ontario. There are 60 such specialists in the province. Most practise in the urban centres.

Decision Cost-Analysis Model

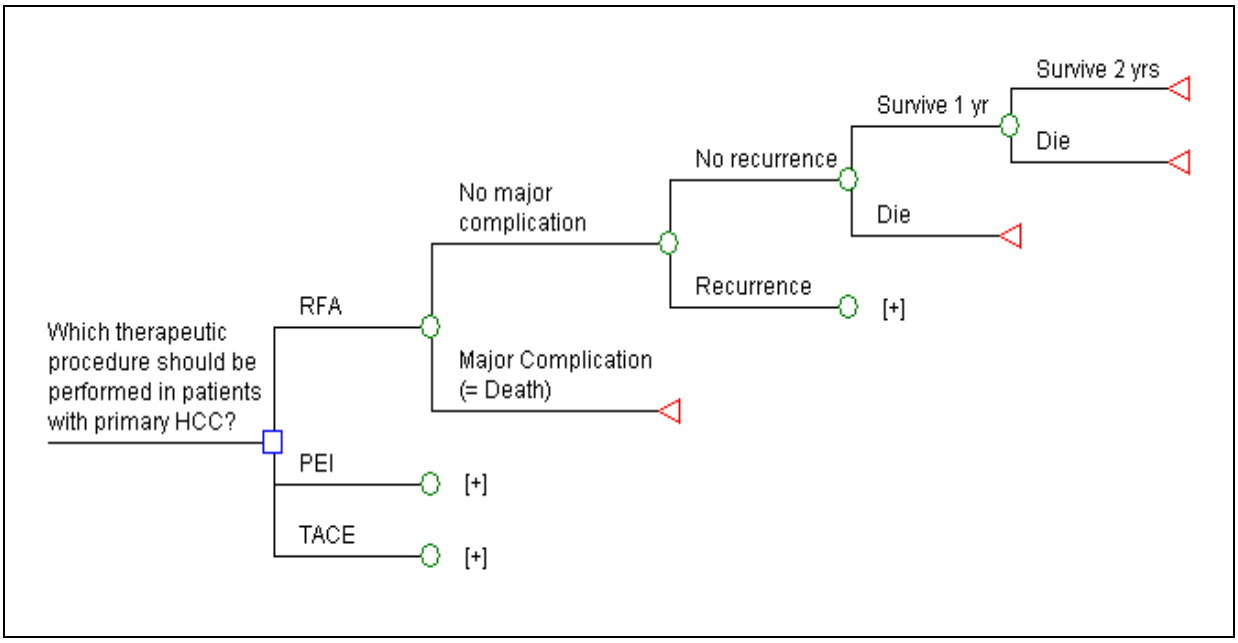
Methods

Model Structure and Assumptions

Deterministic and probabilistic decision models were developed to compare health outcomes and cost options for RFA, PEI, and TACE for patients with primary liver cancer that were ineligible for surgery and that had 4 or fewer small (5 cm or less) liver lesions (Figure 5). TACE was included as a direct comparator because this treatment may be offered in this patient population where ablation techniques are not available. The model adopted a time horizon of 2 years. The cost-effectiveness analysis estimated costs per LYG from the health care payer perspective.

In this analysis the probability of procedure-related death was included as a complication because the complications noted in the literature were usually mild and self-limiting (fever, pain). Patients also may experience local recurrences, so that was included (as a probability) in the model. Survival was measured 1 and 2 years after treatment began. Patients dying halfway through the year contributed 0.5 years to the life expectancy (half-cycle correction). While the model structure is the same for all treatments, probabilities and costs differed across the 3 strategies.

Figure 5: Decision Tree for Primary Liver Cancer Treatment Options*



*Similar branches are represented by [+] in the model structure

Deterministic Analysis

The deterministic analysis used each model parameter as its specified point value during each calculation. There is typically no randomness in this type of analysis.

Probabilistic Analysis (Second-Order Monte Carlo Simulation)

The probabilistic analysis (Monte Carlo Simulation) used random numbers to develop the model parameters. The underlying model variables were allowed to vary over a given range within a given distribution. When recalculating the model multiple times, values that are sampled from the probability distributions were assigned to the model parameters. Sampling parameter values from probability distributions places a greater weight on the likely combinations of parameter values and simulation results quantify the total impact of uncertainty on the model.

Data and Analysis Assumptions

The model was based on published clinical trial data by Lencioni (17) and Llovet (34) and on Ontario unit cost data (Personal communication, Medical Consultant, 2004). Table 12 shows the probabilities used in the model. Comparable patient populations were observed across the 3 treatments on indication (unresectable primary liver cancer), age, gender, cause of cirrhosis (hepatitis C and B), and Child-Turcotte-Pugh Class A (about 70%). However, patients receiving TACE had, on average, larger (52 mm) and more tumours (73% with multiple lesions) than patients receiving RFA (28 mm, 38% with multiple lesions) or PEI (28 mm, 23% with multiple).

Aside from mortality, the probability of local recurrence was included as the primary outcome in the model. Unfortunately, similar data were not available for TACE. It was therefore conservatively assumed that no local recurrences occurred under TACE within the 2-years. Beta distributions (n, r) were used for the probabilistic analysis.

