Local Recurrence After Hepatic Radiofrequency Coagulation

Multivariate Meta-Analysis and Review of Contributing Factors

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Objective: The purpose of this study was to analyze the factors that influence local recurrence after radiofrequency coagulation of liver tumors.

Summary Background Data: Local recurrence rate varies widely between 2% and 60%. Apart from tumor size as an important risk factor for local recurrence, little is known about the impact of other factors.

Methods: An exhaustive literature search was carried out for the period from January 1, 1990 to January 1, 2004. Only series with a minimal follow-up of 6 months and/or mean follow-up of 12 months were included. Univariate and multivariate meta-analyses were carried out.

Results: Ninety-five independent series were included, allowing the analysis of the local recurrence rate of 5224 treated liver tumors. In a univariate analysis, tumor-dependent factors with significantly less local recurrences were: smaller size, neuroendocrine metastases, nonsubcapsular location, and location away from large vessels. Physician-dependent favorable factors were: surgical (open or laparoscopic) approach, vascular occlusion, general anesthesia, a 1-cm intentional margin, and a greater physician experience. In a multivariate analysis, significantly less local recurrences were observed for small size ($P < 0.001$) and a surgical (versus percutaneous) approach ($P < 0.001$).

Conclusions: Radiofrequency coagulation by laparoscopy or laparotomy results in superior local control, independent of tumor size. The percutaneous route should mainly be reserved for patients who cannot tolerate a laparoscopy or laparotomy. The short-term benefits of less invasiveness for the percutaneous route do not outweigh the longer-term higher risk of local recurrence.

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Local recurrence rate after radiofrequency coagulation (RFC) of liver tumors varies widely between 2%[1,2] and 60%.[3] While nearly all authors agree that tumor size is an important risk factor for local recurrence, little is known about the impact of other factors, such as tumor pathology, tumor location, or approach. Two reasons account for this uncertainty. First, the number of tumors per series is limited, precluding a meaningful multivariate analysis. Second, length of follow-up is often not sufficient to allow local recurrences to surface. The purpose of this study was to identify and analyze the factors that may influence local recurrence in an exhaustive meta-analysis.

MATERIALS AND METHODS

Data Accrual

We carried out an exhaustive PubMed search of the world literature for the period from January 1, 1990 to January 1, 2004 using keywords (radiofrequency, radio-frequency or radio frequency) and (liver or hepatic or hepatocellular) in English, French, German, Italian, Spanish, Danish, and Dutch. All abstract supplements from the same period published in *Radiology, American Journal of Radiology, Journal of Vascular and Interventional Radiology, European Radiology*, *and Surgical Endoscopy* were searched manually. Relevant papers were also identified from the reference lists of the papers previously obtained through the search and from abstracts from recent international meetings. In case of overlap between 2 reports, only the most detailed report was included. Only series with a minimal follow-up of 6 months and/or or mean follow-up of 12 months were included. Reports about treatments obtained with noncommercial electrodes and treatments with palliative intent (intentional partial debulking) were excluded. When appropriate, authors were contacted to obtain more details about the cases they reported.

Definitions

Local recurrence was defined as radiologic (CT, MRI or contrast-enhanced ultrasound) and/or histologic (tumor cells with intact mitochondrial enzyme staining) detection of residual or recurrent viable tumor at the site of the original tumor, during follow-up and after completion of all (one or more) sessions. Our definition of local recurrence also includes tumors for which no complete coagulation could be obtained despite one or more RFC sessions.

Size

Tumors were classified as small (≤3 cm), medium (3–5 cm), and large (>5 cm) according to a recent international proposal.[4]

Subcapsular tumor was defined as a tumor 1 cm or less under the liver capsule.

Proximity of large vessel was defined as the situation where the tumor invades, abuts, or is situated within 5 mm of a vessel of at least 3 mm in diameter.[1,5]

Partial vascular occlusion was defined as a temporary or permanent occlusion of the hepatic artery or its branches by either an intravascular balloon during the procedure or a (chemo) embolization immediately or a few days before the procedure.

Full vascular occlusion was defined as the performance of a Pringle maneuver (clamping of both the hepatic artery and the portal vein) during the procedure.

Intentional margin was defined as the minimal margin of coagulation at each side of the tumor that was aimed for in each report.

Physician's experience was defined as the total number of tumors treated by RFC, included in the meta-analysis, performed by the same author. For the analysis of this variable, multicenter studies were excluded.

Statistical Analysis

In univariate analysis, recurrence rates were compared between groups by a χ^2 or Fisher exact test when groups were nominal categories and by a Cochrane test when they were ordinal categories. A multivariate analysis was performed by logistic regression with Wald test for assessing the significance of any variable. All statistical tests are 2-tailed. Analysis was performed using SPSS statistical software (SPSS Inc., Chicago, IL).

