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Mantas Trakymas

THE RESEARCH OF RISK FACTORS FOR LOCAL PROGRESSION OF MALIGNANT HEPATIC TUMOURS TREATED BY RADIOFREQUENCY ABLATION

Summary of doctoral dissertation

Biomedical sciences, medicine (07 B, cytology, oncology, cancerology B200)

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The study has been performed at the Institute of Oncology, Vilnius University during the period of 2005-2008.

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VILNIAUS UNIVERSITETAS
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Mantas Trakymas

PIKTYBINIŲ NAVIKŲ, ESANČIŲ KEPENYSE, VIETINIO PROGRESAVIMO RIZIKOS VEIKSNIŲ TYRIMAS TAIKANT RADIJO DAŽNIO ABLIACIJĄ

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Introduction

There are two main types of malignant liver tumours: 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 worldwide (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 virus (HBV) infection is the predominant risk factor in Asia and Africa, and chronic hepatitis C virus (HCV) infection in Western countries and Japan (2). The most common sites of metastases from other primary cancer are lymph nodes, followed by 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, in 30% to 40% of them metastases being 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).

Radiofrequency ablation (RFA) for the treatment of primary hepatocellular carcinoma and metastatic colorectal liver cancer has been applied for about one decade (5-9). This treatment showed to prolong the overall survival of patients treated applying radiofrequency ablation as compared with patients who were untreated or treated with chemotherapy. The 5-year survival after radiofrequency ablation approaches the results of liver resection (10-14). Radiofrequency ablation and its benefits in selected patients 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 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). Despite radiological evidence of local tumour progression, its histological proof is usually preferred.

Before radiofrequency ablation tumours have certain morphological and radiological characteristics that may influence long-term results. Tumour natural growth may differ depending on the morphology of primary tumour. Tumour size is an important risk factor for incomplete ablation as the larger the tumour is the more difficult to treat it. Large hepatic vessels cool the nearby tissue and the ablation of tumours in the vicinity to these vessels becomes complicated. The zone of ablated tumour is not distinguished from the ablation zone on CT scans. The ablation zone itself is hypodense and hypovascular therefore evaluation of the primary effectiveness of radiofrequency ablation of hypodense and hypovascular tumours is very difficult.

The aim of the study

To investigate and evaluate the prognostic value of computed tomography (CT) and ultrasonography (US) along with the histological results of core biopsy material from ablated tumour for the early assessment of radiofrequency ablation effectiveness.

Objectives

1. To evaluate the results of histological assessment of core biopsy material taken from the ablation zone one month after radiofrequency ablation of malignant hepatic tumours and to correlate them with results of radiological follow up;
2. To identify morphological risk factors of local tumour progression after radiofrequency ablation and to determine their significance;
3. To identify radiological risk factors of local tumour progression after radiofrequency ablation and to determine their significance.

Defended statements

1. The result of histological examination of core biopsy material taken from the ablation zone one month after radiofrequency ablation of malignant hepatic tumour does not predict local tumour progression;
2. Tumour size and proximity of hepatic vessels are the risk factors for local tumour progression after radiofrequency ablation of malignant hepatic tumours;
3. Tumour type, tumour density and enhancement pattern in computed tomography and tumour echogenicity are not the risk factors for local tumour progression after radiofrequency ablation of malignant hepatic tumours.

Scientific novelty and originality

The effectiveness of radiofrequency ablation of malignant hepatic tumours is evaluated by periodical radiological follow up. It is defined by local tumour progression. Histological examination of tissue is another way to evaluate the effectiveness of radiofrequency ablation. It could be performed after resection of ablated tumour or after liver transplantation. In the latter case local tumour progression could not be assessed. We have analysed the influence of the result of histological examination on local tumour progression after radiofrequency ablation of malignant hepatic tumours. This has never been reported in the literature before.

We have also analysed the morphological and radiological features of malignant tumours as risk factors for local tumour progression after radiofrequency ablation. The value of morphological tumour's characteristics is inconsistent and not well established. The radiological characteristics of tumours have not been previously analysed as risk factors for local tumour progression.

