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Factors influencing local tumour progression after radiofrequency ablation of malignant liver tumours

Mantas Trakymas,

Albertas Ulys,

Edita Mišeikytė Kaubrienė

Institute of Oncology,
Vilnius University,
Vilnius, Lithuania

Introduction. Local tumour progression remains the main problem after radiofrequency ablation of liver tumours and is usually the only factor of treatment efficacy. The aim of our study was to assess factors predicting local tumour progression after radiofrequency ablation of malignant hepatic tumours that could be evaluated before intervention.

Materials and methods. We have studied 68 malignant primary and metastatic hepatic tumours treated by radiofrequency ablation. Ablation was performed using perfusion electrodes. Evaluation of tumours before ablation and during the follow-up was performed by means of contrast enhanced computed tomography and ultrasonography. Tumour type, size, echogenicity, density, enhancement pattern and proximity to large hepatic vessels closer than 5 mm were analysed as risk factors for local tumour progression. Local tumour progression was assessed by follow-up CT scans and ultrasonography. The Nelson–Aalen cumulative risk estimation method and log rank test were used for statistical analysis.

Results: 58 successfully treated hepatic tumours were suitable for the final analysis. The local progression of nine (15.5%) tumours was detected in the follow-up. The mean follow-up time for the tumours was 16.3 months, range 1.7 to 38.7 months. The size of the tumour more than 30 mm in diameter and its proximity closer than 5 mm to large hepatic vessels were identified as risk factors for local tumour progression after radiofrequency ablation. Tumour type, echogenicity, density and enhancement pattern had no significant influence.

Conclusions. The size of the tumour and its proximity to hepatic vessels closer than 5 mm should be taken into consideration when performing radiofrequency ablation of liver tumours and during the follow-up.

Key words: radiofrequency ablation, hepatic tumours, local tumour progression, risk factors

INTRODUCTION

There are two main types of malignant tumours in liver: primary hepatic cancer and metastases from other malignant tumours in the body. Hepatocellular carcinoma (HCC) is the primary malignant tumour of hepatocyte and the sixth most common cancer worldwide. About 711,000 new cases were estimated to occur in 2007 (1). Hepatocellular carcinoma develops in a cirrhotic liver in 80% of cases, and this pre-neoplastic condition is the strongest predisposing factor. Chronic hepatitis B viral (HBV) infection is the predominant risk factor in Asia and Africa and chronic hepatitis C viral (HCV) infection in Western countries and Japan (2). The most common sites of metastases from other primary cancer are lymph nodes, followed by the liver. Colorectal cancer gives metastases to the liver most commonly. Worldwide, nearly 1.2 million cases of colorectal cancer were expected to occur in 2007 (1). The majority of patients with colorectal cancer eventually develop liver metastases, and in 30% to 40% of them metastases are confined to the liver. Unfortunately, only 10% to 15% of all patients are candidates for hepatic resection which gives a 25% to 33% 5-year survival (3, 4).

For about a decade, radiofrequency ablation (RFA) has been applied for treating primary hepatocellular carcinoma and metastatic colorectal liver cancer (5–9). This treatment has been shown to prolong the overall survival of these patients as compared with untreated patients or results of chemotherapy. The 5-year survival after radiofrequency ablation approaches the results of liver resection (10–14). Radiofrequency ablation and its benefits in selected patients

Correspondence to: Mantas Trakymas, Institute of Oncology, Vilnius University, Santariškių 1, LT-08660 Vilnius, Lithuania.
E-mail: mantas.trakymas@vuoi.lt

with liver metastases from primaries other than colon cancer have also been reported (15–20). The major problem of this method of treatment is local tumour progression (LTP) in the periphery of the ablation zone. As treatment response of radiofrequency ablation and local tumour progression are evaluated with a continuously repeated radiological follow-up, the lack of direct documented treatment radicality is the main limitation of all local ablation techniques as opposed to surgery which may directly assess the resection margin through histological analysis (21). The ablation margin is usually assessed indirectly from pre- and post- ablation radiological images. This evaluation may in some cases be imprecise and result in local tumour progression detected later (22). The aim of our study was to assess factors predicting local tumour progression after radiofrequency ablation, which could be evaluated before intervention. We have hypothesised that the type, size, echogenicity, density, enhancement pattern of tumour and its proximity closer than 5 mm to large hepatic vessels are the risk factors of local tumour progression.

