Horizon Scanning in Surgery: Application to Surgical Education and Practice

Radiofrequency-assisted (bloodless) liver resection

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Division of Education

Disclaimer

This report is not a comprehensive systematic review. Rather, it is an assessment of an emerging surgical procedure or technology in which the methodology has been limited in one or more areas to shorten the timeline for its completion.

Therefore, this report is a limited evidence-based assessment that is based on a search of studies published in the peer-reviewed literature. This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements in health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

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Objective

This horizon scanning assessment provides short, rapidly completed, 'state of play' documents. These provide current information on technologies to alert clinicians, planners and policy makers of the advent and potential impact of a new or emerging procedure or device. This information can then assist clinicians, planners and policy makers to control and monitor the introduction of new health technologies as well as assist in the prioritization and allocation of resources to promote efficient utilization of available resources.

Introduction

Indications

Elective surgical resection of the liver (partial hepatectomy) is performed for the treatment of both benign and malignant liver tumors (Belghiti et al 1993). Common benign liver tumors include hepatic hemangioma and focular nodular hyperplasia (Arnoletti and Brodsky 1999):

- Hepatic hemangiomas result from dilated blood vessels within the liver, commonly occur in individuals between the ages of 30 and 50 years and, depending on their location, may cause bleeding or interfere with organ function (PubMed Health 2009).

- Focular nodular hyperplasia is almost always asymptomatic, has no malignant potential, and rarely causes hemorrhage; the main reason for resection of these types of benign tumors is the difficulty distinguishing them from hepatic adenoma (Semelka et al 2005).

Malignant liver tumors may be primary or secondary/metastatic, the latter most commonly arising from the bowel, breast, pancreas, stomach, esophagus, ovary or lung. Of the two main types of primary liver cancer, hepatocellular carcinoma and cholangiocarcinoma, hepatocellular carcinoma is more common and may be a sequela of cirrhosis (Lee and Marks 2011). Secondary liver cancer is > 20 times more common than primary liver cancer (Cancer Council 2011).

The stage of liver cancer is one of the most important factors to consider when determining treatment options. The most common staging system used is the American Joint Committee on Cancer TNM system, where staging is based on the number and size of the primary tumor (T), the extent of the spread to nearby lymph nodes (N) and the presence of distant metastases (M) (American Cancer Society 2011). Numbers and letters following T, N and M are used to provide more detail about each of the factors. The numbers 0 to 4 are used to indicate increasing severity and the letter X means ‘cannot be assessed’ because information is unavailable (American Cancer Society 2011).

Surgical resection remains the gold standard for the treatment of both primary and secondary liver tumors. Other treatment options include chemotherapy, radiotherapy, percutaneous ethanol injection, cryoablation, microwave coagulation therapy, laser-induced thermotherapy and radiofrequency ablation (Ayav et al 2007a, Kahn and MacDonald 2007).

Burden of disease

According to the United States Centers for Disease Control and Prevention (2010), liver cancer (primarily hepatocellular carcinoma) is the third leading cause of cancer deaths worldwide and the ninth leading cause of cancer deaths in the United States. The average annual incidence rate of hepatocellular carcinoma in the United States for 2001 to 2006 was 3.0 per 100,000 persons. This increased significantly from 2.7 per 100,000 in 2001 to 3.2 in 2006; the average annual percentage change in incidence rate was 3.5% (Centers for Disease Control and Prevention 2010).

The median age for diagnosis of hepatocellular carcinoma was 64 years; 62 years for males and 69 years for females and the highest incidence rate was among persons aged 70 to 79 years (13.7%), followed by those aged ≥ 80 years (10.0%), 60 to 69 years (9.6%), 50 to 59 years (6.8%) and 40 to 49 years (2.1%). The incidence rate for males (5.0 per 100,000 persons) was approximately three times higher than the rate for females (1.3 per 100,000 persons) (Centers for Disease Control and Prevention 2010).

Approximately 5% of patients with cirrhosis will develop liver cancer. In the United States, the most common causes of cirrhosis are chronic alcoholism and hepatitis (MedlinePlus 2011). It has been reported that about 1 in 12 adults in the United States are alcohol dependent, equating to 17.6 million people country-wide (National Institute on Alcohol Abuse and Alcoholism 2007).

Technology

The Couinaud classification of liver anatomy divides the liver into eight functionally independent segments, each with its own vascular inflow, outflow and biliary drainage. In the center of each Couinaud segment is a branch of the portal vein, hepatic artery and bile duct and in the periphery of each segment there is vascular outflow through the hepatic veins (Smithuis 2011). Liver resection can be anatomical resection, that is resection of Couinaud segments or non-anatomical resection where wedge resection or resection extending across Couinaud's segmental planes occurs. Every liver resection is considered major surgery; however, resection of three or more Couinaud segments is considered to be major liver resection (Belghiti et al 1993).

Liver resections are demanding operations that may have life threatening complications and bleeding. The need for blood transfusions is a significant factor affecting postoperative morbidity and mortality as well as long-term outcomes (Delis et al 2007; Xia et al 2008). Various techniques have been developed to reduce the risk of intraoperative blood loss during liver resection, including radiofrequency-assisted liver resection.

The use of heat to create coagulative necrosis is not new as radiofrequency ablation of liver tumors has been performed (Curley et al 1999). Radiofrequency-assisted liver resection induces necrosis in healthy liver tissue at the resection plane to seal vascular and biliary structures and thereby facilitate bloodless dissection of the parenchyma during resection (Ayav et al 2007a). The procedure is novel because coagulation of normal liver tissue, which responds much more quickly than cancerous tissue, can result in bloodless surgical resection and reduce the risks associated with intraoperative blood loss (Weber et al 2002).

Stage of development

Radiofrequency-assisted liver resection appears to be in limited use throughout Europe and the United States. Published clinical trials took place in Australia, Belgium, China, France, Germany, Greece, Italy, Japan, Switzerland, the United Kingdom and the United States.

Regulatory approval

The radiofrequency-assisted dissection devices used in the identified published studies (including studies not eligible for inclusion in this report) included: the Habib 4X Sealer, the Habib 4X Laparoscopic Sealer, the Radionics Cool-Tip RF System and the TissueLink Dissecting Sealer, all of which have received marketing approval from the United States Food and Drug Administration (FDA) (see Table 1) (FDA 2011). The TissueLink Dissecting Sealer was recalled by the manufacturer in February 2005 because 'the tip may separate from the device and render it unusable'. The manufacturer requested users return the devices in inventory (FDA 2005).

Table 1: FDA-approved radiofrequency-assisted liver resection devices

Device name	Manufacturer	FDA 510(k) number	Approval date
Habib 4X Sealer	Emcision, Ltd.	K051420	15/08/2005
Habib 4X Laparoscopic Sealer	Rita Medical Systems	K062935	13/10/2006
Cool-Tip RF System	Radionics, Inc.	K984552	05/03/1999

(Retrieved April 2011)

Current clinical trials

Searches of the Current Controlled Trials *meta*Register (which encompasses searches of multiple trial registers including NHS in England and US clinicaltrials.gov) for current clinical trials, using broad search terms such as 'liver resection' and 'radiofrequency', did not reveal any relevant ongoing trials.

Current treatment and alternatives

Various intraoperative techniques have been attempted to reduce blood loss during liver resection (Gurusamy et al 2009):

- Lowering central venous pressure (CVP) via vasodilators or limiting infusion so that venous engorgement of the liver is reduced and there is less tendency for the liver to bleed on transection (Hasegawa et al 2002; Jones and Rees 2010).
- Hypoventilation, which reduces respiratory tidal volume so, under positive pressure, lung inflation directly compresses the heart and lowers CVP (Hasegawa et al 2002).
- Vascular occlusion (Pringle technique), where clamping the vascular pedicle (hepatic artery and portal vein) reduces venous engorgement and hemorrhage (Nickloes et al 2011).