Table 12: Input Data Comparing Probabilities for RFA, PEI, and TACE Treatment Outcomes*

Variable	RFA†	PEI (17)	TACE (34)
Survival at 1 year, %	100	96	82
Survival at 2 years, %	98	88	63
Major complication (death), %	0	0	3
Recurrence, %	6	29	§

*RFA represents radio frequency ablation; PEI, percutaneous ethanol injection; TACE, transcatheter arterial chemoembolization

§ Data on local recurrence not available, therefore conservatively assumed to be 0.

This study included only direct costs related to the procedures (Table 13). All costs were Ontario cost estimates. (Ontario Health Insurance Program 2002, Personal communication, Consultant, 2004) Each treatment course consisted of 1 or more cycles with 1 or more treatment sessions. Typically, for complete ablation, RFA requires a mean of 1.3 sessions; (17) PEI requires 7.3 sessions. (17) TACE usually requires 2.8 sessions (34) in 2 years.

The cost per procedure ranged from $266 (Cdn) for PEI to $6,000 for TACE. TACE required 2 to 3 days hospitalization and was therefore far more expensive than RFA and PEI, which are outpatient procedures. For resource use and unit cost, data triangular distributions (minimum, most likely, and maximum) were used for the probabilistic analysis.

Table 13: Input Data of Ontario Unit Costs Per Procedure*

Variable	RFA† Unit cost, $Cdn	PEI† Unit Cost, $Cdn	TACE† Unit cost, $Cdn
Physician time	500	69	250
Needle	800	63	‡
Generator§	125	‖	‖
Drug (ethanol/lipiodol)	‖	5	‡
Ultrasound	30	30	‡
Computed tomography	99	99	‡
Hospitalization	‖	‖	5,750
Total cost per procedure	1,554	266	6,000

*Unit costs estimated from Ontario Health Insurance Plan 2002, where available, and from Personal communication, Consultant 2004.

†RFA represents radio frequency ablation; PEI, percutaneous ethanol injection; TACE, transcatheter arterial embolization

‡ Included in hospitalization cost

§ Calculated per procedure as follows: Generator costs $20,000 to $30,000 (Personal communication, Consultant 2004) and is assumed to depreciate in 5 to 10 years. Based on a projected 20% to 30% of patients with HCC receiving ablation in one Ontario hospital, 30 to 45 patients were assumed to be treated with RFA per generator per year. Therefore, the costs per procedure were assumed to be between $200 ($30,000, 30 patients, and 5 years) and $45 ($20,000, 45 patients, and 10 years).

‖Not applicable

Results: Deterministic analysis

From an economic perspective, PEI has the lowest expected costs per patient. Therefore, it is the preferred strategy in terms of unit costs (Table 14). RFA was somewhat more expensive than PEI, but it was also more effective. Compared with PEI, RFA was highly cost-effective, at about $3,000 per year of life gained. TACE was more expensive and less effective than PEI and RFA; therefore, it is considered to have been dominated. Even if values are changed to favour TACE in a sensitivity analysis, it remains the least attractive strategy.

Table 14: Results of Deterministic analysis Comparing RFA, PEI, and TACE in Ontario*

Strategy	Cost, $Cdn	Incremental Cost, $Cdn	Effectiveness (life-year gained)	Incremental Effectiveness (LYG)	ICER ($/LYG)†
PEI	1,949		1.91		
RFA	2,186	236	1.99	0.08	**2,940**
TACE	16,800	14,614	1.60	-0.39	**Dominated**

*RFA represents radio frequency ablation; PEI, percutaneous ethanol injection; TACE, transcatheter arterial embolization

†ICER represents incremental cost-effectiveness ratio; LYG, life-year gained

Several sensitivity analyses were performed. Figure 6 shows 2-way sensitivity analyses on the unit costs per procedure and the number of procedures required for PEI and RFA. A small change in unit costs per procedure and/or number of procedures performed for complete ablation could change the results so that RFA could save costs compared with PEI.

Figure 6: 2-Way Sensitivity Analyses on the Unit Costs per Procedure and the Number of Procedures

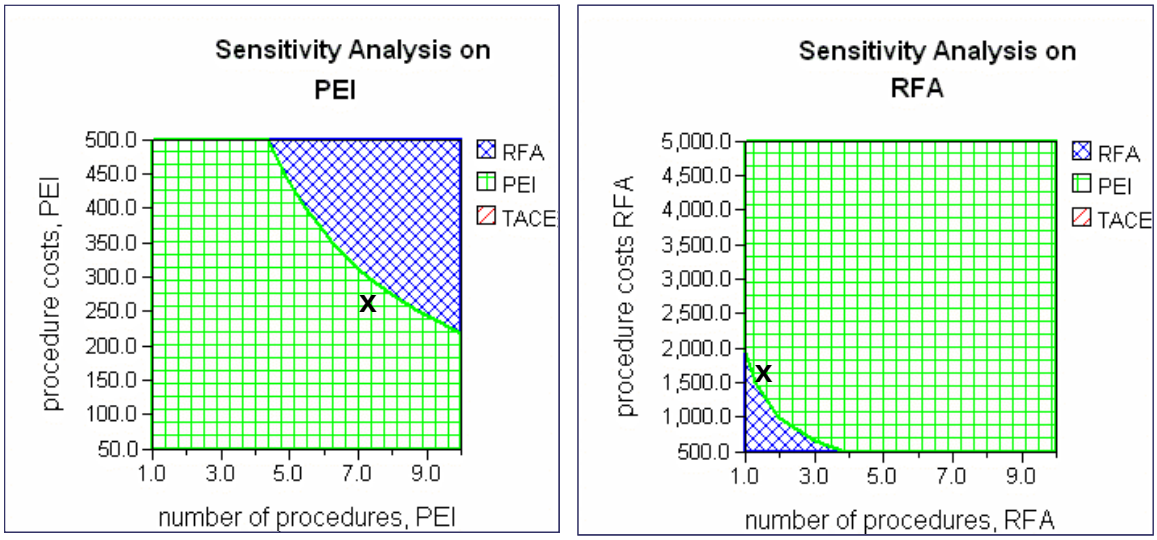


Table 15 shows the mean, and minimum and maximum costs for costs and effectiveness (LYG) for the 3 strategies. Strikingly, the minimum costs for TACE are about double the maximum costs for PEI and RFA. The maximum effectiveness of TACE reaches just about the minimum effectiveness of RFA.

