Quality Improvement Guidelines for Radiofrequency Ablation of Liver Tumours

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Introduction

The development of image-guided percutaneous techniques for local tumour ablation has been one of the major advances in the treatment of liver malignancies. Among these methods, radiofrequency (RF) ablation is currently established as the primary ablative modality at most institutions. RF ablation is accepted as the best therapeutic choice for patients with early-stage hepatocellular carcinoma (HCC) when liver transplantation or surgical resection are not suitable options (1,2). In addition, RF ablation is considered as a viable alternate to surgery for inoperable patients with limited hepatic metastatic disease, especially from colorectal cancer, in patients deemed ineligible for surgical resection, because of extent and location of the disease or concurrent medical conditions (3).
These guidelines are written to be used in quality improvement programs to assess RF ablation of HCC and liver metastases. The most important processes of care are 1) patient selection, 2) performing the procedure, and 3) monitoring the patient. The outcome measures or indicators for these processes are indications, success rates, and complication rates.

Definitions

Ablative margin: the region ablated beyond the borders of the tumour, to achieve complete tumour destruction. It should be ideally 0.5–1.0-cm wide.

Complete ablation: Non-enhancing area at contrast-enhanced imaging modalities, including the tumour and the ablative margin.

Complications: Complications can be stratified on the basis of outcome by using the SIR standard table. *Major* complications result in: admission to a hospital for therapy (for outpatient procedures), an unplanned increase in the level of care, prolonged hospitalization, permanent

adverse sequelae, or death. *Minor* complications result in no sequelae; they may require nominal therapy or a short hospital stay for observation (generally overnight). Major and minor complications and side effects should be reported on the basis of the number of ablation sessions on a per-session basis.

Electrode: RF applicator. One or multiple eletrodes have to be insertered directly into the tumour to deliver RF energy current. Electrodes can be monopolar or bipolar and thay can have different designs (multitined expandable, internally cooled, perfused).

- Monopolar electrode: there is a single active electrode, with current dissipated at one or several return grounding pads.
- Bipolar electrode: there are two active electrode applicators, which have to be placed in proximity
- Multitined expandable electrode: multiple electrode tines that expand from a larger needle cannula.
- Internally cooled electrode: the electrode has an internal lumen which is perfused by saline without coming into direct contact with patient tissues
- Perfused electrode: the tip of the electrode has small apertures that allows the fluid (usually saline) to come in contact with the tissue

Heat sink effect: convective cooling by adjacent blood vessels usually 3 mm or larger when ablated tissues are heated. It can negatively affect the results of RF ablation because it can potentially remove heat before complete tumour ablation is achieved

Hydro/Gas dissection : instillation of liquid (dextrose 5%, sterile water) or gas (air, CO_2) between the area of ablation and the structure vulnerable to heating damage (usually the bowel)

Incomplete ablation: Presence of residual unablated tumour that is seen as peripheral irregular enhancement at imaging. It often grows in scattered, nodular, or eccentric pattern.

Local tumour progression: Appearance at follow-up of foci of untreated disease in tumours that

were previously considered to be completely ablated.

Overall survival: Time from inclusion in the study to death. Patients alive at the end of follow-up are censored.

Radiofrequency Ablation: coagulation induction from all electromagnetic energy sources with frequencies less than 30 MHz. For tumour ablation purposes the frequency is usually in the 375–500 kHz range.

Technical success: The treatment of the tumour was perfomed according to protocol and the complete tumour coverage is assessed, either during or immediately after the procedure.

Transient hyperechoic zone: transient (up to 30–90 minutes) zone of increased echogenicity seen at US within and surrounding a tumour during and immediatelyafter RF ablation

Indications

HCC: RF ablation is the therapy of choice in very early and early HCC according to the Barcelona Clinic Liver Cancer (BCLC) classification (Table 1) when patients are not candidates for either liver resection or transplantation. Patients are required to have a single tumour smaller or as many as three nodules smaller than 3 cm each, no evidence of vascular invasion or extrahepatic spread, performance status test of 0, and liver cirrhosis in Child-Pugh class A or B.