RESULTS

Ninety-five independent series were included, allowing the analysis of the local recurrence rate of 5224 treated liver tumors.[2,5–98]

Tumors were coagulated percutaneously (67.9%), laparoscopically (11.6%), or by laparotomy (20.5%). Total local recurrence rate was 12.4% (647 of 5224). In a univariate analysis (Table 1), tumor-dependent factors with significantly less local recurrences were: small size, neuroendocrine metastases, nonsubcapsular location, and location away from large vessels. Physician-dependent favorable factors were: surgical (open or laparoscopic) approach, vascular occlusion, general anesthesia, a 1-cm intentional margin, and a greater physician experience.

In a multivariate analysis, significantly less local recurrences were observed for small size ($P < 0.001$) and a surgical (versus percutaneous) approach ($P < 0.001$).

Local recurrence rates were lower after a surgical approach for each size category, even for small tumors (Table 2).

DISCUSSION

Meta-Analysis

Local recurrence rate after RFC of liver tumors varies widely between 2%[1,2] and 60%.[3] While nearly all authors agree that tumor size is an important risk factor for local recurrence, little is known about the impact of other factors, such as tumor pathology, tumor location, or approach. The few series that have looked at factors influencing local recurrences have produced conflicting results, probably because of a limited number of tumors in most of them, precluding a meaningful multivariate analysis.[5,52,58,63,99–103]

Awaiting multivariate analyses in large prospective trials, this meta-analysis comes as close as one can currently get to study the factors influencing local recurrence after RFC. As every meta-analysis, it has its strengths and weaknesses. As for its strengths, several measures have been taken to obtain the most correct reflection of daily RFC practice in the world (as opposed to the practice in a handful selected high-volume centers of excellence). Reports with a limited number of cases, including small centers and centers that have only recently started with this technique, were included. To have broader coverage, reports in 7 languages were included. To counter a publication bias (ie, that bad results are less likely to be published), not only peer-reviewed articles but also abstracts from international meetings were included.

As for its weaknesses, the individual series in this meta-analysis may not be entirely comparable. Definitions may differ slightly between reports. Some authors have collected their data retrospectively rather than prospectively. Follow-up duration varies, even if a minimum follow-up of 6 months was required. Electrode and generator technology have evolved rapidly and may be different between early and recent series. We found however no significant impact of the year of publication on local recurrence rate (Table 1).

A second weakness is that not all series reported the data on all of the analyzable factors or did not report them on an individual tumor basis. The lacking of some of the individual data did not hamper the univariate analysis as much as the multivariate analysis, in which all the data had to be present simultaneously. Only 2 of the 9 factors that had a statistically significant impact on local recurrence in the univariate analysis remained significant in the multivariate

TABLE 1. Local Recurrence Rate: Univariable Analysis of Contributing Factors

Factor	Category	% of Recurrences	No. of Cases	No. of Recurrences	*P*
Diameter	>5 cm	58.1	31	18	<0.001
	3–5 cm	24.5	106	26	
	<3 cm	14.1	1,680	237	
	Total		1,817		
Pathology	Hepatocellular carcinoma	14.9	2,369	352	<0.001
	Colon cancer metastases	14.7	763	112	
	Unspecified metastases	9.8	1,046	102	
	Breast cancer metastases	8.2	97	8	
	Neuroendocrine metastases	3.3	330	11	
	Total		4,605		
Proximity major vessel	Yes	36.5	104	38	<0.001
	No	6.3	271	17	
	Total		375		
Location	Subcapsular	61.5	13	8	<0.001
	Nonsubcapsular	15.8	57	9	
	Total		70		
Approach	Percutaneous	16.4	3,002	493	<0.001
	Laparoscopic	5.8	515	30	
	Open	4.4	907	40	
	Total		4,424		
Intentional margin	0 cm	14.5	3,293	478	<0.001
	0.5 cm	16.4	440	72	
	1 cm	6.5	1,491	97	
	Total		5,224		
Vascular occlusion	No	12.8	4,262	547	0.038
	Yes	9.3	428	40	
	Total		4,690		
Anesthesia	Local/sedation	14.3	949	136	<0.001
	General	6.2	1,542	95	
	Total		2,491		
Imaging	MRI	22.7	22	5	0.054
	CT	19.6	56	11	
	Ultrasound	11.7	4,263	499	
	Total		4,341		
Physician's experience	<20 tumors	17.7	249	44	<0.001
	21–50 tumors	15.9	904	144	
	51–100 tumors	13.8	976	135	
	>100 tumors	9.6	2,366	227	
	Total		4,495		
Year of publication	1998–1999	11.6	155	18	0.074
	2000	12.2	1,212	148	
	2001	15.4	1,309	201	
	2002	10.9	1,008	110	
	2003	11.0	1,540	170	
	Total		5,224		

TABLE 2. Local Recurrence Rate According to Size and Approach

	Percutaneous (%)	Laparoscopy/Laparotomy (%)
≤3 cm	16.0	3.6
3–5 cm	25.9	21.7
>5 cm	60.0	50.0

analysis. For the reason mentioned, this should not be interpreted as proof of absence of an independent impact of the 7 other factors. In other words, because of the lack of some data on an individual tumor basis, the multivariate analysis probably underestimates the number of factors with an independent influence on local recurrence.