Table 15: Results of Probabilistic Analysis Comparing RFA, PEI, and TACE in Ontario*

Strategy	Cost ($Cdn) Mean (Min; Max)	Effect. (LYG) † Mean (Min; Max)
PEI	1,952 (872; 3,280)	1.91 (1.55; 2.00)
RFA	2,185 (1,296; 3,460)	1.99 (1.90; 2.00)
TACE	16,777 (7,084; 29,242)	1.60 (1.09; 1.89)

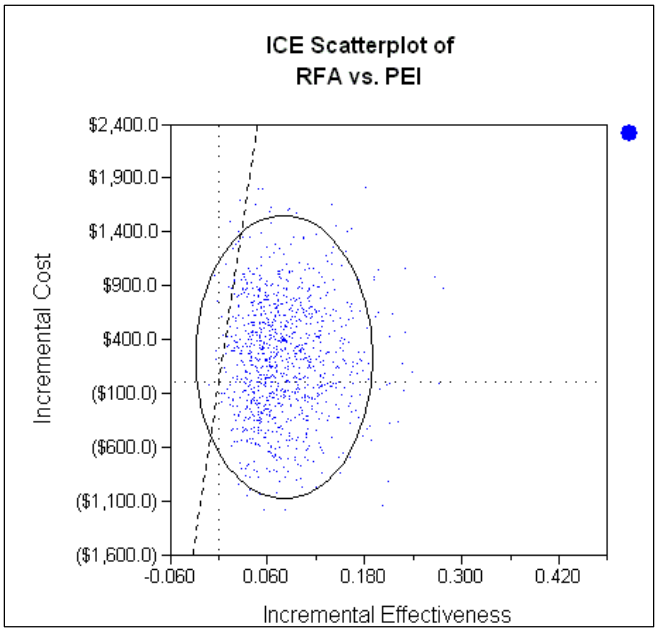
* RFA represents radio frequency ablation; PEI, percutaneous ethanol injection; TACE, transcatheter arterial embolization

†LYG represents life-year gained

The distribution of the expected costs and effectiveness (LYG) of the 100,000 simulations is shown in Figure 7 as a scatterplot comparing RFA with PEI. Figure 8 provides more information about the density of the scatterplot. Both figures assumed a willingness-to-pay threshold of $50,000 per LYG, seen on the diagonal line. All points to the right of this threshold show simulations where RFA is cost-effective compared with PEI at the willingness-to-pay threshold of $50,000. All points in the lower right quadrant show simulations where RFA dominates PEI, such that RFA is less costly and more effective than PEI.

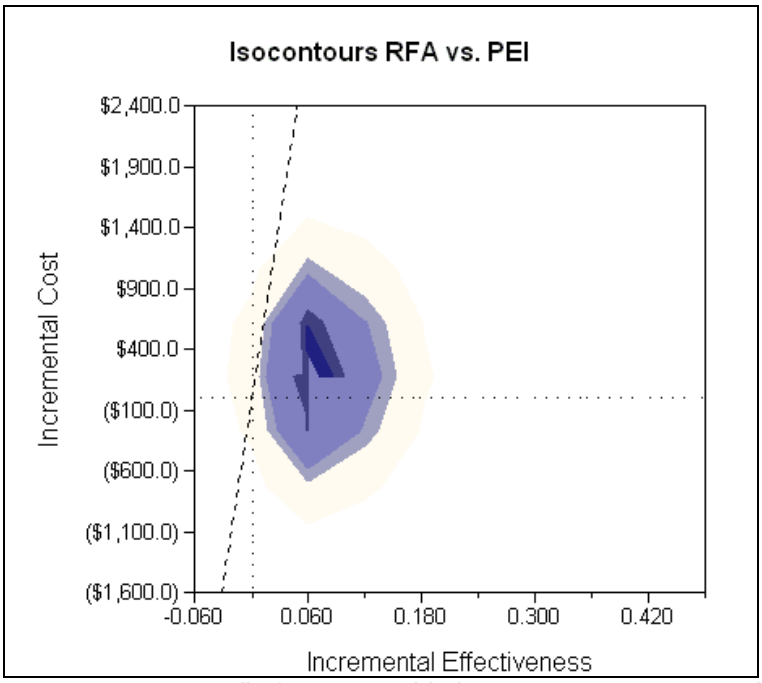
Additionally, to see the proportion of simulations being cost-effective at various willingness-to-pay thresholds, a cost-acceptability graph was generated (Figure 9). Even at a very low willingness-to-pay threshold of $25,000 per LYG, RFA cost-effective compared with PEI in more than 90% of the simulations.

