REVIEWS

Radiofrequency ablation of liver tumors (II): clinical application and outcomes

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Summary. *Radiofrequency ablation is one of the alternatives in the management of liver tumors, especially in patients who are not candidates for surgery. The aim of this article is to review applicability of radiofrequency ablation achieving complete tumor destruction, utility of imaging techniques for patients' follow-up, indications for local ablative procedures, procedure-associated morbidity and mortality, and long-term results in patients with different tumors. The success of local thermal ablation consists in creating adequate volumes of tissue destruction with adequate "clear margin," depending on improved delivery of radiofrequency energy and modulated tissue biophysiology. Different volumes of coagulation necrosis are achieved applying different types of electrodes, pulsing energy sources, utilizing sophisticated ablation schemes. Some additional methods are used to increase the overall deposition of energy through alterations in tissue electrical conductivity, to improve heat retention within the tissue, and to modulate tolerance of tumor tissue to hyperthermia. Contrast-enhanced computed tomography, magnetic resonance imaging, ultrasound or positron emission tomography are applied to control the effectiveness of radiofrequency ablation. The long-term results of radiofrequency ablation are controversial.*

Open surgery is the gold standard for the treatment of hepatocellular carcinoma (HCC) and liver metastases of colorectal cancer (1). However, the great majority of patients with liver tumors present with unresectable disease. Radiofrequency ablation (RFA) is one of the options for the treatment of otherwise unresectable hepatic tumors (2). Outcome following RFA is difficult to interpret since most studies report recurrence per lesion rather than per patient and outcomes in patients with mixed tumor types using different techniques (3). Although the optimal use of radiofrequency ablation remains to be determined, the importance of fundamental understanding of the basic mechanisms, practical strategies, and current technologic limitations cannot be overstressed. Thorough understanding of the underlying processes is essential to achieve successful ablation in clinical practice (4). The aim of this article is to review methods to achieve complete tumor area destruction, imaging techniques for patients' follow-up, indications for ablative procedures, procedure-associated morbidity and mortality, and survival rates.

The success of local thermal ablation consists in creating adequate volumes of tissue destruction. The main aim of thermal tumor ablation therapy is to destroy the entire tumor mass without damaging adjacent vital structures. An essential objective is to achieve and maintain cytotoxic (50–100°C) temperature throughout the entire target volume for at least 4–6 minutes (5). However, the relatively slow thermal conduction from the electrode surface through the tissues increases the duration of application to 10–30 minutes. An additional margin of 0.5–1 cm ("surgical margin") of apparently normal tissue adjacent to the tumor should preferentially be ablated to eliminate microscopic foci of disease. It may be achieved improving the delivery of RF energy, modulating tissue biophysiology, and using a combined therapy. Historically, the first RFA electrodes were monopolar and enabled induction of areas of coagulative necrosis as large as 1.6 cm in diameter (6). With the enlargement of the active electrode, the coagulation zone appeared to be sausage-shaped and did not approximate with the spherical geometry of the majority of tumors. Several technologies were developed in attempt to improve the tissue energy interactions targeting to increase the area of induced coagulation. The development of umbrella electrodes

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with multiple hooked arrays, or tines, enabled the creation of larger zones of coagulation. Hooked electrodes enabled to achieve tissue coagulation up to 3–5 cm in diameter. Bipolar systems were noted to induce the coagulation zone as large as 3.5 cm in diameter (7). Introduction of internally cooled electrodes increased coagulation area when compared with conventional RF electrodes. In the proximity of internally cooled electrode, tissue hyperthermia is reduced, allowing for the improved current deposition without tissue carbonization or increase in impedance. In clinical practice with liver metastases, Solbiati et al. (8) noted a coagulation diameter of 2.8±0.4 cm. Larger volume of coagulation necrosis is achieved by simultaneous application of RF current to a cluster of three closely spaced (0.5–1 cm) internally cooled electrodes (9). Pulsing energy, combining high- and low-energy deposition periods, was also used with RF generators. Preferential tissue cooling occurs adjacent to the electrode during periods of low-energy deposition without a significant decrease of temperature in more distant tissues. An automated algorithm for pulsed, high-power percutaneous RF ablation optimized by Goldberg et al. produced 3.7 cm of necrosis in the liver in vivo and 6.5 cm in muscle in vivo (10).

The ability to create hyperthermia in large tissue volumes in different environments depends on several factors encompassing both heat delivery and local physiologic tissue characteristics. The relationships between these above-mentioned parameters were described by Pennes as the bio-heat equation (11). This equation was further simplified by Goldberg et al. (12). It describes relationship, guiding thermal ablation-induced coagulation necrosis, as follows:

Coagulation necrosis = energy deposited ×
× local tissue interactions – heat loss.