Duration of Follow-up

In the present study, a minimum follow-up of 6 months for each tumor and/or a mean follow-up of at least 12 months for the whole series was required for inclusion. When applying a more strict inclusion criterion (minimum follow-up of 6 months for each tumor), only 3010 tumors were available for analysis, but the statistical results were the same. Extending the minimum follow-up period to 12 months or more did not allow inclusion of a sufficient number of tumors for a meaningful analysis.

A minimal follow-up of 6 months very probably underestimates the real local recurrence rate. Radiologic local recurrences have been reported after 12 months or longer,[2,7,10,31,35,52,57,70,77] 18 months or longer,[2,31,52,77] and even up to 23 months.[77] In one series, local recurrence rate at 12, 24, and 36 months was 3, 5, and 7 times, respectively, higher than after 6 months.[101]

Another indication that a 6-month follow-up period most likely underestimates the true local recurrence rate comes from reports of histologic examination after resection of tumors that had been treated by RFC. Eleven studies reported cases of microscopic residual viable tumor despite a negative CT.[9,31,71,104–106,175] Only with time will these tumor nests grow sufficiently large to appear on imaging. For these reasons, future authors are encouraged to restrict reporting results after RFC to patients with a minimal follow-up of 12 months.

Importance of Local Recurrence

A local recurrence seriously jeopardizes the chances of cure, as re-treatment is often impossible or has a high risk of failure. In an exhaustive review of 153 reports on RFC up until January 1, 2004, we found only 18 authors (12%) who reported an attempt at local re-treatment.[18,25,32,61,63,64,70,91,100,107–109,175] Of these reports, 13 were sufficiently detailed for analysis.[18,25,32,61,63,64,70,107,108,175] In total, of 64 recurrent tumors, only 35 (55%) were re-treated and a complete coagulation was obtained in only 23 cases (36%). One report described 64 patients with local recurrences, of which only 34 received re-treatment.[109] This report did not mention the success rate of re-treatment. Reasons for not considering re-treatment were unfavorable geometry[108] and diffuse metastases.[18,107]

The poor local results of patients with established recurrent tumor during follow-up after completion of one or more sessions of RFC should not be confused with the better results of repeat RFC in cases where incomplete tumor coagulation is detected on immediate follow-up imaging, a common practice after a percutaneous approach. For example, in a series of 364 hepatocellular carcinomas (HCC) smaller than 3.5 cm, 1 percutaneous session achieved a complete coagulation at immediate post-RFC CT in 77% of tumors. Immediately after the second session in the incompletely treated cases, 99.7% of tumors appeared completely coagulated on CT.[110]

Importance of Number of Tumors

In this meta-analysis, we defined the local recurrence rate on a tumor base, for reasons of technical comparability. What counts for a patient, however, is the patient-based local recurrence rate. The more tumors a patient has, the more he is at risk for having at least one local recurrence. The deleterious effect of every factor that increases local recurrence rate on a single tumor level is being amplified in patients with multiple tumors.

Tumor-Dependent Factors

Size

Nearly all authors agree that size is an important factor determining local recurrence rate,[3,12,22,24,31,37,49,52,54,58,63,70,80,83,94,99–102,105,108,109,111–114] with rare exceptions.[5,103]

Several factors may contribute to the higher local recurrence rate for larger tumors. First, the fact that the size of individual RFC lesions is limited. A single coagulation may be sufficient to cover a small tumor and its 1-cm safety margin at both sides, but not to cover a large tumor. Unfortunately, when more than one treatment session is needed to obtain a complete coagulation, a higher risk of local recurrence has been described.[7]

For large tumors, in mathematical models, a large number of precisely calculated overlapping coagulations is necessary.[115] For example, to cover a 3-cm tumor and its safety margin with an electrode that produces a perfectly spherical coagulation of 3 cm, 14 overlapping coagulations are required.[115] Many authors, however, restrict the number of overlapping coagulations to 2 or 3. The technique of overlap is not easy: using ultrasound, it is difficult to visualize the tumor after the first coagulation session due to the appearance of a hyperechogenic microbubble cloud.[103] Performing the overlaps in a mathematically regular fashion is difficult, especially percutaneously. As a result, nests of viable tumor cells will remain in the clefts between the incompletely fused coagulation zones. As an alternative to overlapping coagulations, new electrodes that claim to produce larger coagulation zones in a single session have been introduced recently.[116] Regrettably, no scientific data on size and geometry obtained by these electrodes[116] were available by January 1, 2004.

A second factor is that larger tumors more frequently have irregular borders than small tumors.[113] They also more frequently present satellite lesions that are at a greater distance from the main tumor. This is true for colorectal metastases[117,118] as well as for HCC.[119,120] These satellite lesions are often invisible on pre-RFC imaging.[120] If the coagulation is restricted to the main tumor without safety margin, spiky irregular extensions and satellites will be left untreated.

