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Percutaneous Radiofrequency Ablation for treatment of hepatocellular carcinoma

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by

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Invitation.

This document was developed to assist decision-making in the McGill University Health Centre. All are welcome to make use of it. However, to help us estimate its impact, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way.

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ABBREVIATIONS AND ACRONYMS

BCLL	Barcelona Clinic Liver Cancer
Class	Child-Pugh Class
CLM	Colorectal Liver Metastases
CT	Computed Tomography
EA	Efficacy Analysis
HCC	Hepatocellular Carcinoma
HTA	Health Technology Assessment
INAHTA	International Network of Agencies for Health Technology Assessment
IRFA	Intraoperative Radiofrequency Ablation
LRFA	Laparoscopic Radiofrequency Ablation
LRS	Laparoscopic Resection
MCT	Microwave Coagulation Therapy
PEI	Percutaneous Ethanol Injection
PRFA	Percutaneous Radiofrequency Ablation
RFA	Radiofrequency Ablation
SRFA	Surgical Radiofrequency Ablation
SRS	Surgical Resection
TACE	Transarterial Chemoembolization
US	United States

SOMMAIRE

Avant-propos :

La résection chirurgicale (RC) est considérée comme l'étalon-or pour des carcinomes hépatocellulaires précoces. Il y a un intérêt accru dans l'ablation percutanée par radiofréquences (APR) des carcinomes hépatocellulaires précoces parce que cette technique est moins invasive et coûte moins cher. En 2008 au CUSM, cette procédure fut utilisée environ 40 fois lors de cancers du foie. Cependant, pour des raisons budgétaires, ce nombre fut inférieur à la demande pour ce type de procédure.

Objectif :

L'objectif premier de ce rapport est de comparer l'ablation percutanée par radiofréquences et la résection chirurgicale en termes d'efficacité clinique et de coûts.

Méthodologie :

Revue systématique de la littérature : Une revue systématique de la littérature fut faite parmi les articles rédigés en anglais, en français ainsi qu'en chinois à partir de bases de données d'articles médicaux, de revues systématiques et de rapports d'évaluation.
Méta-analyse : Une méta-analyse d'études observationnelles fut aussi complétée en regard du taux de survie de ces interventions.

Résultats :

Revue de la littérature : Nous avons identifié 21 études répondant à nos critères d'inclusion (3 études randomisées, 10 études comparatives et 8 séries de cas d'APR). De ces études, seulement une étude randomisée et 6 études de cohortes comparaient l'APR vs la RC lors de carcinomes hépatocellulaires précoces.
Survie : Les résultats de l'étude randomisée montraient que les résultats des deux traitements étaient similaires. (Les taux de survie à 1 et 3 ans étaient 94% et 69% pour le groupe APR comparés à 93% et 73% pour le groupe RC, respectivement). Le taux moyen de survie des 6 études comparatives était conforme avec cette conclusion (taux

de survie à 5 ans de 56% (22%, 90%) et de 58% (38%, 77%) pour l'APR et la RC, respectivement.

Récurrence : Dans l'étude randomisée, les taux de récurrence étaient de 23% pour l'APR vs 25% pour la RC. Pour les 4 études comparatives rapportant un taux de récurrence, ce taux était plus élevé suite à l'APR. Par contre, les taux de récurrence n'ont pu être utilisés dans une méta-analyse car les périodes d'observation étaient différentes.

Période de suivie sans maladie : La méta-analyse de trois études comparatives suggère que la RC est associée à une période de survie supérieure à celle suivant l'APR et que ce phénomène s'accentue avec le temps. Cependant, il est à noter que des différences systématiques étaient présentes dans les données de base entre les cohortes de l'APR et la RC.

Analyse des coûts :

Les dépenses communes aux deux traitements n'ont pas été considérées. L'analyse des coûts nous montre que lorsque les deux options sont possibles, l'APR coûte 7 428$ de moins que la RC pour chaque intervention. Actuellement, 40 interventions par APR sont menées par année pour le traitement du cancer du foie (37 cas) au coût de 92 000$. Ce montant est inférieur de 268 000$ à celui correspondant au même nombre d'interventions par RC. Si l'on considère 50 interventions (46 cas) par année, l'impact budgétaire annuel serait de 114 000$. Ce montant serait inférieur de 333 000$ à celui correspondant au même nombre d'interventions par RC.

Conclusion :

Pour les cancers précoces du foie où les options APR et RC sont disponibles, les évidences nous suggèrent que les taux de survie sont comparables. Cependant, plusieurs études de cohortes (avec des biais de sélection possibles) nous suggèrent que les taux de récurrence sont plus élevés et que la survie sans maladie est plus courte suivant l'APR plutôt que la RC. Par contre, les complications sont plus fréquentes et la durée d'hospitalisation plus longue après la RC et ce, de façon significative pour ces

deux paramètres. Le coût d'une intervention par APR est de 7 428$ inférieur à celui d'une RC (au CUSM). Il est à noter que toute économie potentielle résultant de l'utilisation de l'APR ne se concrétiserait pas mais se traduirait par une augmentation d'autres procédures chirurgicales, résultant en une augmentation d'efficacité.

Recommandation :

Si l'on considère les évidences présentes, le CUSM devrait financer sans restriction l'utilisation de l'APR pour le traitement de certains cancers du foie. Cependant, ces évidences devraient être revues fréquemment et la présente recommandation devrait être reconsidérée si de nouvelles évidences démontraient des taux de récurrence plus élevés ainsi que des périodes de survie sans maladie plus courtes suivant l'utilisation de l'APR.

EXECUTIVE SUMMARY

Background:

Surgical resection (SRS) is regarded as the gold standard therapy for early stage Hepatocellular Carcinoma (HCC). There is an increasing interest in percutaneous radiofrequency ablation (PRFA) for early stage HCC patients because it is not as invasive as surgery and also less costly. At the MUHC in 2008 there were 40 such procedures for liver cancer. However, for budgetary reasons, this number was less than the demand.

Objective:

The primary objective of the following document is to compare PRFA and SRS in terms of clinical effectiveness and cost.

Methods:

Systematic literature review: A systematic literature search of articles in English, French and Chinese was performed using online databases of medical articles, systematic reviews and health technology assessment reports.

Meta-analysis: A meta-analysis of observational studies was carried out to estimate the survival rate following PRFA or SRS treatment.

Cost analysis: To estimate the cost of each treatment from the perspective of the MUHC, we obtained information on costs and resource use from the Department of Finance and relevant service departments at the MUHC. Univariate sensitivity analyses were used to study the relative importance of each component cost.

Results:

Literature review: We identified 21 unique studies meeting our inclusion criteria (3 RCTs, 10 comparative cohort studies, 8 single-arm cohort studies of PRFA treatment). Of these 1 RCT and 6 comparative cohort studies evaluated PRFA vs. SRS for early stage HCC focused on our principal question of interest (a comparison of the effectiveness and costs of PRFA versus SRS).

Survival. The 1-, 2-, 3- and 4-year overall survival rates in the PRFA group (94%, 80%, 69%, 66%) were almost identical to those in the SRS group (93%, 82%, 73%, 64%). The average outcomes of the six observational studies were consistent with this conclusion (Survival rates at five years, 42% (95% CI: 11%, 73%) and 54% (95%CI: 40%, 68%) for PRFA and SRS respectively).

Recurrence. In the RCT, recurrence rates were 23% in the PRFA group vs. 25% in the SRS group. However, in each of the four cohort studies that reported recurrence rates[1-4] there was a higher recurrence rate following PRFA. Recurrence rates could not be meta analyzed because of differences of observation period.

Disease Free Survival. In the RCT by Chen et al., disease free survival (DFS) rates at the 4-year follow-up were 48% and 52% following PRFA and SRS, respectively, (P> 0.05). Meta analysis of the four observational studies suggests that SRS is associated with a longer disease free survival than PRFA, and that this becomes increasingly evident over time. However, there were systematic differences in baseline clinical characteristics between SRS and PRFA cohorts in these studies.

Cost analysis:

Costs that would be common to both treatments were not considered. Cost analysis showed that in those cases in which both options are possible, performing PRFA would cost $7,244 less per case than SRS. Currently 40 PRFA procedures per year are carried out for the treatment of liver cancer (37 cases), at a cost of $92,000. This is $268,000 less than the cost of the same number of SRS procedures. For 50 procedures (46 cases) per year, the annual budget impact would be $114,000. This would be $333,000 less than the cost of the same number of SRS.

Conclusions:

For relatively early liver cancer where either SRS or PRFA are available options, the evidence suggests that survival rates are comparable. However, several cohort studies (with possible selection bias) suggest that recurrence rates are higher and disease free

survival shorter following PRFA than SRS. Complications are significantly more frequent and hospitalization significantly longer following SRS. The costs of PRFA are $7,244 less per case than SRS (to the MUHC). Note that any potential budgetary saving resulting from use of PRFA would not be realized but would result in an increase in other types of surgical procedures, thus causing an increase in efficiency.

Recommendation:

On the basis of the evidence currently available, the MUHC should fully fund the use of PRFA for the treatment of appropriate liver cancers. However, the evidence should be frequently reviewed, and this recommendation should be reconsidered, should any new evidence, confirming higher recurrence rates and shorter disease free survival following PRFA become available.

1: INTRODUCTION

On November 18, 2008 the TAU was requested by Dr. L. Stein (Radiologist-in-charge, Royal Victoria Hospital), Dr. R. Lisbona (Chairman, Department of Radiology, McGill University Health Centre(MUHC)) and Ms. P. Rozanski (Director, Therapeutic & Diagnostic Services) to undertake an evaluation of the effectiveness and costs of Percutaneous Radiofrequency Ablation (PRFA) for the management of primary or secondary hepatocellular cancer.

The primary objective of the following document is to compare the clinical effectiveness of this technology with the principle alternate form of management, namely surgical resection (SRS), based on a systematic review of the literature. In addition we compared the costs of these two therapeutic approaches from the point of view of the MUHC.

A number of studies have reported that the clinical outcomes associated with PRFA are influenced by the use of a concomitant therapy, particularly transarterial chemoembolisation (TACE) . Accordingly, we also carried out a comparison of the clinical effectiveness of the following therapeutic combinations:

1). Percutaneous radiofrequency ablation (PRFA) + transarterial chemoembolisation (TACE) vs. surgical resection (SRS).

2). PRFA +TACE vs. TACE alone or PRFA alone.

These comparisons are reported in the Appendices.

2: BACKGROUND

2-1: Treatment of liver cancer

Choosing treatment strategies for patients with Hepatocellular Carcinoma (HCC) requires consideration of the tumor size and stage, the number, location and distribution of nodules, hepatic function, and the patient's overall health and the availability of resources[5, 6]. Surgical resection (SRS) is generally regarded as the gold standard therapy[7-9] for patients with few tumors. For patients at a more advanced stage of cancer who are not suitable candidates for curative surgical resection, percutaneous radiofrequency ablation (PRFA) is the preferred treatment [7-10]. However, recent studies have reported comparable clinical outcomes with either PRFA or SRS for early stage HCC patients[11, 12].

