Tumour ablative procedures for colorectal liver metastases

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Introduction

At this stage, resection should still be considered the "gold standard" for the treatment of colorectal liver metastases. However, in many patients with colorectal liver metastases confined to the liver, resection of the metastases cannot result in adequate clearance of all tumour tissue from the liver. This may be the case either because of the number of metastatic liver lesions or because of the location of the metastases. Examples are patients with diffuse bilobar disease or with unresectable recurrence after previous liver surgery. It is in this group of patients with unresectable colorectal liver metastases in which most of the pioneering work has been performed with local tumour ablative techniques.

Initially, these techniques were used by surgeons when they were confronted in theatre with unresectable metastatic disease. In these circumstances, local tumour ablative techniques were often used complementary to surgical resection. Lesions easily accessible to resection were resected by surgery, while local tumour ablation was used to treat all unresectable lesions. During the past few years, techniques on local tumour ablation have evolved significantly. New techniques became available which could also be used by laparoscopic or percutaneous approaches. This development resulted in an increasing use of local ablative techniques over Europe. Although many methods proved to be safe, the precise impact on survival of local ablative tumour therapy in patients with colorectal metastases is still unclear. This chapter will give a global overview of the results thus far.

Techniques

The basic idea behind local tumour ablation is to selectively destroy tumour tissue (including a rim of normal tissue around the tumour) without significantly interfering with liver anatomy and vasculature and hence losing large areas of normal liver tissue. During the last years, several techniques of local tumour destruction have been developed, based on the application of either extreme cold, like cryoablation [1–13], or the generation of heat, like radiofrequency (RF) [8,9,13–20], microwave and laser techniques [21,22]. Of these methods, cryoablation and RF have been the most widely used.

Cryoablation

During cryosurgery, tumours are frozen with the aid of liquid nitrogen (at $-196°C$) circulating through a probe which is placed within the tumour. Tumour destruction during cryoablation is obtained by a freeze–thaw process of the tumour tissue resulting in direct cell death and microvascular thrombosis. The procedure is generally performed at open surgery or under general anaesthesia. Laparoscopic and percutaneous approaches have been described, but are far more difficult to perform. After localisation of the liver metastases, the cryoprobe is introduced under ultrasonographic guidance into the centre of the tumour. The volume of tumour that can be frozen with one cryoprobe depends on the diameter of the probe. Cryoprobes with a diameter of 5 mm and 10 mm generally result in an ice ball of 4 cm and 6 cm, respectively. By introducing more than one probe, an adequately frozen area with a diameter of 10 cm can be obtained. The time of freezing is dependent on the production of an adequate ice ball, but generally, one freeze period lasts for 20 min. Most authors perform two freeze–thaw cycles per lesion to assure complete tumour treatment.

Radiofrequency and other thermal techniques

During RF, a small electrode is placed within the tumour used to deliver RF energy to the tissue. RF current generates ionic agitation, which is converted into frictional heat. As tissue temperatures increase between 60°C and 100°C, there is an instantaneous induction of irreversible cellular damage with breakdown of proteins and cell membranes referred to as coagulation necrosis. There are several electrode designs available. One principle is based on water-cooled electrodes and is available as one stiff electrode of 19 G or three parallel electrodes forming a cluster needle (Tyco Healthcare, USA). Two other systems show an expandable design. The expandable electrodes are introduced collapsed within a hollow needle (14–15 G). Once positioned within the tumour, multiple prongs are deployed resulting in a final umbrella-like configuration (RITA Medical systems, California, USA and Radiotherapeutics, California, USA). A fourth system, using stiff needles, combines high-frequency energy with needle fluid perfusion (Berchtold, Tuttlingen, Germany).

With current devices, tumours up to 4–5 cm in diameter can be treated by RF. Since needles are thin, the technique can be performed percutaneously next to the laparoscopic or open surgical approach. Depending on the extent of treatment, percutaneous treatment can be performed under conscious sedation or under general anaesthesia. Ultrasonography is the most widely used imaging technique, but computerised tomography (CT) and magnetic resonance imaging (MRI) may provide a higher accuracy in monitoring the treatment procedure.

Other thermal techniques for tumour destruction include laser, microwave ablation and high intensity focused ultrasound (HIFU) [23]. During microwave treatments, heat is generated in the tissue due to vibration and intermolecular collision of polar molecules in the tissue exposed to the high-frequency electromagnetic waves emitted from the tip of a probe. Interstitial laser photocoagulation involves delivery of high-energy light to the tumour, resulting in thermal injury. Different wavelengths have been investigated such as neodymium yttrium–aluminium–garnet (Nd YAC, 1064 nm) and diode light (890 nm). To optimise tumour destruction, several laser fibres are positioned in the tumour centre. Procedures are generally performed under local anaesthetic and conscious sedation.