Table 1: BCLC classification in patients diagnosed with HCC

Very Early Stage:	PS 0, Child-Pugh A, single HCC < 2 cm
Early Stage:	PS 0, Child-Pugh A-B, single HCC or 3 nodules < 3 cm
Intermediate Stage:	PS 0, Child-Pugh A-B, multinodular HCC
Advanced Stage:	PS 1-2, Child-Pugh A-B, portal neoplastic invasion, nodal metastases,

	distant metastases
Terminal Stage:	PS>2, Child-Pugh C

PS: performance status

Liver metastases:

- **Primary tumour histotype:** RF ablation is generally indicated for nonsurgical patients with colorectal cancer oligometastases isolated to the liver. Selected patients with limited hepatic and pulmonary colorectal metastatic disease, however, may qualify for percutaneous treatment provided that extrahepatic disease is deemed curable. In patients with hepatic metastases from other primary cancers, promising initial results have been reported in the treatment of breast and endocrine tumours.
- **Number of lesions:** The number of lesions should not be considered an absolute contraindication to RF ablation if successful treatment of all metastatic deposits can be accomplished. Nevertheless, most centres preferentially treat patients with five or fewer lesions.
- **Tumour size:** The target tumour should not exceed 3 cm in longest axis to achieve best rates of complete ablation with most of the currently available devices.

Tumour location:

Pretreatment imaging must carefully define the location of each lesion with respect to surrounding structures:

- Lesions located on the surface of the liver can be considered for RF ablation, although their treatment requires adequate expertise and may be associated with a higher risk of complications.
- Thermal ablation of superficial lesions that are adjacent to any part of the gastrointestinal tract must be avoided because of the risk of thermal injury of the gastric or bowel wall. The colon appears to be at greater risk than the stomach or small bowel for thermally mediated perforation. Gastric complications are rare, most likely owing to the relatively greater wall thickness of the stomach or the rarity of surgical adhesions along the gastrohepatic ligament. The mobility of the small bowel may also provide the bowel with greater protection compared with the

relatively fixed colon. The use of special techniques - such as intraperitoneal injection of dextrose to displace the bowel - can be considered in such instances.
- Treatment of lesions adjacent to the hepatic hilum increases the risk of thermal injury of the biliary tract. This tumour location represents a relative contraindication to RF ablation. In experienced hands, thermal ablation of tumours located in the vicinity of the gall-bladder has been shown to be feasible, although associated in most cases with self-limited iatrogenic cholecystitis.
- Thermal ablation of lesions adjacent to hepatic vessels is possible, since flowing blood usually protects the vascular wall from thermal injury: in these cases, however, the risk of incomplete treatment of the neoplastic tissue close to the vessel may increase because of the heat loss by convection.

Physician Credentialling

Prior to treatment, all patients with liver tumours who are considered for RF ablation should undergo a thorough clinical evaluation by a multidisciplinary team including interventional radiologist, hepatologist, oncologist, surgeon, and anesthesiologist. The body? core of knowledge required for the interventional radiologist includes understanding of liver anatomy, liver tumour diagnosis and radiological and non radiological treatment options .

Imaging guidance/monitoring

Targeting of the lesion can be performed with ultrasound, CT, or MR imaging. The guidance system is chosen largely on the basis of tumour visibility,operator preference and local availability of dedicated equipment such as CT fluoroscopy or open MR systems. The transient hyperechoic zone that is seen at ultrasound within and surrounding a tumour during and immediately after RF ablation can be used as a rough guide to the extent of tumour destruction. It is not sufficient to evaluate treatment effectiveness and follow-up imaging is mandatory. MR is currently the only imaging modality with validated techniques for real-time temperature monitoring.

Anesthesiology care

Thermal ablation is usually performed under intravenous sedation or general anesthesia with standard cardiac, pressure, and oxygen monitoring. In some centres (American spelling- suggest centre if this is a CIRSE doc) general anesthesia is used. (similarly tumour is American spelling- tumour is preferable if this doc is not a combined SIR doc)
American Society of Anesthesiologists (ASA) score (Appendix 1) can be used to assess patient physical status prior to RF ablation. Patients up to ASA III score can be treated.