Median survival with "untreated" HCC ranges from 1 to 8 months[5]. For patients with early hepatocellular cancer, strategies such as surgical resection, liver transplantation and PRFA all result in greatly improved 5-year survival rates in comparison to no intervention (40-70% versus (vs.) <20%) [10, 13]. For patients with more advanced cancers who receive either TACE or chemotherapy, the median survival time is less than 24 months[14]

2-2: Radio Frequency Ablation (RFA)

RFA was introduced in the early 1990s[1]. Figure 1 illustrates the percutaneous procedure (PRFA) [15]. Under computed tomography (CT) or ultrasound guidance, the radiologist inserts a needle through the skin into the tumor. Electrodes at the tip of the needle deliver energy created by radiofrequency waves, and the energy induces thermal injury in proportion to the temperature achieved and the duration of heating[10]. To destroy tumor tissue, the temperature is typically maintained at 50° to 100°C for 4 to 6 minutes, according to the size of the tumour[10]. The destroyed tumor tissue shrinks and slowly forms a scar[15]. Traditionally, PRFA has been used for tumors of less than 3 cm[5], but

some studies now describe its use in tumors of 3-5 cm[5, 6, 16-18], and even larger [16]. It was also preferred for patients with poor hepatic function. Other contraindications of RFA therapy include tumor proximity to major vascular or biliary structures, and the presence of more than 3 tumours [19].

RFA can be administered percutaneously (PRFA), at the time of surgery (SRFA), or via laparoscopy (LRFA)[20]. PRFA is the most common approach. SRFA is also referred to as open RFA, intraoperative RFA, laparotomy RFA, or celiotomy RFA. LRFA is currently used less frequently than the other two approaches. SRFA can be combined with hepatic resection. A number of studies show that when RFA is carried out at the time of liver resection blood loss is dramatically reduced [21]. In general RFA is a safe procedure and procedure related mortality is very rare.

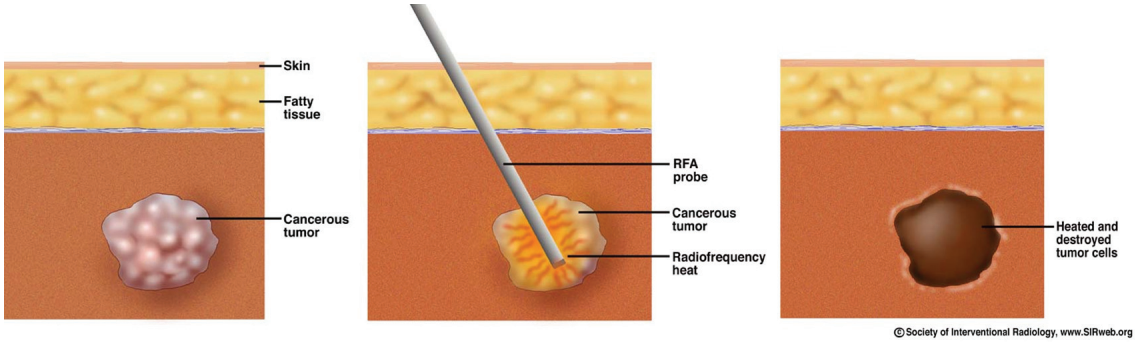

Figure 1: The procedure of percutaneous radiofrequency ablation

2-3: PRFA therapy for liver cancer at the MUHC

Radiologists at the MUHC have considerable experience in the use of PRFA in liver and kidney tumors. The first procedures were carried out in 2003, and since that time approximately 200 procedures have been completed. In 2008 there were 40 procedures for liver cancer but numbers were restricted due to a budget shortage. It is estimated that the average annual demand is approximately 50 procedures per year. PRFA is restricted to patients in which there are no more than three tumours, <4 cm in diameter. Allocation of cases to PRFA or SRS is decided by a multidisciplinary cancer board. TACE is

only used for about 10% of patients at the MUHC. It is equally likely to be used after PRFA or SRS treatment.

The complication rate for PRFA procedures in the MUHC has been recently reviewed by Doctor L Stein, based on 114 procedures carried out in 2007 and 2008:

Abscess…… 2%

Haemorrhage…. ..0.2-0.5%

Mortality……. 1.0%

Track seeding …….0%

Residual tumour… 5.0 %.

Repeat PRFA…… 8.0%

Hospitalization: The average length of hospitalization following SRS is 11.7 (5th to 95th percentile, 5—35) days.[i]

[i] Percentile (or centile): the value of a variable below which a certain percent of observations fall[22].

3: SYSTEMATIC REVIEW OF PRFA THERAPY FOR LIVER CANCER

3-1: Methods

3-1-1: Literature search

A systematic literature search of articles in English, French and Chinese was performed using PubMed, MEDLINE and EMBASE databases. Publications in other languages were considered, if their English abstracts/Tables/Figures were understandable and added information to the existing evidence base. We used the key words (radiofrequency OR radio frequency OR radio-frequency OR catheter ablation) AND (liver carcinoma OR liver cancer OR hepatocellular carcinoma OR liver cell carcinoma). We also searched the databases maintained by the International Network of Agencies for Health Technology Assessment (INAHTA), Cochrane Collaboration and the Centre for Reviews and Dissemination (CRD) using the key words above in order to identify health technology assessment reports and systematic reviews. A further search was conducted by tracking references in publications identified. The date of the last literature search was January 15, 2009.

3-1-2: Inclusion criteria

RCTs, non-randomized comparative cohort studies, and cohort studies with only PRFA treatment were considered for this review. We excluded reviews, editorials, letters, and animal studies. The comparisons of primary interest were PRFA vs. SRS. However, we also included PRFA + TACE vs. PRFA alone or TACE alone or SRS alone for patients with either primary HCC or colorectal liver metastases (CLM). In addition, we included cohort studies with one type of PRFA therapy in order to extract any relevant information on risk of complications or adverse effects.

We required that studies had a minimum sample size (N) depending on their design, as follows:

RCTs or quasi-RCTs: no minimum requirement;

Comparative cohort studies: average N per group ≥ 50;

Cohort studies with only one type of PRFA treatment: N ≥ 200.

If an article mixed similar treatments together, such as ablation treatment including PRFA, PEI and MCT, the sample size of the PRFA group had to be more than 50% of the total and the estimated sample size of the PRFA group had to meet the minimum sample size requirements above. If multiple publications were based on the same data only one of them was included. The main considerations for selecting among multiple publications were study design (comparative studies or studies with single arm), sample size, follow up time, and aim of studies (Appendix 2).

We further excluded studies based on the following criteria:
For comparative studies, when clinical outcomes were not grouped by either the initial treatment or the treatment received.
When articles did not report survival rates.
When the mean or median follow-up time was less than 1 year.
When papers compared efficacy/effectiveness among different types of PRFA equipment (e.g. devices, needles, electrodes).
When papers compared efficacy/effectiveness among different RFA approaches (e.g. percutaneous RFA, PRA at the time of surgery (SRFA), or laparoscopic RFA (LRFA)).
When papers compared efficacy/effectiveness of SRFA/LRFA to other approaches (e.g. LRFA vs. laparoscopic resection).
When papers compared efficacy/effectiveness of PRFA to other ablation methods (e.g. PEI and MCT)
When studies were not reported in peer-reviewed journals.

3-1-3: Data extraction

We read the abstracts of all articles published in 2006 or later and retrieved them if they met our inclusion criteria. We identified eligible studies published before 2006 mainly from systematic reviews[7, 8, 10, 23]. We extracted specific clinical outcomes, including

survival rates and disease free survival rates, typically at 3 years and 5 years, local and distant recurrence rates and major complications. The first author conducted the preliminary data extraction. Data extraction and results were cross-checked by the second author. When necessary, we contacted authors to clarify issues.

HCC patients often receive multiple treatments during the course of the disease. Our analyses were primarily based on the clinical effectiveness among patients who were being treated for the first time, but to utilize all available data maximally, we also included studies that were grouped according to administered treatments. In general the starting date relative to which survival is estimated in our analysis is the date of first receiving treatment. However, in some studies the starting date was the date of diagnosis, especially in those studies grouped by initial treatment. In effect, whether the starting date is timed from diagnosis or from first receipt of therapy is relatively unimportant, since HCC patients are generally treated within a short period after liver cancer is diagnosed. If articles did not report cumulative survival rates in the text or tables, but presented them in figures, such as in a Kaplan-Meier survival curve, we estimated cumulative survival rates from the curve. We also extracted from each study all relevant information on recurrence and complications. We also extracted details on the stage of HCC, tumor size, number of tumors, demographic characteristics, sample size and year of publication.

3-1-4: Meta-analysis

When studies had similar baseline characteristics, and no obvious selection bias (for non-randomized comparative studies), we conducted meta-analysis to estimate the pooled 3- and 5-year survival rate of each treatment strategy. We used the random effects generalized linear mixed model for meta-analysis of 3- and 5-year survival rates. We used an exact likelihood approach based on the binominal distribution rather than the approximate approach used in the DerSimonian and Laird random effects model[24]. This model was particularly suited to situations where the normal approximation to the

binomial is poor due to a sample size or small cumulative survival rates [24, 25]. Meta-analyses were conducted using SAS 9.1.

3-2: Clinical results:

The literature search history in Medline and Embase can be found in Appendix 1. In total we identified 838 abstracts published between January 2006 to January 2009. We identified 4 Health Technology Assessment (HTA) reports in the INAHTA database, 3 of them published in 2004, and the other one published in 2006. We found several instances where multiple publications were based on the same sample (Appendix 2). In total, we identified 21 unique studies meeting our inclusion criteria (3 RCTs, 10 comparative cohort studies, 8 single-arm cohort studies of PRFA treatment). Seventeen of the 21 articles were published in 2006 or later. Of the 21 selected articles one RCT [11] and six observational studies [1, 2, 4, 18, 26], [3] focused on the comparison between PRFA and SRS in patients with early stage HCC with small tumors among whom SRS is the standard treatment. These studies are discussed in the following text. Results from the remaining studies are described in Appendix 3.

3-2-1: PRFA vs. SRS

Survival: The baseline characteristics of patients in studies comparing PRFA to SRS are summarized in Table 1. The RCT by Chen et al. included patients with ≤ 5cm HCC[11]. Although 19 out of 90 patients withdrew after randomization to the PRFA group and did not receive PRFA, the results of intention-to-treat (ITT) and efficacy analyses (EA) were very similar, and both ITT and EA demonstrated that PRFA is as good as the gold standard therapy, SRS, in terms of survival rate and disease free survival rate. The 1-, 2-, 3- and 4-year overall survival rates in the PRFA group (94%, 80%, 69%, 66%) were almost identical to those in the SRS group (93%, 82%, 73%, 64%) (See Table 2).