Route of tumour ablation

Cryoablation

Cryoablation is generally performed during open surgery. The method has mainly been used by surgeons complementary to resection. In this approach, resection is often performed to deal with the main tumour mass, and some residual tumour that cannot be resected, is treated by cryoablation. In later studies, the laparoscopic approach was also used. The diameter and the stiffness of cryoprobes as well as the risk of bleeding due to cracking of the icefall, however, generally preclude a percutaneous approach. Another potential use of cryoablation is treatment of the resection edge. Several studies describe the use of cryoablation in case a very close or histologically-positive resection margin is anticipated. For this purpose, flat cryoprobes are held against the resection edge [24]. Adequate freezing is obtained for at least 1.5 cm into the remaining liver tissue.

Radiofrequency

From the beginning, thermal ablation was positioned within the field of surgery as well as radiology. Due to the small diameter of the electrodes, thermal ablation techniques are far better suited for percutaneous and laparoscopic approaches than cryoablation. Nevertheless, as with cryoablation, RF is used by many surgeons to increase the number of patients who may benefit from resection. In these cases, RF is used in addition to resection in order to treat some unresectable lesions that are left over after resection of the main tumour mass. In case resection is not planned, RF can be performed either by the laparoscopic route or percutaneously [14–20]. No reliable data are available comparing these two approaches. Often the approach used is dependent on the profession of the clinician. The percutaneous approach is least invasive, carries a lower morbidity and can be performed as an out-patient procedure. In contrast, laparoscopy with supplementary laparoscopic ultrasonography, will give additional information on small and superficial liver lesions as well as on extrahepatic disease. For example, in a study by Rahussen and colleagues [25], 25% of the patients with colorectal liver metastases showed additional findings to conventional work-up during laparoscopy and laparoscopic ultrasound. Moreover, the laparoscopic approach can be advantageous when the tumour is adherent to structures that can be damaged by thermal ablation such as the colon and stomach.

Thermal ablative techniques, like RF, are highly reliable as long as the tumour volume can be treated with one probe insertion. Large lesions, requiring multiple probe insertions with overlapping treatment zones, are often insufficiently treated resulting in a high local recurrence rate. It is in these patients, which show large lesions combined with unresectable small lesions, that open RF during laparotomy is preferred. This approach enables resection of the larger lesions and RF of the remaining unresectable smaller ones.

Monitoring local tumour destruction, quality control

Local tumour destruction aims to destroy all tumour tissue including a rim of normal liver tissue around the tumour. In order to ascertain complete tumour destruction, on-line monitoring of the ablative procedure is crucial.

Cryoablation

For cryoablation, ultrasonography has generally been used to assess the completeness of the procedure. During the freezing process an "ice ball" is formed which is clearly visible as a hypoechogenic area around the tip of the cryoprobe. Continuous ultrasonographic monitoring of the procedure should be carried out to assure that the diameter of this hypoechogenic area exceeds the diameter of the tumour lesion by about 1 cm.

Radiofrequency and other thermal techniques

For thermal ablative procedures, imaging of the procedure is dependent on the approach. During laparotomy or laparoscopic approach, ultrasonography is used. During thermal ablation, a hyperechoic area is formed around the tip of the electrode caused by the formation of bubbles from evaporated water. The precise boundaries of this hyperechoic area, however, may be difficult to identify and the formation of the hyperechoic area does not automatically correlate with the coagulative damage. So, ultrasonography provides only a rough estimation of the size of the ablation. Moreover, the image becomes heterogeneous within minutes, which limits treatment accuracy of large lesions in particular, in which multiple probe insertions are necessary to cover the whole lesions. Both CT and MRI have been reported to be more reliable in this regard [26]. For this reason, several investigators prefer CT or MRI when using the percutaneous approach. After thermal treatment, CT shows a round or teardrop-shaped hypoattenuated area which is sharply demarcated from normal liver tissue and which allows accurate monitoring of the treatment effect. Vogl used on-line MRI during percutaneous laser treatment which allowed very accurate monitoring of the treatment effects [21]. Tumour volume and volume of coagulative necrosis were determined using three-dimensional MR images. Moreover, selected sequences could monitor temperature elevations in the tumour and surrounding tissue which increased treatment efficacy. Nevertheless, for the percutaneous approach of thermal ablation, ultrasonography is still the most common method, used mainly because of its real-time capabilities, availability, speed, and low cost.