Therefore, effective ablation can be achieved by optimizing heat production and minimizing heat loss within the area to be ablated. Taking this equation into account, the efficacy of RF ablation was optimized modulating tissue-energy interactions, such as energy deposition and blood flow. Attempting to improve tumor ablation, some adjuvant ablative therapies were created modifying the underlying tumor physiologic characteristics. Based on the bio-heat equation, these adjuvant therapies were classified as (a) strategies to increase the overall deposition of energy through alterations in tissue electrical conductivity, (b) strategies to improve heat retention within the tissue, and (c) strategies to modulate tolerance of tumor tissue to hyperthermia (12). The power deposition is highly dependent on local electrical conductivity. Increase in ablative effect is achieved using saline solutions to alter physiologic characteristics and biologic environment of the liver tissue and to improve the tissue electric conductivity (13). Goldberg et al. obtained the maximum hyperthermia 20 mm from the electrode (102.9±4.3°C) and an increased coagulation area (7.1±1.1 cm) with injection of 6 mL of 38.5% NaCl solution prior to RF deposition (14). Schmidt et al. reported that the size of the induced lesion correlates well with the injected volume of saline, increased power delivery, and duration of the procedure. The most homogeneous and spherical lesions were observed when power settings of 40 to 60 W and saline solution flow rate of 90 to 120 mL/h were used with the maximum energy deposition of 120–190 kJ (15, 16). Miao et al. (17) infused 1 mL/min of 5% hypertonic saline solution in ex vivo liver for 12 min during RF application and achieved coagulation volume measuring 5.5 cm in diameter. Significantly larger necrosis zones were produced increasing the saline perfusion rate – doubling of the perfusion rate makes it possible to reach high temperatures (>60°C) within significantly shorter time. Increased concentration of NaCl solution, however, does not translate directly to significantly larger coagulation volumes (18). The advantages of both internally cooled and saline-enhanced electrodes were used creating the cooled-wet electrode. It contains two coaxial lumina that enable the circulation of cooling water through the electrode and a separate channel for interstitial saline infusion. Ablation volume achieved with this device appeared to be larger than that reported up to now with other monopolar electrodes (19).

The heat retention may be improved by modifying hepatic blood flow. The blood flow reduces the extent of thermally induced coagulation, as the perfusion-mediated "heat-sink" phenomenon prevents achievement of the cytotoxic temperature (50–55°C). Coagulation in vivo is often shaped by vasculature in the vicinity of the ablation region. Specifically, Hansen et al. (20) have shown that vessels larger than 3 mm in diameter prevent complete ablation of liver tissue. Furthermore, experiments in which hepatic perfusion is altered by pharmacological or mechanical tools show that blood flow is essentially responsible for the reduction of coagulation volume. There were several strategies proposed to reduce blood flow during ablative procedures. Total portal inflow occlusion (Pringle maneuver) may be used at open

and laparoscopic procedures and may be safely applied to a noncirrhotic liver for up to 1 hour. Some reports have shown the enlarged extent of radiofrequency coagulation with Pringle maneuver vs. no inflow occlusion (21). Angiographic balloon occlusion has been proposed to occlude inflow via the hepatic artery. Due to the dual hepatic blood supply, isolated hepatic arterial inflow occlusion seems inadequate though. Embolization of sinusoids with an absorbable gelatin sponge or Lipiodol may overcome this limitation (22). Pharmacologic modulation of blood flow, antiangiogenesis therapy were discussed; however, they should be currently considered experimental (23). Goldberg et al. have combined ethanol injection into the tumor site prior to RF ablation achieving almost 60% enlargement of coagulation diameter (24).

Increased tumor destruction has been observed combining RF ablation with systemic or local chemotherapy. Combination of intratumoral injection of free doxorubicin with RFA has been shown to be superior to RF ablation alone or doxorubicin alone. Even better results have been obtained by administering intravenously liposomal doxorubicin 24 hours prior to ablation procedure (25). The possible synergistic effect of these two therapies includes increased agent deposition secondary to vascular permeability changes in viable tumor tissue exposed to sublethal thermal doses and separate cytotoxic activity of both agent components (i.e. lipid vehicle and chemotherapy agent).