Post-treatment assessment and follow-up

Contrast-enhanced CT or MR imaging are recognized as the standard modalities to assess treatment outcome. CT and MR images obtained 4-6 weeks after treatment show successful ablation as a nonenhancing area with or without peripheral enhancing rim. The enhancing rim that may be observed along the periphery of the ablation zone appears a relatively concentric, symmetric, and uniform process in an area with smooth inner margins. This is a transient finding that represents a benign physiologic response to thermal injury (initially, reactive hyperemia; subsequently, fibrosis and giant cell reaction). Benign periablational enhancement needs to be differentiated from irregular peripheral enhancement due to residual tumour that occurs at the treatment margin. In contrast to benign periablational enhancement, residual unablated tumour often grows in scattered, nodular, or eccentric patterns. Contrast-enhanced ultrasound can be performed after the end of the procedure and may allow an initial evaluation of treatment effects. Later follow-up imaging studies should be aimed at detecting local tumour progression, the development of new hepatic lesions, or the emergence of extrahepatic disease. A recommended follow-up protocol includes CT or MR examinations at 3-, 6-, 9-, 12 months after the treatment and at 6 months interval thereafter for the subsequent 3 years.

Contraindications

Contraindications for RF ablation are:

1. Tumour located <1cm main biliary duct due to risk of delayed stenosis of the main biliary tract

2. Intrahepatic bile duct dilation
3. Anterior exophytic location of the tumour, due to the risk of tumour seeding
4. Bilioenteric anastomosis
5. Untreatable/unmanageable coagulopathy

Clinical results: Hepatocellular carcinoma

Technique effectiveness:

RF ablation yields satisfactory local tumour control in treating small HCC, with a complete ablation rate on imaging of about 90% in tumours less than 3cm (4-8). Histological data from explanted liver specimens in patients who have undergone RF ablation showed that tumour size and presence of large (3 mm or more) abutting vessels significantly affect local treatment effect. Complete tumour necrosis was pathologically shown in 83% of tumours <3 cm and 88% of tumours in nonperivascular location (9). Comparison with percutaneous ethanol injection (PEI) in five randomized trials (4-8) has shown that RF ablation has a higher local anticancer effect than PEI, leading to better local control of the disease (Table 2). Consequently there is no room per PEI in HCC amenable to RF ablation.

Survival:

Five randomized trials compared RF ablation with PEI for local ablation of early-stage HCC (Table 2). The two European trials failed to show a statistically significant difference in overall survival between patients who received RF ablation and those treated with PEI (4,8) . However, survival advantages were identified in three Asian studies (5-7). These data were recently pooled in two independent meta-analysis and the survival benefit of patients with small HCC submitted to RF ablation was confirmed (10,11). Therefore, RF ablation is the preferred percutaneous treatment for patients with early-stage HCC on the basis of a more consistent local tumour control and better survival outcomes.

Recently, the long-term survival outcomes of RF ablation-treated patients were reported (Table 3) (12-17). In patients who underwent RF ablation, survival depended on the severity of the underlying cirrhosis and the tumour stage. Patients in Child class A with early stage HCC had a 5-

year survival rate of 61-77%; in patients with single tumour ≤ 2 cm 5-years survival rate was 68% .

Table 2. Randomized studies comparing RF ablation and PEI in the treatment of early-stage HCC

Author	No. of patients	Tumour size	Complete ablation (%)	Treatment failure (%) *	3-yrs overall survival	p
Lencioni et al (4) RF PEI	52 50	1 HCC<5cm or 3 < 3 cm	91 82	8 34	81 73	>0.05
Lin et al (5) RF PEI	52 52	1-3 HCC <4 cm	96 88	17 45	74 50	0.014
Shiina et al (6) RF PEI	118 114	1-3 HCC <3 cm	100 100	2 11	80 63	0.02
Lin et al (7) RF PEI	62 62	1-3 HCC <3 cm	97 89	16 42	74 51	0.031
Brunello et al (8) RF PEI	70 69	1-3 HCC <3 cm	96 66	34 64	59 57	>0.05

* Includes initial treatment failure (incomplete response) and late treatment failure (local recurrence/progression)

Table 3. Studies reporting long-term survival outcomes of patients with early-stage HCC who underwent percutaneous RF ablation

Author	No. of patients	Survival (%)	
		1 year 5 years	3 years

Lencioni et al (12)				
Child A, 1 HCC < 5 cm or 3 < 3 cm	144	100	76	51
1 HCC < 5 cm	116	100	89	61
Child B, 1 HCC < 5 cm or 3 < 3 cm	43	89	46	31
Tateishi et al (13)				
Naive patients *	319	95	78	54
Nonnaive patients **	345	92	62	38
Cabassa et al (14)	59	94	65	43
Choi et al (15)				
Child A, 1 HCC < 5 cm or 3 < 3 cm	359	NA	78	64
Child B, 1 HCC < 5 cm or 3 < 3 cm	160	NA	49	38
Takahashi et al (16)				
Child A, 1 HCC < 5 cm or 3 < 3 cm	171	99	91	77
Hiraoka et al (17)				
Child-Pugh A-B	105	NA	88	59