Monitoring after local tumour ablation

Contrast-enhanced CT scan is generally used for follow-up after local ablative treatment. The sharp hypoattenuated areas seen immediately after treatment usually decrease in size in the months after treatment. By 3–6 months, there may be a marked regression of the necrotic area, although treatment effects may remain visible long after this time. In case of tumour recurrence, a faint, irregular, hypoattenuated area becomes visible around the margins of the ablated tissue that increases in size on the follow-up scans. With MRI, comparable images are obtained. More recently, fluorodeoxyglucose positron emission tomography (FDG–PET) scan has been used to follow up local ablative treatment [27]. After successful treatment, metastatic lesions become photopenic. Persistent activity after local tumour treatment is highly suspicious for inadequate treatment. Moreover, the reappearance of activity in photopenic areas is strongly indicative for tumour recurrence. In a recent study, the positive predictive value for the detection of local recurrence in lesions with a positive FDG–PET scan after treatment was 80%, the negative predictive value was 100%. Moreover, FDG–PET showed tumour recurrence also outside the treated area considerably earlier than CT. Carcinoembryonic antigen (CEA) levels are only a reliable parameter for successful treatment in those patients with elevated CEA levels at the time of tumour ablation. In these patients, CEA levels should return to normal values after local tumour treatment.

Morbidity and mortality

Since no well controlled studies are performed, mortality and morbidity rates in the different series generally reflect the overall results of local treatment of several tumour types, such as hepatocellular carcinomas (HCC) and different types of metastatic liver disease (Tables 1 and 2).

Radiofrequency and other thermal techniques

RF is a well-tolerated procedure. Common side effects following the procedure include mild transient fever and nausea as well as asymptomatic right pleural effusion. The complication rate of the procedure is

Table 1

Results of cryoablation of colorectal liver metastases

[Ref.]	Pt	Lesions	Patients CRC	Patients HCC	Patients other	Diameter lesions Number lesions	Lesions per pt	Approach	Mortality (%)	Additional therapy	Median follow-up (months)	Local recurrence Lesion-based Pt-based	Liver	Extra-hepatic	DFS at median follow-up	Overall survival 1 yr	Overall survival 2yr	Overall survival 5yr
[1]	18	72	18			Diameter ng $n = 1–12$	4	Open	0	Resection	29	5.5% les-based 22% pt-based	ng		22%	ng		
[2]	32		24	3	5	1–8 cm $n = 1–3$	ng	Open	0	Resection	24	9% pt-based	86%	68%	28%	82%	72%	58%
[3]	47	141	47			Diameter ng $n = 1–12$	3	Open		Resection	30	0	ng		11%	82%	62%	15%
[4]	136	136	–	–		1–13 cm median 4 cm $n = 1–10$	3	Open	3.7	Resection	ng	ng	82%	66%	Median DFS 13 months	82%	62%	20%
[5]	25	25				64% < 3 cm $n = 1–10$	> 3	Open	3	Resection Chemo pre + post	16	44% pt-based	60%	40%	20%	77%	52%	
[6]	116	452	116			1–15 cm mean 4.4 cm $n = 1–12$	3.9	Open	0.9	Resection + IA chemo	20.5	ng	ng		ng	82%	56%	3 yr 13.4%
[7]	27	57	27			1–8 cm mean 2.6 cm n = ng	2.1	Open	7		15	2% les-based 7% pt-based	78%	26%	1 yr 30%	83%	50%	
[8]	54	88	44	7		1–9 cm median 3.6 cm $n = 1–5$	ng	Open	2	Resection	15	13.6%les-based 22% pt-based	ng		ng	ng		
[9]	240	762	180	20	40	1–22 cm median 5 cm $n = 1–16$	3	Open	2.5	Resection	28	5% les-based 15% pt-based > 3 cm 17% pt-based	ng		34%	ng		
[10]	30	115	30			1–9 cm median < 4 cm $n = 1–10$	3	Open	3.3	Resection	26	9% les-based 20% pt-based	72%	56%	17%	83%	68%	
[11]	185	185	114	71		1–15 cm median 4 cm $n = 1–15$	3 4	Open	2	 Resection Resection + IA chemo	20	11% pt-based 12% pt 4% les 10% pt 4% les	83%	16%	34% 22% 52%	 85% 95%	 35% 75%	
[12]	24	144	24			1–10 cm mean 4.5 cm $n = 1–12$	6	Open	0	Resection + Chemo pre-, post-	48	4% les-based 18% pt-based	75%	70%	1 yr 68% 2 yr 40%	92%	78%	36%
[13]	31	42	ng	18	ng	< 5 cm mean 2.2 cm $n = \leq 3$	1.4	Perc	3.2	Chemo	21	53% les-based 60% pt-based	64%	58%	16%	80%		

ng, not given; les, lesion; pt, patient; yr, year; CRC, colorectal cancer; HCC, hepatocellular carcinoma; Chemo, chemotherapy; DFS, disease-free survival.