Figure 7: Incremental Cost-Effectiveness Scatterplot for RFA Versus PEI*



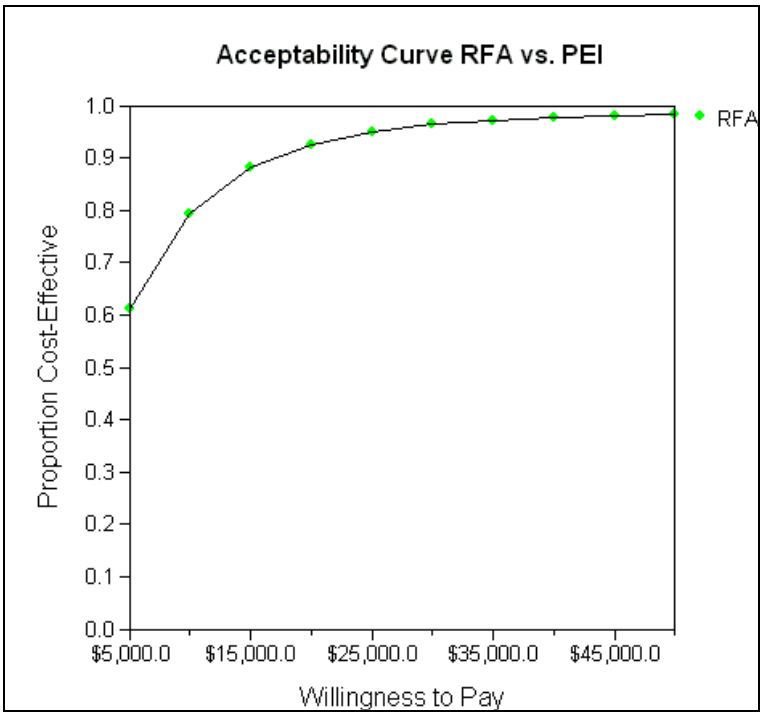
*RFA represents radio frequency ablation; PEI, percutaneous ethanol injection

Figure 8: Cost-Effectiveness Scatterplot for RFA Versus PEI*



*RFA represents radio frequency ablation; PEI, percutaneous ethanol injection

Figure 9: Cost-Acceptability Curve for RFA Versus PEI*



*RFA REPRESENTS RADIO FREQUENCY ABLATION; PEI, PERCUTANEOUS ETHANOL INJECTION

The Medical Advisory Secretariat's Commentary on the Decision-Cost Analysis

These results are conditional on the baseline probabilities and cost data available, such that there is a lack of accurate information about the natural history of primary liver cancer in relation to the effectiveness of the 3 interventions investigated. All baseline probabilities stem from only 2 publications. While the uncertainty related to the input values was dealt with by deterministic and probabilistic sensitivity analyses, it was not possible to populate a Markov model, an economic analysis that is typically used for cancer and chronic diseases. The lack of data also restricted the analysis to 2 years. This may have underestimated the level of effectiveness. Additionally, recurrences have no impact on LYG, and this may have underestimated the effectiveness of RFA.

The impact of the studied interventions on quality of life could not be assessed because of lack of appropriate data. Quality of life outcomes are particularly important for patients in end-of-life care. Death was included as the only complication because RFA, PEI, and TACE are relatively safe procedures with few complications that would affect costs and LYG appreciably. Complications were more frequently noted with TACE than with the other 2 procedures. Finally, the model is based on a very specific patient population and results may not be transferable to patient populations with other characteristics and indications.

Conclusion of Decision Analysis

This analysis found that RFA is less costly and more effective than TACE (i.e., it dominates TACE), and that RFA is highly cost-effective at $3,000 per LYG, compared with PEI, from a health care payer perspective. The probability of RFA being cost-effective, taking into account uncertainties related to input values, is very high (> 90%), even at low willingness-to-pay thresholds ($25,000/LYG).

Policy Appraisal

Recommendation Considerations/Implications

Demographics/Epidemiology of Liver Cancer

- Primary liver cancer usually affects people with underlying liver disease (e.g., alcohol cirrhosis or hepatitis).
- Liver cancer affects 4 times more men than women in Ontario.
- The incidence of liver cancer in Ontario is relatively low (crude 5.8 cases per 100,000 men and 1.8 cases per 100,000 women in 2002); increases in incidence may occur, as seen in other developed countries, because of immigration of populations from hepatitis-endemic areas.
- An estimated 450 people in Ontario may be diagnosed with liver cancer each year.

Treatment and Patient Outcomes

- The rate of survival in untreated patients in the early stage of the disease ranges from 50% to 82% at 1 year and 26% to 32% at 2 years. The rate of survival in patients with more advanced disease ranges from 0% to 36% at 3 years.
- The first line of treatment for HCC is surgical resection or transplantation, which are associated with a rate of survival of 40% to 70% at 5 years. Only 15% to 20% of patients with primary liver cancer are eligible for resection (based on their clinical characteristics). About 5% of eligible patients may receive a transplant, depending on organ and resource availability.