In addition, various intraoperative maneuvers have been designed to reduce the risk of bleeding during liver resection:

- Finger fracture technique (or 'digitoclasy') where the liver tissue is fractured between the forefinger and thumb to stop hemorrhage (Jones and Rees 2010).
- Sharp dissection (separation of liver tissue via the sharp edge of a knife, scalpel or scissors).
- Clamp-crush technique (Kelly's technique), where a Kelly Clamp is used to occlude blood flow (Kim and Lee 2008).
- Ultrasonic dissector whose high frequency ultrasonic waves divide liver parenchyma whilst sparing structures greater than 2 mm in diameter (Jones and Rees 2010).
- Hydrojet where a pressurized jet of water achieves transection (Jones and Rees 2010).
- Radiofrequency dissecting sealer (radiofrequency-assisted liver resection).

Direct comparators to radiofrequency-assisted liver resection include radiofrequency ablation of liver tumors, standard surgical resection, hepatic arterial infusion chemotherapy, percutaneous ethanol injection, cryoablation, microwave coagulation therapy and laser-induced thermotherapy (Kahn and MacDonald 2007).

Literature review

Search criteria

Keyword/MeSH terms utilized:
Radiofrequency resection; radiofrequency assisted resection; bloodless resection; liver tumo*r, hepatic tumo*r; liver resection; hepatectomy

Databases utilized:
PubMed, OVID

Inclusion criteria

Table 2: Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Systematic reviews; randomized controlled trials (RCTs); non-randomized comparative studies
Patient	Patients with hepatic tumors requiring partial hepatectomy
Intervention	Radiofrequency-assisted liver resection
Comparator	Conventional liver resection, other bloodless resection techniques
Outcome	Blood loss, transfusion requirement, operative time, liver enzyme levels, mortality, complications
Language	English only

Included studies

A total of 632 studies were retrieved using the above search strategy. Closer examination of these studies with application of the inclusion criteria revealed a total of nine studies eligible for inclusion. Of these, three were RCTs (Lupo et al 2007; Arita et al 2005; Lesurtel et al 2005) and six were non-randomized comparative studies (Di Carlo et al 2010; Delis et al 2009; Xia et al 2008; Ayav et al 2007; Hompes et al 2007; Mitsuo et al 2007). Excluded studies, along with the reasons for their exclusion, are presented in Appendix A. Table 3 describes the level of evidence and characteristics of the nine included studies.

Table 3: Characteristics of included studies

Study authors / Location	Level of Evidence[1]	Total n	Intervention	Comparator
Lupo et al ((2007), Italy	II	50	RF-assisted, n=24	Clamp-crush, n=26
Arita et al (2005), Japan	II	80	RF-assisted, n=40	Clamp-crush, n=40
Lesurtel et al (2005), Switzerland	II	100	RF-assisted, n=25	Clamp-crush, n=25; Ultrasonic dissector, n=25; Hydrojet, n=25
Di Carlo et al (2010), Italy	III-1	71	RF-assisted, n=27	Clamp-crush, n=44
Delis et al (2009), US	III-1	196	RF-assisted, n=109	Clamp-crush, n=87
Xia et al (2008), China	III-1	122	RF-assisted, n=61	Clamp-crush, n=61
Ayav et al (2007), UK	III-3	78	RF-assisted, n=27	Total vascular occlusion, n=51
Hompes et al (2007), Belgium	III-1	45	RF-assisted, n=20	Conventional resection, n=25
Mitsuo et al (2007), Japan	III-1	48	RF-assisted, n=20	Conventional resection, n=28

[1]See Appendix B for NHMRC Evidence Hierarchy.
RF-assisted: radiofrequency-assisted liver resection; UK: United Kingdom; US: United States.

Study profiles

RCT evidence

Lupo et al (2007) compared patient outcomes following liver resection via radiofrequency-assist versus the clamp-crush technique. Patients with primary and secondary liver cancer considered for curative liver resection between January 2003 and October 2004 were eligible for inclusion. Random-number tables were used to assign patients to a treatment group once they were in the operating room (OR); even numbers were allocated to the radiofrequency group (n=24) and odd numbers to the clamp-crush group (n=26). All procedures were carried out under general anesthesia by two surgeons equally skilled in liver resection using both techniques. In the radiofrequency group, the resection plane was precoagulated by radiofrequency waves delivered using two cooled triple needles (≤ 100 W for 3 to 6 minutes per single application, with the power suspended when the impedance rose). A few stitches were used on major vessels that had already been closed by radiofrequency. Patients in the control group underwent resection with clamp-crushing and bipolar diathermy. In some patients, fibrin glue was spread on the cut surface at the end of resection to ensure hemostasis. At baseline, the treatment groups were similar in terms of age, sex ratio, diagnosis and type of resection.

Arita et al (2005) compared the effects of radiofrequency-assisted liver resection (intervention) on blood loss with the use of the clamp-crushing technique (control). Consecutive patients scheduled to undergo hepatic resection at a single center between October 2003 and April 2004 who met the inclusion criteria (aged 20 to 79 years and acceptable clotting profile) and agreed to participate were randomized into one of two treatment arms (n=80). Randomization took place in the OR by means of an internet-accessed registration system administered by an independent randomization service. The randomization was achieved using the minimization procedure with stratification by age, indocyanine green retention rate at 15 minutes and the type of resection. Two consultants and three trainee surgeons performed all procedures. In the radiofrequency group (n=40), the dissecting sealer received radiofrequency energy at 90 W with saline dripping from the tip of the device at a rate approximately 4 mL/minute. Patients in the crush-clamp group (n=40) underwent clamping for 15 or 30 minute intervals followed by 5 minutes of release to achieve intermittent inflow occlusion. Macroscopically observed biliary leakage was controlled by fine suturing and fibrin glue was spread on the cut surface to ensure hemostasis in all patients. Patient characteristics were similar at baseline between the treatment groups.

Lesurtel et al (2005) sought to compare the efficiency of four liver resection techniques in 100 consecutive non-cirrhotic and non-cholestatic patients undergoing liver resection at a single center between June 2003 and September 2004. Patients were randomly allocated to: radiofrequency-assist (n=25), clamp-crush (n=25), ultrasonic dissector (n=25) or Hydrojet (n=25). Inclusion criteria were a need for partial hepatectomy (≥ 2 segments) for benign or malignant tumors and an acceptable clotting profile. Randomization took place the night before surgery using sealed envelopes; however, operative staff was not informed of the allocation until the time of surgery. The clamp-crushing technique was performed under routine inflow occlusion (Pringle maneuver); the remaining procedures were performed without the Pringle maneuver. A single hepatobiliary surgeon with ≥ 30 procedures experience for each intervention performed all surgeries. Details of the surgical procedures are as follows:

- For radiofrequency-assist, radiofrequency energy was coupled with a conductive fluid to seal the liver tissue in order to pre-coagulate the parenchyma and isolate small and larger intrahepatic structures prior to resection.
- The clamp-crush technique was performed under continuous Pringle maneuver, small vessels (< 2 mm) were coagulated with irrigated bipolar forceps set at 120 W and all other major intrahepatic bile ducts were ligated or clipped.
- Ultrasonic dissection took place with the device set at 70 W and fluid flush or 4 mL/minute. The use of bipolar forceps, ligatures, and clips was identical to the clamp-crush technique.
- In the Hydrojet group, a high-pressure pump was used to pressurize the jet of water used to 30-40 bar water pressure. The use of bipolar forceps, ligatures and clips was identical to the ultrasonic dissection group.

Patient age, gender, the surface of liver resection, use of chemotherapy prior to resection and the type of hepatectomy performed were comparable between the groups at baseline.