The important difference between surgical resection and RF ablation of hepatic tumors is the possibility to achieve documented free resection margins, i.e. to complete the R0 resection. There is a general agreement that R0 resection is mandatory to achieve long-term and disease-free survival. Majority of authors suggest the extent of free resection margin to be not less than 1 cm (26, 27). With RF ablation, it is not always possible to adhere to these principles though. Consequently, this failure results in an unacceptably high rate of local tumor recurrence. Taking into account the local format of RF lesion, 360˚ 1-cm-thick tumor-free margins should be achieved around the whole tumor site, translating into increased diameter of the ablated zone by 2 cm (28). Regular RF devices produce thermal injury that hardly exceeds 3–3.5 cm in diameter, indicating that only 1–1.5-cm tumors are available for destruction with a single RF application. Three different ablation strategies have been proposed to enhance ablation volumes. Six- (Fig.) and fourteen-ablation schemes are six or
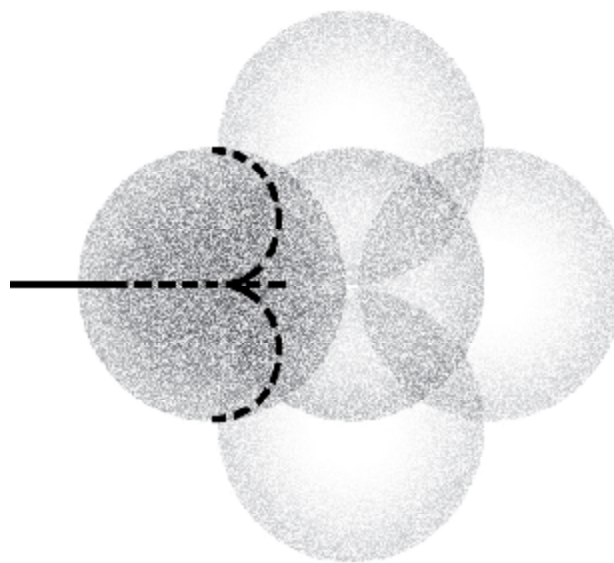

Fig. A six-ablation scheme. Six perfectly placed ablations (four along the *x-y* plane, two along the *z* plane) will yield a composite thermal sphere (After Gerald D. Dodd III)

fourteen perfectly placed 3-cm-diameter ablation zones that yield composite spheres of 3.75 cm and 5 cm in diameter (i.e. complete destruction of 1.75-cm- or 3-cm-diameter tumors).

Unfortunately, 14-ablation scheme is inoperable in a clinical setting. A feasible alternative is to create thermal cylinders, where hyperthermic spheres are overlapping to create a cylinder, and cylinders are overlapping to totally ablate the target volume. This model is geometrically less efficient when compared with the 14-ablation scheme; yet, it might be implemented with success (4, 28).

Accurate imaging techniques are needed to achieve complete tumor destruction and to institute competent patients' follow-up. As microcirculation is an excellent marker of tissue viability, imaging techniques targeted to identify microcirculation may be of service. Contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US) are generally applied (29). Multiphase helical CT plays a central role in the assessment of therapeutic response allowing confident discrimination between nonviable and viable (residual) tumor tissue. Coagulation necrosis appears as a homogeneously hypoattenuating area with well-defined borders. Lack of enhancement throughout the entire lesion volume is considered the hallmark of a complete response. The hypointense regions with loss of gadolinium enhancement in dynamic postcontrast MRI studies are considered characteristic markers of coagulation necrosis, whereas viable tumor tissue appears as areas

with the same signal intensity as on pretreatment T2-weighted spin-echo images (4). Heat-sensitive sequences of MRI are helpful assessing real time coagulation volume during energy application procedure. The microbubble contrast-enhanced wideband harmonic gray-scale US has been reported to reveal blood flow in residual tumors with an accuracy comparable to that of helical CT (30). Employment of contrast-enhanced US during the RF ablation session allows for detection of viable tissue and complementary targeted ablation therapies. Experimental and clinical data suggest high congruence of data acquired with contrast enhanced US, CT, and MRI, with the difference confined to 2–3 mm, i.e. the current degree of image resolution (31). As per protocol, CT and/or MR should be performed 1–2 weeks before RFA to compare with the postablation images done within 1 week after. The latter allows for detection of residual tumor tissue requiring immediate re-ablation (4). At CT evaluation within the first few days postablation, a hyperattenuating rim around the destruction site is often visible on CT scan, reflecting postinterventional hyperemia or tissue regeneration (32). The local hyperemia is determined by temporary outflow obstruction. Tissue regeneration in the periphery of the ablated zone results in a persistently increased contrast uptake for a longer period of time (12). This halo of contrast enhancement on CT scan regresses during the first month after ablation procedure, whereas it can persist for several months on MR images. Hepatocellular carcinomas and metastases from neuroendocrine tumors in the liver present an early contrast enhancement rim in the arterial phase of investigation (33). In these cases, the differentiation of arterial hyperemia from residual tumor will be troublesome. Some authors, therefore, recommend waiting to perform follow-up procedures after 6–12 weeks to avoid this physiologic contrast enhancement (34). On the other hand, hepatic metastases from the gastrointestinal tract are imaged as hypodense (CT), hypointense (MR), or hypoechoic (US) lesions surrounded by contrast-enhanced liver tissue. Consequently, this hyperattenuating rim does not compromise image assessment and is not mistaken for residual tumor. The functional imaging with fluorine-18-labeled deoxyglucose at positron emission tomography (18 F-FDG PET) has been shown to be advantageous detecting residual tumor after RF ablation (32). Based on the homogeneous glucose utilization in normal liver parenchyma, residual tumor becomes detectable as a hot spot or rim-like increase in glucose metabolism in the periphery of the ablative site. The additional CT component of combined PET/CT en-