Table 2
Results of radiofrequency ablation of colorectal liver metastases

[Ref.]	Pt	Lesions	Patients			Diameter lesions Number lesions	Lesions per pt	Approach	Mortality (%)	Additional therapy	Median follow-up (months)	Local recurrence Lesion-based Pt-based	Liver	Extra hepatic	DFS at median follow-up	Overall survival
			CRC	HCC	other											
[14]	84	231	37 Lesions 70	11 18	36 143	1–9 cm median 2 cm n = ng	2.8	Perc 29% Open 71%	4	Resection	9	6.5% les-based (> 3 cm 33%) 18% pt-based	50%	ng	26%	74% at median follow up
[15]	123	169	61	48	14	1–12 cm median 3.4 cm $n = 1–4$	1.4	Perc 25% Open 75%	0	Resection	15	2% les-based 2.5% pt-based	ng		73%	ng
[8]	92	138	46	34	12	1 –12 cm median 3.8 cm $n = 1–5$	Ng	Open	0	Resection	15	2.2% les-based 3.3% pt-based	ng		ng	ng
[16]	86	121	76	–	10	< 4.5 cm median 1.9 cm $n =< 5$	1.8	Perc 69% Open 31%	0	Resection	14	9% les-based 16% pt-based	ng		50%	1 yr 81%
[9]	68	181	30	9	29	1–9 cm median 2 cm $n = 1–13$	2	Perc 24% Open 38% Lapsc 38%	3	Resection	12	3% les-based 7% pt-based > 3 cm 38% pt-based	ng		52%	1 yr 80%
[17]	117	179	117	–	–	< 9.5 cm median 2.6 cm $n =< 4$	1.5	Perc 100%	0	Chemo	24	39% les-based ≥ 4 cm 68% les-based	ng		1 yr 49% 2 yr 35%	1 yr 93% 2 yr 69%
[18]	76	328	39	25	12	1–18 cm median 3 cm $n = 1–14$	3.3	Perc 58% Open 34% Lapsc 8%	1	Chemo	15	9% les-based 26% pt-based	ng		33%	1 yr 80% 2 yr 50%
[19]	153	447	59	21	73	1–13.5 cm median 2.5 cm $n = 1–13$	2.9	Perc 51% Open 35% Lapsc 14%	0	Resection	11	12% les-based 21% pt-based	ng		29%	1 yr 61%
[13]	33	43	ng	18	ng	< 5 cm median 2.8 cm $n = \leq 3$	1.3	Perc	0	Chemo	16	18% les-based 16% pt-based	51%	54%	27%	1 yr 58%

Abbreviations as in Table 1. Perc, percutaneous; Lapsc, laparoscopic.

below 10%. An excellent review on the complications of RF of liver tumours was published by Mulier [28]. A total of 3670 cases of RF for metastatic disease as well as for primary liver tumours were included. The mortality rate was 0.5%. Complications occurred in 8.9% of the patients. This included abdominal bleeding (1.6%), abdominal infection (1.1%), biliary tract damage (1%), liver failure (0.8%), and pulmonary complications (0.8%). Other complications, less frequently encountered, were visceral damage, cardiac complications, coagulopathy, dispersive pad skin burn and tumour seeding. Abscess formation in the treated area can be one of the worst complications and may result in prolonged hospital stay.

The morbidity rate of the RF procedure was similar for the percutaneous (7.2%), laparoscopic (9.5%) and open approach using laparotomy (9.9%). Mortality rates during these three different approaches were respectively 0.5%, 0% and 0%. Patients treated by a combined approach during laparotomy of RF plus hepatic resection, however, showed a significant higher morbidity rate (31.8%) and mortality rate (4.5%).