- There is no considered standard of practice for unresectable primary liver cancer.
- One small clinical trial (level 2 evidence) suggests that RFA has a 2-year recurrence-free survival benefit compared with PEI (96% vs. 62%, P=.002) and a significant 2-year event-free survival benefit (64% vs. 43%, P=.012). The same trial found no overall comparative survival benefit for RFA compared with PEI.
- Case series suggest that patients with a few, small (< 3 cm) surface tumours benefit from RFA, with rates of event-free survival up to 70% at 3 years. Heterogeneous patient populations and study outcomes render aggregation of these data difficult.
- RFA may be performed percutaneously (as day surgery), laparoscopically, or as open surgery. The last 2 methods require a stay of 2 to 3 days in the hospital.
- Few side effects are associated with RFA, although the ablation procedure may be painful. Needle track seeding (diffusing cancerous cells as the needle is retracted) has been noted, but may be of concern only where practitioners are not adequately trained in RFA.
- Expertise in doing RFA, specifically percutaneous RFA, is needed to optimize outcomes.
- Only 1 treatment session of 1.5 to 4 hours is usually necessary to ablate a series of small tumours completely, compared to multiple, short (20-minute) sessions for PEI.

Utilization and Diffusion – International, National, Provincial

- Public funding has been recommended for RFA in Australia, and guidance has been proposed for its use for primary liver tumours in the United Kingdom. RFA has been recommended for coverage for small unresectable HCC in at least one American Health Maintenance Organization.
- The distribution of treatments provided for patients with unresectable HCC in Ontario is unknown.
- There is currently no way to track the use of RFA in Ontario. It is estimated that 90 to 135 patients had RFA in the past 12 months (May 2003 to May 2004) in 9 Ontario teaching hospitals in Ontario, mostly in the Greater Toronto Area (Personal communication, Consultant, 2004).
- Administrative data are not sensitive enough to capture RFA specifically. A physician claims fee code for RFA is under consideration in 2 Canadian provinces. An application for a new fee code for RFA in Ontario's Schedule of Benefits has been submitted.
- RFA has been used to treat patients with colorectal and neuroendocrine liver metastases and primary cancer of the kidney, lung, breast, and bone, despite the paucity of published evidence of effectiveness. Because about 25% colorectal cancers will metastasize into the liver, the use of RFA could increase dramatically if it was expanded to this patient population. Clinical trials are underway in many of these areas. Examination of RFA for these indications as new evidence becomes available is necessary.

Cost

- An RFA generator costs from $20,000 to $30,000 (Cdn). Each disposable electrode probe costs $600 to $1200 (Cdn).
- An estimated 140 RFA procedures have been performed in the past year in Ontario.
- Percutaneous RFA is an outpatient procedure.
- Ultrasound guidance is usually used during the procedure. Follow-up with CT scan is done 2 to 3 weeks after the procedure and then every 6 months thereafter.
- There is no professional fee claims code in Ontario for RFA.
- One treatment session is usually necessary for complete ablation using RFA, whereas short, multiple sessions may be required for PEI.
- Aside from initial capital costs, physician time, professional costs, outpatient day surgery costs, and indirect costs incurred by patients need assessment.
- RFA is marginally more costly than PEI but is more cost-effective at about $3,000 per LYG.

- The probability of RFA being cost-effective, taking into account uncertainties related to input values, is very high (> 90%), even at low willingness-to-pay thresholds ($25,000/LYG).

Stakeholder Analysis

- Interventional radiologists perform RFA. There are about 60 interventional radiologists practising in Ontario, about half in teaching hospitals. Adequate training and time to add this procedure to the list of other clinical responsibilities would affect the diffusion of RFA.
- The workload of radiologists and diagnostic imaging technicians would be affected, because CT scans are required for pretreatment and post-treatment assessments. RFA is typically performed using ultrasound guidance.
- Practitioners who treat and coordinate liver cancer patients and patients in Ontario may not be aware of RFA or other ablative treatments for unresectable HCC.

System Considerations

- Hospital global budgets could incur the cost of equipment for RFA. Potential hospital resource savings could be envisioned if outpatient ablation replaced TACE owing to transfer of inpatient to outpatient service (saving expenses of operating room time and personnel, bed days, complications). Direct costs of PEI are slightly less than RFA.
- Some hospitals may be performing very low volumes of RFA. This practice may be unsafe for patients.
- The Ministry of Health and Long-Term Care would be responsible for professional costs for RFA if a fee claims code was approved.
- Increased system costs could be incurred if RFA were used for indications for which there is no published evidence of effectiveness.
- Expansion of expertise in performing RFA could be required, depending on diffusion.
- Guidelines for use and the appropriate dissemination of these guidelines through either Cancer Care Ontario or another designated body would be needed.
- Monitoring the literature for the use of RFA for other indications would be necessary, as would updating the guidelines as appropriate.

Appendices

Appendix 1: Summary of Conclusions From International Systematic Reviews of Radio Frequency Ablation for Primary and Metastatic Liver Cancer, 2002 to 2004