sures the accurate localization of the residual tumor site. Thus, even on 18 F-FDG PET, the differentiation of local tissue regeneration from residual tumor may be difficult since both go along with increased glucose metabolism. Tissue regeneration typically requires several days to develop; therefore, 18 F-FDG PET performed immediately after the ablation procedure may be expected to specifically reveal residual tumor.

The indications for RFA are well described in the literature. RFA is indicated for the *patients with unresectable tumors* – multifocal disease, poor liver function, proximity of the tumor to major intrahepatic vessels leading to margin-positive resection. RFA is also indicated for *large tumors*. Multiple procedures with overlapping hyperthermic zones may produce satisfactory results. Patients with *tumors in complicated anatomical location*, including subcapsular, perivascular tumors and those located in the hilum of the liver, are also candidates for RFA. In resent years, RFA is increasingly used as an alternative to surgery *in recurrent hepatic tumors*. Regarding the hemostatic effect, RFA is indicated *for acute management of ruptured HCC*. In this particular situation, complete hemostasis and tumor ablation may be achieved. RFA is also applicable in patients with *liver metastases from noncolorectal cancer,* including metastases from breast, adrenocortical cancer, neuroendocrine and carcinoid tumors (2).

RFA-associated mortality and morbidity were analyzed by several groups and were reported to occur in 0.5–1.4% and 5.7–12.0% of cases, respectively (35, 36). Deaths occurred as a sequel of intra-abdominal sepsis, intraperitoneal bleeding, liver failure, cardiac complications, bile duct stricture-associated complications (37). The RFA-associated morbidity is usually subdivided into major and minor complications. The former occur in up to 6% of cases and are described as abdominal bleeding, intra-abdominal sepsis, liver abscess, bile duct injury, liver failure, cardiac and pulmonary complications, skin burn at the ground pad site, hepatic vascular damage, portal vein thrombosis, visceral damage, myoglobinemia or myoglobinuria, renal failure, tumor seeding along the needle-track, coagulopathy, and hormonal complications (35, 37). The morbidity rate is rather low after percutaneous, laparoscopic, or open procedures; however, it was substantially higher (31.8%) when patients were treated by open RFA combined with cryotherapy, hepatic or extrahepatic resection (37). The major risk factors for post-RFA morbidity are impaired liver function, liver cirrhosis, subcapsular or central tumor location (38). RFA in subcapsular tumors may result in intraperitoneal bleeding or damage of neighboring

organs, whereas central tumors are risky for damaging bile ducts and intrahepatic blood vessels. Poon et al. (36) revealed other four variables – *hyperbilirubinemia* (>20 *μ*mol/L), *multiple tumor nodules*, *surgical approach of ablation*, and *early experience* (<50 cases) – as the significant risk factors for treatment-associated morbidity. Hyperbilirubinemia and early experience were identified as the independent risk factors by multivariate analysis.

The long-term results of RFA for liver metastases are controversial. According to the literature, median survival in patients with colorectal liver metastases treated with RFA varies from 27 to 37 months (Table 1). One-, two-, and three-year survival rates are in the range of 90–93%, 60–69%, and 34–68%, respectively. Moreover, survival has been shown to be not signifi-

cantly related to number of metastases treated (39). Elias et al. (40) have reported superior local recurrence rate (5.7%) after RFA procedures when compared with anatomical (12.5%) and wedge resections (12.5%) in 88 patients with liver metastases. Similar survival rates following RFA or liver resection (median survival, 41% vs. 37%; 3-year survival, 55.4% vs. 52.6%) were reported in another study (41). On the contrary Abdalla et al. (3) has shown that RFA is associated with higher recurrence rates and decreased survival when compared to liver resection. Rate of true local (9% vs. 2%) and liver-only recurrence rates (44% vs. 11%) favored liver resection. The 3- and 4-year overall survival rates were also worse in RFA patients (37% vs. 73% and 22% vs. 65%, respectively).