Pathology

The impact of pathology on local recurrence rate is unclear in the literature.[3,5,83,99,102,103] The univariate analysis of all cases shows that local control is best for neuroendocrine metastases, followed by breast cancer metastases. Local recurrence rates for HCC and colorectal metastases were similar.

Differences in local recurrence rate between various tumor types may be due to differences in the mean natural growth rate. In this hypothesis, local recurrences of slow-growing tumors (such as neuroendocrine metastases) will appear later than recurrences of fast-growing tumors. For medium (3–5 cm) and large (>5 cm) HCC, an infiltrating growth pattern (irregular margins, peripheral portal invasion, extranodal growth) is associated with a clearly higher risk of local recurrence than a noninfiltrating growth pattern (smooth, well-circumscribed margins or surrounded by a capsule).[94,113] For small HCC (≤3 cm), however, presence or absence of a capsule did not influence risk of local recurrence.[94,101]

Proximity of Large Vessels

The literature is not clear about the influence of the proximity of large vessels on the risk of local recurrence. Residual or recurrent tumor near large vessels was reported by 20 authors[30,32,35,47,49,70,80,108,111,112,114,121–123,175] and 3 comparative studies found an increased risk,[5,12,63] but 2 other studies did not.[52,101] This meta-analysis, however, clearly confirms the negative impact of the proximity of large vessels on the risk of local recurrence.

In animal experiments with perfused liver, a rim of viable tissue around the vessel is observed in 100% of vessels >5 mm; in 29% of vessels 3 to 5 mm, and in 3% of vessels <3 mm.[124] After percutaneous RFC or laser therapy, residual tumor was observed in 100% of tumors adjacent to the vena cava, in 57% of tumors adjacent to the portal vein, and in 33% of tumors adjacent to the hepatic veins.[121]

Two strategies that may counter the perivascular heat-sink[4] effect include the Pringle maneuver and manipulation of the electrode.

Pringle Maneuver. Compared with RFC in perfused liver, the very common distortion near blood vessels disappears almost completely with a Pringle maneuver.[116,125–127] Two biophysical phenomena govern the shape of an RFC lesion near a blood vessel. The first is the well-known heat-sink effect, in which the cooler blood carries away part of the generated heat and causes a type 1 distortion of the RFC lesion.[116] The second is the much less known attraction of the RFC current to the vessel because of the higher electrical conductivity of blood.[128] With preserved blood flow, the dominating heat-sink effect annihilates the effect of the second phenomenon. With interrupted blood flow only, the second phenomenon will play a role, and it will cause a preferential perivascular heating, which is exactly what is needed.

A Pringle maneuver has to be used with caution, as it may cause hepatic vessel thrombosis. In a recent review of complications of RFC, the clinical risk of portal vein thrombosis was 0.2% in 3227 patients with normal blood flow versus 4.2% in 96 patients with a Pringle maneuver throughout the whole RFC procedure.[129] Interestingly, in a series of 123 patients treated with a short (2–3 minutes) Pringle maneuver, no patient developed a portal thrombosis despite the fact that 71.6% of the tumors were within 5 mm of large vessels[1]; and the local recurrence rate after a median follow-up of 15 months was only 1.8%. The risk of hepatic vein thrombosis seems to be much lower (2 in 3670 patients) than for portal vein thrombosis.[129]

Manipulation of the Electrode. Several tips and tricks have been described to counter the heat-sink effect of perivascular tumors. The first tip is to apply the current first to the deepest (ie, most central) part of the tumor, which contains the afferent vessels, to enhance coagulation of the devascularized remaining part of the tumor. Preferably, using color Doppler, the electrode tip is positioned precisely near the feeding vessel.[130,131] A second tip was recommended for the 4-prong model 30 RITA electrode, which is now less frequently used. When target temperatures were not reached at the 4 prongs due to the presence of a large vessel, the prongs were retracted after the first coagulation, the electrode was twisted 45°, and the prongs were redeployed to perform a second coagulation.[114,123,131] A third tip is to deploy the prongs only halfway, to concentrate current and heating in a smaller area, and to overcome tissue cooling by the blood flow.[58,132] This way, complete coagulation of 3 perivascular tumors has been reported.[132] A drawback of all 3 tips and tricks is that experimental evidence of their efficacy is lacking, and proof of their clinical efficacy is only anecdotal.