Materials and methods

The study was performed from 2005 to 2008 with the permission of the Lithuanian Bioethics Committee. All tumours had been assessed with CT and ultrasound before radiofrequency ablation, 1 month after radiofrequency ablation and then every 3

months. Three-phase CT scans were obtained in the axial plane with spiral equipment (Lightspeed 32 PRO, GE). The tumour size, density, contrast enhancement pattern and vicinity closer than 5 mm to hepatic vessels larger than 3 mm in diameter were registered. Ultrasound examinations were done with Voluson 730 PRO, GE apparatus 3.5-5 MHz convex probe using tissue harmonic imaging, colour and power Doppler technique. The tumour size and echogenicity were registered.

Radiofrequency ablation was performed using Elektrotom Hitt® 106, Integra™, a 375 kHz impedance regulated generator which operates at 10 to 60 W power, 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 the 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 for 20 minutes. Tumours up to 10 mm in diameter were treated with a single electrode placement. Larger tumours were treated with multiple electrode placements by overlapping ablations to ensure a 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 the transient hyperechoic zone and mean transverse diameter of the 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 seeding of the tumour, we first ablated the part of the tumour proximal to the electrode and then the more distal parts of the tumour. 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 late major 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 was assessed on CT scans. The size of the ablation zone was also assessed by

ultrasonography. If both diagnostic methods showed ablation zone to encompass the entire tumour and no contrast enhancement was observed in the ablation zone or in contact with it, this was considered as a technically effective ablation. Otherwise the ablation was repeated until complete response. Percutaneous core biopsies from the ablation zone were performed under ultrasound guidance one month after radiofrequency ablation using a Bard® Magnum or Manan® ProMag automatic biopsy device and a 18 G (1.2 mm outer diameter) biopsy needle with the 22 mm biopsy sample notch. One to five tissue samples were harvested for one tumour depending on tumour size. Biopsy specimens were fixed in 10% formalin, sectioned, stained with hematoxylin and eosin and examined by conventional optical microscopy.

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 was nodular contrast enhancement along the periphery of the ablation zone. The second was a halo pattern of the irregular rim of enhancement around the ablative zone. The third was 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 follow up.

Local tumour progression rates are expressed as the percentage progressing for three years calculated using the Nelson Aalen cumulative risk estimation method. The Nelson Aalen curves comparing local tumour progression probability for the result of histological examination of ablation zone biopsy material, different histological type, size, proximity closer than 5 mm to large hepatic vessels, density as well as contrast enhancement pattern on CT and echogenicity of tumours are shown in up to 3 years of follow up. The log rank test was used to test the difference between the curves. The difference between the mean values of tumour size from CT and ultrasonography were tested by a paired *t* test. All analyses were carried out in STATA version 10. The significance level was taken as $p < 0.05$.

Results

In total 68 primary and metastatic hepatic tumours were enrolled in the study, but only 58 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 vicinity to a large portal vein. Ultrasonography after one month showed a 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 as one patient with one tumour refused to continue participating in this study, one patient with two tumours developed anaphylactoid adverse reaction to intravenous contrast media on initial evaluation, and three phase CT scan was not repeated after radiofrequency ablation; three other patients did not come for technique effectiveness evaluation after radiofrequency ablation.

Fifty-eight 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).

Table 1. Characteristics of analysed tumours.

Histological type	**Frequency**	**Percent**	**Median size (range) (mm)**
Colorectal cancer metastases	35	60.3	20 (6-43)
Hepatocelullar carcinoma	5	8.6	36 (13-39)
Breast cancer metastases	5	8.6	12 (8-39)
Ovarian cancer metastases	1	1.7	44
Ocular melanoma metastases	5	8,6	12 (9-28)
Sarcoma metastases	4	6.9	29 (13-35)
Renal cancer metastases	2	3.4	34 (25-43)
Gallbladder cancer metastases	1	1.7	26
Total	58	100.0	23,5 (6-44)

The primary effectiveness rate of ablation for these tumours was 100%. The mean follow up time for analysed tumours was 16.3 months with a range from 1.7 to 38.7 months. For nine tumours (15.5 %) local tumour progression was detected on follow up both on CT scans and ultrasonography within 18 months after ablation. The maximal diameter of the tumours measured on CT scans and ultrasonography differed. The median maximal tumour diameter on CT scans was 20.7 mm whereas on ultrasonography 22.8 mm, range 6 - 44 mm. The difference was significant ($p = 0.008$) and only the lager diameters were taken for the analysis (Table 2).