Non-randomized comparative evidence

Di Carlo et al (2010) retrospectively analyzed 71 consecutive patients who underwent hepatic resection between January 2003 and July 2009 at a single center using either radiofrequency (n=27) or kellycasia with the Pringle maneuver (n=44). Patients were cirrhotic and non-cirrhotic. In the clamp-crush group, clamping was performed by (< 4) cycles of 15 minute inflow occlusion following by 5 minutes of release. In the radiofrequency group were 16 male and 11 female patients, with a mean age of 60 years (range, 20-79 years); in the clamp-crush group were 18 males and 26 females, with a mean age of 54 years (range, 32-79 years). The significance of the differences between the treatment groups was not discussed.

Delis et al (2008) assessed the outcomes of 196 consecutive patients with primary or metastatic hepatic tumors who were treated with hepatic resection at a single center from January 2002 to March 2007. Treatment allocation was determined by the tumor characteristics of each patient; the crush-clamp method was used in patients whose tumor was in close proximity to major vasculature. All resections were performed under low CVP anesthesia under the supervision of two hepatobiliary and pancreas surgeons. Radiofrequency-assisted liver resection was achieved using a cool-tip device with a single 3 cm needle. Radiofrequency energy was used to instigate coagulative necrosis prior to resection of the liver tissue with a surgical scalpel. In the crush-clamp group, small vessels (< 2 mm) were coagulated with monopolar forceps and bigger structures were ligated or clipped. Intermittent portal triad clamping was performed in cycles of inflow occlusion for 10 minutes following by reperfusion for 5 minutes. There were no significant differences between the treatment groups pre-operatively.

Xia et al (2008) prospectively assessed 122 consecutive patients with cirrhosis who underwent liver resection for liver cancer over 3 years (2004 to 2007) at a single medical center. Patients received radiofrequency-assisted liver resection (n=61) or liver resection using the clamp-crush technique (n=61). One team of liver surgeons performed all of the procedures; the reasons for choosing one procedure versus the other were not explained. An intermittent Pringle maneuver consisting of 5 minutes break after 15 minutes of clamping was routinely used with the clamp crushing technique. Inflow occlusion was achieved using the tourniquet technique around the portal triad with a 4 mm tape. Liver transection was carried out using parenchyma crushing with a

Kelly clamp. All clamped structures were ligated or sutured. In the radiofrequency group, hepatic resection was achieved using a saline-linked radiofrequency dissecting sealer connected to a compatible electrosurgical generator with an output power set at 70 W. Radiofrequency energy (480 kHz) was focused at the tip and was conveyed into the liver tissue by a low flow of saline solution (one drop per second). The pointed tip of the cone-shaped dissector allowed dissection of the liver parenchyma after coagulation without the need for clamp crushing. There were no significant differences between the two treatment groups in terms of patient characteristics at baseline.

Ayav et al (2007) reported on a time series of patients undergoing major (> 3 Couinaud segments) liver resections performed with radiofrequency assistance without vascular clamping or with total vascular occlusion. All patients treated between January 1994 and August 2004 at a single medical center in London were eligible for inclusion. Patients treated prior to January 2002 underwent total vascular occlusion (n=51) and after this date they underwent radiofrequency-assisted liver resection (n=27). In the case of major liver resection using radiofrequency, dissection of the hepatic pedicle was not performed unless the tumor was close to the hilus when separation of the tumor from the hilar structures was indicated. Hepatic veins were dissected only when the tumors lay close to them in order to separate the tumor from the main vascular structures. Radiofrequency energy was applied along the transection line so coagulative necrosis was induced in normal liver tissue, using a cooled-tip radiofrequency probe and a 500 kHz generator. The zone of coagulative necrosis sealed the vascular and biliary structures along the line of resection so that the liver parenchyma could be divided with a scalpel. The hepatic veins were then coagulated with radiofrequency or ligated (when > 1 cm); neither the Pringle maneuver nor any other vascular clamping technique was applied in this group. Both patient groups were of similar age and gender distribution, with similarities in the nature, size and number of tumors.

Hompes et al (2007) compared the outcomes of 45 patients undergoing laparoscopic liver resection with or without radiofrequency assistance over 3 years (2002 to 2005). Treatment allocation was based on the judgment of the (one of two) hepatobiliary surgeon performing the procedure; the surgeon decided ‘at random’ whether or not to use radiofrequency assistance. In the radiofrequency group, the transection plane was precoagulated using radiofrequency energy applied during 1 to 2 minutes every 2 cm using a monopolar radiofrequency generator and a single cool-tip electrode. Parenchymal transection was performed through the precoagulated plane using a harmonic scalpel and ultrasonic aspirator. Patient, tumor and surgery characteristics were comparable in both study groups.

Finally, Mitsuo et al (2007) retrospectively compared outcomes for 48 patients who received hepatectomy with or without radiofrequency ablation to determine whether the technique reduced blood loss and affected perioperative outcomes. Patients undergoing partial hepatectomy (resection of a portion of liver smaller than a single Couinaud segment) between January 2002 and October 2005 at a single center were eligible for inclusion. Twenty patients underwent hepatectomy with radiofrequency assistance and 28 without radiofrequency assistance. Two surgeons with over 15 years’ experience with hepatectomy performed the procedures using the same protocol agreed upon prior to the study. Patients in the radiofrequency group received radiofrequency ablation by applying a cool-tip system to the target site with a single insertion at approximately 100 W prior to resection; otherwise, the two patient groups received the same liver resection procedure. Resection was achieved using an electrosurgical knife. Hepatic blood inflow was controlled by clamping (10 minutes) and unclamping (5 minutes) during the resection in both treatment groups. Hemostasis of the cut surface was attained by electrosurgical knife, fibrin glue or the application of thrombin-soaked gelatin foam sheets. Patients in each treatment group were comparable at baseline in regards to age, sex, and disease type and severity.

Critical appraisal

The overall quality of the current evidence base for radiofrequency-assisted liver resection is good, with three RCTs available for inclusion. The critical appraisal of the included studies is presented below by level of evidence. Patient follow-up was generally limited to the immediate postoperative period.

RCT evidence

Randomization methods were well described and deemed to be adequate. The use of consecutive patient enrolment in two RCTs (Artia et al 2005, Lesurtel et al 2005) reduced chance of bias. Participants were generally well matched at baseline in terms of demographics and disease and procedural characteristics. Apart from the OR staff generally being unaware of treatment allocation until the beginning of surgery, allocation concealment was not described; however, this would be a challenge when different surgical procedures were being employed.

Maximizing patient numbers assists in the generalizability of a study's findings and reduces the likelihood of the results obtained being due to chance alone. All three RCTs performed statistical calculations to determine the adequate number of patients required to detect differences between the treatments to a desired level of significance – in all three cases this number was achieved. All RCTs took place at a single center which reduces the generalizability of their findings but may have improved their validity by reducing the effects of random bias. Two of the included studies had multiple experienced surgeons completing the assigned procedures and one of the studies had a single experienced surgeon complete all procedures. The utilization of experienced surgeons using the same treatment protocol in the entire patient population within a trial is important to produce valid findings.

Non-randomized comparative evidence

In the non-randomized comparative evidence base, statistical calculations to determine minimum sample size did not occur. It is therefore not possible to determine that the statistically significant differences seen between treatment groups with small patient populations were not due to chance alone. Four studies enrolled consecutive patients and participants were generally well matched between treatment groups at baseline. Allocation concealment was not reported. Most studies took place at a single center, perhaps reducing generalizability but also improving validity by reducing biases such as variations in OR staff and protocols.

As previously mentioned the overall quality of the evidence base available for radiofrequency-assisted liver resection was good. Refinements in study protocol, including patient and assessor allocation concealment, would be useful in improving the validity of this report's conclusions.