Subcapsular Location

A subcapsular location was found to significantly increase local recurrence rate in 2 studies,[52,101] which was confirmed in our meta-analysis. A third study, published after the deadline of inclusion in the meta-analysis, found no difference in local recurrence rate between subcapsular and nonsubcapsular tumors.[133] All subcapsular tumors of the meta-analysis, including those of the first 2 studies,[52,101] had been approached percutaneously under local anesthesia with or without sedation, whereas 75% of subcapsular tumors in the third study[133] had been approached surgically under general anesthesia. Therefore, 2 factors may account for the different outcome between these studies. First, it is possible that in the percutaneous approach, subcapsular tumors have been undertreated for fear of burning adjacent organs, diaphragm, or the abdominal wall.[52,101,112] Second, a percutaneous treatment of subcapsular tumors under local anesthesia with or without sedation can be painful,[133] which may have prevented a correct complete coagulation.[112] In conclusion, a subcapsular location is probably not a risk factor for local recurrence per se, but only if RFC is performed percutaneously. For this reason, as well as for the increased risk of bleeding and seeding when treated percutaneously,[129] a laparoscopic or open approach is favored for subcapsular tumors.[52,101,129]

Physician-Dependent Factors

Approach

RFC was pioneered by interventional radiologists. They reported the first experiments of RFC on ex vivo liver[134] and in vivo animal livers[135] in 1990 and the first clinical results in 1992.[136] Surgeons entered the field only in 1996.[137] When RFC was first introduced clinically, it was entirely experimental and considered as a palliative treatment. In that context, the percutaneous route was justified as it was the least invasive and a less costly approach. Even today, the majority of RFC procedures are still performed percutaneously. In this meta-analysis, tumors were coagulated percutaneously in 67.9%, by laparotomy in 20.5%, and laparoscopically in 11.6%.

Given the absence of randomized trials, there is no consensus among experts about which approach is best.[138] Some authors that used more than one approach found better local control after a surgical approach,[3,5,11,102,103,122,139] while other reports found no statistically significant difference.[1,12,22,54,63,111,114,140] One author[99] found worse results after the percutaneous approach in the univariate analysis of his results, but not in the multivariate analysis.

In the present meta-analysis, a surgical approach (laparotomy or laparoscopy) clearly yielded statistically significantly ($P < 0.001$) superior results than a percutaneous approach, independent of the size of the tumors (Table 2).

Several factors may contribute to better results after a surgical approach. Intraoperative ultrasound greatly improves spatial resolution. The probe is placed directly on the liver surface, without sound attenuation by skin and subcutaneous tissue. Further, the acoustic window is much wider compared with external ultrasound, which is hampered by the interposition of ribs and bowel.[141] Many studies have demonstrated a ±30% increase in tumor detection rate by intraoperative ultrasound during laparoscopy[18,80,114,175] or laparotomy[62,114,175] compared with preoperative imaging. Several authors have reported improved visibility of the tumor itself, although no firm literature data are available, probably because this is much more difficult to quantify. These authors claim better tumor visualization compared with external ultrasound, especially of tumors located in the superior right lobe of the liver.[63,71,106,142,175] They also report better identification of tumor margins and small satellite nodules.[3,7,80,111,143] Improved visibility will lead to a more correct insertion of the electrodes and an increased chance of complete covering of the tumor, including its irregular margins, satellites, and a 1-cm safety margin.

RFC by a surgical approach allows an easy access to tumors located in the superior right lobe of the liver, which are often hard to reach percutaneously.[63,71,106,142,175] The surgical, especially the open approach, provides a larger degree of freedom for inserting the electrodes under an optimal angle, with mobilization of the liver if necessary.[142,144] In the percutaneous approach, the electrodes have to be inserted through a narrow access window, between ribs or subcostally.[3] In the laparoscopic approach, because of the pneumoperitoneum and the upward movement of the diaphragm, liver movement is minimal, facilitating precise electrode placement.[145] The surgical route allows multiple parallel reinsertions of the electrode in cases where overlapping coagulations are necessary, which is difficult percutaneously.[106] In the future, novel RFC electrodes that would allow a large and reliable coagulation zone with a single insertion could take away this current disadvantage of the percutaneous route.

Intraoperative RFC allows the use of a full Pringle maneuver, which has been shown to result in larger, more complete, and less distorted coagulation zones when compared with normal hepatic flow or interrupting the flow in the hepatic artery only.[116] Even if the surgeon does not perform a Pringle maneuver during laparoscopy, a 12-mm Hg pneumoperitoneum by itself causes a 40% decrease of portal vein flow, with a subsequent increase in RFC size.[146]

For fear of burning adjacent organs, diaphragm, or the abdominal wall, subcapsular tumors are often undertreated by a percutaneous approach, leading to higher local recurrence rates compared with deeper tumors.[52,101,112]

Finally, it appeared that an intended safety margin of 1 cm, which was found to be associated with less local recurrence in our univariate analysis, was used much less in the percutaneous approach than in the surgical approach (Table 3). The surgical route is used mainly by surgeons (although in some centers an interventional radiologists scrubs and performs the RFC), while the percutaneous route is used mainly by radiologists (although surgeons also perform percutaneous RFC for selected indications). It is likely that surgeons more rigorously apply the 1-cm oncologic margin in RFC because they have been using it in hepatic surgery for over 20 years.

