



**Australian Government**  
**Department of Health and Ageing**



**Horizon Scanning Technology**  
**Prioritising Summary**  
**Radiofrequency assisted liver resection**

**May 2007**



**Australian  
Safety  
and Efficacy  
Register  
of New  
Interventional  
Procedures -  
Surgical**



**Royal Australasian  
College of Surgeons**

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The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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# PRIORITISING SUMMARY

**REGISTER ID:** S000032

**NAME OF TECHNOLOGY:** RADIOFREQUENCY-ASSISTED LIVER RESECTION

**PURPOSE AND TARGET GROUP:** PATIENTS WITH LIVER TUMOURS REQUIRING HEPATECTOMY

## STAGE OF DEVELOPMENT (IN AUSTRALIA):

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established  |
| <input type="checkbox"/> Experimental             | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational          | <input type="checkbox"/> Should be taken out of use   |
| <input type="checkbox"/> Nearly established       |   |

## AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- |   |             |     |
|---|-------------|-----|
| <input type="checkbox"/> Yes            | ARTG number | N/A |
| <input checked="" type="checkbox"/> No  |             |     |
| <input type="checkbox"/> Not applicable |             |     |

## INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia	✓		
Europe		✓	
United Kingdom	✓		
United States		✓	

## IMPACT SUMMARY:

Radiofrequency-assisted liver resection is designed for blood loss reduction, reduced operating time and decrease in the occurrence of biliary leaks. The Habib 4X liver resection sealer is currently the only device which has received approval from the FDA and is also licensed for use in Europe. The device is currently not available in Australia.

## BACKGROUND

Hepatectomy is the term given to surgical resection of the liver. Hepatectomies are generally performed for the treatment of benign or malignant liver tumours. The most common benign tumours include hemangioma and focal nodular hyperplasia (Arnoletti and Brodsky 1999). The most common malignant tumours of the liver include metastases which may arise from any primary malignant neoplasm, however those arising from the colon, lung, stomach, pancreas and breast are the most common (Kahn and Macdonald 2007). In terms of primary tumours of the liver, hepatocellular carcinoma (HCC) is the most common, accounting for over 80% of all primary liver cancers (Kassahun et al. 2006).

Although other treatment options including chemotherapy, radiotherapy, percutaneous ethanol injection, cryoablation, microwave coagulation therapy, laser-induced thermotherapy and radiofrequency ablation exist, surgical resection remains the gold standard for the treatment of both primary and secondary liver tumours (Ayav et al. 2007, Kahn and Macdonald 2007). Unfortunately, very few patients are suitable for surgical resection due to a variety of reasons related to the stage of the disease and the patient's liver function (McGahan and Dodd 2001). In the instances where surgery is possible, intra-operative blood loss presents a major hazard (Dixon et al. 2005). Intra-operative blood loss is associated with higher rate of post-operative complications and shorter long-term survival (Weber et al. 2002, Kooby et al. 2003). Liver failure is also a concern for patients undergoing liver resection with approximately 1% to 2% of patients dying as a result of liver failure after surgery (Personal Communication 2007, Guy Maddern).

Methods including vascular clamping and Pringle's manoeuvre during liver resection surgery permit the surgeon to clamp the inflow vessels during surgery and reduce bleeding during resection (Ayav et al. 2007). The use of these techniques has led to a significant reduction in intra-operative blood loss and the requirement for intra-operative blood transfusion (Jarnagin et al. 2002). Unfortunately, these methods are not completely effective and some even carry a further risk of causing liver dysfunction in patients suffering liver disease (Farges et al. 1999).

Radiofrequency-assisted liver resection involves the induction of necrosis in healthy liver tissue at the resection plane with the aim of creating a safe and bloodless way of dissecting the parenchyma during minor and major resections by sealing vascular and biliary structures (Ayav et al. 2007). The use of heat to create coagulative necrosis is not new. Radiofrequency ablation of liver tumours has been performed previously (Curley et al. 1999). Radiofrequency-assisted liver resection is novel because coagulation of normal liver tissue, which coagulates much quicker than cancerous tissue, is performed in order to obtain bloodless surgical resection, thus reducing the associated risks with intra-operative blood loss (Weber et al. 2002).