Review	*Country, Date Published*	*Comparators*	*Literature*	*Conclusions*
Galandi and Antes for the Cochrane Collaboration (16)	*United Kingdom, February 2004*	*Percutaneous RFA and PEI*	*Review to October 2003* 2 RCTs	*RFA seems to provide a recurrence-free survival benefit compared with PEI* Clinically relevant quality research needed
Blue Cross Blue Shields (14)	*United States, November 2003*	*RFA and PEI*	*Review to October 2003* *RFA: 1 RCT, 2 comparative studies, 12 case series* *PEI: 1 RCT (same as above), 3 comparison studies, 11 case series*	"RFA of small surgically unresectable HCC lesions and no extrahepatic disease appears to be at least as good as and possibly better than PEI in achieving complete ablation and preventing local recurrence" No evidence for colorectal liver metastases
National Institutes of Clinical Excellence (4;20)	United Kingdom, Guidance July 2003 Overview March 2003	*RFA and any other technique for liver cancer*	*Review to October 2002* Based on ASERNIP-S systematic review, 2002 (14) and 4 additional comparison studies to October 2002	Appropriate selection of patients for RFA and adequate training of specialists and surgeons will decrease the likelihood of complications and increase the likelihood of positive patient outcomes Procedure should be monitored by imaging device to ensure accurate electrode placement Patients should be monitored after procedure Patients should told the risks and benefits of the procedure for their clinical condition
Medical Services Advisory Committee (9)	Australia, May 2003	*RFA for:* *Hepatocellular carcinoma* *Metastatic colorectal liver tumours* *Metastatic neuroendocrine liver tumours compared with surgical resection, percutaneous ethanol injection, transarterial chemoembolization, hepatic arterial infusion chemotherapy, hepatic artery embolization with ocreotide separately* Plus: economic	*Review to January 2003 (only comparative trials for liver cancer; all studies for metastatic colorectal and neuroendocrine liver tumours)* *Primary liver cancer:* *1 small RCT, 3 RCT abstracts, 3 non-RCTs* Colorectal liver metastases: case series studies only	*Public funding should be supported for the percutaneous RFA treatment of nonresectable hepatocellular carcinoma* *Insufficient evidence to support RFA for colorectal or neuroendocrine liver metastases* Incremental cost-effectiveness ratio per local recurrence-free survival for the 1st session of RFA vs. PEI ranged from $6,000–$10,000 (25% benefit of RFA) to $215,000–$248,333 (3% benefit for RFA)

		evaluation		
Australian Safety and Efficacy Register of New Interventional Procedures-S (10)	Australia, October 2002	*Surgical intervention (surgical resection and hepatic artery infusion chemotherapy)* *Ablative treatment (RFA, PEI, cryoablation, microwave coagulation therapy, and laser-induced thermotherapy)* For HCC or metastatic colorectal liver cancer	*Systematic review to May 2002* *4 RCTs, 1 quasi-randomized trial, 7 retrospective non-RCTs* Case series were retrieved but only included where necessary	*No trials assessed RFA adequately* *Recommendations for further research:* *Further controlled trials necessary* *Long-term outcomes and recurrence should be a research focus* *Adequate sample sizes and standard outcome measurements needed in studies* *Comparison of percutaneous RFA with other RFA approaches and RFA as adjunct to resection could be considered* *RFA is safe compared with other available procedures* A registry should be developed by surgeons who are performing this procedure

Appendix 2: Multiple-site Case series (Level 4b) on RFA included for Medical Advisory Secretariat Systematic Review, January 2003 to April 2004

Author/Country/ Year	Patient Recruitment Date	Population	Follow-up	Outcomes	Results
Komorizono (22) Belgium, 2003	January 2000 – December 2001 at 2 centres	56 patients with 65 unresectable HCC tumours Child-Turcotte-Pugh Class: -59% class A -38% class B -3% class C Exclusion criteria: extrahepatic, vascular invasion, refractory ascites, tumour size > 3 cm, > 3 tumours, platelet count < 30,000/mm^3, prothrombin activity < 40% Number of tumours: -86% had 1 -13% had 2 -1% had 3 -39% previous treatment for HCC (15% TACE + RFA) Median tumour size=2.2 cm (range, 0.8–3.0)	2-5 days after RFA Median=16 months (range, 9–26 months) Single session, single application of RFA	Local recurrence:	18% of patients had distant recurrence at primary site (tumours more likely to be > 2 cm [P=.001] and subcapsular [P=.002] compared with tumours in patients without recurrence) Electrode impedance with cooled-tip electrode > hooked electrodes (P=.001)
				Overall cumulative local recurrence-free intervals: 1-year local recurrence-free survival rate:	12 months: 76% (95% CI, 70.9, 81.7%) 15 month: 74% (95% CI: 68.2,79.6%) Tumour ≤ 2 cm: 92% (95% CI: 87.4, 96.4%) Tumours > 2 cm: 51% (95% CI: 41.7, 61.1%) Subcapsular: 35% (95% CI: 19.0, 51.0%) Non-subcapsular: 81% (95% CI: 75.3, 86.6%)
				Independent risk factors for recurrence:	Tumour size: RR=4.9 (95% CI, 1.3–16.4, P=.019) Subcapsular location: RR=5.2 (95% CI, 1.7–16.6, P=.005)
				Complications: -Pain requiring analgesia -Intraperitoneal hemorrhage	9 patients (16%) 3 patients (7%)

Appendix 3: Single-site Case series (Level 4c) on RFA Included in Medical Advisory Secretariat Systematic Review, January 2003 to April 2004