While formal proof of the therapeutic value of RFC awaits the results of randomized trials such as the recently opened CLOCC 40004 trial (chemotherapy + local ablation versus chemotherapy) of the European Organisation for Research and Treatment of Cancer, there are currently good indications that RFC may potentially lead to curative treatment of individual metastases. If cure is possible, then the most reliable treatment protocol should be chosen, even if it is more invasive and costly. This meta-analysis indicates that RFC by laparoscopy or laparotomy results in superior local control, independent of tumor size. While some authors argue that a percutaneous approach is acceptable for small tumors, our data indicate that the superiority of the surgical approach is even more evident for small than for larger tumors (Table 2). The surgical route is the first choice approach for any patient who can tolerate a laparoscopy or laparotomy. The short-term benefits of less invasiveness for the percutaneous route do not outweigh the longer-term higher risk of local recurrence, as a local recurrence may jeopardize cure.

The percutaneous route remains valuable for certain indications. First, it is indicated for patients that are too fragile to undergo laparoscopy or laparotomy. Second, tumors that are invisible on ultrasound imaging can be treated by a CT- or MRI-guided percutaneous procedure. Third, it is not excluded that some highly specialized centers through expertise and patient selection can produce equivalent results by the percutaneous approach to those obtained after a surgical route. Such centers, however, are rare. For percutaneously treated tumors ≤3 cm, only one of 5 reports with at least 50 tumors came close (0%) to the 3.6% local recurrence rate of the surgical approach.[94] The other 4 series obtained local recurrence rates between 13% and 26%.[52,77,83,84]

Margin

The importance of a 1-cm oncologic safety margin in RFC of liver metastases[2,12,18,46,62,63,67,70,74,87,97,103,112,114,116,175] and HCC[12,18,22,46,63,70,87,97,103,112,114,116,133,175] has been stressed mainly by surgeons. Some authors, mainly in the radiologic literature, have lowered the proposed safety margin to 0.5 cm for metastases[5,13,17,23,25,30,39,41,42,55,60,61,80,88,104,113,175] and HCC.[5,8,11,17,23,25,39,41,42,57,80,88,94,96,104,175] A third group of authors explicitly state that a margin is not necessary for HCC.[13,113,175]

At present, there is only one study relating the local recurrence rate to the peritumoral coagulation margin. In this short-term follow-up study, much less local recurrences were observed after RFC of HCC with a margin of 5 mm versus no margin.[147] Our meta-analysis found that local recurrence rates are higher when the physician does not aim at coagulating a peritumoral margin of 1 cm. Local recurrences at the edge of an initially complete radiologic coagulation have been reported by many authors.[2,7,15–17,22,27,30,34,35,37,39,40,43,48,50,51,55–58,61,70,72–75,77,87–89,91,94,96] The underlying reason may be that the tumor can microscopically extend further than macroscopically suspected.

In HCC, viable satellite nodules were found in 57% of patients who underwent transplantation after RFC, despite a complete marginal necrosis of the main tumor.[68] In medium (3–5 cm) and large (>5 cm) HCC, microscopic tumor extends more than 2 cm beyond macroscopic borders in 67%.[119] In small HCC (≤3 cm), microscopic tumor extends more than 1 cm beyond macroscopic borders in 60%.[119] Even in the most favorable subgroup, nodular-type HCC of less than 2 cm, satellites 10 mm from the nodule were observed in 10% of cases and microscopic portal invasion in up to 25% of cases.[148]

In resected colorectal metastases, microscopic bile duct, portal, or hepatic vein invasion or peritumoral micrometastases is found in 31% to 50%, up until 9 to 21 mm from the macroscopic tumor edge.[118,149]

The histologic data and the results of our meta-analysis provide the rationale to recommend a minimal safety margin of 1 cm for both primary and secondary liver tumors. A marginal coagulation of neuroendocrine metastases may be sufficient when the intent is purely palliative.[10,18,40,54,93]

TABLE 3. Intentional Margin According to Approach

Approach	No. of Cases	No Margin	0.5 cm Margin	1 cm Margin	*P*
Percutaneous	3046	88.4% (2692)	5.4% (165)	6.2% (189)	<0.001
Surgical	1248	28.8% (360)	13.6% (170)	57.5% (718)	<0.001

Correctly obtaining a minimal 1-cm coagulation margin at all sides is not that easy. First, in the transverse plane perpendicular to the electrode, the electrode tip may not be placed perfectly in the center. In an experimental study, the mean distance between the center of the tumor and the center of the thermal coagulation was 3.8 ± 1.5 mm.[150] In patients, after satisfactory placement of an electrode under 2-dimensional imaging, 3-dimensional imaging disclosed unacceptable eccentric device placement in 40% to 45%.[151,152] Second, in the axial plane parallel to the electrode, the exact position of the electrode tip is not always easy to verify and a straight electrode may slide after placement.[123] Moreover, there are no data in the literature on the precise position of the coagulation zone in relation to the electrode tip.[116] Third, the diameter of coagulation lesions is rather variable, with a wide range between minimum and maximal diameter.[116,153] Data on size and geometry obtained by current RFC electrodes have recently been published.[116]