All six comparative observational study cohorts consisted of early stage HCC patients (Child-Pugh class A or B), tumor sizes ≤ 3-6 cm and 3 or fewer lesions. Some studies[2, 26]

attempted to adjust for baseline differences in PRFA and SRS groups by either study design or statistical analysis, but it is likely that, selection bias between PRFA and SRS groups still existed. In one study the difference between the groups was clearly apparent [26]. In this study Child-Pugh Class A and single HCC cases were considered for surgery, whereas Class B and multiple HCC cases were considered for PFRA. This was the only study in which 3- and 5-year cumulative survival rates favored SRS over PRFA (64% and 48% vs. 42% and 20%)[26], despite adjusting for the differences in baseline characteristics using a multivariate model(See Table 2). In the remaining 5 studies differences between the two treatments in survival were not statistically significant [1-4, 18].

The pooled 1-, 3- and 5-year survival rates in the PRFA and SRS groups in the 6 observational studies that did not find a significant difference between the two treatments was as follows:

	1-year survival(95% CI)	3-year survival(95% CI)	5-year survival(95% CI)
PRFA	98%(95%,100%)[1-4, 18, 26]	71% (54%, 87%)[2-4, 18, 26]	42% (11%, 73%)[2, 18, 26]
SRS	96%(93%, 99%)[1-4, 18, 26]	74% (65%, 83%)[2-4, 18, 26]	54% (40%, 68%)[2, 18, 26]

Since the 5-year survival rates in PRFA differed greatly between Guglielmi et al. (20%)[26], Takahashi et al. (77%)[2] and Lupo et al. (32%)[18] , the pooled estimates had very wide confidence intervals.

Recurrence and disease free survival: In the RCT by Chen et al.[27], recurrence rates following both interventions were also comparable, with 3-year cumulative recurrence rates of 23.4% and 24.6% for PRFA and SRS, respectively. Four out of 6 cohort studies reported recurrence rates[1-4]. In all four there was a higher recurrence rate following PRFA (See Table 2). However, overall recurrence rates varied greatly. Following PRFA and SRS the overall recurrence rates were 47% and 43% at 3 years[3], 55% and 36% at 2

years[1], 58% and 45% at 3 years[4] and 85% and 73% at 5 years[2], respectively. Recurrence rates were not comparable across studies because of different follow-up times.

In the RCT by Chen et al., disease free survival (DFS) rates at the 4-year follow-up were 48% and 52% following PRFA and SRS, respectively, (P> 0.05) [11]. Five out of the 6 observational studies reported DFS (See Table 2). In all, disease-free survival was longer following SRS, but in only one was this statistically and clinically significant [26]. However, as stated above, there was obvious selection bias in this study[26]. In Guglielmi et al.[26], disease free survival was longer following SRS (1-, 3-, and 5-year DFS, 60%, 22% and 22% with PRFA and 83%, 56% and 27% with SRS (p=0.001)). In Takahashi et al.[2], the median DFS was 23 and 25 months following PRFA and SRS, respectively (p=0.012). However, DFS at 1-, 3- and 5-year follow up was not reported.

The pooled 1-, 3- and 5-year disease free survival in the PRFA and SRS groups in the 4 observational studies was as follows:

	1-year DFS rate, (95% CI)	3-year DFS rate, (95% CI)	5-year DFS rate, (95% CI)
PRFA	68% (63%, 74%)[3, 4, 18, 26]	27% (19%, 35%)[3, 4, 18, 26]	2% (0%, 13%)[18, 26]
SRS	76% (72%, 82%)[3, 4, 18, 26]	47% (37%, 57%)[3, 4, 18, 26]	22% (12%, 32%)[18, 26]

Thus, meta analysis of these three studies suggests that SRS has longer disease free survival than PRFA, and that this becomes increasingly evident with time. (Note, however, that these are observational studies, not RCTs.)

Additional treatment: Patients in the PRFA group are more likely to have multiple treatments to achieve complete necrosis. In the RCT by Chen et al., 23 (32%) patients in the PRFA group needed additional treatment with PRFA, PEI or TACE because the 1 month follow-up CT scan showed incomplete tumor necrosis. The authors believe that without the additional treatment the subsequent intrahepatic recurrence rate would

have been very high. In the study by Guglielmi et al, patients treated with PRFA received between 1-4 treatment sessions, with those with smaller tumors (<3cm) being more likely to achieve complete necrosis than those with larger tumors (93.3% vs. 80.3%). Based on the expert opinion of Doctor L. Stein, the repeat procedure rate at the MUHC is roughly 8%.

Complications: The most common major complications following PRFA are hemorrhage, skin burn (under the electrode), pleural effusion and hepatic abscess. While skin burns are only associated with the use of PRFA, the other complications also occur following surgical resection. In the RCT by Chen et al.[11], major complications (liver failure, gastrointestinal bleeding, ascites, persistent jaundice) were significantly more frequent in the SRS group (50 of 90 procedures (55%) vs. 3 of 71(4%)) and one patient died, following SRS treatment. Three out of 6 cohort studies reported complications. Complication rates for PRFA and SRS in these studies were 10% and 36% [26], 10% and 17% [18] and 6.5% and 5% [3], respectively (See Table 2). One hospital death was observed following SRS[18]. Two studies also found that SRS was associated with significantly longer hospitalization[11, 18]. In Chen et al., the hospital stay (mean± SD) in SRS and PRFA groups were 19.7±5.6 and 9.2 ± 3.1 days, respectively; and in Lupo et al., the median (range) hospital stay in SRS and PRFA groups were 5.5(3—43) and 2(1—16) days, respectively.

The frequency of complications following PRFA reported in the four studies can be summarized as follows:
Chen et al., skin burn at the site where the electrode pads were passed: 3 out of 71 patients.
Lupo et al., out of 60 patients undergoing PRFA, 2 liver failure, 2 pleural effusion, 1 hepatic abscess and 1 cutaneous metastasis.
Cho et al., out of 99 patients undergoing PRFA there were 5 cases of complications (chest wall metastasis, cholecystitis, iatrogenic burn, ileus and hepatic infarction).

Guglielmi et al mentioned that 10% of patients experienced minor complications, but did not report types of complication.
3 studies did not report complications.

In addition, the following complications were reported in three large observational studies of PRFA treatment. (These studies are included in Appendix 3 but not in the main document.)
Tateishi et al.[28], 40 major complications in 1,000 PRFA procedures (4%), including intraperitoneal hemorrhage (4), pleural effusion requiring drainage (4), hepatic abscess requiring drainage (7) neoplastic seeding (15) etc. No procedure-related deaths.
Choi et al.[29], a total of 11 complications were found in 570 patients (1.9%), including abscess (3), infarction (4), cancer seeding (2) etc. No procedure-related deaths.
Yan et al.[30], 10 complications were found in 284 patients (3.5%), including intraperitoneal hemorrhage (2), biliary duct stricture (1), hemothorax (1), bowel perforation (1) and needle tract seeding (5).

3-3: Discussion of systematic review

In the evaluation of PRFA and its alternatives we have had to largely rely on non-controlled studies, and, although, to facilitate analysis, we have grouped patients into specific treatment groups, it is difficult, for many reasons, to be certain of the real role of any one therapy in the management of these liver cancers. For example, many of the observational studies did not report the criteria by which treatment was selected. Furthermore, some studies categorized patients by the therapies they received, rather than by their initial treatments, (This occurred particularly in Appendix 3, which included CLM or more advanced HCC patients). Irrespective of the initial therapy, patients are likely to experience many other forms of treatment as their disease progresses. Therefore, even though patients with similar characteristics can be grouped together, selection bias still cannot be excluded.

However, despite the potential confounding, most studies show comparable results. In terms of survival rate, PRFA appears to be as effective as SRS in early stage HCC. For patients with unresectable liver cancer, in comparison to PRFA alone or TACE alone, TACE+ PRFA appears to substantially improve survival rates, by around 20% in 5 years[31, 32](see Appendix 3). It must be stressed however that the magnitude of survival benefits varies considerably across studies, possibly due to variations in stage of HCC, or other factors such as tumor size, number of tumors and Child-Pugh Class.

Strengths and weaknesses: We have carried out a comprehensive review of PRFA treatment for liver cancer covering the two major languages. With increasing use of PRFA, a number of studies have been published in recent years. Consequently, most studies included in our analysis were published after 2006, and are not included in previous HTA reports. Since the incidence rates of liver cancer are higher in East Asia[33], 15 out of 21 publications were based on populations from those regions. Seven out of 21 articles were from China[11, 16, 30, 31, 34-36], 2 of them in Chinese[16, 36]. As explained above, our results are limited by the quality of the individual studies, particularly those that used a non-randomized design. Ideally, individual-level data should have been used for the meta-analyses in order to account for time-varying covariates and censoring. Due to the aggregate nature of the reported data we were limited to using standard meta-analysis methods for combining of proportions.

4: COST ANALYSIS

In this section, we compare the costs of using percutaneous radio frequency ablation (PRFA) with the cost of surgical resection (SRS), at the MUHC, for those early stage hepatocellular cancer cases in which either treatment approach may be used. Since our systematic review demonstrated that 5-year survival rates following either treatment are comparable, we simply compared the costs of the two approaches. We assumed that recurrence rates are also comparable following either treatment as this was the conclusion of the sole RCT.

4-1: Methods

Our primary interest was to estimate the difference in cost of the two treatments, seen from the perspective of the MUHC. Physician's fees were excluded as these are not covered by the MUHC.

We obtained information on costs and resource use from the Department of Finance and relevant service departments at the MUHC. Since patients undergoing PRFA and SRS are managed identically during pretreatment and follow-up, the costs incurred during these phases of management are ignored. Moreover, the rates, types, and definitions of complications varied so much across different studies, that it was impossible to quantify and transform these events into monetary terms. Therefore, we also excluded the cost of complications from our analysis (Their inclusion would have further increased the cost of SRS.). Since the costs considered do not reflect the total costs, we refer throughout to the *compared costs* of SRS and PRFA. All cost information is per patient and not per tumor.

Below we describe how we estimated the total cost of each treatment:

4-1-1: Costs of liver resection surgery

Cost estimates were based on 57 SRS procedures carried out by 4 surgeons at the MUHC. (Procedure code: 301200 & 301205 (Laparotomy resection liver left & right) (2008—2009)). Details are shown in Appendix 4. The average (compared) cost to the MUHC per procedure was \$9,722 (5^{th} to 95^{th} percentile, \$5,101— \$19,389).

4-1-2: Costs of PRFA

The average and range of resource and personnel used per procedure, was estimated by Doctor David Valenti, Department of Radiology, Royal Victoria Hospital (RVH) (May 7^{th} 2009). Costs to the MUHC were obtained from Nicolas Robert, Department of Finance,

MUHC. The details are shown in Appendix 4. The average (compared) cost per PRFA procedure was $2294.