Several risk factors for complications can be identified. For example, subcapsular tumours carry a higher risk of abdominal bleeding. Bleeding was most often encountered during the percutaneous and laparoscopic approach and was generally self-limiting and did not require transfusion. Careful cauterisation of the electrode track can prevent this complication. Thermal damage of neighbouring organs is found exclusively in the percutaneous approach. For this reason, an open or laparoscopic approach is advised for subcapsular tumours within 2 cm of adjacent viscera. Biliary tract damage exclusively occurs in central tumours. Tumours closer than 1 cm to the main biliary ducts are generally considered a contraindication to RF. The risk of electrode seeding is limited to the percutaneous approach and is generally assumed to be between 0.2% and 2.8%. One group describes a rate of 12.5%. Careful cauterisation of the electrode track should be performed to prevent this complication. RF of subcapsular tumours carries a higher risk of track seeding than deeper situated tumours. For this reason, subcapsular tumours should not be approached by a perpendicular route during the percutaneous approach. For these tumours, a laparoscopic approach or open approach is often a better choice.

With regard to other thermal ablation methods, such as laser and microwave, percutaneous application results in a complication rate comparable to percutaneous RF.

Cryoablation

In many series, cryoablation is used during laparotomy in combination with hepatic resection. This means that the complication rate in these series can often not be attributed to cryoablation *per se*. These studies report a morbidity rate between 10% and 30%, with a mortality rate varying from 0% to 7% [24]. Cracking of the ice ball is a typical feature related to the cryosurgical procedure. In a large overview on cryosurgery, this was encountered in 19% of the cases and could result in significant haemorrhage. Complications of cryoablation mentioned in this overview are chest infection (12.9%) haemorrhage (3.9%), coagulopathy (3%), biloma (2.9%), abscess formation (1.7%) and acute renal failure (1.4%). Some of these complications, such as acute renal failure and coagulopathy, may fit into the phenomenon of cryoshock. This is a syndrome of multiorgan failure, severe coagulopathy and diffuse intravascular coagulation, similar to septic shock. Massive tissue destruction and cytokine release, as can occur during cryoablation of large tumour volumes, are probably at the basis of this phenomenon. Three studies directly compared the complication rate during cryotherapy and RF [8,9,13]. In a retrospective study [9], the complication rate during cryosurgery ($n = 130$) was 17% compared with 0% during RF of small lesions ($n = 28$). Complications increased significantly for larger lesions treated by RF. RF for lesions larger than 3 cm ($n = 13$) resulted in a complication rate of 47% mainly caused by abscesses (23%), compared with 24% for cryoablation ($n = 130$). In a prospective series [8] comparing intraoperative cryoablation ($n = 54$) with RF ($n = 92$) the complication rate was 41% and 3%, respectively. Mortality rates were 2% and 0%. The median greatest diameter of the tumours treated was comparable for both groups, 3.6 cm for cryo and 3.8 cm for RF. In this series, no intrahepatic abscess formation was observed in the RF group compared to 19% in the cryo group. In a recent series [13], percutaneous cryoablation was compared to percutaneous RF. The distribution of tumour types (±45% metastatic disease), tumour number and tumour size was similar between both groups. The mean largest tumour diameter treated per patient was 22 mm in the cryo group versus 28 mm in the RF group. Complication rates in the cryo group and the RF group were respectively 29% and 24%.

Failure of treatment

Local tumour control is the primary aim of local tumour destruction. Hence, local tumour recurrence should be considered as primary failure of therapy. However, whether local tumour destruction of colorectal liver metastases is useful is a completely different issue which should be judged by the effect of this treatment modality on disease-free and overall survival rates.

Local tumour recurrence after radiofrequency and other thermal techniques

Despite the fact that many studies report on the effect of RF on local tumour control, it remains difficult at this stage to define specifically the results of RF in colorectal liver metastases. In the analysis of most studies, several different tumour types are included, ranging from colorectal liver metastases to melanoma metastases, as well as other tumour types, such as HCC and endocrine tumours. Moreover, additional treatment by chemotherapy may obscure the primary effect of RF treatment. In addition, results on local tumour recurrence are often reported in a different way, either as the number of failures on a lesion basis, or as the number of patients with local recurrence in relation to the total number of patients treated.