MATERIALS AND METHODS

The study was performed in 2005–2008 with the permission of the Lithuanian Bioethics Committee. Sixty-eight primary and metastatic hepatic tumours were enrolled in the study, but only 58 successfully treated hepatic tumours were suitable for the final analysis. These were hepatocellular carcinoma, liver metastases from colorectal, breast, ovarian, renal and gallbladder cancer as well as from sarcoma and ocular melanoma (Table 1). All tumours were assessed with CT and ultrasound before radiofrequency ablation, one month after radiofrequency ablation and then every three months. Three phase CT scans were obtained in the axial plane with the spiral equipment (Lightspeed 32 PRO, GE). Tumour size, density, contrast enhancement pattern and proximity closer than 5 mm to hepatic vessels larger than 3 mm in diameter were registered. Ultrasound examinations were done with a Voluson 730 PRO, GE apparatus 3.5–5 MHz convex probe using tissue harmonic imaging, colour and power Doppler technique. Tumour size, echogenicity and vascularisation were registered.

Radiofrequency ablation was performed using an Elektrotom Hitt® 106, Integra™, a 375 kHz impedance regulated generator which operates at power 10 to 60 W, with 16 G and 20 mm active tip straight needle type perfusion electrodes. All procedures were done percutaneously under general anaesthesia and guided by ultrasound. They were all monopolar single electrode ablations. During radiofrequency ablation, the flow of sterile saline was automatically controlled by a power-related perfusion system depending on tissue impedance. The power of radiofrequency current was gradually increased by 10 W from 30 W to 60 W every 5 minutes. One application lasted 20 minutes. Tumours up to 10 mm in diameter were treated with a single electrode placement. Lager tumours were treated with multiple electrode placements by overlapping ablations to ensure 10 mm ablation margin. The number of electrode placements for overlapping ablations ranged from 3 to 6. The overlapping cylinders strategy was used. The ablation zone was predicted according to a transient hyperechoic zone and the mean transverse diameter of ablation zone of 27 mm, estimated and reported by other authors (23–25). Ablation was considered technically successful, if the tissue impedance during ablation remained pulsing and was not automatically stopped. To prevent tumour seeding, we first ablated the part of the tumour proximal to the electrode and then its more distal parts. When the predicted ablation zone encompassed the entire tumour with a 10-mm ablation margin, the ablation was completed. Haemorrhage and needle tract seeding after radiofrequency ablation were prevented by coagulation of the electrode tract using a power setting of 25 W with the perfusion system switched off. Neither periprocedural nor major late complications after radiofrequency ablation developed.

Three-phase CT scan and ultrasound examination were repeated following one month after radiofrequency ablation to assess the effectiveness of the technique. The size of the ablation zone and contrast enhancement in the ablation zone or in contact with it were assessed on CT scans. The size of the ablation zone was also assessed by ultrasonography. If both diagnostic methods showed an ablation zone encompassing the entire tumour and no contrast enhancement was observed in the ablation zone or in contact with it, this was considered as technically effective ablation. Otherwise, ablation was repeated until a complete response. Only radiologically complete ablations were analysed for local tumour progression-free survival. In one case, the technique effectiveness was not reached even after repeated ablations as the tumour was in a close proximity to a large portal vein. Ultrasonography after one month showed hypoechoic tumour near the ablation zone. This tumour was not included in the analysis. The other nine tumours were also excluded from the further analysis because one patient with one tumour refused to continue participating in the study, one patient with two tumours developed an anaphylactoid adverse reaction to intravenous contrast media on initial evaluation and the three-phase CT scan was not repeated after radiofrequency ablation, and three patients did not arrive for technique effectiveness evaluation after radiofrequency ablation.

The follow-up consisted of CT scans and ultrasound examination every three months until local tumour progression. The local tumour progression on follow-up CT scans was defined by three patterns, the first being nodular contrast enhancement along the periphery of the ablation zone, the second a halo pattern of the irregular rim of enhancement around the ablative zone, and the third a gross enlargement of the ablation zone (26, 27). Local tumour progression on ultrasonography was defined either by nodular growth in the periphery of the ablation zone or by a gross enlargement of the lesion on the follow-up.

Table 1. **Characteristics of the tumours**

Histological type	Frequency	Percentage
Colorectal cancer metastases	35	60.3
HCC	5	8.6
Breast cancer metastases	5	8.6
Ovarian cancer metastases	1	1.7
Ocular melanoma metastases	5	8.6
Sarcoma metastases	4	6.9
Renal cancer metastases	2	3.4
Gallbladder cancer metastases	1	1.7
Total	58	100.0

Local tumour progression rates are expressed as the percentage progressing for 3 years calculated using the Nelson–Aalen cumulative risk estimation method. The Nelson–Aalen curves comparing local tumour progression probability for different histological type, size, echogenicity, density, contrast enhancement pattern and proximity closer than 5 mm to large hepatic vessels of tumours are shown for up to 3-year follow-up. The log rank test was used to test the difference between the curves. All analyses were carried out in STATA version 8. The significance level was taken as $p < 0.05$.