In the present summary, studies reporting the results of radiofrequency-assisted liver resection using different radiofrequency devices are presented. However, all devices appear to have great similarities to the Habib 4X sealer (RITA Medical Systems; California, United States). The Habib 4X sealer is currently the only device designed for open-surgery radiofrequency-assisted liver resections. The device consists of an array of four cooled-tip radiofrequency probes connected to a generator. These probes contain an exposed electrode and a thermocouple on the tip (to monitor temperature and impedance of the tissue) to produce controlled necrosis of healthy parenchyma. A laparoscopic version of the Habib 4X sealer is also available and use of this device has been noted.

## **CLINICAL NEED AND BURDEN OF DISEASE**

In 2001, the Australian incidence of liver cancer was 617 cases per 100,000 males and 236 cases per 100,000 females (AIHW 2004). The mortality rates for sufferers of liver cancer during 2001 were 538 deaths per 100,000 males and 239 deaths per 100,000 females (AIHW 2004). Projections for the number of new cases of liver, gallbladder and pancreas cancer show that the new cases of this group of cancers is projected to increase by 27% from 1,469 in 2001 to 1,863 in 2011 (95% prediction interval from 1,426 to 2,489) for females. For males, an increase of 43% from 1,836 in 2001 to 2,624 in 2011 (95% prediction interval from 2,223 to 3,160) is projected (AIHW 2005).

Additionally, liver metastases have been identified in approximately 30% to 70% of cancer sufferers making the liver the second most common site of metastasis (Virtual Medical Centre 2006). In Western countries such as Australia liver metastases are more common than primary liver cancer (Virtual Medical Centre 2006).

## **DIFFUSION**

The Habib 4X sealer and the Habib 4X Laparoscopic sealer have both received marketing approval from the FDA. They are the only systems specifically designed and marketed for the performance of liver resection. The Habib 4X sealer is also licensed for use in Europe. The Habib 4X sealer is currently not available in Australia.

## **COMPARATORS**

Intra-operative manoeuvres to reduce risk of intra-operative bleeding during liver resection surgery (Jarnagin et al. 2002):

- Hypotensive anaesthetics
- The Pringle manoeuvre
- Total vascular exclusion

Comparators to radiofrequency-assisted liver resection (Kahn and Macdonald 2007):

- Radiofrequency ablation of liver tumours
- Standard surgical resection
- Hepatic arterial infusion chemotherapy
- Percutaneous ethanol injection
- Cryoablation
- Microwave coagulation therapy
- Laser-induced thermotherapy

## **SAFETY AND EFFECTIVENESS ISSUES**

Ayav and colleagues reported their experience of radiofrequency-assisted liver resection in 156 consecutive patients over four years (Ayav et al. 2007). The patients involved had a mean of 1.77 (range: 1 to 10) tumours each with a mean size of  $44 \pm 30$  mm. A total of thirty major hepatectomies<sup>1</sup> and 126 minor hepatectomies<sup>2</sup> were performed with 275 tumours resected. In this series, a cooled-tip radiofrequency probe and a 500 kHz radiofrequency generator (model RFG-3D, Radionics Europe, NV, Wettdren, Belgium) were used. The procedures were performed in a mean ( $\pm$  standard deviation) operative time of  $241 \pm 89$  minutes including a mean resection time<sup>3</sup> of  $75 \pm 51$  minutes.

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<sup>1</sup> Major hepatectomy: defined as resection of more than three segments.

<sup>2</sup> Minor hepatectomy: defined as tumorectomy, segmentectomy or bi-segmentectomy.

<sup>3</sup> Resection time: time from start of radiofrequency ablation to completion of parenchymal transection.

The mean intra-operative blood loss for all patients was  $139 \pm 222$  mL with major hepatectomy patients experiencing significantly greater blood loss than minor hepatectomy patients ( $271 \pm 256$  mL versus  $109 \pm 203$  mL,  $p = 0.005$ ). Intra-operative blood transfusion was required in nine patients (16% transfusion rate; six major hepatectomy and three minor hepatectomy patients) with the transfusion requirement being greater for patients who had undergone major hepatectomy ( $p = 0.001$ ). This compares favourably to previously reported median volumes of 450 mL to 1450 mL and transfusion rates of 55% reported in the scientific literature (Cunningham et al. 1994, Melendez et al. 1998, Poon et al. 2004).