Table 2. The largest diameter of tumours established by ultrasonography (US) and computed tomography (CT).

Method	**Median**	**Mean**	**Standard deviation**	**Min**	**Max**
US	23	22.8	10.7	6	44
CT	20	20.7	10.3	6	44
US and CT	23,5	23.7	11.1	6	44

We have evaluated the value of the results of histological examination of ablation zone biopsy material, histological type, size, proximity to large hepatic vessels, density and contrast enhancement pattern on CT and echogenicity for the prognosis of local tumour progression (Table 3).

Table 3. 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**
The result of histological examination of biopsy tissue	Viable tumour	40 (17.5%)	p = 0.472
	Complete necrosis	18 (11%)	
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%)	
Proximity closer than 5 mm to large hepatic vessels	Close to large vessels	14 (36%)	**p = 0.0126**
	Far from large vessels	44 (9%)	
Tumour density in CT	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%)	
Echogenicity of the tumour	Hypoechoic	35 (20%)	p = 0.5392
	Isoechoic	19 (10.5%)	
	Hyperechoic	4 (0%)	

The data in Table 3 show the size of the tumour larger or equal to 30 mm and its proximity closer than 5 mm to large hepatic vessels to be significant risk factors of local tumour progression after radiofrequency ablation of malignant liver tumours.

The Nelson Aalen cumulative hazard estimates and log rank test haven't shown the result of a histological examination of the ablation zone biopsy material to be of a significant prognostic value for local tumour progression after radiofrequency ablation (Figure 1).

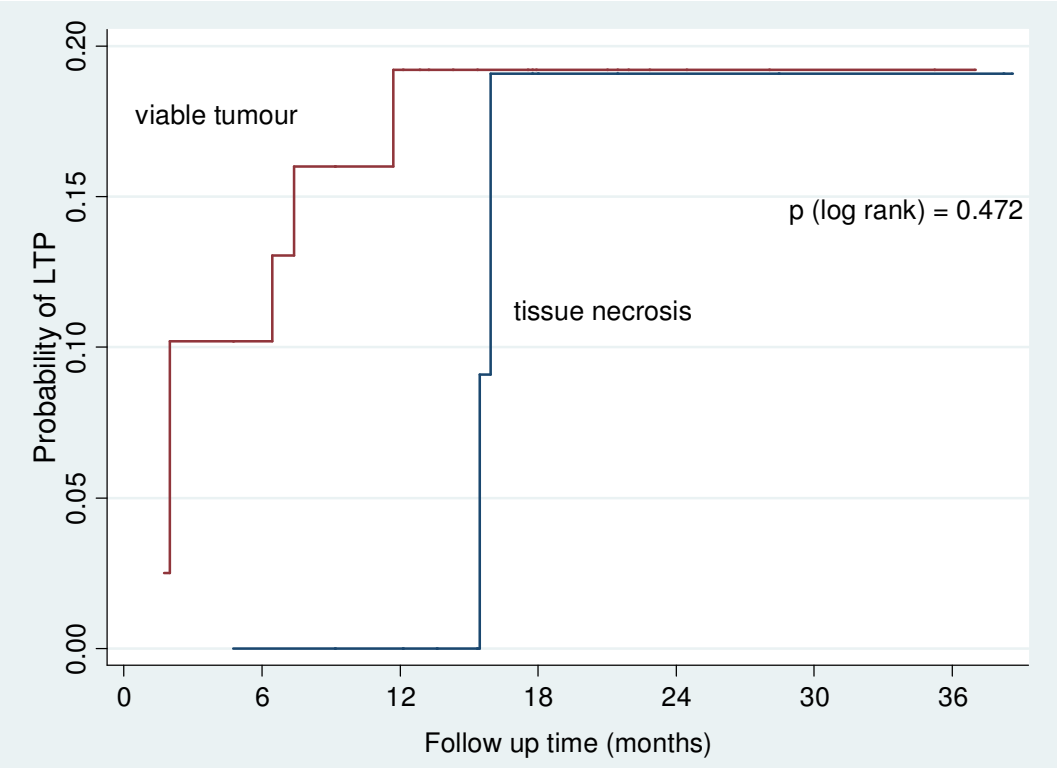

Figure 1. Nelson Aalen cumulative hazard curves depicting local tumour progression based on the result of histological examination of ablation zone biopsy material. The probability of local tumour progression for viable tumour was similar to complete necrosis.