Table 1. Characteristics and long-term results of patients with only nonresectable colorectal liver metastasis treated by radiofrequency ablation

Authors	No. of patients	Tumor size (range), cm	Mean F/U, months	Median survival time, months	Relapse, %	Survival rates, %
Gillams and Lees, 2000 (42)	69	3.9 (1–8)	–	27	–	1-year SR, 90 2-year SR, 60 3-year SR, 34 4-year SR, 22
Solbiati et al., 2001 (43)	117	(0.9–9.9)	7.9	36	39	1-year SR, 93 2-year SR, 69 3-year SR, 46 Tumor-free SR, 66
Oshowo et al., 2003 (41)	25	3 (1–10)	–	37	–	3-year SR, 52.6
Lencioni et al., 2004 (44)	423	–	–	–	–	3-year SR, 47 5-year SR, 24
Gillams and Lees, 2004 (45)	167	3.9 (1–12)	17	33	–	5-year SR, 30
Jacobs et al., 2006 (46)	68	2.3 (0.5–5.0)	21	–	–	38-month SR, 68

F/U, follow-up; SR, survival rate.

In patients with HCC, the 1-, 2-, 3-, and 5-year survival rates are 95%, 90%, 75%, and 59%, respectively. The independent predictors of survival are serum albumin level (risk ratio, 3.216; 95% CI, 1.407–7.353; *P*=0.0056) and initial treatment response (risk ratio, 2.474; 95% CI, 1.076–5.692; *P*=0.0330) (47). The long-term results in HCC patients are also controversial in different studies. Some authors have observed no difference between RFA and liver resection. The 1-, 2-, 3-, and 4-year overall survival rates after RFA and surgery were 95.8%, 82.1%, 71.4%, 67.9% and 93.3%, 82.3%, 73.4%, 64.0%, respectively. The corresponding disease-free survival rates were not different also (85.9%, 69.3%, 64.1%, 46.4% and 86.6%, 76.8%, 69%, 51.6%, respectively) (48).

Conversely Wakai et al. (49) have shown that hepatectomy provided both better local control and long-term survival when compared with RFA (median survival, 122 vs. 66 months; *P*=0.0123). The Cox proportional hazards regression model revealed that hepatectomy and tumor diameter (≤2 cm) was independently associated with better survival (Table 2).

Thermal ablative therapies have demonstrated some benefits in management of liver tumors, especially in patients who are not candidates for surgery. The overall results to date are promising with high success rates, at least in some reports. However, we need to admit that comparison of RFA and surgical treatment groups in a prospective randomized trial is hardly feasible in terms of inability of the former to

Table 2. Characteristics and long-term results of patients with hepatocellular carcinoma treated by radiofrequency ablation

Study	No. of patients	Mean F/U, months	Relapse, %	Survival rate, %
Curley et al., 2000 (50)	110	19	45.5	2-year SR, 71.8
Nicoli et al., 2000 (51)	47	11.8	–	2-year SR, 83
Buscarini et al., 2001 (52)	39 49	34	29 14	5-year SR, 33
Guglielmi et al., 2003 (53)	53	18	28.3	2-year SR, 63 3-year SR, 45
Giovannini et al., 2003 (54)	56	14	17.8	1-year SR, 96.2 2-year SR, 94.2
Vivarelli et al., 2004 (55)	79	15.6	48.1	1-year SR, 78 3-year SR, 33
Wakai et al., 2006 (49)	21	69	33	Median survival time, 66 months
Chen et al., 2006 (48)	71	27.9	–	1-year SR, 95.8 2-year SR, 82.1 3-year SR, 71.4 4-year SR, 67.9
Morimoto et al., 2007 (47)	110	34	53	1-year SR, 95 2-year SR, 90 3-year SR, 75 5-year SR, 59

F/U, follow-up; SR, survival rate.

produce comparable results in small patient series. On the other hand, available scarce clinical data are being biased by patient selection and the nonhomogeneity of the patient groups under comparison. Further investigation of the mechanisms of local thermal destruction in pursuit of enlargement of the ablation volume may lead toward more successful application of RF ablation techniques in clinical practice.

Kepenų navikų radiodažninė abliacija (II). Klinikinis pritaikymas ir rezultatai

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Raktažodžiai: radiodažninė abliacija, kepenų navikas, rezultatai.