* Patients who received radiofrequency ablation as primary treatment

** Patients who received radiofrequency ablation for recurrent tumour after previous treatment including resection, ethanol injection, microwave ablation, and transarterial embolization

NA not available

Clinical results: Colorectal Cancer Liver metastases

Technique effectiveness:

Many studies have investigated the use of RF ablation in the treatment of limited colorectal cancer hepatic metastatic disease in patients who were excluded from surgery. Two early studies reported rates of complete response that did not exceed 60% to 70% (18,19). Subsequently, owing to the advances in RF technique and probably to the treatment of smaller tumours, reported rates of successful local tumour control following RF treatment substantially increased.

In two series, RF ablation allowed eradication of 91% of 100 metastases and 97% of 74 metastases, respectively (20,21).

Survival:

Recently, data on long-term survival of nonsurgical patients with hepatic colorectal metastases who underwent RF ablation have been reported (Table 4) (22-28). In particular, in three series including patients with 5 or fewer lesions, each 5 cm or less in diameter, the 5-year survival rate ranged 24–44% at 5 years (22,23,26). When RF ablation was performed in patients with small (<4 cm), solitary hepatic colorectal metastases, 40% 5-year survival rate was demonstrated (29). These figures are substantially higher than those obtained with any chemotherapy regimens and provide indirect evidence that RF ablation therapy improves survival in patients with limited hepatic metastatic disease. This conclusion is supported by the interim analysis of a randomized controlled trial comparing chemotherapy plus RF ablation vs. chemotherapy alone in colorectal cancer metastatic to the liver (34).

Table 4. Studies reporting long-term survival outcomes of patients with colorectal hepatic metastases who underwent percutaneous RF ablation

Author	No. of patients	Survival (%)		
		1 year	3 years	5 years
Solbiati et al (22)	117	93	46	-
Lencioni et al (23)	423	86	47	24
Gillams et al (24)	73	91	28	25
Machi et al (25)	100	90	42	30
Jackobs et al (26)	68	96	68	-
Sorensen et al (27)	102	87	46	26[a]
Veltri et al (28)	122	79	38	22

NA, not available

[a]4-year survival

Complications

Early major complications associated with RFA occur in 2.2-3.1% of patients and include intraperitoneal bleeding, liver abscess, intestinal perforation, pneumo/haemothorax and bile duct stenosis and tumour seeding (0.5%); the procedure mortality rate is 0.1-0.5% (Table 5). The minor complication rate ranges from 5% to 8.9%. The most common causes of death were sepsis, hepatic failure, colon perforation, and portal vein thrombosis, while the most common complications were intraperitoneal bleeding, hepatic abscess, bile duct injury, hepatic decompensation, and grounding pad burns. Minor complications and side effects were usually transient and self-limiting (31-33). An uncommon late complication of RF ablation can be tumour seeding along the needle track. In patients with HCC, tumour seeding occurred in 8 (0.5%) of 1610 cases in a multicentre survey (31) and in 1 (0.5%) of 187 cases in a single-institution series (12). Lesions with subcapsular location and an invasive tumoural pattern, as shown by a poor differentiation degree, seem to be at higher risk for such a complication (39).

Table 5: Reported and acceptable rate of major complications

Specific Major Complications per session	Reported Rate	Suggested Threshold
HEMORRHAGE REQUIRING TRANSFUSION	1%	2%
BOWEL PERFORATION	0.3%	0.6%
ABSCESS	0.3%	0.6%
HEMOTHORAX	0.1%	0.2%
TUMOUR SEEDING	0.5%	1%
HEPATIC DECOMPENSATION	0.3%	0.6%
BILE DUCTS INJURY	0.1%	0.2%

GROUNDING PAD BURNS	0.1%	0.2%
DEATH	0.5%	1%

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Appendix A

American Society of Anesthesiologists (ASA) physical status classification system

I: A normal healthy patient
II: A patient with mild systemic disease
III: A patient with severe systemic disease
IV: A patient with severe systemic disease that is a constant threat to life
V: A moribund patient who is not expected to survive without the operation
VI: A declared brain-dead patient whose organs are being removed for donor purposes