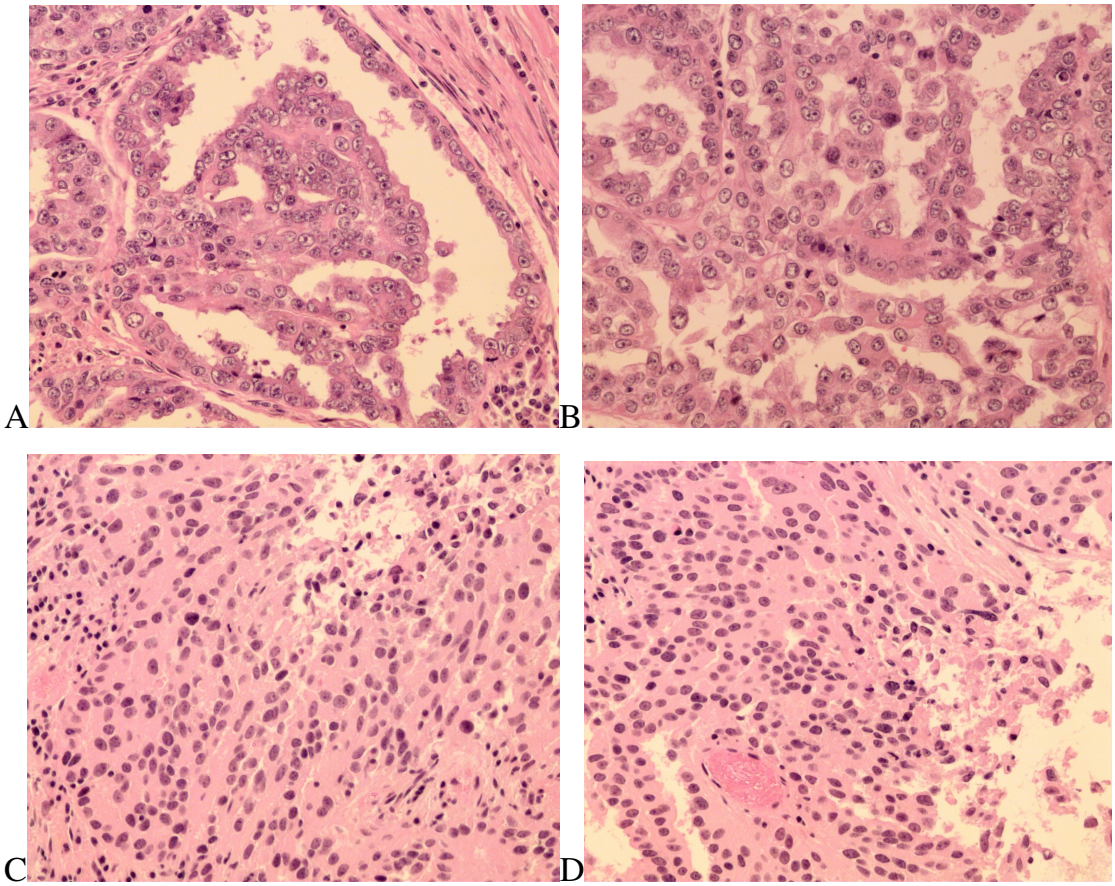

Figure 2. (A-D) Biopsy specimens obtained before and after radiofrequency ablation. The sections have been stained with hematoxylin and eosin (original magnification x200). A, B – biopsy specimens obtained before radiofrequency ablation. C, D biopsy specimens obtained one month after radiofrequency ablation.

Figure 2 shows the histological picture of biopsy specimens obtained before and after radiofrequency ablation. Specimens obtained one month after radiofrequency ablation showed tumour cells with a homogeneous eosinophilic staining in the cytoplasm and a dense homogeneous basophilic staining of oval nuclei when stained with hematoxylin-eosin, compared with the findings for cells obtained before the radiofrequency ablation. However, the stained sections did not meet the definite histological criteria for coagulative necrosis. This result of histological examination of biopsy material was qualified as a viable tumour.