Santrauka. Rezekcinės operacijos išlieka kepenų navikų gydymo „auksiniu standartu". Viena iš alternatyvų, apibrėžtų griežtomis indikacijomis, yra radiodažninė abliacija. Šis metodas dažniausiai naudojamas pacientams, kuriems rezekcinės operacijos negalimos. Šio straipsnio tikslas – apibendrinti naviko destrukcijos padidinimo, efektyvumo kontrolės būdus, metodo indikacijas, sergamumą, mirtingumą ir išgyvenamumą. Lokalios abliacijos sėkmė priklauso nuo to, ar sukuriamas pakankamas destrukcijos plotas su pakankamu „chirurginiu kraštu". Tą galima pasiekti pagerinus energijos perdavimą, keičiant audinio biofiziologiją, derinant radiodažninę abliaciją su kitais gydymo būdais. Didesni destrukcijos tūriai gaunami naudojant įvairių tipų elektrodus, kintamą energiją, šešių arba keturiolikos abliacijų schemas. Taip pat naudojami tam tikri pagalbiniai metodai: a) sukauptos energijos bendro kiekio padidinimas, keičiant audinio elektrinį laidumą; b) energijos praradimo audinyje sumažinimas; c) šiluminio atsparumo sumažinimas. Tam tikru laiku atliekama kompiuterinė tomografija su intraveniniu kontrastavimu, branduolinio magnetinio rezonanso ir ultragarsinis tyrimai, funkcinis vaizdavimas pozitronų emisijos tomografijoje su 18-fluorinu žymėta deoksigliukoze, kurie naudojami radiodažninės abliacijos efektyvumo kontrolei. Kepenų navikų radiodažninės abliacijos rezultatai yra labai kontraversiški, tačiau dauguma studijų patvirtina, kad šis metodas susijęs su didesniu atkryčio ir blogesniu išgyvenamumo dažniu nei kepenų rezekcinės operacijos.

References

1. Hansler J, Wissniowski TT, Schuppan D, Witte A, Bernatik T, Hahn EG, et al. Activation and dramatically increased cytolytic activity of tumor specific T lymphocytes after radio-frequency ablation in patients with hepatocellular carcinoma and colorectal liver metastases. World J Gastroenterol 2006;12(23):3716-21.

2. Ng KK, Poon RT. Radiofrequency ablation for malignant liver tumor. Surg Oncol 2005;14(1):41-52.

3. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004; 239(6):818-25.

4. Rhim H, Goldberg SN, Dodd GD, Solbiati L, Lim HK, Tonolini M, et al. Essential techniques for successful radiofrequency thermal ablation of malignant hepatic tumors. Radiographics 2001;21:S17-S35.

5. Goldberg SN, Solbiati L, Halpern EF, Gazelle GS. Variables affecting proper system grounding for radiofrequency ablation in an animal model. J Vasc Interv Radiol 2000;11(8): 1069-75.

6. Goldberg SN, Gazelle GS, Dawson SL, Rittman WJ, Mueller PR, Rosenthal DI. Tissue ablation with radiofrequency: effect of probe size, gauge, duration, and temperature on lesion volume. Acad Radiol 1995;2(5):399-404.

7. McGahan JP, Gu WZ, Brock JM, Tesluk H, Jones CD. Hepatic ablation using bipolar radiofrequency electrocautery. Acad Radiol 1996;3(5):418-22.

8. Solbiati L, Goldberg SN, Ierace T, Livraghi T, Meloni F, Dellanoce M, et al. Hepatic metastases: percutaneous radiofrequency ablation with cooled-tip electrodes. Radiology 1997;205(2):367-73.

9. Goldberg SN, Solbiati L, Hahn PF, Cosman E, Conrad JE, Fogle R, et al. Large-volume tissue ablation with radio frequency by using a clustered, internally cooled electrode technique: laboratory and clinical experience in liver metastases. Radiology 1998;209(2):371-9.

10. Goldberg SN, Stein MC, Gazelle GS, Sheiman RG, Kruskal JB, Clouse ME. Percutaneous radiofrequency tissue ablation: optimization of pulsed-radiofrequency technique to increase coagulation necrosis. J Vasc Interv Radiol 1999;10(7):907-16.

11. Ahmed M, Goldberg SN. Thermal ablation therapy for hepatocellular carcinoma. J Vasc Interv Radiol 2002;13 (9 Pt2):S231-44.

12. Goldberg SN, Gazelle GS, Mueller PR. Thermal ablation therapy for focal malignancy: a unified approach to underlying principles, techniques, and diagnostic imaging guidance. AJR Am J Roentgenol 2000;174(2):323-31.

13. Barauskas R, Gulbinas A, Barauskas G. Finite element modeling and experimental investigation of infiltration of sodium chloride solution into nonviable liver tissue. Medicina (Kaunas) 2007;43(5):399-411.