As it was the aim of most of these studies to determine the effect of radiofrequency-assisted liver resection on intraoperative blood loss the duration of follow-up in most cases was limited to the immediate postoperative period. In order to fully understand the effectiveness of radiofrequency-assisted liver resection, in particular in regards to disease recurrence, additional high-quality studies with longer-term follow-up are needed.

Safety and efficacy

Safety

All nine included studies reported safety outcomes including death and perioperative complications such as biliary leakage, wound infection, pleural effusion and abscess.

RCT evidence

Mortality

Lesurtel et al (2005) reported the death of four patients within 30 days of major hepatectomy. Deaths were due to mesenteric arterial infarction in one patient at 5 days post-surgery and sepsis with multi-organ failure in three patients at 10 to 28 days post-surgery. These patients had cholangiocarcinoma (n=2) and gallbladder carcinoma (n=2), and underwent liver resection using ultrasonic dissection (n=2) and Hydrojet treatment (n=2); therefore, no deaths occurred in the radiofrequency-assisted liver resection group. Arita et al (2005) reported no operative deaths in either treatment group; however, the authors did not define their follow-up period. No deaths were reported by Lupo et al (2007).

Complications

All RCTs reported complications (Table 4). Arita et al (2005) reported five patients in the radiofrequency group who developed biliary leakage, three of which were considered major leakages; two underwent percutaneous drainage and one required re-laparotomy. In the clamp-crush group, four patients developed biliary leakage, two of which were considered major leakages; one patient required re-laparotomy and the other percutaneous drainage. Other major complications consisted of two cases of peritoneal abscess in the radiofrequency group, both of which were drained percutaneously. In the study by Lesurtel et al (2005), overall complication rates were similar between the treatment groups; there was no significant difference observed between minor and major complication rates. Abdominal ultrasound at postoperative day 5 and computed tomography scans at 3 months showed moderate levels of asymptomatic intraperitoneal collections in each group. These were documented in 8 (32%), 9 (36%), 6 (24%) and 8 (32%) patients in clamp-crush, ultrasonic dissector, Hyrdojet and radiofrequency groups, respectively (P = 0.82).

Table 4: Complications reported in the RCTs

Study	Treatment group (N)	Complication (n; %)
Lupo et al (2007)	RF-assisted (24)	Abscess (n=6; 25%) Biliary fistula (n=3; 13%) Biliary stenosis (n=1; 4%)
	Clamp-crush (26)	None
Arita et al (2005)	RF-assisted (40)	Major biliary leakage (n=3; 8%) Biliary leakage (n=2; 5%) Peritoneal abscess (n=2; 5%) Ileus (n=1; 3%) Ascites (n=1; 3%)
	Clamp-crush (40)	Major biliary leakage (n=2; 5%) Biliary leakage (n=2; 5%) Ileus (n=1; 3%) Ascites (n=2; 5%)
Lesurtel et al (2005)	RF-assisted (25)	Wound infection (n=6; 24%) ***Total minor complications (n=6; 24%)*** Bilioma (n=3; 12%) ***Total major complications (n=3; 12%)***
	Clamp-crush (25)	Wound infection (n=1; 4%) Pneumonia (n=1; 4%) Urine infection (n=2; 8%) ***Total minor complications (n=4; 16%)*** Bilioma (n=2; 8%) Hepatic failure (n=1; 4%) Pulmonary embolism (n=1; 4%) ***Total major complications (n=4; 16%)***
	Ultrasonic dissector (25)	Cardiac arrhythmia (n=2; 8%) Pneumonia (n=2; 8%) ***Total minor complications (n=4; 16%)*** Bilioma (n=1; 4%) Hepatic failure (n=1; 4%) ***Total major complications (n=2; 8%)****
	Hydrojet (25)	Cardiac arrhythmia (n=1; 4%) Urine infection (n=1; 4%) ***Total minor complications (n=2; 8%)*** Intra-abdominal bleeding (n=1; 4%) Hepatic failure (n=1; 4%) Renal failure (n=1; 4%) ***Total major complications (n=3; 12%)****

*In Lesurtel et al (2005), death was classified as a major complication.
RF-assisted: radiofrequency-assisted liver resection.

Non-randomized comparative evidence

Mortality

All studies reported mortality. In the study by Di Carlo et al (2010) death due to a pulmonary embolism was reported in one patient in the crush-clamp group on the second day following hepatic resection; there were no deaths reported in the radiofrequency group. Delis et al (2009) reported the death of one patient in the radiofrequency group on postoperative day 8 as a result of hepatic insufficiency. Xia et al (2008) reported the deaths of two patients in the clamp-crush group due to liver failure (n=1) and heavy postoperative bleeding (n=1); there were no deaths reported in the radiofrequency group.

Mortality rates in the study by Ayav et al (2007) were 3% (n=1) and 11% (n=6) in the radiofrequency group and the total vascular exclusion group, respectively. No details were provided. No deaths were reported in the studies by Hompes et al (2007) and Mitsuo et al (2007).

Complications

Reported complications are summarized in Table 5. Di Carlo et al (2010) reported complications in the clamp-crush group only (n=2). One patient had ascites that regressed after 3 weeks and the other had an infected hematoma with right pleural effusion and fever that regressed after 15 days. Conversely, Delis et al (2009) reported a higher incidence of complications in the radiofrequency group (n=31) compared with the clamp-crush group (n=15) (significance not reported). Significantly more patients in the radiofrequency group experienced abscess and biliary fistula ($P = 0.04$); all were successfully treated with computer tomography-guided drainage or conservative treatment, respectively. It was also reported that more patients in the radiofrequency group experienced bile leak and infectious complications (data not provided).

Xia et al (2008) reported a higher incidence of complications in the clamp-crush group compared to the radiofrequency group (15 versus 8, respectively); however this difference was not statistically significant. Details for five 'other' complications in the radiofrequency group were not reported (one of these was considered a major complication and the remaining four minor complications).

In the study by Ayav et al (2007), the incidence of postoperative complication rates were similar between the two treatment groups: 14 complications in 11 patients in the radiofrequency group (52%) and 32 complications in 24 patients in the total vascular occlusion group (63%). However, occurrence of liver failure was significantly different with no cases reported in the radiofrequency group versus nine in the total vascular occlusion group ($P = 0.05$). Reoperation was not required in any case.

Hompes et al (2007) reported three patients required conversion from laparoscopic to open hepatic resection due to uncontrollable bleeding from various portal veins; however, it was unclear which treatment arm the patients were in. Finally, in the study by Mitsuo et al (2007) there was no significant difference in rates of postoperative complications between the treatment groups with the exception of bile leakage (significantly higher in the radiofrequency group ($P < 0.05$)). These patients were all successfully managed by the insertion of a drain into the site of bile accumulation.