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 (Figures 3 and 4).

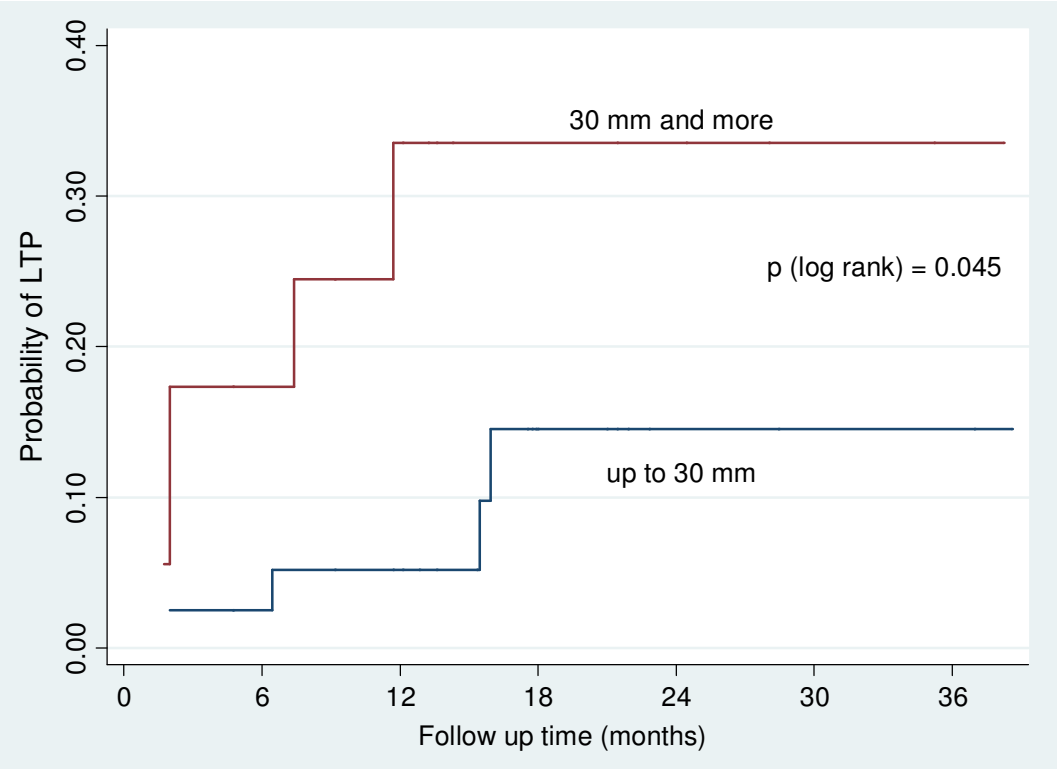

Figure 3. Nelson Aalen cumulative hazard curves depicting local tumour progression based on tumour size up to 30 mm and 30 mm and more. The probability of local tumour progression for small tumours was significantly lower than for intermediate tumours.