14. Goldberg SN, Ahmed M, Gazelle GS, Kruskal JB, Huertas JC, Halpern EF, et al. Radio-frequency thermal ablation with NaCl solution injection: effect of electrical conductivity on tissue heating and coagulation-phantom and porcine liver study. Radiology 2001;219(1):157-65.

15. Schmidt D, Trubenbach J, Brieger J, Koenig C, Putzhammer H, Duda SH, et al. Automated saline-enhanced radiofrequency thermal ablation: initial results in ex vivo bovine livers. AJR Am J Roentgenol 2003;180(1):163-5.

16. Barauskas R, Gulbinas A, Barauskas G. Investigation of radiofrequency ablation process in liver tissue by finite element modeling and experiment. Medicina (Kaunas) 2007; 43(4):310-25.

17. Miao Y, Ni Y, Mulier S, Wang K, Hoey MF, Mulier P, et al. Ex vivo experiment on radiofrequency liver ablation with saline infusion through a screw-tip cannulated electrode. J Surg Res 1997;71(1):19-24.

18. Frieser M, Haensler J, Schaber S, Peters A, Mohelsky E, Bernatik T, et al. Radiofrequency ablation of liver tumors: how to enlarge the necrotic zones? Eur Surg Res 2004;36(6): 357-61.

19. Ni Y, Miao Y, Mulier S, Yu J, Baert AL, Marchal G. A novel "cooled-wet" electrode for radiofrequency ablation. Eur Radiol 2000;10(5):852-4.

20. Hansen PD, Rogers S, Corless CL, Swanstrom LL, Siperstien AE. Radiofrequency ablation lesions in a pig liver model. J Surg Res 1999;87(1):114-21.

21. Goldberg SN, Hahn PF, Tanabe KK, Mueller PR, Schima W, Athanasoulis CA, et al. Percutaneous radiofrequency tissue ablation: does perfusion-mediated tissue cooling limit coagulation necrosis? J Vasc Interv Radiol 1998;9(1 Pt 1):101-11.

22. Rossi S, Garbagnati F, Lencioni R, Allgaier HP, Marchiano A, Fornari F, et al. Percutaneous radio-frequency thermal ablation of nonresectable hepatocellular carcinoma after occlusion of tumor blood supply. Radiology 2000;217(1): 119-26.

23. Goldberg SN, Hahn PF, Halpern EF, Fogle RM, Gazelle GS. Radio-frequency tissue ablation: effect of pharmacologic modulation of blood flow on coagulation diameter. Radiology 1998;209(3):761-7.

24. Goldberg SN, Kruskal JB, Oliver BS, Clouse ME, Gazelle GS. Percutaneous tumor ablation: increased coagulation by combining radio-frequency ablation and ethanol instillation in a rat breast tumor model. Radiology 2000;217(3):827-31.

25. Goldberg SN, Girnan GD, Lukyanov AN, Ahmed M, Monsky WL, Gazelle GS, et al. Percutaneous tumor ablation: increased necrosis with combined radio-frequency ablation and intravenous liposomal doxorubicin in a rat breast tumor model. Radiology 2002;222(3):797-804.

26. Lee SG, Hwang S, Jung JP, Lee YJ, Kim KH, Ahn CS. Outcome of patients with huge hepatocellular carcinoma after primary resection and treatment of recurrent lesions. Br J Surg 2007;94(3):320-6.

27. Xu L, Shi M, Zhang YQ, Li JQ. [Influence of surgical resection margin in hepatectomy on survival of patients with hepatocellular carcinoma]. Zhonghua Zhong Liu Za Zhi 2006; 28(1):47-9.

28. Dodd GD 3rd, Soulen MC, Kane RA, Livraghi T, Lees WR, Yamashita Y, et al. Minimally invasive treatment of malignant hepatic tumors: at the threshold of a major breakthrough. Radiographics 2000;20(1):9-27.

29. Tacke J. [Percutaneous radiofrequency ablation – clinical indications and results]. Rofo 2003;175(2):156-68.

30. Numata K, Tanaka K, Kiba T, Saito S, Isozaki T, Hara K, et al. Using contrast-enhanced sonography to assess the effectiveness of transcatheter arterial embolization for hepatocellular carcinoma. AJR Am J Roentgenol 2001;176(5): 1199-205.

31. Goldberg SN, Gazelle GS, Compton CC, Mueller PR, Tanabe KK. Treatment of intrahepatic malignancy with radiofrequency ablation: radiologic-pathologic correlation. Cancer 2000;88(11):2452-63.

32. Antoch G, Vogt FM, Veit P, Freudenberg LS, Blechschmid N, Dirsch O, et al. Assessment of liver tissue after radio-frequency ablation: findings with different imaging procedures. J Nucl Med 2005;46(3):520-5.