4-1-3: Sensitivity analyses

We conducted univariate sensitivity analyses to identify key variables impacting the incremental cost. For the cost of each component of liver resection surgery, we used the 5^{th} to 95^{th} percentile to define the possible range. For the cost of each component of PRFA therapy, the range was elicited using expert opinion.

In 2008 at the MUHC 40 PRFA procedures were performed for liver cancer. As noted, numbers were restricted by budgetary constraints. It is estimated that the future annual demand will be for 70 PRFA procedures per year, of which 50 will be for liver cancer. Assuming 8% of patients require a second procedure, the demand for hepatic PRFA will be for approximately 46 patients (50 procedures) per year.

4- 2: Results

Compared cost. The compared costs of SRS and PRFA (including 8% repeat procedures) are $ 9,722 and $ 2,478 per case, respectively. Thus, when both options are possible, performing PRFA would cost $ 7,244 less per case. Results of the sensitivity analysis are shown in Appendix 4. Most variables only have a small impact on the cost. The most important variables impacting the total cost are costs of nursing & ICU and operating room use for SRS.

Budget impact. The procedure costs (excluding costs of preoperative workup and post-operative follow-up, which are comparable for either procedure), of the current level of use of PRFA (37 patients (40 procedures) per year) are $ 92,000. The comparable costs of surgical management of the same number of cases would be approximately $360,000, or approximately $268,000 more. If annual use of PRFA for liver cancer were to increase

to 46 cases (50 procedures) per year, the annual budget impact would be $ 114,000, with a potential saving of $ 333,000 per year, compared to surgical resection.

5: DISCUSSION

It should be noted that the costs of liver resection surgery were based on the actual records of 57 cases, while resource uses of PRFA were based on the estimates of an expert.

Furthermore, we did not consider complications and recurrences in our cost analysis. Based on the available literature, the complication rate is higher in the SRS arm suggesting that if we had taken complications into account the cost of SRS vs. PRFA would have been even higher. Recurrence rates, however, appear to be either comparable (based on the RCT[27]) or somewhat lower following SRS (based on 4 observational studies[1-4]).

Cost analysis demonstrated the potential cost saving associated with PRFA use for patients with early stage hepatocellular carcinoma. Specifically, the cost of PRFA is only one quarter of the cost of surgical resection ($ 2,478 vs. $ 9,722). However, the realisation of such potential savings through reduction of surgical procedures is not feasible. Thus, the preferential use of PRFA instead of surgery, does not represent an actual budget saving, but reflects instead a substantial increase in efficiency.

6: CONCLUSIONS

Outcomes. For relatively early liver cancer where either SRS or PRFA are available options, the evidence suggests that *survival* rates following these two interventions are comparable. Disease-free survival, however, may be longer following SRS and recurrence rates may be lower.

Complications are significantly more frequent and hospitalisation significantly longer following SRS.

Unit costs. On average, use of PRFA costs the MUHC $7,244 less per case than SRS.

Budget impact. Use of PRFA instead of SRS for 46 cases per year would result in a *potential* budget saving of $333,000. However, this saving would not be realised, but would cause an increased in other types of surgical procedure. Thus the overall result would be a major increase in the efficiency of the institution.

7: RECOMMENDATION

On the basis of the evidence currently available the MUHC should fully fund the use of PRFA for the treatment of appropriate liver cancers. However, the evidence, should be frequently reviewed, and this recommendation should be reconsidered, should any new evidence, confirming higher recurrence rates and shorter disease free survival following PRFA become available.

8: ADDITIONAL OBSERVATIONS

Though not pertinent to the principal question (a comparison of the effectiveness and costs of PRFA versus SRS) the other analyses reported in Appendix 3 revealed interesting information which should be shared with the relevant physicians:

Both RCTs and cohort studies showed substantial survival benefits with PRFA+TACE therapy when compared to TACE alone or to PRFA alone (See Appendix 3-1).

In general evidence is consistent to the effect that in terms of overall and disease free survival, recurrence, and complication rates[37], results following PRFA + TACE were comparable or superior to SRS therapy for HCC in Child-Pugh class A level,.(See Appendix 3-2)

Meta-analysis of the outcomes of patient groups categorised as early, intermediate and advanced, gave 3- and 5-year survival rates that were comparable to those arrived at in the PRFA vs. SRS section reported above (3 year survival, 78%[28-30, 36, 38, 39] vs. 74%; and 5 year survival, 58%[28-30, 36, 38, 39] vs. 54%[2, 2, 18, 18, 26]).(See Appendix 3-3).

Table 1: Patient characteristics in studies of PRFA vs. SRS

Author(y) Country	Population	Treatment	N	Tumor Size (cm)	TN	Age Mean (SD or range)	Sex, Male, n(%)
RCTs							
Chen[11] (2006) † ; China	Solitary HCC, no metastasis; TS ≤ 5 cm; Child-Pugh Class A; good liver function; no previous treatment.	PRFA	90	≤3: 52%; 3.1-5: 48%	1	51.9(11.2)	56(79)
		SRS	90	≤3 : 47%; 3.1-5: 53%	1	49.4(10.9)	75(83)
Comparative cohort studies							
Guglielmi[26] (2008); Italy	HCC; TS < 6 cm; TN≤3; Class A and single HCC considered for surgeries; Class B and multiple HCC considered for PFRA; 76% and 59% pts with Class A in SRS and PRFA group.	PRFA	109	≤3, 34%; 3-6, 66%	60%SG	65%> 65y	88(81)
		SRS	91	≤3: 30%; 3-6, 70%	76%SG	48%> 65y	73(80)
Hasegawa[1] (2008); Japan	HCC; TS≤3cm; TN≤3; Class A or B; 2570 of 2875 (90%) and 2288 of 3022 (76%) with Class A in SRS and PRFA groups, respectively; a database from national survey of 795 institutions.	PRFA	3,022	2.0(1.0, 3.0) ‡	72%SG	69(52,80) ‡	1,937 (64)
		SRS	2,857	2.2(1.2, 3.0) ‡	84%SG	67(48,77) ‡	2,114 (74)
Takahashi[2] (2007); Japan	Naïve HCC; Class A; 47 of 171 receiving TACE before PRFA, 124 of 171 pts treated by PRFA alone; no information of criteria for treatment SRS or PRFA.	PRFA	171	2.1(0.7-4.8) #	73%SG	69(44-84)#	120(70)
		SRS	53	2.5(1-5) #	77%SG	66(41-80)#	39(74)
Lupo[18] (2007); Italy	Single HCC; TS 3 to 5 cm; Class A or B; no previous treatment for HCC; criteria for choosing PRFA: a localization of the tumor requiring too much parenchymal loss at SRS or patient's refusal of surgery; in PRFA, Class A of 73%; in SRS, Class A of 67%.	PRFA	60	Median: 3.7	1	68(42-85) #	47(78)
		SRS	42	Median: 4.0	1	67(28-80) #	33(79)
Cho[3] (2005);	HCC; TS < 5 cm; TN ≤3; Class A; no evidence of extrahepatic	PRFA	99	3.1±0.8	NA	58	76(77)

Korea	metastasis; no information on criteria for using PRFA or SRA.	SRS	61	3.4±1.0	NA	57	48(79)
Hong[4] (2005); Korea	Single HCC; Pts with liver cirrhosis whose Child-Pugh score is 5 (Class A) or without cirrhosis; TS ≤ 4 cm; no previous treatment of HCC; reasons for undergoing PRFA, refusal of surgery or general anesthesia (33 pts), insufficient postoperative hepatic reserve.	PRFA	55	2.4±0.6	1	59.1±9.6	41(75)
		SRS	93	2.5±0.8	1	49.2±9.9	69(74)

Abbreviations: RFA= radiofrequency ablation; PRFA= percutaneous RFA; SRS= surgical resection/ partial hepatectomy/ hepatectomy/ resection; HCC= hepatocellular carcinoma tumors; CLM= colorectal liver metastases; TN=number of tumors; SG=single tumor; y= year/ years; Class = Child-Pugh class; Korea= South Korea; US= United States.

†: Intention to treat analysis was conducted. However, for PFRA group, descriptive demographic statistics in Table 1 were based on 71 patients who received PRFA treatment, and excluded 19 patients who withdrew their consent.

‡: Median (5^{th} percentile, 95^{th} percentile).

#: Median/mean (range).

Table 2: Clinical outcomes in studies of PRFA vs. SRS

Author (Year)	Type of Treatment (N)	Survival (%) T1	T2	T3	P value	DFS (%) T1	T2	T3	P value	Recurrence (%) T1	T2	T3	Mortality n (%)	Complications n (%)
RCTs		1 y	3 y	4 y		1 y	3 y	4 y		1y	2y	3y		
Chen[11, 27]	PRFA (90)	94	69	66	P> 0.05	91	60	48	P> 0.05	9	19	23	0(0)	3 (4.2)
(2006) #	SRS (90)	93	73	64		87	70	52		11	18	25	1(1.1)	50(55)
Comparative cohort studies														
		1 y	3 y	5 y		1 y	3 y	5 y						
Guglielmi[26]	PRFA(109)	83	42	20	P= 0.01	60	22	22	P=0.001	NA	NA	NA	0(0)	11 (10)
(2008)‡	SRS (91)	84	64	48		83	56	27		NA	NA	NA	0(0)	33 (36)
		1 y	2 y							1 y	2 y			
Hasegawa[1]	PRFA(3,022)	99	93		P> 0.05	NA	NA	NA		26	55		NA	NA
(2008)	SRS(2,857)	98	95			NA	NA	NA		17	36		NA	NA
		1 y	3 y	5y						1 y	3 y	5y		
Takahashi[2] (2007)	PRFA(171)	99*	90*	77	P> 0.05	Median DFS: 23 months			P=0.012	26	68	85	NA	NA
	SRS (53)	96*	81*	70		Median DFS: 25 months				20	49	73	NA	NA
		1y	3y	5y		1y	3y	5y						
Lupo[18]	PRFA (60)	96	53	32	P> 0.05	68	18	0	P> 0.05	NA	NA	NA	0(0)	6 (10)
(2007)	SRS (42)	91	57	43		74	35	14		NA	NA	NA	1(2.4)	7 (17)
		1y	2y	3y		1y	2y	3y		1y	2y	>2y		
Cho[3]	PRFA (99)	96	87	80	P> 0.05	73	51	31	P> 0.05	24	40	46	0(0)	4 (6.5)
(2005)	SRS (61)	98	87	77		72	51	37		26	38	43	0(0)	5 (5.0)

		1y	2y	3y		1y	2y	3y		1y	2y	3y		
Hong[4]	PRFA (55)	100	88*	73	P> 0.05	74	57	40	P> 0.05	26*	45*	58	NA	NA
(2005)	SRS (93)	98	92*	84		76	63	55		24*	43*	45	NA	NA

Abbreviations: RCTs= randomized controlled trials; NA= not applicable; PRFA= percutaneous radiofrequency ablation; SRS= surgical resection; DFS =disease free survival; T1, T2, T3=time point (in years) when clinical outcomes were reported; N=Total sample size; n=number with outcome; y=year/years; Mortality= procedure related mortality or hospital mortality.