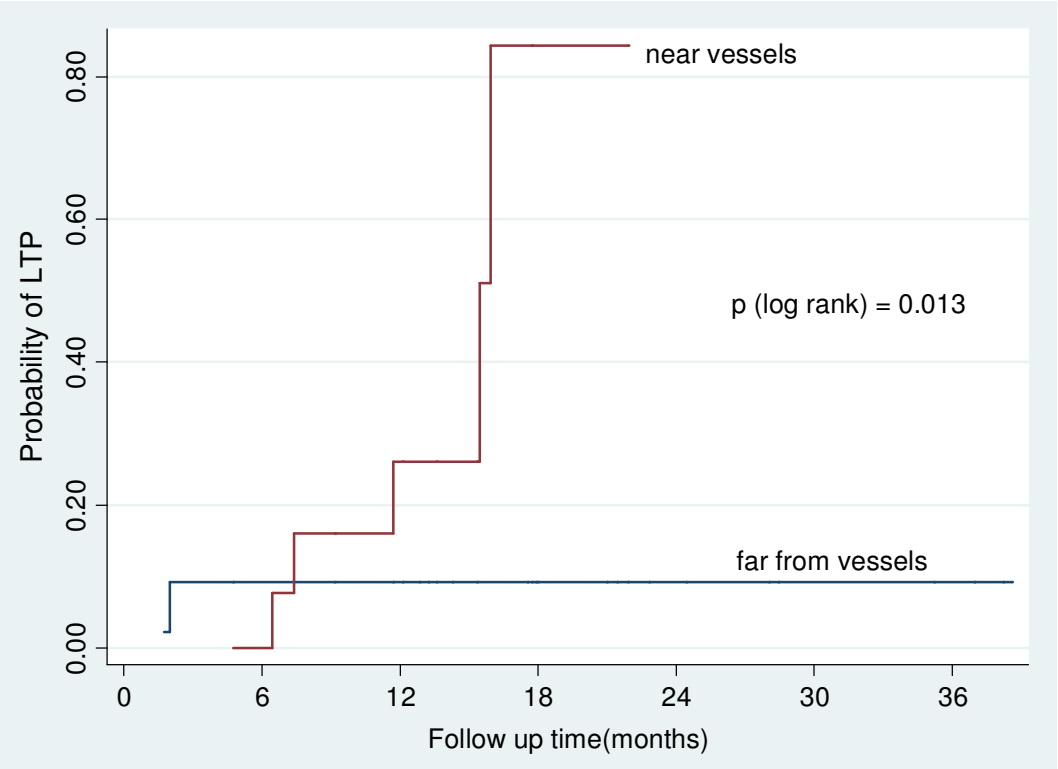

Figure 4. Nelson Aalen cumulative hazard curves depicting local tumour progression based on tumour proximity to hepatic vessels larger than 3 mm in diameter. The probability of local tumour progression for tumours far from large hepatic vessels was significantly lower than for those near the vessels.

Discussion

The rate of local tumour progression in the literature ranges from 2% to 60% (28-30). Mulier et al. in metaanalysis reported the overall local tumour progression to be 12.4% from the analysed 5224 tumours (31). Local tumour progression is the most important determinant of the radiofrequency ablation technique effectiveness. It is detected by means of periodical radiological follow up. The time of the follow up also plays a great role in the detection of local tumour progression as many authors report local tumour progression detected 6 up to 23 months after radiofrequency ablation (31). In our study, the mean follow up period lasted 16.3 months. The results of our study demonstrated an overall local tumour progression of 15.5%. Other authors present similar results regarding local tumour progression – 22% (32), 20% (33), 23%(34) and 9% (35) although there are also much higher rates reported (36).

The results of our study showed 69% of tumours to be viable according to the histological result of ablation zone biopsy taken one month after radiofrequency ablation. Meanwhile radiological follow up showed only nine tumours (15.5%) to progress locally and two of them were from the tissue necrosis group.

Morimoto et al. investigated tissues from hepatocellular carcinoma tumours after radiofrequency ablation (n = 36). Specimens obtained 3 days and 4 weeks after radiofrequency application did not show any classic manifestations of coagulative necrosis, characterized by the conversion of a cell to an acidophilic, opaque tombstone, usually with a loss of the nucleus but with the preservation of the basic cellular shape, permitting recognition of the cell outlines and tissue architecture when stained with hematoxylin and eosin. However, evidence of irreversible cellular damage, including the absence of lactase-dehydrogenase in the cytosol and the absence of mitochondrial enzyme (maleate-dehydrogenase and nicotinamide-adenine dinucleotide phosphate-diaphorase) function, suggested cellular death. The hematoxylin-eosin staining technique relies on visual examination of cell membranes and intracellular structures to assess cell viability (37). Research of Goldberg et al. has shown that the hematoxylin-eosin stain gives inconsistent rankings of the extent, or completeness, of tissue necrosis when assessments are made less than 24 hours after the application of radiofrequency ablation. On the other hand, cytosolic lactate-dehydrogenase staining, a marker for cytosolic glycolytic enzime activity, was absent in the ablation zone, suggesting functional disorder within the cells (9). Ni et al. differentiate between classical coagulation necrosis and thermal coagulation necrosis and thus explain our results. The moderately elevated temperature of 50^{o}C to 100^{o}C during radiofrequency ablation produces an area of tissue coagulation. This constitutes the major portion of the radiofrequency ablation lesion and occupies the area between the immediate perielectrode zone and the periphery of the lesion. The affected live structures and substances including cytosolic enzyme proteins in particular are subjected to an instantaneous thermal fixation, an effect equivalent to that with formalin used for routine histopathology. Because of such thermally induced structural denaturalization and functional deactivation of the enzyme proteins, all the aforementioned progressive enzymatic tissue or cell degradation as seen in the process of traditionally defined coagulation necrosis becomes impossible. As a consequence, with conventional staining techniques, the tissue architecture and cytological details appear

well preserved, despite an absence of any activity on enzymatic histochemical assays. This is called thermal tissue fixation (38).