33. Paul SB, Gulati MS. Spectrum of hepatocellular carcinoma on triple phase helical CT: a pictorial essay. Clin Imaging 2002;26(4):270-9.

34. Lencioni R, Cioni D, Bartolozzi C. Percutaneous radio-frequency thermal ablation of liver malignancies: techniques, indications, imaging findings, and clinical results. Abdom Imaging 2001;26(4):345-60.

35. de Baere T, Risse O, Kuoch V, Dromain C, Sengel C, Smayra T, et al. Adverse events during radiofrequency treatment of 582 hepatic tumors. AJR Am J Roentgenol 2003;181(3):695-700.

36. Poon RT, Ng KK, Lam CM, Ai V, Yuen J, Fan ST, et al. Learning curve for radiofrequency ablation of liver tumors: prospective analysis of initial 100 patients in a tertiary institution. Ann Surg 2004;239(4):441-9.

37. Mulier S, Mulier P, Ni Y, Miao Y, Dupas B, Marchal G, et al. Complications of radiofrequency coagulation of liver tumours. Br J Surg 2002;89(10):1206-22.

38. Curley SA, Marra P, Beaty K, Ellis LM, Vauthey JN, Abdalla EK, et al. Early and late complications after radiofrequency ablation of malignant liver tumors in 608 patients. Ann Surg 2004;239(4):450-8.

39. Solbiati L, Ierace T, Tonolini M, Osti V, Cova L. Radiofrequency thermal ablation of hepatic metastases. Eur J Ultrasound 2001;13(2):149-58.

40. Elias D, Baton O, Sideris L, Matsuhisa T, Pocard M, Lasser P. Local recurrences after intraoperative radiofrequency ablation of liver metastases: a comparative study with anatomic and wedge resections. Ann Surg Oncol 2004;11(5):500-5.

41. Oshowo A, Gillams A, Harrison E, Lees WR, Taylor I. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg 2003;90(10):1240-3.

42. Gillams AR, Lees WR. Survival after percutaneous, image-guided, thermal ablation of hepatic metastases from colorectal cancer. Dis Colon Rectum 2000;43(5):656-61.

43. Solbiati L, Livraghi T, Goldberg SN, Ierace T, Meloni F, Dellanoce M, et al. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. Radiology 2001;221(1):159-66.

44. Lencioni R, Crocetti L, Cioni D, Della PC, Bartolozzi C. Percutaneous radiofrequency ablation of hepatic colorectal metastases: technique, indications, results, and new promises. Invest Radiol 2004;39(11):689-97.

45. Gillams AR, Lees WR. Radio-frequency ablation of colorectal liver metastases in 167 patients. Eur Radiol 2004;14(12):2261-7.

46. Jakobs TF, Hoffmann RT, Trumm C, Reiser MF, Helmberger TK. Radiofrequency ablation of colorectal liver metastases: mid-term results in 68 patients. Anticancer Res 2006;26(1B):671-80.

47. Morimoto M, Numata K, Sugimori K, Shirato K, Kokawa A, Oka H, et al. Successful initial ablation therapy contributes to survival in patients with hepatocellular carcinoma. World J Gastroenterol 2007;13(7):1003-9.

48. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006;243(3):321-8.

49. Wakai T, Shirai Y, Suda T, Yokoyama N, Sakata J, Cruz PV, et al. Long-term outcomes of hepatectomy vs percutaneous ablation for treatment of hepatocellular carcinoma < or =4 cm. World J Gastroenterol 2006;12(4):546-52.

50. Curley SA, Izzo F, Ellis LM, Nicolas VJ, Vallone P. Radio-frequency ablation of hepatocellular cancer in 110 patients with cirrhosis. Ann Surg 2000;232(3):381-91.

51. Nicoli N, Casaril A, Marchiori L, Mangiante G, Marini G, Colombari R, et al. Intraoperative and percutaneous radiofrequency thermal ablation in the treatment of hepatocellular carcinoma. Chir Ital 2000;52(1):29-40.

52. Buscarini L, Buscarini E, Di SM, Vallisa D, Quaretti P, Rocca A. Percutaneous radiofrequency ablation of small hepatocellular carcinoma: long-term results. Eur Radiol 2001;11(6):914-21.

53. Guglielmi A, Ruzzenente A, Battocchia A, Tonon A, Fracastoro G, Cordiano C. Radiofrequency ablation of hepatocellular carcinoma in cirrhotic patients. Hepatogastroenterology 2003;50(50):480-4.

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

55. Vivarelli M, Guglielmi A, Ruzzenente A, Cucchetti A, Bellusci R, Cordiano C, et al. Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma on cirrhotic liver. Ann Surg 2004;240(1):102-7.