#: Originally, this paper was published in Chinese in 2005[27]. Thereafter authors added additional patients and republished, including all patients in 2006[11] . However, the 2006 article did not report recurrence rates, so we derive these from the 2005 study [27].

*: Estimated value, extracted from the graphs of the articles.

‡: in PRFA group, 89 out of 109 with complete necrosis were included in disease free survival analysis.

Appendix 1: Literature search history in Medline or Embase

	Keyword(s)	Results
1	radiofrequency.mp. [mp=ti, ot, ab, nm, hw, sh, tn, dm, mf]	25,490
2	radio frequency.mp. [mp=ti, ot, ab, nm, hw, sh, tn, dm, mf]	4,276
3	radio-frequency.mp. [mp=ti, ot, ab, nm, hw, sh, tn, dm, mf]	4,276
4	catheter ablation.mp. [mp=ti, ot, ab, nm, hw, sh, tn, dm, mf]	19,860
5	4 or 1 or 3 or 2	37,612
6	liver carcinoma.mp. [mp=ti, ot, ab, nm, hw, sh, tn, dm, mf]	2,229
7	liver cancer.mp. [mp=ti, ot, ab, nm, hw, sh, tn, dm, mf]	10,570
8	hepatocellular carcinoma.mp. [mp=ti, ot, ab, nm, hw, sh, tn, dm, mf]	39,441
9	liver cell carcinoma.mp. [mp=ti, ot, ab, nm, hw, sh, tn, dm, mf]	24,085
10	8 or 6 or 7 or 9	56,799
11	10 and 5	2,740
12	limit 11 to human	2,432
13	limit 12 to yr="2006 - 2009"	1,098
14	remove duplicates from 13	838

Appendix 2: Criteria used for selecting from among studies based on overlapping samples

All studies below met the inclusion criteria individually, however studies in each row shared all or a part of the same data.

Study selected (Entry time)	Studies excluded (Entry time)	Institutions, city, country	Main considerations in the article selection
Guglielmi[26] (1996-2006)	Vivarelli[40] (1998-2002)	Guglielmi study: at University of Verona Medical School; Vivarelli study: SRS group at University of Bologna and PRFA at UVMS; Verona & Bologna, Italy	Guglielmi et al. study was a comparative study conducted in one institute, while SRS and PRFA were conducted at two different institutes in Vivarelli et al. study.
Tateishi[28] (1999-2003)	Ohki[41] (1995-2003); Omata[42] (1992-2003)	Department of Gastroenterology, University of Tokyo, Japan	Tateishi et al. study (the non-SRS group) only included PRFA patients, while the other two studies mixed PRFA, PEI and MCT together.
Chen[11] (1999-2004) (RCT)#	Chen[27] (2000-2003) (RCT)#	Cancer Centre of Sun Yay-Sen University, Guangzhou, China	Chen et al. study[11] had larger sample size.
Chen[36] (1999-2007)	Peng[43](1999-2005)	Cancer Centre of Sun Yay-Sen University, Guangzhou, China	Chen et al. study[36] had larger sample size.
Yamakado[37] (2000-2006) Yamagiwa[12] (1995-2004)	Takaki[44] (2000-2006); Fuke[45] (2000-2006)	Mie University Hospital, Shima City, Japan	Yamagiwa et al. study had the largest sample size. Yamakado et al. study focuses on our interested subgroup, the early stage of HCC and included a comparison of PRFA vs. SRS.
Choi[29] (1999-2005); Hong[4] (1999-2001)		Sungkyunkwan University School of Medicine, Seoul, Korea	Hong study is a comparative study, while Choi et al. study is a single arm study with large sample size. Only a small proportion population was

			overlapped i.e., so, we included both studies.
Liu[46] (1994-2003)	Liu[35] (1994-2003)	First Hospital□Xi'an Jiaotong University□Xi'an, China	These two studies were very similar, except one was in English, and the other in Chinese. We selected the English article.
Raut[47](1997-2002)	Curley[48](NA)	The University of Texas M.D. Anderson Cancer Center, Houston, US; and the G. Pascale National Cancer Institute, Fondazione, Italy	Raut et al. study had a larger sample size and longer follow-up time.
Yan[46] (1999-2006)	Chen[49] (1999-2005); Chen[50] (2000-2007); Chen[51] (2000-2007)	Peking University school of Oncology, Beijing Cancer Hospital & Institute, Beijing, China	Yan et al. study had a 5-year follow-up, while others have 3-year follow-up.

#: We contacted the authors for these two RCTs. Originally, this paper was published in Chinese in 2005[27]. Then, the authors continued the study with a cohort of new patients. The authors re-analyzed all cases and published it in 2006[11] .

We also excluded two studies which were included in some reviews. The RCT by Lu et al. compared the SRS with percutaneous thermal ablation for early stage HCC[52]. But, since most ablation procedures were performed by MCT (37 of MCT vs. 14 of PRFA), so we excluded it. Two reviews by Lencioni et al. included their own study of 423 cases[10, 53], which was indicated as in press in the publication in 2004[53], but the original article was not found by tracking references, so we excluded it.

References in Appendix 2 and 3 share the same reference list with the main text.

Appendix 3: Summary of other studies involving PRFA

This Appendix is divided into 3 sub-sections. In the first two sections, we present the results of studies of the effectiveness of PRFA when used together with the concomitant therapy transarterial chemoembolisation (TACE). In Appendix 3-1 we present results from studies comparing PRFA+TACE to either TACE alone or PRFA alone. In Appendix 3-2 we present results of studies comparing PRFA+TACE to SRS. In Appendix 3-3 we present meta-analyses summarizing the survival rate following PRFA for patients at various different stages of liver cancer. Baseline characteristics of patients are summarized in Table 3 and clinical outcomes (survival, recurrences and complications) are summarized in Tables 4a and 4b, respectively. The methods of data extraction and meta-analyses in this section are the same as those in the main text.

Appendix 3-1: TACE+ PRFA vs. TACE alone or PRFA alone

Two RCTs and three comparative cohort studies that made these comparisons were identified[12, 31, 32, 34, 46] (See Table 3).

Survival: Two RCTs compared the survival benefit of TACE combined with PRFA to PRFA alone and TACE alone[31, 34]. In these studies, patients were not eligible for SRS. In the RCT by Cheng et al.[31], the 1-, 3-, 5-year survival rates were 67%, 32%, 8% with PRFA; 74%, 32%, 13% with TACE; and 83%, 55% and 31% with PRFA+TACE, respectively; compared with PRFA alone or TACE alone, PRFA+TACE improved survival significantly ($p< 0.001$). In the Yang et al. RCT[34], the inclusion/exclusion criteria and statistical methods were unclear; the sample size was very small in the PRFA and TACE groups (12 and 11, respectively); and the follow up time was short (a maximum of 18-month survival rate was presented). The RCT by Cheng et al. did not have these drawbacks. In Yang et al., 6-, 12-, 18-months survival rates were 60%, 58%, 52% with PRFA ; 62%, 53%, 45% with TACE ; 79%, 68%, 67% with TACE +PRFA, respectively[34]. Yang et al. did not report whether survival rates of TACE +PRFA vs. TACE/PRFA were statistically different.

Three comparative cohort studies compared TACE+ PRFA vs. TACE alone[12, 32, 46] (See Table 4a). Survival was significantly better with the former treatment in all three studies. In the study of Helmberger et al., the 1-, 3- and 5-year survival rates were 94%, 65%, 27% and 57%, 15%, 6%, in TACE+ PRFA and TACE groups ($p<0.01$), respectively; in the study of Liu et al. the 1- and 3-year survival rates were 75%, 37% and 69%, 22% in TACE+ PRFA and TACE alone($p<0.05$), respectively[46] . In the study of Yamagiwa et al. the 5-year survival rates were 72% in the TACE+ PRFA group and 15% in the TACE group[12] ($P<0.01$).

Recurrence: In the RCT by Cheng et al., the overall recurrence rates were 81%, 80% and 59% in PRFA, TACE and TACE+PRFA groups, respectively[31](TACE+ PRFA vs. TACE, $p=0.001$; TACE+ PRFA vs. PRFA, $p<0.001$). In the RCT by Yang et al. the overall recurrence rates were 35%, 46% and 29% in PRFA, TACE and TACE +PRFA groups, respectively[34]. Among the observational studies, only the one by Yamagiwa et al. reported recurrences[12]. The recurrence rates were 41% and 40% with TACE+ PRFA and TACE alone, respectively[12].

Complications: In the RCT by Cheng et al. the complication rates were similar for all three therapies[31] (See Table 4a). Only one cohort study reported complications, in which the complication rates were 11% and 8% with TACE+ PRFA and TACE alone, respectively[12].

Interpretations: All studies consisted of HCC patients at a stage at which resection was contraindicated. Both RCTs and cohort studies showed substantial survival benefits with PRFA+TACE therapy compared to TACE alone or to PRFA alone. Absolute survival benefits of PRFA+TACE therapy were around 20% at 5 years in 2 studies[31, 32], 48% at 5 years[12], 15% at 3 years[46], and 20% at 1.5 years[34]. Also, two RCTs showed that the combination therapy is associated with a low recurrence rate. Moreover, PRFA+TACE did not significantly increase complications[12, 31].

Appendix 3-2: TACE+ PRFA vs. SRS alone

Survival: Three comparative cohort studies compared TACE+ PRFA vs. SRS for HCC patients [12, 32, 37] (See Table 4a). Two studies in Japan included patients from the same institute and were carried out during the same period of time. One study by Yamakado et al. only included early stage HCC patients (Child-Pugh class A)[37] (See Appendix 2). The two strategies did not show significant clinical differences for the early stage HCC in this study[37]. The 1-, 3- and 5-year survival rates following TACE+PRFA (98%, 94%, and 75%, respectively) were similar to those following SRS (97%, 93%, and 81%, respectively) [37]. However, in the study by Yamagiwa et al., that included more severe HCC patients, clinical outcomes were significantly better following TACE+PRFA therapy, with better 5-year survival rates (72% vs. 59%)[12].

In the study by Helmberger et al. in Germany, compared with SRS, TACE+PRFA therapy show significantly better survival ($P<0.01$) for HCC patients presented with the Vienna Survival Model (VISUM) score stage 1[32]. The 1-, 3- and 5-year survival rates by TACE-PRFA were 95%, 65% and 27%, respectively; the 1-, 3- and 5-year survival rates by SRS were 78%, 53% and 29%, respectively.