	Giovanni (23)	Ruzzenente (26)	HORI (24)	Salama (27)	Poon (25)
Study focus	Percutaneous RFA only -Survival	Ablation rates	Ablation rates and recurrence	-	Tumour size: Group 1: ≤ 3 cm Group 2: 3.1 –8 cm
Population	Patients with HCC N=56	Patients with HCC N=87	Consecutive patients with HCC N=69 (104 tumours)	Patients with unresectable HCC N=158	N=86 HCC: -open and percutaneous RFA (45% and 71% open in Groups 1 and 2, respectively) -10 patients in Group 1 had resectable tumours but were part of another study where they received RFA -Group 2 patients had significantly more comorbidity (diabetes; cardiovascular, respiratory, and renal disease)
Follow-up	Mean, 20 months (range, 6–36 months)	19.2 months	18 months (6–38 months)	1 month, 6 months, 1.5 years	< 3 cm: 11.5 months 3-8 cm: 11 months (5–24 months) Monitored every 3 months
Child-Turcotte-Pugh Class, %	A:80 B: 20	A: 55 B: 45	A: 58 B: 29 C: 13	A: 100	Class C excluded
Number of Tumours	-	-	104 tumours, total	81% had 1 13% had 2 6% had 3	79% had 1 15% had 2 6% had 3 or 4
Tumour Size, cm	-	< 7 (inclusion criterion)	Mean=2.03 (1.0–3.3)	81% < 3 14% 3-5 5% > 5	59% < 3 41% 3-8 (29 patients with 3.1–5; 6 with 5.1–8)
Complications	-	10% minor 6% major (130 procedures)	-	-	12% < 3 cm (6 patients) 17% Group 2 (6 patients)
Complete Ablation, %	89%, patients at 30 days 80, patients at 1 year	73, overall (73/104 HCCs) 100, tumours < 3 cm 88, tumours 3–5 cm 57, for tumours 5–7 cm	95, complete necrosis (99/104 tumours	100, of 128 patients with tumour < 3 cm 27, of 30 patients with tumour > 3 cm Incomplete ablation: -3/8 patients with	-94, < 3 cm -91, 3-8 cm -88, open RFA (21/24 patients) -100, percutaneous RFA (9/9 patients) -96, < 2 cm (69/72 patients) -93, 3.1–5 cm (27/29 patients) -83, 5. –8 cm (5/6 patients)

				tumour > 5 cm -4/30 patients with more than 1 tumour -100% of those successful at 1 month	
Recurrence	4 patients local at 1 year	19% local (17/87 tumours) 34% new intra-hepatic (30/37 patients)	Overall at 1, 2, 3 years: -10%, 15%, 20% -8% of tumours recurred < 2.5 cm at 2 years: -30% of tumours recurred 2.5 cm or more at 2 years (P=.0051) -Tumours close to surface at 1, 2, 3 years: -20%, 35%, 51% -Tumours deep in liver at 1, 2, 3 years: 8%, 11%, 11% (P=.0034)	At 1.5 years: -9 patients needed further ablation -47 patients had liver cell failure (occurring at 5–14 months) -22 patients referred to chemoembolization with or without chemotherapy	Local: -8% < 3 cm -3% 3-8 cm Distant Recurrence: -26% < 3 cm -24% 3 –8 cm
Recurrence-Free Survival	70% complete remission at 30 months	-	-	-	-
Risk Factors	-	AFP < 200 kU/L (χ^2, P<.4) tumour location (peripheral vs. near main portal) (χ^2, P<.4)	Tumour size and location of tumour independent risk factors for recurrence	-	-
Overall Survival	96% at 1 year 94% at 2 years 94% at 3 years	-	-	-	6 month, 12 month, 18 month survival: -98%, 86%, 90% < 3 cm -85%, 81%, 76% 3–8 cm At 1 year: -80%, 5.1–8 cm -83%, 3.1–5 cm
Event-Free Survival	82% at 1 year 74% at 2 years* 70% at 3 years (*significant difference between alcoholic and post-viral cirrhosis)	-	-	-	

Appendix 4: Retrospective Study (Level 4d) on RFA Included in Medical Advisory Secretariat Systematic Review, January 2003 to April 2004

Author/Country/Year	Patient recruitment dates	Population	Follow-up, length	Outcomes	Results
Arch-Ferrari (28)	*March 1999 to June 2002*	*26 patients with unresectable HCC < 4 cm (49 lesions)* *Turcotte-Pugh class:* *-27% A* *-39% B* *-35% C* *Number of tumours:* *-62% had 1* *-23% had 2* *-15% had 3* *Mean tumour size: 3.2 cm (SD, 0.9 cm)* *58% laparoscopic RFA* *15% percutaneous RFA* *27% open RFA*	*13.5 months*	*Complete ablation* *Operative mortality* *Hemorrhage* *Recurrence* *Disease-free survival* *RFA+ transplant compared to RFA:* *Overall survival* *Disease-free survival*	*89% (23 patients)* *0%* *4% (1 patient)* *3 patients (12%)* *9.3 months in 9 patients who subsequently had transplant* *P=.023* *P=.047*

References

(1) Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology 1999; 29(1):62-67.

(2) Canadian Cancer Society. Canadian Cancer Statistics 2004

(3) Garcea G, Lloyd TD, Aylott C, Maddern G, Berry DP. The emergent role of focal liver ablation techniques in the treatment of primary and secondary liver tumours. European Journal of Cancer 2003; 39(15):2150-2164.

(4) NICE. Interventional procedure overview of radiofrequency ablation for the treatment of liver tumours. United Kingdom: National Institute for Clinical Excellence 2003.

(5) Cancer Care Ontario. Ontario Cancer Fact. Vol 2 No. 4. 2004.

(6) Carr BI, Flickinger JC, Lotze MT. Hepatobiliary Cancers. In DeVita, Jr VT, Hellman S, and Rosenberg SA. (eds). Principles and Practice of Oncology 5th edition. Philadelphia: Lippincott-Raven Publishers 1997 pp. 1087-1114.

(7) Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60:646-649.

(8) Ryder SD for the British Society of Gastroenterology. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut 2003; 52:Suppl-8.