Morimoto et al. and Goldberg et al. analyzed only the histological response of tumour to radiofrequency ablation. Sofocleous et al. investigated the evidence of Ki-67 positive tumour cells found on the electrode after hepatic radiofrequency ablation as a predictor of local tumour progression (n = 68). The authors showed it to be an independent risk factor. They found 74% of tumours viable when stained with hematoxylin and eosin. Imunohistochemical staining for apoptosis marker caspase-3 and cell proliferation marker Ki-67 revealed only 19% of tumours to be viable. Local tumour progression was radiologically detected for 92% of Ki-67 positive tumours compared with 29% of complete necrosis group (39). We investigated the value of histological response of tumour by the conventional staining technique for local tumour progression. Our results have not shown it to be a significant risk factor. The reason is thermal fixation of tissue, which makes standard histology to be inconclusive about tissue viability.

Our study also concentrated on other risk factors for local tumour progression. 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 of 30 mm or less), intermediate (diameter of 30-50 mm) and large (diameter of 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 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 reported different sizes of tumours to be significant risk factors for local tumour progression: more than 20 mm (40), 23 mm (34), 25 mm (7). There are some papers reporting tumour size not to be a risk factor (39, 41-43). 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 in to several groups according to the percentage of necrosis in tumour. When considering LTP, only 100%

necrosis assures LTP-free survival (41). Nakazawa et al. analysed only tumours smaller than 30 mm in diameter (42). Rodriguez et al. also analysed posttransplant specimens, but nevertheless incompletely ablated tumours were larger, the significance was not detected (43). Sofocleous et al. analysed small and intermediate primary and metastatic liver tumours. The only significant risk factor in his study was the presence of viable tumour tissue adherent to the radiofrequency electrode, but not the size of the tumour. Our data showed the tumours larger than 30 mm in diameter to progress significantly more frequently, and in the opinion of other authors this size remains crucial (44, 45).

Data on tumour vicinity to large hepatic vessels as a risk factor for local tumour progression differ. A large hepatic vessel obviously alters the distribution of temperature near it. Heat sink phenomenon is widely known in the radiofrequency ablation related literature, but the literature is not clear about the influence of vessels contiguous to 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, 42). Some authors selected a 5 mm distance to a large vessel as a risk factor (42), but 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 the strategy for radiofrequency ablation of such tumour.

The histological type of the 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 possibility of local tumour progression, but it was compared to neuroendocrine metastases which have significantly slower natural growth (32). We did not analyse neuroendocrine metastases, but no significant differences in local tumour progression-free survival among hepatic malignancies in our study were observed. Sofocleous et al. evaluated local tumour progression for patients with hepatocellular carcinoma and colorectal cancer metastases. No significant differences in local tumour progression survival between these two groups were found (39).

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 the tumour were not visible on CT or ultrasonographical images and would progress in the follow up. However the differences among these groups were not significant. This is possible because usually a visible tumour is ablated, but microscopic tumour invasion that may extend up to 9 to 21 mm remains not ablated (31). Paulet et al. reported the hyperechogenicity and hypodensity of the tumour to be 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 usually are hypo- or isoechoic, while larger tumours due to keratinisation become hyperechoic as they grow (33).

Conclusions

1. The result of histological examination of ablation zone biopsy material taken one month after radiofrequency ablation of malignant liver tumour is not predictive of local tumour progression;
2. Tumour size 30 mm and larger is a significant risk factor for local tumour progression after radiofrequency ablation of malignant liver tumours;
3. Tumour proximity closer than 5 mm to hepatic vessels larger than 3 mm is significant risk factor for local tumour progression after radiofrequency ablation of malignant liver tumours;
4. Tumour type, tumour density and enhancement pattern in computed tomography and tumour echogenicity are not the risk factors for local tumour progression.