Changes in haemoglobin (Hb), bilirubin, albumin, aspartate transaminase (AST) and alanine transaminase (ALT) were measured pre-operatively and post-operatively on days one and seven to demonstrate the effect of radiofrequency-assisted liver resection on liver function. All variables except haemoglobin were significantly ( $p < 0.001$ ) altered on post-operative day one but returned to near pre-operative levels by day seven (Table 1).

**Table 1 Mean values of indicators of liver function presented by Ayav et al. (2007)**

Indicator	Pre-operative	Day 1	Day 7
Hb (g/dL)	$12.9 \pm 1.7$	$11.9 \pm 1.6$	$12.1 \pm 1.4$
Bilirubin (mmol/L)	$11.1 \pm 9.6$	$25.7 \pm 15.6$ *	$19.7 \pm 14.7$
Albumin (g/L)	$36.4 \pm 4.4$	$28.8 \pm 7.9$ *	$35.8 \pm 8.9$
AST (IU/L)	$32 \pm 17$	$569 \pm 509$ *	$51 \pm 29$
ALT (IU/L)	$30 \pm 20$	$518 \pm 436$ *	$102 \pm 85$

\*  $p < 0.001$

Post-operative complications were reported in 36 (23%) patients, with six developing more than one complication. Complications included pleural effusion ( $n = 18$ ), intra-abdominal collection ( $n = 17$ ), biliary leak ( $n = 4$ ), post-operative liver failure ( $n = 2$ ) and hepatic ischemia ( $n = 1$ ). One re-operation was required to reconstruct a right hepatic artery injured during extended left hepatectomy and hepaticojejunostomy for cholangiocarcinoma in the case of hepatic ischemia. In two of the four cases of biliary leak, leakage was reported from the resection margin perhaps indicating incomplete coagulation in that specific region of the resection plane. Despite this the authors state that none of the complications reported were directly reported to the resection technique used.

There were no deaths intra-operatively, however, five patients died post-operatively (period at which the patients died was not reported). Two died from post-operative liver failure while the remaining patients died of multi-organ failure (none began with liver failure). A further five patients were admitted into the intensive care unit post-operatively (two for prolonged general anaesthesia and three for pre-operative respiratory and cardiac problems).

Fifty one patients (33%) experienced recurrence of the disease (26 hepatic, 15 extrahepatic and 10 both). In 34 of the 36 cases of hepatic recurrence, the recurrence was distant (more than 1 cm away) from the resection margin. In the remaining two patients initial histology demonstrated a negative resection margin suggesting that these two new tumours were new. When compared with nine other liver resection series presented by the authors, the present study had comparable rates of morbidity (23% versus range: 16 to 45%) and mortality (3.2% versus range: 0 to 5%) but much lower mean blood loss (139 mL versus range: 250 to 1700 mL) and transfusion rate (5% versus range: 6.9 to 62.3%).

Navarra et al. (2004) reported the results of radiofrequency-assisted liver resection in 42 patients, possibly reporting on a subset of patients also reported by Ayav et al. 2007. Thirteen major and 29 minor resections were performed. The number and size of tumours as well as the operating time of the patients was not reported. Despite this, a median resection time of 50

minutes (range: 30 to 110 minutes) was reported. The median intra-operative blood loss was reported at 30 mL (range: 15 to 992 mL) with no requirement for intra-operative blood transfusion in any patient. As with the study by Ayav et al. (2007) the results compared favourably to the blood loss and transfusion rates reported in the literature.

Changes in haemoglobin, bilirubin, aspartate transaminase and alanine transaminase were measured pre-operatively and post-operatively on days one and seven to demonstrate the effect of radiofrequency-assisted liver resection on liver function. Bilirubin, aspartate transaminase and alanine transaminase levels were increased following the procedure but decreased to near-normal levels by the seventh post-operative day (Table 2). No statistical tests were performed.