The effect of the addition of all these small errors is illustrated by an experiment in which simulated 1-cm tumors were coagulated with an expandable electrode with an expected thermal coagulation diameter of 3 cm. Instead of obtaining a 1 cm safety margin around the tumor, the mean margin was only 0.16 cm with a positive margin in 23%.[150]

Reporting the extent of the resection margin is essential in any publication on hepatectomy for tumor. In the RFC literature, similar information on the peritumoral coagulation margin is inexistent, with a rare exception.[147,154,155] By comparing pre- and post-RFC CT/MR images with superimposing of hepatic anatomic landmarks, the minimal coagulation margin can be measured.[154] Some reports compared pre-RFC tumor volumes with post-RFC coagulation volumes or pre-RFC tumor diameter with post-RFC coagulation diameter. These surrogate measures are not recommended: the margin can be positive when the coagulation zone is asymmetric or eccentric, even when the coagulation diameter exceeds the tumor diameter or the coagulation volume triples the tumor volume.

Vascular Occlusion

The clinical value of vascular occlusion has been regarded as controversial. For HCC treated percutaneously, 3 studies found better local control of HCC when RFC was combined with occlusion of the hepatic artery,[8,96,156] while 2 did not.[50,52] No studies were available that evaluate the influence of a Pringle maneuver on local recurrence for the surgical approach. In this meta-analysis, local control was better with vascular occlusion than with normal blood flow. The benefit of vascular occlusion is proven only for large tumors (Table 4).

The differences in local control rate can be explained by the negative effects of a perfusion-mediated tissue cooling on size and geometry of RFC lesions.[4,116] Compared with RFC in perfused liver, thermal coagulations are larger and more regular when performing RFC during blood flow interruption. These findings are more pronounced in case of complete interruption of inflow (Pringle maneuver) or outflow (occlusion of hepatic veins), than with partial occlusion, ie, only the hepatic artery or the portal vein.[104,116,125–127,157,158]

A Pringle maneuver (clamping the hepatic artery and portal vein at the level of the porta hepatis) can be performed

TABLE 4.

Effect of Hepatic Artery Occlusion on Local Recurrence (Percutaneous Approach)

≤3 cm	No. of Cases	No. of Recurrences	% Recurrences	*P*
Hepatic artery occlusion	39	9	23.1%	NS
Normal flow	1,319	208	15.8%	NS
>3 cm	**No. of Cases**	**No. of Recurrences**	**% Recurrences**	***P***
Hepatic artery occlusion	105	17	16.2%	<0.001
Normal flow	164	67	40.9%	<0.001

Effect of Pringle on Local Recurrence (Surgical Approach)

≤3 cm*	No. of Cases	No. of Recurrences	% Recurrences	*P*
Pringle	50	0	0%	NS
Normal flow	109	6	5.5%	NS

*For tumors >3 cm treated by a surgical approach, too few data were available for analysis.

during laparotomy[22,30,62,63,70,74,85,93,99,143] as well as during laparoscopy.[36,127,175]

For patients treated by a percutaneous approach, a hepatic artery occlusion can be performed by balloon catheter occlusion,[33,72,96,159] by selective embolization,[13,33,72,94] or by chemoembolization.[8,27,50,156] Selective occlusion of a hepatic vein may in theory be as effective as a Pringle maneuver,[116,126] but it is less frequently performed.[25,33,175] Hypotensive anesthesia[160] yields larger coagulation lesions than normotensive anesthesia, but the effect on local recurrence rates has not yet been reported. Percutaneous balloon occlusion of the portal vein is still experimental[161] and unlikely to be of any benefit, given the predominantly arterial vascularization of liver tumors.[162]

Based on our current findings, vascular occlusion is recommended for the treatment of tumors >3 cm.

Anesthesia

We found no studies that looked at the effect of the type of anesthesia on local recurrence, although one author reported higher coagulation volumes after RFC under general anesthesia versus local anesthesia with or without sedation.[112] Our meta-analysis of the whole series indicates that local control is superior for RFC performed during general anesthesia compared with local anesthesia with or without sedation (Table 1). As surgical cases are always done under general anesthesia, analysis was repeated for the percutaneous cases only, which showed no significant differences in local recurrence rate.