Table 5: Complications reported in the non-randomized comparative studies

Study	Treatment group (n)	Complication (n; %)
Di Carlo et al (2010)	RF-assisted (27)	'No incidence of fluid collection or biliary fistulas'
	Clamp-crush (44)	Ascites (n=1; 2%) Infected hematoma (n=1; 2%)
Delis et al (2009)	RF-assisted (109)	Abscess (n=8; 7%) Biliary fistula (n=10; 9%) Pleural effusion (n=13; 12%)
	Clamp-crush (87)	Abscess (n=1; 1%) Biliary fistula (n=1; 1%) Pleural effusion (n=13; 15%)
Xia et al (2008)	RF-assisted (61)	Biliary leakage (n=2; 3%) Other minor (n=4; 7%) ***Total minor complications (n=6; 10%)*** Major biliary leakage (n=1; 2%) Other major (n=1; 2%) ***Total major complications (n=2; 3%)***
	Clamp-crush (61)	Biliary leakage (n=3; 5%) Ascites (n=2; 3%) Incision infection (n=2; 3%) Ileus (n=1; 2%) ***Total minor complications (n=8; 13%)*** Major biliary leakage (n=3; 5%) Postoperative bleeding (n=2; 3%) Intra-abdominal sepsis (n=1; 2%) Total incision dehiscence (n=1; 2%) ***Total major complications (n=7; 11%)***
Ayav et al (2007)	RF-assisted (27)	Pleural effusion (n=8; 29%) Intra-abdominal collection (n=5; 18%) Biliary fistula (n=1; 3%)
	Total vascular occlusion (51)	Pleural effusion (n=9; 17%) Intra-abdominal collection (n=9; 17%) Biliary fistula (n=5; 9%) Liver failure (n=9; 17%)
Hompes et al (2007)	RF-assisted (20)	Biliary leakage with intraabdominal abscess (n=1; 5%) Pulmonary infection (n=1; 5%) Bleeding (n=6; 30%)
	Conventional resection (25)	Bleeding (n=3; 12%)
Mitsuo et al (2007)	RF-assisted (20)	Pleural effusion (n=2; 10%) Infection of a drain (n=1; 5%) Bile leakage (n=3; 15%) Subcutaneous abscess (n=2; 10%)
	Conventional resection (28)	Pleural effusion (n=5; 18%) Infection of a drain (n=2; 7%) Subcutaneous abscess (n=4)

RF-assisted: radiofrequency-assisted liver resection.

Efficacy

Outcomes reported in the nine studies included intraoperative blood loss, the need for blood transfusion, operative time, transection time and speed, length of hospital stay (LOHS), liver enzyme levels, and several other outcomes.

RCT evidence

Intraoperative blood loss

Two studies reported intraoperative blood loss (Arita et al 2005; Lesurtel et al 2005), but their findings were contradictory. In Arita et al (2005), there were no significant difference in blood loss between the radiofrequency and clamp-crush techniques, although there was a trend to increased blood loss for the latter, i.e., median intraoperative blood loss was greater in the clamp-crush group, with a loss of 733 mL (range, 40-2550 mL) versus 665 mL (range, 30-2840 mL) (P = 0.45) total blood, and 7.0 mL/cm^2 (range, 0.7-32.4 mL/cm^2) versus 5.3 mL/cm^2 (range, 0.3-25.9 mL/cm^2) (P = 0.187) blood per unit transection area, respectively. Whereas, Lesurtel et al (2005) reported mean blood loss per resection surface to be lower in the crush-clamp group (1.5 mL/cm^2 (standard deviation [SD], 0.3 mL/cm^2) compared with the ultrasonic dissector, Hydrojet and radiofrequency groups (4 mL/cm^2 (SD, 0.7 mL/cm^2), 3.5 mL/cm^2 (SD, 0.5 mL/cm^2) and 3.4 mL/cm^2 (SD, 0.4 mL/cm^2), respectively) (P = 0.003). They reported no difference in hemostasis time (from the end of transection until completion of hemostasis) among the treatment groups (P = 0.41).

Blood transfusion

All three RCTs reported the number of patients who required blood transfusions although in only one study did the differences reach statistical significance. In Lesurtel et al (2005), significantly fewer patients in the crush-clamp group required blood transfusions (n=1; 4%) compared to the other three study groups, i.e., ultrasonic dissector (n=8; 32%), Hydrojet (n=8, 32%) and radiofrequency-assisted (n=5, 20%) (P = 0.06). Significance was not achieved in the remaining two RCTs where two patients (5%) in the radiofrequency group versus none in the crush-clamp group required transfusion (P = 0.494) (Arita et al 2005) and fewer patients required transfusion in the radiofrequency group versus the crush-clamp group (8/24 (34%) versus 13/26 (50%) (P = 0.232) (Lupo et al 2007).

Operative time

OR time was reported in Lupo et al (2007), but differences did not reach statistical significance (crush-clamp group versus radiofrequency group, 278 versus 292 minutes; P = 0.340). In each treatment group four patients with metastasis from colorectal cancer developed recurrence during the study's follow-up period (mean 19 months; range 14-25).

Transection time and speed

Mean transection time and speed were measured in Arita et al (2005) and Lesurtel et al (2005). In the study by Arita et al (2005), median transection times were similar between treatment groups:

radiofrequency 79 minutes (range 18-162); crush-clamp 80 minutes (range 17-202) ($P = 0.740$). Median transection speeds were also similar: 0.99 cm^2/minute (range 0.32-2.17) versus 0.89 cm^2/minute (range 0.36-2.09), respectively ($P = 0.777$). Lesurtel et al (2005) pooled the overall mean transection time from all four treatment groups (46 minutes; SD, 4 minutes; range, 14-128 minutes). The mean transection speed was fastest for the crush-clamp group (3.9 cm^2/minute) compared with the ultrasonic dissector, Hydrojet and radiofrequency groups (2.3, 2.4, and 2.5 cm^2/minute, respectively) ($P = 0.001$).

LOHS

Intensive care unit (ICU) and postoperative LOHS were similar in the three RCTs. Lupo et al (2007) reported median LOHS to be 12 days for both groups (no SDs or ranges were provided). Arita et al (2005) reported median LOHS to be similar between groups with a duration of 16 days (range, 9-65 days) and 18 days (range, 9-30 days), respectively ($P = 0.941$). In the study by Lesurtel et al (2005) all four patient groups had a median ICU stay of 1 day (range, 0-26 days; $P = 0.35$) and a median LOHS of 9 days (range, 4-34 days; $P = 0.67$).

Liver enzyme levels

In the two studies reporting these outcomes (Arita et al 2005; Lesurtel et al 2005), differences did not reach statistical significance.

Additional efficacy outcome: use of the Pringle maneuver

In Lesurtel et al (2005) the Pringle maneuver (inflow occlusion) was applied to all 25 patients in the clamp-crush group and only 5 (20%), 7 (28%) and 9 (36%) in the ultrasonic dissector, Hydrojet and radiofrequency groups, respectively ($P < 0.001$ for clamp-crush versus other techniques). The overall mean Pringle time (pooled) was 28 minutes (standard error, 2 minutes; range, 10-60 minutes).

Non-randomized comparative evidence

Intraoperative blood loss

Five of the six studies reported the volume of intraoperative blood loss. In four of the five studies the differences between procedure types were not statistically significant, although there was often a trend favoring the radiofrequency group. Di Carlo et al (2010) reported no significant difference in median intraoperative blood loss although the trend was towards higher blood loss in the crush-clamp group (122 mL; range, 20-545 mL versus 100 mL; range, 50-500 mL) ($P = 0.22$).

In Delis et al (2009), the same pattern emerged with lack of significant differences but a trend towards higher median intraoperative blood loss in the crush-clamp versus radiofrequency group (580 mL; range, 200-850 mL versus 490 mL; range, 100-900 mL) ($P = 0.09$). Xia et al (2008) also reported a non-statistically significant increase in median intraoperative blood loss in the crush-clamp group compared with the radiofrequency group (750 mL; range, 150-6800 mL versus 350 mL; range, 40-2000 mL) ($P = 0.047$). The median time to reach hemostasis in the crush-clamp group was significantly longer than in the radiofrequency group (25 minutes; range, 8-48 minutes versus 4 minutes; range, 0-12 minutes) (P < 0.001).

Hompes et al (2007) reported median operative blood loss to be the same in both of its treatment groups (200 mL). Despite this, significant variability was observed in the volume of blood loss dependent on the type of surgery performed, irrespective of whether radiofrequency was used or not, i.e. laparoscopic right/left hemihepatectomy, left lateral lobectomy and segmental hepatectomy resulted in a median blood loss of 2000 mL, 200 mL and 100 mL, respectively. Furthermore, median blood loss was 150 mL in patients with cirrhosis and/or those who underwent preoperative chemotherapy (n=8 and 9 in the radiofrequency-assisted and non-radiofrequency-assisted groups, respectively), compared with 200 mL in patients without cirrhosis and/or those who did not undergo preoperative chemotherapy (n=12 and 16 in the radiofrequency-assisted and non-radiofrequency-assisted groups, respectively).