**Table 2 Mean ( $\pm$  SD) values of indicators of liver function presented by Navarra et al. (2004)**

Indicator	Pre-operative	Day 1	Day 7
Hb (g/dL)	13.7 $\pm$ 1.6	11.8 $\pm$ 1.4	n/a
Bilirubin (mmol/L)	11.1 $\pm$ 5.0	23.6 $\pm$ 12.6	17.6 $\pm$ 12.7
AST (IU/L)	30.4 $\pm$ 13.7	730.7 $\pm$ 653.5	57.5 $\pm$ 23.5
ALT (IU/L)	40.1 $\pm$ 61.6	702.3 $\pm$ 516.1	128.8 $\pm$ 67.4

No operative or post-operative deaths were reported. Most patients tolerated the surgery well with all but one being sent to the surgical ward soon after surgery. The remaining patient was sent to the ICU due to concomitant heart failure. Five days post-operatively another patient was transferred to the ICU due to a biliary leak from hepatico-jejunostomy. One week post-operatively blood transfusion was required in one patient due to another biliary leak from hepatico-jejunostomy. Two additional post-operative complications were also reported: subphrenic abscess (one patient) and chest infection (one patient). Only the occurrence of subphrenic abscess was related to the technique.

Hompes and colleagues reported the first series of patients who had undergone laparoscopic radiofrequency-assisted liver resection (Hompes et al. 2007). Forty-five patients were enrolled in the study with 25 undergoing laparoscopic liver resection without radiofrequency assistance and 20 undergoing laparoscopic liver resection with radiofrequency assistance. Allocation to radiofrequency was performed by the surgeon and was not random. Patients had a median number of one (range: 1 to 3) tumours with a median maximum diameter of 40 mm (range: 8 to 170 mm). Thirty-eight minor and nine major resections were performed. The study used a monopolar radiofrequency generator (frequency not reported) and a single cool-tip electrode manufactured by Tyco Healthcare and Radionics Europe respectively.

The median operative time for all patients was 115 minutes (range: 45 to 360 minutes) with the resection time not reported. A comparison between both groups demonstrated similar operation times for the non-radiofrequency assisted and the radiofrequency assisted groups (105 and 120 minutes, respectively). Median intra-operative blood loss was the same for both groups at 200 mL. Additionally, there were no significant differences between groups in terms of complications, mortality (none reported) and length of hospital stay. This small short term study suggests that when performing laparoscopic liver resection, radiofrequency assistance offers little (if any) advantage. This is in contrast to observations from open-surgery studies in which radiofrequency assistance is associated with a reduction in bleeding and better patient outcomes. The study also identifies that the surgical procedure is the main determinant in amount of intra-operative blood loss.

## **COST IMPACT**

A search of the published literature and website of the manufacturer of the Habib 4X Sealer (Rita Medical Systems; California, United States) did not reveal the cost of performing radiofrequency-assisted liver resection.

The Medicare Benefits Schedule reimbursement fees for procedures related the resection of liver tumours is listed in Table 3:

**Table 3: Medical Benefits Schedule of fees for procedures related to resection of liver tumours (Department of Health and Ageing 2007)**

<b>Category</b>	<b>Item Number</b>	<b>Benefit (AUD)</b>	<b>Number of Claims (July 2005 to June 2006)</b>
Subsegmental resection of liver	30414	\$609.55	204
Segmental resection of liver	30415	\$1219.05	192
Lobectomy of liver	30418	\$1058.70	221
Tri-segmental resection (extended lobectomy) of liver	30421	\$1764.30	59

## **ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**

No issues were identified from the retrieved material.

## **OTHER ISSUES**

No issues were identified from the retrieved material.

## **RECOMMENDATION:**

The evidence currently available on radiofrequency-assisted liver resection is limited. There are currently no randomised comparative studies available, however the evidence presented in this summary suggests that under open surgery settings radiofrequency assisted liver resection may be associated with intra-operative blood loss and transfusion rate improvements. Given the potential high impact of this technology and lack of comparative studies it is recommended that this technology be monitored.

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#### **LIST OF STUDIES INCLUDED**

Total number of studies            3  
Level IV intervention evidence

#### **SEARCH CRITERIA TO BE USED:**

Radiofrequency  
Radio-frequency  
Liver resection  
Resection  
Radiofrequency assisted liver resection  
RFALR  
Hepatectomy  
Liver  
Liver cancer

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