RESULTS

A total of 58 successfully ablated tumours were included in this analysis. The primary effectiveness rate of ablation for these tumours was 100%. The mean follow-up time for the tumours was 16.3 months (range, 1.7 to 38.7 months). For nine tumours (15.5%), local tumour progression was detected during the follow-up both on CT scans and ultrasonography within 18 months after ablation. The maximal diameter of the tumours measured on CT scans and on ultrasonography differed. The median maximal tumour diameter on CT scans was 20.7 mm and on ultrasonography 22.8 mm (range, 6 to 44 mm). The difference was not significant, and only the larger diameters were taken for the analysis.

We have evaluated the influence of the histological type, size, echogenicity, density, contrast enhancement pattern of the tumours and their proximity to large hepatic vessels on local tumour progression (Table 2).

The Nelson–Aalen cumulative hazard estimates and log rank test showed the size of the tumour and its proximity to hepatic vessels larger than 3 mm in diameter to be significant prognostic factors for local tumour progression after radiofrequency ablation (Figs. 1 and 2).

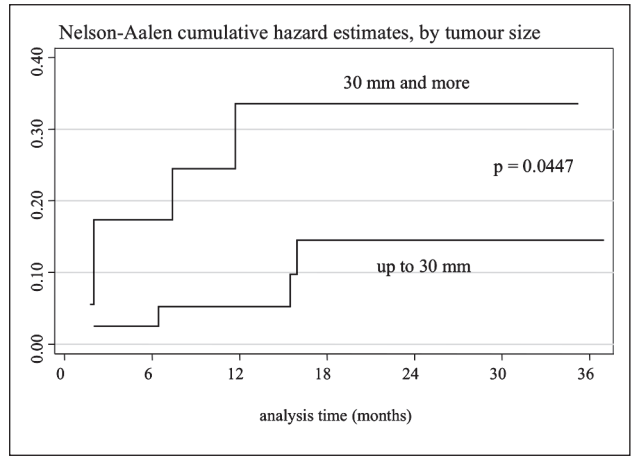

Fig. 1. Nelson–Aalen cumulative hazard curves depicting local tumour progression based on tumour size up to 30 mm and 30 mm and more. The probability of local tumour progression for small tumours was significantly lower than for intermediate tumours

Table 2. **Determinants of local tumour progression (LTP) after radiofrequency ablation of malignant hepatic tumours (n = 58)**

Factor for LTP	Categories, number of tumours (LTP rate)		Log rank test
Histological type	Colorectal liver metastases	35 (20%)	p = 0.234
	Other	23 (8.7%)	
Tumour size	Up to 30 mm	40 (10%)	**p = 0.0447**
	30 mm and more	18 (28%)	
Tumour echogenicity	Hypoechoic	35(20%)	p = 0.5392
	Isoechoic	19 (10.5%)	
	Hyperechoic	4 (0%)	
Tumour density	Hypodense	45 (20%)	p = 0.1137
	Isodense	13 (0%)	
Contrast enhancement pattern	Hypovascular	16 (6%)	p = 0.1393
	Slightly enhancing	35 (23%)	
	Arterial	7 (0%)	
Proximity closer than 5 mm to large hepatic vessels	Close to large vessels	14 (36%)	**p = 0.0126**
	Far from large vessels	44 (9%)	

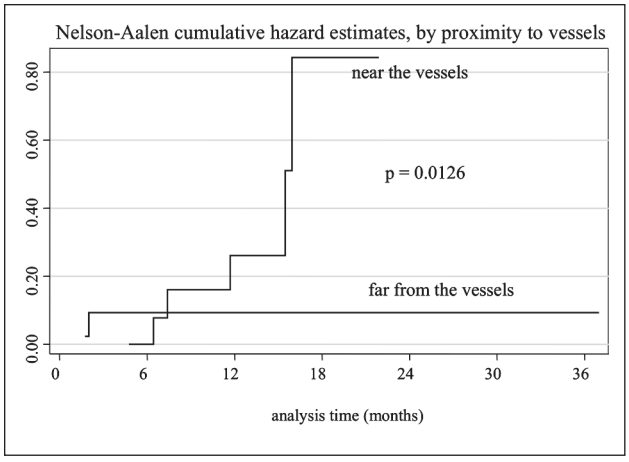

Fig. 2. Nelson–Aalen cumulative hazard curves depicting local tumour progression based on tumour proximity to hepatic vessels larger than 3 mm in diameter. The probability of local tumour progression for tumours far from large hepatic vessels was significantly lower than for those near the vessels