The only study to show a statistically significant difference was Mitsuo et al (2007) where the estimated mean intraoperative blood loss was significantly higher in the non-radiofrequency-assisted group compared with the radiofrequency-assisted group: 429 mL (SD 389 mL) versus 209 mL (SD 180 mL), respectively (P < 0.05).

Blood transfusion

Four studies reported on the need for blood transfusions but only two reported statistically significant differences, both favoring radiofrequency (Xia et al (2008); Ayav et al (2007). In Xia et al (2008), more crush-clamp patients required blood transfusions compared with the radiofrequency patients (n=26; 59% versus n=7; 12%) (P < 0.001). The median volume of blood administered per transfusion was also higher in the crush-clamp group (950 mL; range, 0-6500 mL versus 600 mL; range, 0-1500 mL) (P = 0.031). Ayav et al (2007) also reported significantly more blood transfusions in patients in the total vascular occlusion group compared with those in the radiofrequency group (53% versus 26%) (P = 0.04).

In Delis et al (2009), fewer patients in the radiofrequency group required transfusion in the first 48 hours postoperative than in the crush-clamp group (n=22 (20%) versus n=27 (31%) but this difference was not significant) (P = 0.06). Similarly, Mitsuo et al (2007) reported that three of 28 patients in the non-radiofrequency-assisted group required blood transfusions, compared to zero of 20 in the radiofrequency-assisted group, a difference that was not statistically significant.

Operative time

Four of the six studies reported OR time (Table 6). Of these studies, one reported a statistically significant difference in operative time, favoring the clamp-crush method.

Table 6: Operative time reported in non-randomized comparative studies

Study	Median operative time (minutes [range])		
	RF-assisted	Comparator	P value
Di Carlo et al (2010)	160 (60-482)	160 (60-510)	0.96
Delis et al (2009)	240 (150-300)	170 (110-290)	0.04
Hompes et al (2007)	120 (50-310)	105 (45-360)	NR*
Mitsuo et al (2008)	Mean 141 (SD, 49)	Mean 163 (SD, 39)	NS

RF-assisted: radiofrequency-assisted liver resection; NR: not reported; SD: standard deviation; NS: not significant.
*it was reported that radiofrequency-assistance did not reduce operative time; however the significance of this was not reported.

Transection time and speed

Three studies reported data on transection times, with two reporting shorter times for the crush-clamp procedure (Delis et al 2009; Xia et al 2008) and one reporting no significant difference (Di Carlo et al 2010). Significant differences were reported by Delis et al (2009) who reported a shorter median transection time in the crush-clamp group (60 minutes; range, 20-120 minutes) compared with the radiofrequency group (105 minutes; range, 50-180 minutes) (P = 0.01). Xia et al (2008) also reported significantly faster median transection times in the crush-clamp group compared with the radiofrequency group (32 minutes; range 8-102 minutes versus 85 minutes; range 20-182 minutes) (P < 0.001). Non-significant differences were seen in the study by Di Carlo et al (2010) who reported lower median transaction times in the crush-clamp group compared with the radiofrequency group (47.5 minutes; range, 15-120 minutes versus 60 minutes; range, 30-150 minutes, respectively) (P = 0.69).

LOHS

All studies reported on LOHS, with two of six reporting significant differences. LOHS was significantly different between the treatment groups in the study by Delis et al (2009) who reported significantly longer median LOHS for the radiofrequency group (9 days; range, 4-15 days) compared with the crush-clamp group (7 days; range, 4-12 days) (P = 0.04). Also, 25 (23%) and 33 (38%) patients, in each group respectively, were required to stay in the ICU for a day or more (P = 0.15). Ayav et al (2007) reported two patients (6%) in the radiofrequency group were admitted to ICU, compared with 47 patients (92%) in the total vascular occlusion group (P < 0.0001). The median LOHS was also significantly lower in radiofrequency patients compared to total vascular occlusion patients (10 versus 17 days) (P = 0.04).

Studies reporting non-significant differences in LOHS between treatment groups included Di Carlo et al (2010) who reported similar LOHS for both the radiofrequency and crush-clamp groups (median 7 versus 9 days) (P = 0.66). Xia et al (2008) reported comparable LOHS as well (14 days; range, 9-32 days versus 16 days; range, 9-42 days) (P = 0.216). In Hompes et al (2007), both groups required a mean LOHS of 7 days (range, 5-41 days in the radiofrequency-assisted group and 3-18 days in the control group). In Mitsuo et al (2007), patients in the radiofrequency-assisted group required a longer LOHS than those in the control group (mean 17.2 days (SD 15.5 days) versus mean 13.3 days (SD 7.4 days), respectively); however, this did not reach statistical significance.

Liver enzyme levels

Five studies reported changes in liver enzyme levels following hepatic resection (Table 7). Di Carlo et al (2010) reported significantly higher alanine transaminase levels in the crush-clamp group of patients compared with radiofrequency patients at 2 days postoperative (P = 0.01). In the study by Xia et al (2008), median aspartate transaminase levels were also significantly higher in the crush-clamp group compared with the radiofrequency group at 3 and 7 days postoperative, and median bilirubin levels were significantly higher in the crush-clamp group compared with the radiofrequency group at 3 days postoperative.

In contrast, Mitsuo et al (2007) observed a significantly higher concentration of bilirubin in the radiofrequency-assisted group compared with the control group at day 3 postoperative. Mean alanine transaminase levels were also significantly higher in the radiofrequency-assisted group at days 1, 3 and 7.

Overall, most patients, in both treatment groups, experienced a peak in liver enzyme levels in the immediate postoperative period, which generally normalized within one week of the procedure.

Table 7: Transaminase and liver biomarker levels before and after surgery

	ALT (units/L)		AST (units/L)		Bilirubin (µmol/L)		Albumin (g/L)	
Xia et al (2008)[1]	***RF***	***C-C***	***RF***	***C-C***	***RF***	***C-C***	***RF***	***C-C***
Preoperative	NR	NR	61 (12-496)	54 (14-528) (P=0.679)	14 (5-48)	17 (8-54) (P=0.325)	36 (26-51)	34 (24-52) (P=0.358)
3 day postoperative	NR	NR	112 (58-864)	246 (34-1569) (P=0.035)	48 (25-154)	132 (18-434) (P=0.011)	NR	NR
7 day postoperative	NR	NR	32 (15-168)	104 (12-1124) (P=0.003)	NR	NR	NR	NR
Ayav et al (2007)[2]	***RF***	***TVO***	***RF***	***TVO***	***RF***	***TVO***	***RF***	***TVO***
Preoperative	38 ± 24	32 ± 14	33 ± 11	87 ± 20	31 ± 20	31 ± 47	36 ± 3	37 ± 4
1 day postoperative	576 ± 389	686 ± 465	550 ± 381	689 ± 562	38 ± 65	63 ± 65 (P=0.006)	27 ± 10	30 ± 10
7 day postoperative	85 ± 54	148 ± 132	47 ± 24	52 ± 30	36 ± 3	84 ± 95 (P=0.005)	35 ± 10	31 ± 7 (P=0.02)
Mitsuo et al (2007)[3]	***RF***	***Control***	***RF***	***Control***	***RF***	***Control***	***RF***	***Control***
1 day postoperative	1019 ± 968	190 ± 103 (P<0.05)	NR	NR	NR	NR	NR	NR
3 day postoperative	261 ± 130	130 ± 74 (P<0.05)	NR	NR	1.4 ± 0.3	1.0 ± 0.3 (P<0.05)	NR	NR
7 day postoperative	67 ± 27	40 ± 18 (P<0.05)	NR	NR	NR	NR	NR	NR

[1]Data expressed as median (range); [2]Data expressed as mean ± standard deviation; [3]Data expressed as mean ± standard deviation.
ALT: alanine transaminase; AST: aspartate transaminase; RF: radiofrequency-assisted liver resection; C-C: crush-clamp; NR: not reported; TVO: total vascular occlusion.