(9) Medical Services Advisory Committee. Radiofrequency ablation of liver tumours. Canberra: Medical Services Advisory Committee (MSAC) 2003.

(10) Sutherland LM, Williams JAR, Padbury RTA, Gotley DG, Stokes B. A systematic review of radiofrequency ablation for the treatment of liver tumours. Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) 2002.

(11) Camma C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology 2002; 224:47-54.

(12) Suguria NTK, Ohto M. Treatment of small hepatocellular carcinoma by percutaneous injection of ethanol into tumour with real-time ultrasound scanning. Acta Hepatol Jpn 1983; 24:920.

(13) Giorgio A, Tarantino L, de Stefano G, Francica G, Esposito F, Perrotta A et al. Complications after interventional sonography of focal liver lesions: a 22-year single-center experience. Journal of Ultrasound in Medicine 2003; 22(2):193-205.

(14) TEC Assessment Program. Radiofrequency ablation of unresectable hepatic tumours. Vol 18, No. 13. United States: Blue Cross and Blue Shields Association 2003.

(15) NICE. Interventional procedure overview of radiofrequency ablation for the treatment of colorectal liver metastases. United Kingdom: National Institute for Clinical Excellence 2003.

(16) Galandi D, Antes G. Radiofrequency thermal ablation versus other interventions for hepatocellular carcinoma. Cochrane Database of Systematic Reviews(2):CD003046 2004.

(17) Lencioni RA, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 2003; 228(1):235-240.

(18) Shibata T, Limuro Y, Yamamoto Y, Maetani Y, et al. Small hepatocellular carcinoma: comparison of radiofrequency ablation and percutaneous microwave coagulation therapy. Radiology 2002; 223:331-337.

(19) Olschewski M, Lencioni R, Allgaier HP, et al. A randomised comparison of radiofrequency thermal ablation and percutaneous ethanol injections for the treatment of small hepatocellular carcinoma. American Society of Clinical Oncology, Abstract 126A 2001.

(20) NICE. Interventional procedure guidance 2 - Radiofrequency ablation of hepatocellular carcinoma. United Kingdom: National Institute for Clinical Excellence. 2003.

(21) Hsieh CB, Chang HM, Chen TW, Chen CJ, Chan DC, Yu JC et al. Comparison of transcatheter arterial chemoembolization, laparoscopic radiofrequency ablation, and conservative treatment for decompensated cirrhotic patients with hepatocellular carcinoma. World Journal of Gastroenterology 2004; 10(4):505-508.

(22) Komorizono Y, Oketani M, Sako K, Yamasaki N, Shibatou T, Maeda M et al. Risk factors for local recurrence of small hepatocellular carcinoma tumors after a single session, single application of percutaneous radiofrequency ablation. Cancer 2003; 97(5):1253-1262.

(23) Giovannini M, Moutardier V, Danisi C, Bories E, Pesenti C, Delpero JR. Treatment of hepatocellular carcinoma using percutaneous radiofrequency thermoablation: results and outcomes in 56 patients. Journal of Gastrointestinal Surgery 2003; 7(6):791-796.

(24) Hori T, Nagata K, Hasuike S, Onaga M, Motoda M, Moriuchi A et al. Risk factors for the local recurrence of hepatocellular carcinoma after a single session of percutaneous radiofrequency ablation. J Gastroenterol 2003; 38(10):977-981.

(25) Poon RTP, Ng KKC, Lam C-M, Ai V, Yuen J, Fan S-T. Effectiveness of Radiofrequency Ablation for Hepatocellular Carcinomas Larger Than 3 cm in Diameter. Arch Surg 2004; 139(3):281-287.

(26) Ruzzenente A, Manzoni GD, Molfetta M, Pachera S, Genco B, Donataccio M et al. Rapid progression of hepatocellular carcinoma after Radiofrequency Ablation. World Journal of Gastroenterology 2004; 10(8):1137-1140.

(27) Salama HM, Hassan NHA, Hassan EM, Amer AR, Nicholls J, Kaddah TAH et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma using a multiple array needle electrode. HPB 2003; 5(1):11-18.

(28) Arch-Ferrer JE, Smith JK, Bynon S, Eckhoff DE, Sellers MT, Bland KI et al. Radio-frequency ablation in cirrhotic patients with hepatocellular carcinoma. American Surgeon 2003; 69(12):1067-1071.

(29) NICE. International procedure consultation document - percutaneous radiofrequency ablation of renal cancer. United Kingdom: National Institute for Clinical Excellence 2004.

(30) Thanos L, Mylona S, Pomboni M, et al. Primary lung cancer: treatment with radiofrequency thermal ablation. Eur Radiol 2004; 14(5):897-901.

(31) Rosenthal DI, Hornicek FJ, Torriani M, Gebhardt MC, Mankin HJ. Osteoid osteoma: percutaneous treatment with radiofrequency energy. Radiology 2003; 229(1):171-175.

(32) Callstrom MR, Carboneau JW, Goetz MP. Painful metastases involving bone: feasibility of percutaneous CT- and US-guided radio-frequency ablation. Radiology 2002; 224(1):87-97.

(33) Shetty SK, Rosen MP, Raptopoulos V, Goldberg SN. Cost-effectiveness of percutaneous radiofrequency ablation for malignant hepatic neoplasms. Journal of Vascular & Interventional Radiology 2001; 12(7):823-833.

(34) Llovet JM, Bruix J, for the Barcelona-Clinic Liver Cancer Group. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003; 37(429):442.