DISCUSSION

The rate of local tumour progression in the literature ranges from 2% to 60% (28–30). In metaanalysis, Mulier et al. reported the overall local tumour progression to be 12.4% from e total of 5224 tumours analysed (31). Local tumour progression is the most important determinant of the technique effectiveness in radiofrequency ablation. It is detected by means of a periodical radiological follow-up. But also the time of this follow-up plays a great role because many authors report local tumour progression detected 6 up to 23 months after radiofrequency ablation (31). In our study, the mean follow-up period embraced 16.3 months. We demonstrated an overall local tumour progression of 15.5%. Other authors present similar data on local tumour progression – 22% (32), 20% (33), 23%(34) and 9% (35), although there are much higher rates reported (36). Our study was concentrated on risk factors for local tumour progression rather than on its general rate. These risk factors were evaluated before radiofrequency ablation. The size of the target tumour is the main risk factor defined as significant by many authors. Tumours are classified as small (diameter 30 mm or less), intermediate (30–50 mm) and large (diameter more than 50 mm) according to the recently proposed standard terminology of image-guided tumour ablation (25). We enrolled only small and intermediate tumours in our study, and we have found small tumours to progress locally significantly less than intermediate ones. As we used single electrode placement for tumours smaller than 10 mm in diameter and the other tumours were treated with overlapping ablations, this factor should not influence the result. Some investigators have reported different sizes of tumours, such as more than 20 mm (37), 23 mm (34), 25 mm (7), to be significant risk factors for local tumour progression. There are some papers reporting tumour size not to be a risk factor (38–41). Netto et al. analysed HCC tumours up to 50 mm in diameter, but the endpoint of this study was histological examination of posttransplant specimens of RFA-treated HCC and not local tumour progression. The extent of coagulation necrosis was divided into several groups according to the percentage of necrosis in tumour. When considering LTP, only a 100% necrosis assures LTP-free survival (38). Nakazawa et al. analysed only tumours smaller than 30 mm in diameter (39). Rodriguez et al. also analysed posttransplant specimens; however, incompletely ablated tumours were larger, and the significance was not detected (40). Sofocleous et al. analysed small and intermediate primary and metastatic liver tumours, but the only significant risk factor in this study was presence of viable tumour tissue adherent to the radiofrequency electrode, but not the size of the tumour. This study demonstrated that both the size and presence of viable tumour tissue adherent to the radiofrequency electrode were significant risks factors for local tumour progression for tumours 30–50 mm in size. Multivariate analysis demonstrated that for tumours smaller than 30 mm in the largest diameter, only the viable tumour on the electrode was an independent risk factor for local tumour progression. Our data showed tumours larger than 30 mm in diameter to progress significantly more frequently. In the opinion of other authors, this size remains crucial (42, 43).

Data on tumour proximity to large hepatic vessels as a risk factor for local tumour progression differ. A large hepatic vessel certainly alters the distribution of temperature in its vicinity. The heat sink phenomenon is widely known in the radiofrequency ablation-related literature. But the literature is not definite regarding the influence of vessels contiguous to a tumour on local tumour progression (31). Some papers report proximity to vessels to be a risk factor (32), while others find it to have no relation to local tumour progression (22, 33, 34, 39). Some authors mention a 5-mm distance to a large vessel as a risk factor (39), whereas other papers indicate a direct contact of tumour with a large hepatic vessel (22, 32). Data on the influence of tumour proximity to large hepatic vessels on LTP-free survival are not consistent, and sometimes a greater distance gives more LTP than do tumours in contact with a vessel. Our data have shown tumour proximity closer than 5 mm to large hepatic vessels to be a significant risk factor for local tumour progression after radiofrequency ablation, and despite heterogeneous data, this fact should be considered when selecting a strategy for radiofrequency ablation of such tumours.

The histological type of a tumour was not detected as a risk factor for local tumour progression in our study. Berber et al. reported colorectal cancer metastases to be associated with a higher level of local tumour progression, but they were compared with neuroendocrine metastases which show a significantly slower natural growth (32). We did not analyse neuroendocrine metastases, but no significant differences in local tumour progression-free survival among hepatic malignancies were found in our study. Sofocleous

et al. evaluated local tumour progression for patients with hepatocellular carcinoma and colorectal cancer metastases, and no significant differences in local tumour progression between these two groups were found (41).