Additional efficacy outcome: use of the Pringle maneuver

Di Carlo et al (2010) routinely used an intermittent Pringle maneuver in the crush-clamp group of patients plus two patients in the radiofrequency group required the Pringle maneuver for 3 and 6 minutes, respectively. In the study by Xia et al (2008), significantly more patients required the

Pringle maneuver in the crush-clamp group than the radiofrequency group (n=53 (86.9%) versus n=7 (11.5%)) ($P < 0.001$). Finally, Hompes et al (2007) reported the use of the Pringle maneuver in two control group patients for a median duration of 25 minutes (range, 20-30 minutes) and four radiofrequency-assisted patients for a median duration of 15 minutes (range, 7-45 minutes).

Cost impact

Lesurtel et al (2005) presented a cost analysis for four reviewed liver resection techniques, based on 2004 currency values (1 Euro = US$1.3) (Table 8). The cost of each procedure was estimated based on the costs of (1) the device, (2) OR time, (3) additional techniques required to control bleeding and (4) transfused red blood cell units. Device cost was based on capital cost with 5-year depreciation, maintenance (dependent on the number of procedures performed annually) and disposable materials. A cost analysis was performed on the basis of three scenarios according to center volume (10, 50 or 100 liver resections/year). The cost of the OR was 466 Euro per hour (excluding physician fees) and physician fees were calculated based on the type of procedure being performed, not the duration of the procedure.

Table 8: Cost (in Euro) of device and cost per liver resection for each technique

Annual center volume	Equipment cost/case*				Total cost/case (mean ± standard deviation)			
	RF-assisted[1]	Clamp-crush	Ultrasonic dissection[2]	Hydrojet[3]	RF-assisted	Clamp-crush	Ultrasonic dissection	Hydrojet
10	0	0	1471	1233	1618 ± 45*	497 ± 38*	2912 ± 73*	2235 ± 97*
50	0	0	294	246	1618 ± 45	497 ± 38*	1735 ± 73	1248 ± 97*
100	0	0	146	123	1618 ± 45	497 ± 38*	1587 ± 73	1125 ± 97*

[1]Disposable material cost/case of 980 Euro; [2]Disposable material cost/case of 661 Euro; [3]Disposable material cost/case of 191 Euro.

*Significant versus all other techniques (P < 0.001).

RF-assisted: radiofrequency-assisted liver resection; pa: per annum.

The clamp-crush technique was deemed to be the least expensive and appeared to provide significant cost savings regardless of the volume of procedures performed per year. The most expensive procedure employed the ultrasonic dissector.

Clinical practice guidelines and consensus statements

Searches of the United States Department of Health and Human Services National Guideline Clearinghouse retrieved two relevant clinical practice guideline (CPG) documents:

- Bruix J, Sherman M. **Management of hepatocellular carcinoma: an update**. Alexandria (VA): American Association for the Study of Liver Diseases; 2010.

- Brown DB, Bakal CW, Weintraub JL, Bass JC, Dickey KW, Gemery JM, Klyde DP, Millward SF, Patel AA, Salem R, Selby JB Jr, Silberzweig JE, Expert Panel on Interventional Radiology. **Hepatic malignancy**. [Online publication]. Reston (VA): American College of Radiology (ACR); 2007.

The first and most recently updated of these documents aimed to provide a data-supported approach to the diagnosis, staging, and treatment of patients diagnosed with hepatocellular carcinoma and patients at high risk for developing the disease. The treatments considered included surgical resection; liver transplantation, including consideration of living donor and preoperative therapy when wait times are long; local ablation by radiofrequency ablation or alcohol injection and non-curative therapy using transarterial chemoembolization or sorafenib, as indicated. These guidelines did not provide direction regarding the use of radiofrequency-assisted liver resection; instead the authors looked at liver resection as a stand-alone therapy and radiofrequency ablation for non-resectable liver tumors.

Recommendations made in regards to these treatments (as well as liver transplantation) include:

- Patients who have a single lesion can be offered surgical resection if they are non-cirrhotic or have cirrhosis but still have well preserved liver function, normal bilirubin, and hepatic vein pressure gradient > 10 mm Hg.
- Pre- or post-resection adjuvant therapy is not recommended.
- Liver transplantation is an effective option for patients with hepatocellular carcinoma that is: a solitary tumor = 5 cm or up to three nodules = 3 cm. Living donor transplantation can be offered for hepatocellular carcinoma if the waiting time is expected to be so long that there is a high risk of tumor progression leading to exclusion from the waiting list.
- Local ablation is safe and effective therapy for patients who cannot undergo resection, or as a bridge to transplantation.
- Alcohol injection and radiofrequency are equally effective for tumors < 2 cm. However, the necrotic effect of radiofrequency ablation is more predictable in all tumor sizes and in addition; its efficacy is clearly superior to that of alcohol injection in larger tumors.

The second US guideline document aimed to evaluate the appropriateness of interventional radiologic (ablative and endovascular) procedures/treatments for hepatic malignancy in patients with hepatic malignancies including hepatocellular carcinoma, neuroendocrine tumors and colorectal metastases to the liver. Similarly, these guidelines did not provide specific guidance on the use of radiofrequency-assisted liver resection. Recommendations included:

- Liver transplantation is the only cure for hepatocellular carcinoma.
- Patients younger than 65 years with limited tumor burden (described at many centers as a solitary tumor = 5 cm or up to three nodules = 3 cm) should undergo evaluation for transplantation.
- Patients with adequate hepatic reserve may undergo resection if obtaining a margin does not leave too small a remnant.
- Chemotherapy and external beam radiation have traditionally been ineffective in treating these tumors.
- Ablative therapies are effective at treating small hepatocellular carcinomas. Since most patients with hepatocellular carcinoma are poor surgical candidates, this option may not be the most appropriate.

No American CPGs were located regarding the use of radiofrequency-assisted liver resection for malignant or benign hepatic tumors. However, CPGs were issued by the NHS National Institute for Health and Clinical Excellence (NICE) in the United Kingdom in February 2007:

- **Radiofrequency-assisted liver resection**. Interventional procedure guidance 211. National Institute for Health and Clinical Excellence, February 2007; ISBN 1-84629-375-8

The NICE CPGs state that the limited evidence on the safety and efficacy of radiofrequency-assisted liver resection appear adequate in supporting its use as one of the options for liver resection for primary and secondary hepatic cancers provided normal arrangements are in place for consent, audit and clinical governance. The analysis noted that it is unclear from the literature whether radiofrequency-assisted liver resection offers any efficacy advantage compared with other methods of surgical resection. Specialist Advisers stated that potential adverse events associated with the procedure may include inadvertent tumor cell spillage and increased risk of postoperative infection and bile leak. They also noted a risk of injury to major vascular and biliary structures if the procedure was used for centrally located tumors.

Training and education impact

No literature was located regarding the training required to undertake radiofrequency-assisted liver resection. It is expected the procedure should be completed by, or under the guidance of, an experienced hepatobiliary surgeon. Patients and peri-operative staff should be well informed about the procedure including its benefits and risks in comparison with alternatives so informed consent (for patients) and informed care (for staff) can be given.