Procedures under local anesthesia with or without sedation are often painful,[1,122] especially when the diameter of the thermal lesion exceeds 3 cm,[163] when the tumor is superficial or in contact to pain-sensitive Glissonian structures,[112,133,163] when treatment power exceeds 100 W, or when electric current exceeds 1 to 1.5 Amp.[163] Pain may force the physician to lower the current intensity, to shorten coagulation duration, or to limit the number of overlapping coagulations. Incomplete tumor coagulation has been explicitly attributed to pain during a procedure under sedation.[112]

For a procedure under local anesthesia, the patient has to breathe in deeply and then hold his breath during electrode insertion.[71] Under general anesthesia, inadvertent breathing movements while inserting the electrode are prevented. The anesthetist can be asked for a short-lasting apnea to facilitate a difficult electrode positioning.[113]

General anesthesia carries the additional advantage that systolic blood pressure can be lowered, aiming at a decreased liver blood flow and an increased coagulation diameter.[157,160]

Electrodes

At present, 6 companies have marketed RFC electrodes: Valleylab, Boulder, CO (formerly, Radionics); RITA Medical Systems, Mountain View, CA; Boston Scientific (formerly, Radiotherapeutics), Natick, MA; Berchtold, Tuttlingen, Germany; Invatec, Roncadelle, Italy; and Celon AG Medical Instruments, Teltow, Germany. The influence of electrodes on local recurrence rate is unknown. Several studies found equal results between electrodes.[5,52,77,103] There are currently more than 28 RFC electrodes on the market,[116] each of which can be used with a number of different protocols.[116,164] Comparison of results with different electrodes in this meta-analysis was not possible.

A recent review[116] showed that scientific data about size and geometry of coagulations obtained by current commercial electrodes are scarce. Data on the most basic parameter, ie, the transverse diameter in perfused pig liver, were available for only 10 of the 28 electrodes on the market. The paucity of data on size and geometry of the coagulation zone was incriminated explicitly as cause of several local recurrences in a recent study.[103] The authors strongly recommend that new electrodes not be approved for release on the market without a complete set of experimental data on the size and geometry of the coagulation. Companies should also quickly provide data for those electrodes that are already for sale.[116]

For those electrodes for which experimental data are available, a substantial variability of coagulation diameters has been observed.[116,153] An electrode used in the same experiment using the same treatment algorithms can yield coagulation lesions with a difference of up to 3.2 cm between minimal and maximal diameter. Overestimation of expected coagulation size may contribute to failure of local tumor control. Future research should focus on the development of novel electrodes that yield coagulations with more predictable diameters and shapes.

Imaging

In the meta-analysis, 98% of tumors have been treated under ultrasound guidance. Percutaneous RFC can also be performed under CT[21,64,89,94,96,105] or MRI.[43,48,88,112,175] Proponents of CT and MRI claim superiority in the treatment of tumors that are less conspicuous on ultrasound, particularly those in less accessible areas, such as the right hepatic dome.[48,94,112] MRI holds the prospect of on-line monitoring of the thermocoagulation process.[48,112] Contrast-enhanced color Doppler allows immediate recognition of remaining viable parts of HCC.[20] There are no comparative studies on outcome after each of these imaging modalities. The meta-analysis found no significant differences.

Physician's Experience

A recent study found significantly more local recurrences in the first group of 50 patients versus the second group of 50 patients treated with RFC in the same center.[103] The present meta-analysis confirms the importance of experience: authors who treated large numbers of tumors had significantly less local recurrences than authors who treated fewer tumors. Measures to shorten the learning curve may include appraisal of the literature, visiting specialized centers, and participating in training workshops with animal models.[103] Physicians have an ethical obligation to acquire a thorough understanding of the physics, the possible complications, and the correct application of RFC prior to using it in patients.[164] Regrettably, a minimally prepared physician who performs his first RFC directly on a patient, guided only by a company representative, is not an exception.

RFC Versus Surgery for Resectable Colorectal Metastases

The local recurrence rates obtained by RFC are encouraging in case of unresectable colorectal metastases. Nevertheless, no data from randomized trials are available evaluating the effect of RFC on overall survival when compared with chemotherapy alone. RFC for unresectable colorectal liver metastases seems justified only when such trials demonstrate a clear benefit on overall survival of RFC over chemotherapy. Currently such a trial (EORTC-CLOCC) is under way.

For patients with resectable colorectal metastases, current local recurrence rates are totally inacceptable, except maybe for the 3.6% local recurrence rate after RFC of small (≤3 cm) tumors by a surgical approach. Surgical RFC for such small resectable colorectal metastases could be acceptable in a randomized trial comparing resection with surgical RFC. For all other situations (percutaneous RFC and surgical RFC for medium and large tumors), RFC is contraindicated for resectable colorectal metastases. Sad cases of solitary, resectable, central lesions that were unsuccessfully treated with RFC and then progressed to incurability because of extension of tumor into major vasculature have been described.[165]

Yet the pressure on oncologists to refer their patients for minimally invasive techniques rather than for hepatic surgery becomes heavier.[60,166–169] On the other hand, surgeons that have no experience with hepatic surgery start to perform RFC on an occasional basis to treat patients with resectable tumors, rather than referring these patients to a center where the resectability of the tumor can be evaluated. An alarming survey from Germany reported that 25.9% of patients undergoing RFC had a resectable tumor.[170]

The search for minimally invasive techniques is laudable. In oncology, however, the goal is not minimal invasiveness but cure.[164,165,171–174] Innovative, less invasive techniques in oncology are welcome, but they should obtain at least the same results as traditional more invasive techniques.

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