Initially, two series were reported on the use of RF for different types of tumours during laparotomy. Wood reported on 84 patients with 231 lesions, of which 70 lesions were of colorectal origin [14]. Seventy one percent of the cases were treated by laparotomy. Overall, a local recurrence rate of 6.5% on a lesion basis and 18% on a patient basis were reported. Curley et al. reported on a comparable group of 123 patients, of which 61 patients had colorectal metastases, a local recurrence rate on a lesion basis of 2% and 2.5% on a patient basis [15]. Median diameter of the lesions in both studies was 2 cm and 3.4 cm, respectively. Later studies also included patients treated by a laparoscopic approach [9,19,20]. These studies observed a local recurrence rate on a lesion basis of between 3% and 12%, while local recurrence on a patient basis varied between 7% and 26%. Median diameter of the lesions treated in these studies varied from 2 cm to 3 cm. For the percutaneous approach, results vary significantly. De Baere et al. treated 86 patients with 121 lesions, of which 76 patients had colorectal liver metastases [16]. Median diameter of the lesion was 1.9 cm. Local recurrence on a lesion basis in this series was 9% vs. 16% on a patient basis. Solbiati et al., however, showed significantly higher local recurrence rates in 117 patients with 179 colorectal liver metastases [17]. In this series, with a median diameter of the lesion of 2.6 cm, the local recurrence rate on a lesion basis was as high as 39%. For lesions over 4 cm in diameter, local recurrence was 68%. This finding was in agreement with Wood et al. [14] and Bilchick et al. [9] who reported local recurrence rates for tumours larger than 3 cm of respectively 33% and 38%.

So far, it seems that for lesions up to 3 cm, RF is effective and can result in definite local tumour control in more than 90% of the lesions treated. For lesions larger than 3 cm, local recurrence rates at the site treated are still high and are reported to be over 30%. With the RF probes that are currently available, a necrotic lesion up to 4 cm can be achieved with one probe insertion. For tumour lesions larger than 4 cm, multiple probe insertions are necessary to obtain a treatment zone large enough to include all of the tumour tissue. It seems that the efficacy of these overlapping treatment zones is still unreliably resulting in high local recurrence rates. However, technology in the design of RF probes will improve and, in due course, probes will become available that can treat lesions larger than 4 cm in diameter. Another reason for local recurrence may be the approximation of tumour tissue to large vessels. Large vessels may be the cause of loss of heat generated during the ablation process and hence insufficient temperatures are obtained in the edge of tumour tissue close to the vessel lumen. Even for tumours smaller than 3 cm, this may result in inadequate treatment. Moreover, the different series give a slight indication that laparoscopic RF and RF performed during open surgery seems slightly more reliable than percutaneous RF. During these approaches, the surgeon has the opportunity to reduce the heat sink effect by the large vessels by clamping the portal ligament.

In colorectal liver metastases, experience with other thermal ablation techniques such as interstitial laser photocoagulation (ILP) and microwave ablation, is still limited [23]. For ILP, reported local control rates vary significantly. Local control is highly dependent on tumour size and can generally only be obtained for lesions smaller than 4 cm in diameter. Vogl reports on percutaneous ILP in a series of 324 patients with liver metastases and primary liver tumours. Local control rates in this series varied from 71% in the first 100 patients to 97% in the last group of patients that were treated by a percutaneous cooled-tip system [29]. Microwave tumour ablation has hardly been used for colorectal liver metastases. In general, local control rates are comparable to those of ILP.

Local tumour recurrence after cryoablation

Lesions treated by cryoablation are considerably larger than those described in series using thermal ablation. In most series using cryoablation, the maximum diameter of the lesions treated varies from 1 cm to 15 cm, with a median diameter of 4 cm. For cryoablation used during laparotomy, local recurrence rates on a lesion basis vary from 2% to 14%; on a patient basis, this figure varies from 7% to 44% [1–13]. Reasons for local recurrence are generally the position of the metastases close to large blood vessels and the diameter of the metastases. As with thermal ablation, cryoablation becomes less accurate in cases where multiple probe insertions with overlapping treatment zones are required in order to incorporate the whole lesion in the treatment zone. This is generally the case in tumours with a diameter larger than 5–6 cm. Indeed, several series describe that local recurrences were only seen when tumour diameter exceeded 5–6 cm.

There are 3 series which directly compare the efficacy of cryoablation and RF. Using an open approach during laparotomy, Pearson et al. described a non-randomised consecutive series of 54 patients treated by cryoablation and 92 patients treated by RF [8]. The indications and diameter of the lesions treated were comparable in both groups. Local recurrences were identified in 13.6% of the lesions treated by cryoablation and in 2.2% of the lesions treated by RF. Bilchik and colleagues observed a local recurrence rate during cryoablation of 5% on a lesion basis versus 3% during RF [9]. On a patient basis, these figures were 15% and 7%, respectively. For lesions larger than 3 cm, however, the local recurrence rate for RF was significantly higher (36% on a patient basis) than for cryoablation (17% on a patient basis). Therefore, in patients with unresectabe lesions they recommend a diversified approach, using cryosurgery during laparotomy for lesions larger than 3 cm and RF either by laparotomy, laparoscopy or percutaneously for unresectable lesions smaller than 3 cm. More recently, a third study described the results of percutaneous cryoablation versus percutaneous RF [13]. In this study only lesions smaller than 5 cm were included. Local recurrence rates after cryoablation were 53% on a lesions basis versus 18% during RF.