Recurrence: In Yamakado et al.[37], overall recurrence rates were 36% and 37% in TACE+ PRFA and SRS, respectively. In Yamagiwa et al. [12], TACE+PRFA group showed a lower recurrence rate than the SRS group (41% vs. 50%).

Complications: In Yamakado et al.[37], the rate of major complications was 2.2% and 3.2% in TACE+ PRFA and SRS, respectively. In Yamagiwa et al. [12], TACE+ PRFA therapy was associated with lower complication rates (11% vs. 22%) (See Table 4a).

Interpretation: In general evidence is consistent to the effect that in terms of overall and disease free survival, recurrence, and complication rates[37] results following PRFA +

TACE were comparable or superior to SRS therapy for HCC in Child-Pugh class A level.(See Appendix 3-2)

Appendix 3-3: PRFA for patients with various stages liver cancer

Survival: Eight cohort studies of patients with liver cancer treated by PRFA were included (See Table 3). We carried out meta-analyses to estimate the survival rate following PRFA within early, intermediate and advanced groups of HCC (See Table 4b). Classification of HCC severity was made according to factors such as tumor size and Child-Pugh class. PRFA procedures were performed as the first therapy or as treatments for recurrences[30, 36]. In estimating survival, the starting time was defined as the date of receiving PRFA treatment. It should be noted that patients may receive other therapies in the follow-up period[36], such as PEI or TACE.

Early. We identified 6 groups of patients as early stage HCC. These were the class A groups in Yan et al.[30], Choi et al.[29], and Lencioni et al.[38], a small tumor group in the study of Chen et al.[36], the naïve tumor group of Tateishi et al.[28], and all patients in Livraghi et al.[39] . The pooled estimates of 3- and 5-year survival rates after commencement of PRFA were 78% (95%CI: 75%, 82%)[28-30, 36, 38, 39] and 58% (95% CI: 55%, 62%)[28-30, 36, 38, 39], respectively. These results were similar to pooled estimates of 3- and 5-year survival rates for early stage HCC treated by PRFA therapy in the PRFA vs. SRS section reported above.

Intermediate. From the literature we identified 7 groups of patients with cancers at intermediate stages of development. These included groups classified as class B in Yan et al.[30], Choi et al.[29], and Lencioni et al.[38], the "medium tumor" groups in Chen et al.[36] and Zhai et al.[16], a group of patients with colorectal liver metastases (CLM) tumors (numbering 5 or fewer metastases, and 5 cm or less in diameter) in Gillams et al.[54], and a group classified as "non-naïve tumors" in Tateishi et al. [28]. The pooled estimates of 3- and 5-year survival rates following PRFA treatment were 51% (95%CI: 43%, 60%)[16, 28-30, 36, 38, 54] and 29% (95%CI: 22%, 37%)[16, 28-30, 36, 38, 54], respectively.

Advanced. We identified 4 groups with advanced cancers. These included, a group of CLM (>5 metastases or > 5 cm in diameter) in Gillams et al.[54], class C groups in Yan et al. [30] , and a large or extra large tumor group in Chen et al. [36] and Zhai et al. [16]. The pooled estimates of 3- and 5-year survival rates following PRFA therapy are 28% (95%CI: 14%, 43%) and 3.7% (95%CI: 0%, 9.5%), respectively.

The pooled estimates:

PRFA treatment	3-year survival rate, (95% CI)	5-year survival rate, (95% CI)
Early	78% (75%, 82%)[28-30, 36, 38, 39]	58% (55%, 62%)[28-30, 36, 38, 39]
Intermediate	51% (43%, 60%)[16, 28-30, 36, 38, 54]	29% (22%, 37%)[16, 28-30, 36, 38, 54]
Advanced	28% (14%, 43%)[16, 30, 36, 54]	3.7%(0%, 9.5%)[16, 30, 36, 54]

Interpretation: Meta-analysis of the outcomes of patient groups categorized as early, intermediate and advanced, gave 5-year survival rates of 58%, 31% and 4.5% for early, intermediate and advanced HCC patients, respectively. Similarly estimated three and five year survival rates are consistent with those arrived at in the PRFA vs. SRS section reported above (3 year survival, 78%[28-30, 36, 38, 39] vs. 77%[2-4, 18]; and 5 year survival, 58%[28-30, 36, 38, 39] vs. 56%[2, 18]). The pooled estimates for the advanced group were less reliable, because of small sample size and absence of information of previous therapies.

Table 3: Patient characteristics at baseline in studies of PRFA+TACE vs. PRFA & PRFA for patients with various stages of liver cancer

Author(y), Country	Population	Treatment	N	Tumor Size (cm)	TN	Age Mean (SD or range)	Sex, Male, n(%)
TACE+PRFA vs. PRFA alone or TACE alone or SRS alone (RCTs)							
Cheng[31] (2008) ; China†	HCC; no indication for resection; TN ≤ 3; 3 cm < TS ≤7.5 cm of each larger; Class A or B; no previous treatment of HCC.	PRFA	100	3.1-5: 48%. 5.1-7: 45%. >7: 7%	45%SG	63.9(5.4)	77(77)
		TACE	95	3.1-5: 48%, 5.1-7: 46%. >7: 5%	45%SG	63.5(5.5)	66(69)
		TACE+ PRFA	96	3.1-5: 48%. 5.1-7: 46%, >7: 6%	45%SG	63.8(5.6)	69(72)
Yang[34] (2008); China	HCC ; not suitable for SRS; 5.2cm ≤TS ≤10.1 cm.	PFRA	12	5.2±0.4	NA	61.0(10.4)	8(67)
		TACE	11	6.4±1.0	NA	57.6(11.8)	8(73)
		TACE+ PRFA	24	6.6±0.6	NA	59.1(11.4)	18(75)
(comparative cohort studies)							
Yamagiwa[12] (2008) ; Japan†	HCC; hepatic resection mainly based on indocyanine green retention test; PRFA procedure for patients in Class A and B with no more than five tumors and TS <5cm; TACE for all, including Class C and main portal vein thrombosis.	PRFA+TACE	115	NA	NA	Of all 345 pts, 65.1	Of all 345 pts, 259 (75)
		TACE	86	NA	NA		
		SRS	101	NA	NA		
Yamakado[37] (2008); Japan	Early stage HCC; Class A; no previous treatment for HCC; TN≤ 3 with TS ≤ 3 cm of each or a single tumor ≤ 5 cm.	TACE+PRFA	104	2.5±0.8	74%SG	66.5±8.7	79(76)
		SRS	62	2.7±1.1	87%SG	64.5±9.6	51(82)
Helmberger[32]	Early HCC; single nodule < 5 cm or three nodules < 3 cm each;	PRFA+TACE	44	NA	NA	65.3±8.3	37 (84)

(2007); Germany	VISUM stage 1 (0–2 points); selecting for liver resection mainly those with solitary HCC and normal liver function.	TACE	107	NA	NA	64.6±10.0	89(83)
		SRS	52	NA	NA	61.9±8.9	42 (81)
Liu[46] (2007); China	HCC; all therapy strategies including TACE; TACE plus PRFA used in pts ineligible or who refused surgical therapies. (This study included multiple groups of pts, and we selected two groups from all.)	TACE +PRFA	106	NA	NA	Of all 1126 pts, 56.2 (32-76)#	Of all 1126 pts, 873 (78).
		TACE alone	387	NA	NA		
PRFA for patients with various stages liver cancer							
Gillams[54] (2009); UK	Unresectable CLM; TN ≤ 5 of TS <5 cm, TN≤ 9 of TS <4 or 4.5 cm, TN=1 of TS <9cm.	PRFA	309	NA	NA	64 (24-92)#	198(64)
Livraghi[39] (2008); Italy	Single HCC in very early stage; Class A; TS ≤ 2 cm; no previous treatment; 100 (45.8%) of 218 patients being resectable, whereas the other 118 (54.1%) ineligible for surgery.	PRFA	218	NA	1	68 (43-88)#	122(56)
Yan[30] (2008); China	284 consecutive pts with HCC; TS ≤7 cm; TN≤5; Class A: 160, Class B: 94, Class C: 12; excluding 18 pts of loss follow up; 223 pts (83.3%) ineligible for surgery.	PRFA	266	<3: 26%; 3-5: 50%; >5: 24%	59%SG	59.4±15.4	216(81)
Choi[29] (2007); Korea	Early stage HCC; Class A or B; single tumor, TS≤5 cm or TN ≤3 and TS≤3 cm; 359 pts (63%) of Class A; no previous treatments by TACE, PEI, resection and IRFA.	PRFA	570	≤2: 40%; 2-5: 60%	83%SG	293 ≤ 58 y and 277 > 58 y.	421 (74)
Chen[36] (2007); China	672 pts with primary liver cancer and 131 with liver metastasis; Class A: 576, Class B 87, Class C: 9; including 5 SRFA and 9 LRFA; 117 with PRFA-PEI; 108 with PRFA-TACE.	PRFA (TS, S: ≤ 3 cm; M: 3-5 cm; L: > 5 cm)	803	≤3: 62%; 3-5: 25%; >5: 13%	77%SG	54 (26-88)#	Of all, 693 (86)
Zhai[16] (2007); China	Primary liver cancer; TS≥ 4cm; ineligible for SRS; 347 pts (79%) of all Class A and 94 pts (21%) of Class B; before PRFA, 365 pts experienced TACE; after PRFA, 272 pts experienced TACE; 163 pts with TACE both before and after PRFA.	PRFA (TS, M: 4-5 cm; L: 5-6 cm; EL: ≥ 6 cm)	441	4.6±0.63; 4-5: 87%; 5-6: 10%; ≥6: 3%.	67%SG	53.7±4.2	389 (88)

Lencioni[38] (2005);†† Italy	HCC; single tumor of TS≤ 5cm or multiple tumors with (≤3) and ≤ 3cm each; Class A or B; 144 of 187 receiving Class A and 43 of Class B; ineligibility for SRS or liver transplantation; no previous treatment for HCC.	PRFA	206 (ITT) / 187 (EA)	2.8±0.7	78%SG	67±7	143(70)
Tateishi[28] (2005); Japan	HCC; 419 (63.1%) with unresectable HCC; in initial group, Class A of 221 (69.3%), Class B of 94 (29.5%) and Class C 4 (1.3%); in non-initial group, Class A of 225(65.2%), Class B of 111 (32.1%) and Class C 9 (2.6%).	PFRA (Initial)	319	≤2: 27%; 2-5: 67%; >5: 5%.	61%SG	67.4± 7.8	212 (67)
		PFRA (Non-initial)	345	≤2: 33%; 2-5: 61%; >5: 7%	40%SG	66.6± 8.4	247 (72)

Abbreviations: RFA= radiofrequency ablation; PRFA= percutaneous RFA; SRS= surgical resection/ partial hepatectomy/ hepatectomy/ resection; TACE= transarterial chemoembolization; pt=patient; HCC= hepatocellular carcinoma tumors; CLM= colorectal liver metastases; TS= tumor size in diameter; TN=number of tumors; SG=single; S=small; M= medium; L=large; EL=extra large; y= year/ years; Class = Child-Pugh class; Korea= South Korea; US= United States; ITT=intention to treat; EA=efficacy analysis.