Our results showed that tumour echogenicity, density and contrast enhancement pattern evaluated before radiofrequency ablation had no influence on local tumour progression. All these are imaging factors that influence tumour visibility after radiofrequency ablation. As only radiologically completely ablated tumours were analysed in our study, we hypothesised that some viable portions of a tumour were not visible on CT or ultrasonographical images and would progress during the follow-up. However, the difference among these groups was not significant, possibly because usually a visible tumour is ablated, but a microscopic tumour invasion, which may extend from 9 to 21 mm, remains not ablated (31). Paulet et al. have reported tumour hyperechogenicity and hypodensity to be a significant risk factors for local tumour progression, but they analysed only hepatocellular carcinoma. This finding was explained by the size of the tumours. Small hepatocellular carcinomas are usually hypo- or isoechoic, while larger tumours, due to keratinisation, become hyperechoic as they grow (33).

CONCLUSIONS

Tumour size and its proximity to large hepatic vessels are significant risk factors for local tumour progression after radiofrequency ablation of malignant liver tumours. These factors should be taken into account when selecting patients with malignant hepatic tumours for radiofrequency ablation because they can influence the further progression of the disease. Such patients at risk should be also closely monitored for a possible local tumour progression to employ adequate treatment measures as soon as possible.

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Mantas Trakymas, Albertas Ulys, Edita Mišeikytė Kaubrienė

VEIKSNIAI, TURINTYS ĮTAKOS VIETINIAM PIKTYBINIŲ KEPENŲ NAVIKŲ PROGRESAVIMUI PO RADIJO DAŽNIO ABLIACIJOS

Santrauka

Įvadas: Nors vietinis naviko progresavimas yra esminė problema atliekant piktybinių navikų kepenyse radijo dažnio abliaciją, visgi dažniausiai tai yra vienintelis rodiklis, apibrėžiantis šio gydymo metodo veiksmingumą. Mūsų tyrimo tikslas buvo nustatyti vietinio naviko progresavimo po radijo dažnio abliacijos rizikos veiksnius, kurie gali būti įvertinami prieš atliekant intervenciją.

Tyrimo medžiaga ir metodai. Į tyrimą buvo įtraukti 68 pirminiai ir metastaziniai navikai kepenyse, kuriems buvo atliekama radijo dažnio abliacija naudojant perfuzijos elektrodus. Navikai prieš abliaciją ir po jos atliekant kontrolinius tyrimus buvo vertinami kompiuterinės tomografijos ir ultragarsinio tyrimo metodais. Navikų tipas, jų

dydis, echogeniškumas, kompiuterinės tomografijos tankis, kontrastinės medžiagos kaupimo pobūdis ir padėtis arčiau nei 5 mm šalia stambių kepenų kraujagyslių buvo nagrinėjami kaip vietinio naviko progresavimo rizikos veiksniai. Statistinei analizei buvo taikomas Nelson–Aalen kumuliacinės rizikos vertinimo metodas, o skirtumai įvertinti naudojant log rank testą.

Rezultatai. Galutinei analizei buvo tinkami 58 sėkmingai abliuoti navikai. Radiologinio stebėjimo metu buvo nustatyti devyni (15,5%) vietinio naviko progresavimo atvejai. Vidutinis analizuotų navikų stebėjimo laikas buvo 16,3 mėnesio (nuo 1,7 iki 38,7 mėnesio). Nustatyta, kad didesni kaip 30 mm skersmens navikai ir tie, kurie lokalizuojasi arčiau nei 5 mm šalia stambių kepenų kraujagyslių, vietiškai progresuoja reikšmingai dažniau. Tuo tarpu navikų tipas, echogeniškumas, kompiuterinės tomografijos tankis ir kontrastinės medžiagos kaupimo pobūdis reikšmingos įtakos vietiniam naviko progresavimui po radijo dažnio abliacijos neturėjo.

Išvados. Atliekant navikų kepenyse radijo dažnio abliaciją reikia ypatingai atsižvelgti į naviko dydį ir jo padėtį šalia stambių kepenų kraujagyslių, nes šie veiksniai turi įtakos vietiniam naviko progresavimui. Taip pat šie navikai turi būti atidžiai stebimi po abliacijos, kad būtų laiku pritaikyti adekvatūs gydymo būdai.

Raktažodžiai: radijo dažnio abliacija, navikai kepenyse, vietinis naviko progresavimas, rizikos veiksniai