The data on local recurrence after different ablative procedures are difficult to interpret, since indications and applications differ considerably between the studies, while data from randomised studies are not available. However, with these limitations in mind, it seems that for lesions up to 3 cm in diameter, local recurrence rates are low for both RF and cryoablation (2–9% on lesion basis). For lesions larger than 3 cm in diameter, local recurrence rates start to increase significantly for RF to over 33% on a lesion basis. For cryosurgery, this increase in local recurrence seems to start from a diameter of 5–6 cm. RF seems to be accurate during the percutaneous approach as well as during laparotomy or laparoscopy. For cryoablation, promising results are only described for the open approach.

Effect of local ablative treatment on survival

The efficacy of local tumour ablation in terms of effect on survival is difficult to assess because most reports include different patient selection criteria, different treatment protocols and sometimes even different types of tumour (Tables 1 and 2). Although nearly all studies mention that local tumour ablation was exclusively used for unresectable lesions, criteria for resection seem to differ considerably between the studies. Accordingly, the extent of metastatic disease treated in the different series may vary significantly and hence may directly influence data on disease-free and overall survival.

Radiofrequency

Overall survival

One year overall survival after RF of unresectable colorectal liver metastases varies generally between 80% and 93%, 2-year overall survival is reported between 50 and 69% [8,9,13–20]. In the patient populations selected in the different studies, the number and diameter of lesions is generally low. In most studies, the mean number of metastases is less than 2, while most lesions treated are smaller than 3 cm. Between the studies, however, there are significant differences between these figures which indeed may reflect differences in resectability criteria. The way RF was applied varies considerably between the different studies. Most series include an open approach as well as the percutaneous or laparoscopic approach. The way in which RF was applied, however, does not seem to affect overall survival. In cases where the open approach was used, RF of unresectable lesions was often combined with resection of resectable lesions.

Disease-free survival

Disease-free survival (DFS) in all series varies considerably. In the series of Bleicher et al., in which a median of 2.9 lesions was treated per patient, DFS at a median follow-up of 11 months was 29%

[19]. Solbiati et al., however, who treated a median number of 1.5 lesions per patient, reported a DFS of 49% at 1 year follow-up by a combined treatment of RF plus chemotherapy [17]. These differences may indeed reflect differences in indications as well as treatment protocols. In general, it seems that, with the exception of one study by Curley et al. [15], who also treated patients with very limited disease (1.4 lesions per patient), DFS at 1 year is below 50%. For more than 90% of the cases, recurrent disease occurs outside the treated area, either within the liver or at extrahepatic sites.

Cryoablation

Overall survival

After cryoablation of colorectal liver metastases 1-year survival varies from 77% to 95%, 2-year survival rates from 50% to 78% [1–13]. Since cryoablation has been used for a longer period than thermal ablation, several studies report on 5 year survival rates which vary between the different series from 13% to 58%. In comparison to patients described in series using thermal ablation, patients selected for cryoablation showed more extensive liver disease. The number of metastases per patient varied from 1 to 16 with a median in most series of 3 or more lesions per patient. Also the diameter of the lesions was significantly larger: in most series median diameter of the lesions was 4 cm or more. Moreover, all series used a combined approach of resection and cryoablation. In most series, this meant that resection was used for resectable lesions and cryoablation as an adjunct for those lesions that could not be resected. In this way, resection criteria in the series using cryoablation seemed more uniform than in the series using thermal ablation and, in this respect, the studies reported on cryoablation probably give a better impression of the results that can be obtained with local tumour ablation in patients with unresectable disease. In two studies, the results of cryoablation in patients with colorectal liver metastases were directly compared with resection. In a series published by Finlay et al., 107 patients were treated, of which 75 patients underwent resection combined with cryotherapy and 32 patients underwent resection only [30]. There was no significant difference in overall survival between the groups. In another study by Rivoir et al., 131 patients with unresectable colorectal liver metastases were first treated by chemotherapy [12]. After 3–6 months of chemotherapy, curative surgery was considered possible in 57 patients, either by resection alone (33 patients) or by resection combined with cryotherapy (24 patients). Overall survival rates at 3 and 4 years were similar in both groups, 58% and 37% in the resection group, 50% and 36% in the resection plus cryotherapy group. In this series, in which all patients received postoperative chemotherapy, median survival after surgery was 39 months. This figure is higher than median survival reported in series without postoperative chemotherapy. For example, in series by Weaver et al. [4] and Ruers et al. [10], median survivals were 30 months and 32 months, respectively. One study directly compared the effect of additional chemotherapy after cryoablation [11]. In this study by Litvak et al., 185 patients underwent cryoablation with ($n = 71$) or without ($n = 114$) additional intrahepatic chemotherapy. Overall survival at 2 years was significantly different between the groups: 35% in the group without chemotherapy versus 75% in the group with additional chemotherapy.