†: TACE-PRFA did not indicate sequences of TACE and PRFA therapies. Patients received PRFA after TACE in some studies[31], while PRFA was prior to TACE in other studies[12].

††: It is a prospective, single-arm clinical trial. Authors also excluded 19 (9%) patients because of tumor location, and then 187 (91%) patients received PRFA. Both ITT and EA were conducted.

#: Median/mean (range).

Table 4a: Clinical outcomes in studies of TACE+PRFA vs. PRFA alone or TACE alone or SRS alone

Author(y)	Intervention	Survival rate (%) T1	T2	T3	P Value	Recurrence n(%)	Complications n(%)
RCTs							
		1 y	3 y	5 y			
Cheng[31] (2008)	PRFA	67	32	8	P<0.01	Overall: 81(81). Local: 16(16); distant: 65(65).	5 (2) procedure-related deaths (PRFA: 1(1); TACE: 2(2); and TACE+ PRFA: 2(2)). Common complications in all 3 groups were fever (temperature >38°C), pain, vomiting etc. Typically not statistically significant between groups.
	TACE	74	32	13	P<0.01	Overall: 76(80). Local: 14(15); distant: 62(65).	
	TACE+ PRFA	83	55	31	Ref	Overall: 57(59). Local: 4(4); distant: 53(55).	
Yang[34]		6 m	12m	18m			
(2008)	PFRA	60	58	52		Overall: (35)	NA
	TACE	62	53	45		Overall: (46)	NA
	TACE+PRFA	79	68	67		Overall: (29)	NA
comparative cohort studies							
		5y					
Yamagiwa[12] (2008)	TACE+ PRFA	72			Vs. TACE P<0.01	Overall: 47 (41).	13 (11) complications, including ascites, pneumo-thorax, bleeding etc.
	TACE	15				Overall: 34 (40).	8 (8) complications, including ascites, and liver failure.
	SRS	59				Overall: 50 (50).	22 (22) complications, including ascites, infection, liver failure, bleeding et al.
		1 y	3y	5y			
Yamakado[37] (2008)	TACE+PRFA	98	94	75	P=0.87	Overall: 37 (36).Local: 3 (3); distant 34(33).	No procedure related mortality. 3 (2) major complications; 3(2) minor complications.

	SRS	97	93	81		Overall: 23 (37).Local: 0(0); distant 23 (37).	No procedure related mortality. 2 (3) major complications; no minor complications.
		1 y	3y	5y			
Helmberger	TACE+PRFA	94*	65*	27*	P<0.01	NA	NA
[32] (2007)	TACE	57*	15*	6*	Ref	NA	NA
	SRS	78*	53*	29*	P<0.01	NA	NA
		1y	3y	5y			
Liu[46] (2007)	TACE+PRFA	75	37	--	1st y: P > 0.05;3rd y: P < 0.05.	NA	NA
	TACE alone	69	22	8		NA	NA

Abbreviations: T=time; m =month/ months; y= year/years; Ref= reference group; PRFA= percutaneous RFA; SRS= surgical resection; TACE= transarterial chemoembolization.

*: Estimated value. We extracted information from the graphs of the articles.

Table 4b: Clinical outcomes in studies of PRFA for patients with various stages of liver cancer

Author (year)	Intervention	Survival rate (%) T1	T2	T3	P Value	Recurrence n(%)	Complications n(%)
		3y	5y				
Gillams[54] (2009)	PRFA (TN≤5 of TS ≤ 5 cm)	40	18		P<0.01	NA	No procedure-related deaths. 29 (5) major complications in 617 sessions, of which 5(1) were "systemic", 1(0.2) "anaesthetic" 23 (4) "local").
	PRFA (TN>5 or TS > 5 cm)	13	3				
		1y	3y	5y			
Livraghi[39]	PRFA (all)	94*	76	55			
(2008)	PRFA (eligible for surgery)	96*	89	68	p= 0.013	Local: 2(1).	No procedure-related deaths; 4 (2) major complications, hemorrhage, hemothorax, neoplastic seeding and hyperbilirubinemia lasting for 1 month.
	PRFA (ineligible for surgery)	92*	75	47			
		1y	3y	5y			
Yan[30]	PRFA (all)	83	58	43		Overall: 109 (41). Local: 28 (11); new tumors occurred in the treated liver segment: 45 (17) ; new tumors in other segments 56 (21); both local progression and new tumors: 20 (8).	No procedure-related deaths; 10(2.4) complications in 420 sessions, including intraperitoneal hemorrhage; 2(0.5); biliary duct stricture 1(0.2), hemothorax: 1(0.2); bowel perforation 1(0.2) and needle tract seeding 5(1.2).
(2008)	PRFA(Class A)	90	73	63	vs. B: P<0.01		
	PRFA(Class B)	77	40	27	vs. C: P>0.05		
	PRFA(Class C)	58	25	25			
		1y	3y	5y			
Choi[29]	PRFA(all)	95	70	58		Distant: 296 (52). Local progression (based on 652 tumors, not 570 patients): 1y: 53(8); 2 y: 71(11); 3 y: 77(12).	No procedure-related deaths; a total of 35(6) complications; of these, 11(2) major complications, including abscess, infarction, cancer seeding et al.
(2007)	PRFA(Class A)	98*	78	64			
	PRFA(Class B)	90*	49	38			

		1y	3y	5y			
Chen[36]	PRFA(all)	95	76	48		Local (overall): (14).	
(2007)	PRFA (S)	97	85	60		Local (S): (8).	Overall, 2 (0.2) procedure-related deaths and 3 (0.4) major complications.
	PRFA (M)	95	70	42		Local (M): (19).	
	PRFA (L)	85	46	0		Local (L): (57).	
		1y	3y	5y			
Zhai[16]	PRFA (M)	78	48	18		Based on data of 359 cases (excluding 9 deaths and 73 loss to follow-up), 141 (39) with hepatic recurrences, and 87 (24) recurrences in other locations..	Overall, 7(2) procedure-related deaths; a total of 92 (21) complications; of these, 42 (10) major complications.
(2007)	PRFA (L)	66	36	10			
	PRFA (EL)	54	28	0			
		1y	3y	5y			
	PRFA (all)	97	67	41		Overall: 1 y: (18); 3 y: (55); 5 y: (83). Distant : 1 y : (14) ; 3 y (49) ; 5 y (81). Local: 1 y: (4); 3 y: (10); 5 y: (10).	No procedure-related deaths; 3 (2) of major complications of hemorrhage, and 9 (5) of minor complications.
Lencioni[38]	PRFA(Class A)	100	76	51	P<0.01		
(2005)	PRFA(Class B)	89	46	31			
		1y	3y	5y			
Tateishi[28]	PFRA (Initial)	95	78	54	NA	Overall: 1 y: (20) ; 2 y : (43) ; 3 y: (60); 4 y: (66).	No procedure-related deaths; 40(4) major complications of 1000 procedures, including intraperitoneal hemorrhage, pleural effusion requiring drainage and hepatic abscess requiring drainage; 17(1.7) minor complications.
(2005)	PFRA (Non-initial)	92	62	38			

Abbreviations: T=time; m =month/ months; y= year/years; S=small; M= medium; L=large; EL=extra large; Class = Child-Pugh class; SRS=hepatic resection.

*: Estimated value. We extracted information from the graphs of the articles.

Appendix 4: Details of cost analysis

4-1: Costs of liver resection surgery

At the MUHC, the average length of hospitalization following SRS is 11.7 (5^{th} to 95^{th} percentile, 5—35) days. We considered the cost of the following components: anesthesia technician fees, operating room and recovery room, nursing and ICU, imaging, laboratory tests and medications. Most cost estimates were based on 57 procedures carried out by 4 surgeons at the MUHC. (Procedure code: 301200 & 301205 (Laparotomy resection liver left & right) (2008— 2009)). To estimate the anesthesia cost per patient, we assumed that the anesthesia would last 4 (3—5) hours, at a technician cost of $ 32.70 per hour. (See Table 5a)

Table 5a: Average Costs of liver resection surgery

Item	Unit cost ($)	Resource use	Average cost ($)	Range used for sensitivity analysis (5^{th} to 95^{th} percentile) ($)
Anesthesia (Technician fees)	32.70 /h	4 (3—5) h	131	(98—164)
Operating room and recovery room	--	--	2,978	(2,337—3,607)
Nursing & ICU	--	--	5,143	(1,757—12,168)
Imaging	--	--	214	(25—729)
Labs	--	--	541	(151— 1,202)

Medications	--	--	715	(157—2,811)
Total cost per patient	--	--	9,722	--

Abbreviations: h=hour/hours.

4-2: Costs of PRFA

The average duration of each PRFA session is 2.25 hours. (Range 45 minutes to 3.5 hours). Three different types of electrodes may be used depending on the size of the tumor. Type 1 ($ 500), used in approximately 20%; type 2 ($ 800), used in approximately 40%; type 3 ($ 2,000), used in approximately 40%. The weighted average price is $ 1,220 per electrode. Anesthesia is used for only for those tumours that require electrodes of type 2 ($ 800) and type 3 ($ 2,000), i.e. for 80% of cases. The average duration of anesthesia use is 2.5 hours (Range: 1.5 to 3.5 hours). Two generators at a total capital cost of $100,000 are "loaned" to the MUHC by the company. The electrode cost above covers both the cost of disposable electrodes and the rental cost of equipment. Procedures are carried out in the X-Ray department under CT guidance (80%) or ultrasound guidance (20%). For 80% of cases done under CT guidance technicians are present 75% of the time, i.e. 75% of 2.5 (1.5—3.5) hours. For the 20% of cases done under ultrasound, technicians are present 50% of the time, i.e. 50% of 1 (0.5—1.5) hours. About 50% of patients need 1 day hospitalization, and the other 50% patients can go home directly from the recovery room. Usually a small amount of medication is used after the PRFA procedure. We did not consider this cost. (See Table 5b)

Table 5b: Average Costs of radio-frequency ablation therapy

Item	Unit cost ($)	Resource use	Average cost ($)	Range used in sensitivity analyses ($)
Anesthesia (Technician fees)	32.70 /h	80% 2.5 (1.5—3.5) h	65	(39—92)
Diagnostic radiology room (Technician fees)	29.60 /h	1.6 (1—2.3) h (weighted values)	47	(28—67)
Single/Cluster needle electrode	500/800/2,000	20%/40%/40%	1,220	(800—1,600)
Recovery room	203.3/h	4 (3—5) h	813	(610—1,017)
Hospitalization	298 /d	0.5 (0—1) d	149	(0—298)
Total cost per procedure	--	--	2,294	--
Total cost per patient (assuming repeat procedure rate: 8%)	--	--	2,478	--

Abbreviations: d= day/days; h=hour/hours.