Summary

The overall quality of the evidence base available for radiofrequency-assisted liver resection was good. Nine studies were eligible for review including three RCTs and six non-randomized comparative studies reporting results for 353 patients undergoing radiofrequency-assisted liver resection, 311 undergoing liver resection using the crush-clamp method, and 25 each undergoing liver resection using the ultrasonic dissector, Hydrojet and 'conventional' methods.

Findings with respect to safety were as follows:

- There were fewer deaths reported in patients receiving radiofrequency-assisted liver resection (n=2) compared with comparator techniques.
- With respect to rates of complications, results among technologies were inconsistent and in none of the included studies were differences statistically significant.
- Radiofrequency-assisted liver resection appeared to be associated with a significantly higher incidence of biliary leak, biliary fistula and infectious complications in some studies.
- One study reported the rate of liver failure to be significantly higher in patients in the crush-clamp group compared with the radiofrequency group.

Efficacy findings were also inconsistent for some outcomes:

- There was a trend for blood loss to be lower in the radiofrequency-assisted group compared with the other techniques but only one study reported a statistically significant difference. One RCT reported significantly less blood loss in the crush-clamp group compared with the radiofrequency, ultrasonic dissector and Hydrojet groups.
- There was a trend towards a reduced need for blood transfusion in patients undergoing radiofrequency-assisted liver resection with three studies (one RCT and two comparative studies) showing statistically significant reductions.
- Transection speed and time were generally longer in the radiofrequency-assisted group, as was operative time. However, LOHS was generally similar between the treatment types.
- Liver enzyme levels peaked and returned to normal levels in the short-term (usually 7 day) postoperative period for all liver resection techniques. Three studies found a significantly lower peak in liver enzymes postoperatively in patients who underwent radiofrequency-assisted liver resection compared with liver resection using conventional techniques.

Recommendation

Radiofrequency-assisted liver resection appears to be a treatment option for patients with resectable liver tumors. However, choice of procedure/technology should be decided on a case-by-case basis considering an individual's disease characteristics and surgeon/patient preferences. CPGs for radiofrequency-assisted liver resection in a United States setting are required to provide guidance to clinicians and institutions offering the procedure. In order to fully understand the effectiveness of radiofrequency-assisted liver resection, in particular with regard to long-term outcomes, additional high-quality studies with longer-term follow-up are needed.

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Appendix A

Studies excluded from this assessment

Burdio et al. A new single-instrument technique for parenchyma division and hemostasis in liver resection: a clinical feasibility study. *Am J Surg* 2010; 200 (6): e75-80.	Case series < 100 patients
Kleinert et al. Radiomorphology of the Habib sealer-induced resection plane during long-time follow up: a longitudinal single center experience after 64 radiofrequency-assisted liver resections. *HPB Surg* 2010; Epub ahead of print Aug 30.	Case series < 100 patients
Sandonato et al. Minor hepatic resection using heat coagulative necrosis. *Am Surg* 2009; 75 (12): 1213-1219.	Case series < 100 patients
Kargozaran et al. Radiofrequency-assisted hepatectomy using bipolar Inline multichannel radiofrequency device (ILMRD): report of initial clinical experience. *Hepatogastroenterology* 2009; 56 (94-95): 1496-1500.	Case series < 100 patients
Stavrou et al. Liver resection using heat coagulative necrosis: indications and limits of new method. *ANZ J Surg* 2009; 79 (9): 624-628.	Case series < 100 patients
Wahman et al. liver resection using a four-prong radiofrequency transection device. *Am Surg* 2009; 75 (10): 991-994.	Case series < 100 patients
Andonian et al. Habib laparoscopic bipolar radiofrequency device: a novel way of creating an avascular resection margin in laparoscopic partial nephrectomy. *J Laparoendosc Adv Surg Tech* 2008; 18 (6): 853-856.	Case series < 100 patients
Curro et al. Radiofrequency-assisted liver resection in patients with hepatocellular carcinoma and cirrhosis: preliminary results. *Transplant Proc* 2008; 40 (10): 3523-3525.	Case series < 100 patients
Jiao et al. Laparoscopic liver resection assisted by the laparoscopic Habib sealer. *Surgery* 2008; 144 (5): 770-774.	Case series < 100 patients
El-Gendi et al. Repeat hepatic resection using a radiofrequency-assisted technique. *Dig Surg* 2008; 25 (4): 293-299.	Case series < 100 patients
Curro et al. Radiofrequency-assisted liver resection in cirrhotic patients with hepatocellular carcinoma. *J Surg Oncol* 2008; 98 (6): 407-410.	Case series < 100 patients
McGahan et al. Imaging findings after liver resection by using radiofrequency parenchymal coagulation devices: initial experiences. *Radiology* 2008; 247 (3): 896-902.	Case series < 100 patients
Ayav et al. Liver resection with a new multiprobe bipolar radiofrequency device. *Arch Surg* 2008; 143 (4): 396-401.	Case series < 100 patients
Delis et al. Radiofrequency-assisted liver resection. *Surg Oncol* 2008; 17 (2): 81-86.	Case series < 100 patients
Delis et al. Current role of bloodless liver resection. *World J Gastroenterol* 2007; 13 (6): 826-829.	Case series < 100 patients
Varshney et al. Pitfalls of radiofrequency assisted liver resection. *Hepatogastroenterology* 2007; 54 (77): 1539-1541.	Case series < 100 patients
Milicevic et al. A radiofrequency-assisted minimal blood loss liver parenchyma dissection technique. *Dig Surg* 2007; 24 (4): 306-313.	Case series < 100 patients
Bachellier et al. Laparoscopic liver resection assisted with radiofrequency. *Am J Surg* 2007; 193 (4): 427-430.	Case series < 100 patients
Zacharoulis et al. Modified radiofrequency-assisted liver resection: a new device. *J Surg Oncol* 2007; 96 (3): 254-257.	Case series < 100 patients
Ferko et al. A modified radiofrequency-assisted approach to right hemihepatectomy. *Eur J Surg Oncol* 2006; 32 (10): 1209-1211.	Case series < 100 patients
Navarra et al. Early results after radiofrequency-assisted live resection. *Tumori*	Case series < 100 patients

2004; 90 (1): 32-35.	
Sakamoto et al. Bloodless liver resection using the monopolar floating ball plus ligasure diathermy: preliminary results of 16 liver resections. *World J Surg* 2004; 28 (2): 166-172.	Case series < 100 patients
Croce et al. Laparoscopic liver resection with radiofrequency. *Hepatogastroenterology* 2003; 50 (54): 2088-2092.	Case series < 100 patients
Stella et al. Radiofrequency-assisted liver resection. *J Gastrointest Surg* 2003; 7 (6): 797-801.	Case series < 100 patients
Sturgeon et al. Early experience employing a linear hepatic parenchyma coagulation device. *J Hepatobiliary Pancreat Surg* 2003; 10 (1): 81-86.	Case series < 100 patients
Weber et al. New technique for liver resection using heat coagulative necrosis. *Ann Surg* 2002; 236 (5): 560-563.	Case series < 100 patients
Dulucq et al. Virtually bloodless laparoscopic liver resection of recurrent hepatoma with a new laparoscopic sealer device: report of our initial laparoscopic experience. *Surg Laparosc Endosc Percutan Tech* 2007; 17 (5): 413-415.	Case report
Jiao et al. Radiofrequency assisted liver resection – a novel technique. *Hepatogastroenterology* 2005; 52 (66): 1685-1687.	Case report

Appendix B

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,5 among consecutive persons with a defined clinical presentation6	A prospective cohort study[7]	A prospective cohort study	A randomized controlled trial
III-1	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation6	All or none[8]	All or none[8]	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Explanatory notes

1. Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

2. The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3. If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilized.

4. A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5. The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6. Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7. At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomized controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

8. All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9. This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C with statistical adjustment for B).

10. Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C but where there is no statistical adjustment for B).

11. Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomized controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.