Apart from postoperative chemotherapy, overall survival was influenced by the size of the metastases treated and the number of lesions per patient. Both Adam et al. [5] and Seifert et al. [6] reported a significantly better overall survival for cryo-treated lesions smaller or equal to 3 cm. Adam et al. reported a 2-year survival rate of 64% for lesions smaller than 3 cm, versus 33% for patients with treated lesions larger than 3 cm. With regard to the number of metastases, Rivoir et al. reported a 4-year survival rate of 18% in patients with 5 to 15 metastases, versus 49% in patients with 4 or less metastases [12].

Disease-free survival

As with RF, DFS rates vary considerably between different series. In general, DFS rates at 2 years are approximately in the range of 20–30% in those series without additional postoperative chemotherapy. Two series with additional postoperative chemotherapy show 2 year survival rates between 40 and 50% [11,12]. In patients with recurrent disease, the liver is involved in 70–85% of the cases, extrahepatic involvement is reported in 40–70% of the cases.

Conclusions

Until now, local tumour ablative techniques have mainly been used in patients with unresectable colorectal liver metastases. In these patients, tumour ablative therapy was used either alone or in combination with hepatic resection. For RF and cryoablation techniques, lesions up to 3 cm and 6 cm, respectively, can be treated effectively, with low local recurrence rates. Cryoablation is accompanied by an acceptable morbidity, but the technique is rather invasive and mainly applicable during laparotomy. In contrast, RF is characterised by a low morbidity rate, while the technique can be performed as a minimally invasive procedure during laparoscopy or percutaneously. For these reasons, RF is now recognised as the most appropriate technique for local tumour ablation within the liver, while cryoablation has been more or less abandoned. However, in patients with unresectable liver metastases, and hence more extensive liver disease, recurrence rates after local ablative treatment are high either as a result of liver recurrence outside the treated area or due to extrahepatic disease. Combined treatment of local ablative therapy plus chemotherapy is therefore currently favoured by several centres.

Whether local tumour ablation in patients with unresectable colorectal liver metastases is of any benefit in terms of survival, however, remains to be determined. Until now, only phase II studies have been performed, showing 2-year survival rates of between 50% and 75%. Although most of these data are derived from studies using cryoablation, it seems likely that in the near future more reports will be published on RF which will show equal or even better results.

Nevertheless, the utmost question that still needs to be answered is whether these local ablative therapies are of any benefit in terms of survival. Several studies on local ablative therapy have shown median overall survival times of more than 30 months. These results have been claimed to be superior to the standard treatment of chemotherapy, which nowadays can result in a median survival of 17–19 months. The superior results of local ablative therapy compared with chemotherapy may certainly be due to patient selection. Especially since patients selected for aggressive local treatment show only a limited number of liver metastases (most studies median number of approximately 4 or less), while patients reported in chemotherapy series may show more widespread liver involvement or even extrahepatic disease.

In order to determine the place of local ablative therapy, controlled clinical trials are highly needed. One trial would concern patients with unresectable colorectal liver metastases in which aggressive local treatment of the metastases with RF plus chemotherapy is compared with the standard treatment of chemotherapy alone. Such a trial is running at the moment as a multicentre Intergroup trial by the European Organisation for Research and Treatment of Cancer, the Arbeitsgemeinschaft für Leber Metastasen in Germany, and the NCRI colorectal cancer group in the UK (information: *nga@eortc.be*). Another study would concern the place of RF in the treatment of resectable colorectal liver metastases. Such a study is running at the moment in France, in which RF treatment is directly compared to resection in patients with resectable colorectal liver metastases. Until the results of these studies are available, local tumour ablation for colorectal liver metastases should be considered experimental and should mainly be performed within well controlled clinical trials.

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