Table 5c: Main results of univariate sensitivity analysis

Variable (Range) ($)	Cost saving by PRFA ($)
Liver resection surgery	
Operating room (2,337—3,607)	6,603—7,873
Nursing & ICU (1,757—12,168)	3,858—14,269
Imaging (25—729)	7,055—7,759
Labs (151— 1,202)	6,854—7,905
Medications (157—2,811)	6,686—9,340
PRFA procedure	
Single/Cluster needle electrode (800—1,600)	7,698—6,834
Recovery room (610—1,017)	7,464—7,024

§: For observational studies with several groups, we only reported results of groups of interest.

REFERENCES

1. Hasegawa K, Makuuchi M, Takayama T et al. Surgical resection vs. percutaneous ablation for hepatocellular carcinoma: a preliminary report of the Japanese nationwide survey. J Hepatol 2008;49(4):589-594.

2. Takahashi S, Kudo M, Chung H et al. Outcomes of nontransplant potentially curative therapy for early-stage hepatocellular carcinoma in Child-Pugh stage A cirrhosis is comparable with liver transplantation. Dig Dis 2007;25(4):303-309.

3. Cho CM, Tak WY, Kweon YO et al. [The comparative results of radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma.]. Korean J Hepatol 2005;11(1):59-71.

4. Hong SN, Lee SY, Choi MS et al. Comparing the outcomes of radiofrequency ablation and surgery in patients with a single small hepatocellular carcinoma and well-preserved hepatic function. J Clin Gastroenterol 2005;39(3):247-252.

5. Cormier JN, Thomas KT, Chari RS, Pinson CW. Management of hepatocellular carcinoma. J Gastrointest Surg 2006;10(5):761-780.

6. Buell JF, Thomas MT, Rudich S et al. Experience with more than 500 minimally invasive hepatic procedures. Ann Surg 2008;248(3):475-486.

7. Marlow N E, et al. Radiofrequency Ablation for the Treatment of Liver Tumours: A systematic Review. ASERNIP-S Report No 56 Adelaide, South Australia: ASERNIP-S 2006.

8. Sutherland LM, Williams JA, Padbury RT, Gotley DC, Stokes B, Maddern GJ. Radiofrequency ablation of liver tumors: a systematic review. Arch Surg 2006;141(2):181-190.

9. Lau WY, Lai EC. The current role of radiofrequency ablation in the management of hepatocellular carcinoma: a systematic review. Ann Surg 2009;249(1):20-25.

10. Lencioni R, Crocetti L. Radiofrequency ablation of liver cancer. Tech Vasc Interv Radiol 2007;10(1):38-46.

11. Chen MS, Li JQ, Zheng Y et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006;243(3):321-328.

12. Yamagiwa K, Shiraki K, Yamakado K et al. Survival rates according to the Cancer of the Liver Italian Program scores of 345 hepatocellular carcinoma patients after multimodality treatments during a 10-year period in a retrospective study. J Gastroenterol Hepatol 2008;23(3):482-490.

13. Lopez PM, Villanueva A, Llovet JM. Systematic review: evidence-based management of hepatocellular carcinoma--an updated analysis of randomized controlled trials. Aliment Pharmacol Ther 2006;23(11):1535-1547.

14. Gillams AR, Lees WR. Five-year survival following radiofrequency ablation of small, solitary, hepatic colorectal metastases. J Vasc Interv Radiol 2008;19(5):712-717.

15. Society of Interventional Radiology. Thermal Ablation Treatments. http://www scvir org/patients/liver-cancer/, 2009.

16. Zhai B, Xu AM, Chen Y, Li XY, Liu S, Wu MC. [Radiofrequency ablation for larger hepatocellular carcinomas]. Di Er Jun Yi Da Xue Xue Bao 2007; 28(6):651-655.

17. Khan MR, Poon RT, Ng KK et al. Comparison of percutaneous and surgical approaches for radiofrequency ablation of small and medium hepatocellular carcinoma. Arch Surg 2007;142(12):1136-1143.

18. Lupo L, Panzera P, Giannelli G, Memeo M, Gentile A, Memeo V. Single hepatocellular carcinoma ranging from 3 to 5 cm: radiofrequency ablation or resection? HPB (Oxford) 2007;9(6):429-434.

19. Kooby DA, Egnatashvili V, Graiser M et al. Changing management and outcome of hepatocellular carcinoma: evaluation of 501 patients treated at a single comprehensive center. J Surg Oncol 2008;98(2):81-88.

20. Amersi FF, Elrath-Garza A, Ahmad A et al. Long-term survival after radiofrequency ablation of complex unresectable liver tumors. Arch Surg 2006;141(6):581-587.

21. Yao P, Morris DL. Radiofrequency ablation-assisted liver resection: review of the literature and our experience. HPB (Oxford) 2006;8(4):248-254.

22. Wikipedia. Definition of percentile. http://en wikipedia org/wiki/Percentile, 2009 (Accessed July 27, 2009 .

23. Garrean S, Hering J, Saied A, Helton WS, Espat NJ. Radiofrequency ablation of primary and metastatic liver tumors: a critical review of the literature. Am J Surg 2008;195(4):508-520.

24. Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. J Clin Epidemiol 2008;61(1):41-51.

25. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. J Clin Epidemiol 2006;59(12):1331-1332.

26. Guglielmi A, Ruzzenente A, Valdegamberi A et al. Radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma in cirrhosis. J Gastrointest Surg 2008;12(1):192-198.

27. Chen MS, Li JQ, Liang HH et al. [Comparison of effects of percutaneous radiofrequency ablation and surgical resection on small hepatocellular carcinoma]. Zhonghua Yi Xue Za Zhi 2005;85(2):80-83.

28. Tateishi R, Shiina S, Teratani T et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. Cancer 2005;103(6):1201-1209.

29. Choi D, Lim HK, Rhim H et al. Percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma as a first-line treatment: long-term results and prognostic factors in a large single-institution series. Eur Radiol 2007;17(3):684-692.

30. Yan K, Chen MH, Yang W et al. Radiofrequency ablation of hepatocellular carcinoma: long-term outcome and prognostic factors. Eur J Radiol 2008;67(2):336-347.

31. Cheng BQ, Jia CQ, Liu CT et al. Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial. JAMA 2008;299(14):1669-1677.

32. Helmberger T, Dogan S, Straub G et al. Liver resection or combined chemoembolization and radiofrequency ablation improve survival in patients with hepatocellular carcinoma. Digestion 2007;75(2-3):104-112.

33. Wong GL, Wong VW, Tan GM et al. Surveillance programme for hepatocellular carcinoma improves the survival of patients with chronic viral hepatitis. Liver Int 2008;28(1):79-87.

34. Yang P, Liang M, Zhang Y, Shen B. Clinical application of a combination therapy of lentinan, multi-electrode RFA and TACE in HCC. Adv Ther 2008;25(8):787-794.

35. Liu YM, Qin H, Wang CB, Fang XH, Ma QY. [Comparision of different interventional therapies for primary liver cancer]. Zhonghua Zhong Liu Za Zhi 2007;29(3):232-235.

36. Chen MS, Zhang YJ, Li JQ et al. [Experience of radiofrequency ablation on liver malignancies: a report of 803 cases]. Zhonghua Wai Ke Za Zhi 2007;45(21):1469-1471.

37. Yamakado K, Nakatsuka A, Takaki H et al. Early-stage hepatocellular carcinoma: radiofrequency ablation combined with chemoembolization versus hepatectomy. Radiology 2008;247(1):260-266.

38. Lencioni R, Cioni D, Crocetti L et al. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology 2005;234(3):961-967.

39. Livraghi T, Meloni F, Di SM et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? Hepatology 2008;47(1):82-89.

40. Vivarelli M, Guglielmi A, Ruzzenente A et al. Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma on cirrhotic liver. Ann Surg 2004;240(1):102-107.

41. Ohki T, Tateishi R, Shiina S et al. Obesity did not diminish the efficacy of percutaneous ablation for hepatocellular carcinoma. Liver Int 2007;27(3):360-367.

42. Omata M, Tateishi R, Yoshida H, Shiina S. Treatment of hepatocellular carcinoma by percutaneous tumor ablation methods: Ethanol injection therapy and radiofrequency ablation. Gastroenterology 2004;127(5 Suppl 1):S159-S166.

43. Peng ZW, Zhang YJ, Chen MS et al. Risk factors of survival after percutaneous radiofrequency ablation of hepatocellular carcinoma. Surg Oncol 2008;17(1):23-31.

44. Takaki H, Yamakado K, Nakatsuka A et al. Radiofrequency ablation combined with chemoembolization for the treatment of hepatocellular carcinomas 5 cm or smaller: risk factors for local tumor progression. J Vasc Interv Radiol 2007;18(7):856-861.

45. Fuke H, Sugimoto K, Shiraki K et al. Predictive factors for distant recurrence of HCV-related hepatocellular carcinoma after radiofrequency ablation combined with chemoembolization. Aliment Pharmacol Ther 2008;27(12):1253-1260.

46. Liu YM, Qin H, Wang CB, Fang XH, Ma QY. Comparison of therapeutic effectiveness of combined interventional therapy for 1126 cases of primary liver cancer. World J Gastroenterol 2006;12(31):5060-5063.

47. Raut CP, Izzo F, Marra P et al. Significant long-term survival after radiofrequency ablation of unresectable hepatocellular carcinoma in patients with cirrhosis. Ann Surg Oncol 2005;12(8):616-628.

48. Curley SA, Izzo F, Ellis LM, Nicolas VJ, Vallone P. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. Ann Surg 2000;232(3):381-391.

49. Chen MH, Wei Y, Yan K et al. Treatment strategy to optimize radiofrequency ablation for liver malignancies. J Vasc Interv Radiol 2006;17(4):671-683.

50. Chen MH, Yang W, Yan K et al. Radiofrequency ablation of problematically located hepatocellular carcinoma: tailored approach. Abdom Imaging 2008;33(4):428-436.

51. Chen MH, Yang W, Yan K et al. [A tailored approach to radiofrequency ablation of hepatocellular carcinoma and its outcome]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2008;30(1):15-21.

52. Lu MD, Kuang M, Liang LJ et al. [Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: a randomized clinical trial]. Zhonghua Yi Xue Za Zhi 2006;86(12):801-805.

53. Lencioni R, Crocetti L, Cioni D, Della PC, Bartolozzi C. Percutaneous radiofrequency ablation of hepatic colorectal metastases: technique, indications, results, and new promises. Invest Radiol 2004;39(11):689-697.

54. Gillams AR, Lees WR. Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. Eur Radiol 2009.