Practical recommendations

1. Local tumour progression after radiofrequency ablation should not be confirmed by standard histological examination of biopsy material in early period, as it may be inconclusive and misleading.
2. Patients with malignant hepatic tumours should be carefully evaluated for tumour size and proximity to large hepatic vessels before radiofrequency ablation. The evaluation of tumour size should be carried out both with contrast enhanced computed tomography and with ultrasonography.

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Santrauka

Jau apie dešimt metų pasaulyje navikams, esantiems kepenyse, gydyti taikoma radijo dažnio abliacija. Šis gydymo metodas dažniausiai naudojamas gydant pirminį kepenų vėžį – hepatoceliulinę karcinomą ir storosios žarnos vėžio metastazes kepenyse (5-8). Tačiau tam tikrais atvejais, kai kitų pirminių navikų metastazės kepenyse kurį laiką išlieka stabilios, radijo dažnio abliacija gali būti vienas iš galimų gydymo metodų (17).

Radijo dažnio abliacija yra vaizdinimo metodais kontroliuojama intervencija, kurios metu dėl temperatūros poveikio sunaikinamas navikas ir dalis aplink jį esančio sveiko audinio, kuris sudaro 1 cm abliacijos kraštą. Po radijo dažnio abliacijos nėra audinių medžiagos, kurią būtų galima tirti morfologiškai, taigi gydymo veiksmingumui vertinti naudojami tik radiologiniai metodai. Dažniausiai radijo dažnio abliacijos veiksmingumui įvertinti naudojamas ir auksiniu standartu laikomas kompiuterinės tomografijos, naudojant intravenines kontrastines medžiagas, metodas (27, 46-48). Jis taikomas po radijo dažnio abliacijos praėjus vienam mėnesiui, kai sumažėja aplinkinių audinių uždegiminė reakcija į temperatūros sukeltą pažeidimą. Ši reakcija pirmosiomis dienomis po radijo dažnio abliacijos radiologiniais tyrimo metodais matoma kaip kontrastinę medžiagą kaupiantis apvadas, kuris trukdo vertinti navikinio audinio, kaupiančio kontrastinę medžiagą, struktūrą. Radijo dažnio abliacijos veiksmingumui vertinti taip pat naudojami ir kiti vaizdinimo metodai, tokie kaip magnetinio rezonanso tomografija, pozitronų emisijos tomografija, kontrastinis ultragarso tyrimas (21, 49-56). Tačiau pagrindinis visų perkutaninių abliacijų trūkumas yra tai, kad negalima tiesiogiai dokumentuoti gydymo radikalumo. Pavyzdžiui, po chirurginės naviko rezekcijos yra atliekamas histologinis ištyrimas, įvertinamas rezekcijos kraštas ir pagal tai vertinamas rezekcijos radikalumas (21). Abliacijos krašto vertinimas yra didžiulė problema, nes po abliacijos kompiuterinės tomografijos ar magnetinio rezonanso tomografijos vaizduose nėra matomos abliuoto naviko ribos, o abliacijos kraštas nustatomas pagal netiesioginių antrinių matavimų rezultatus, kurie dėl nevienodos kepenų padėties skirtingų tyrimų metu ne visada būna tikslūs (57).

Vietinį naviko progresavimą galima nustatyti tik kas tam tikrą laiko tarpą atliekant pakartotinius vaizdinimo tyrimus ir lyginant juos su anksčiau atliktais.

Nustačius abliacijos zonos formos pakitimus, jos tūrio didėjimą arba naujai atsiradusį kontrastinės medžiagos kaupimą joje arba ties ja, galima diagnozuoti vietinį naviko progresavimą. Vietinis naviko progresavimas po radijo dažnio abliacijos, nustatytas radiologiniais metodais, ir yra laikomas standartu, vertinant radijo dažnio abliacijos veiksmingumą (22, 32, 34, 57-62), nors naviko progresavimas vis tiek yra patvirtinamas histologiškai, atliekant punkcinę biopsiją iš įtartinos vietos.

Navikai prieš atliekant radijo dažnio abliaciją turi tam tikras morfologines ir radiologines savybes, kurios gali turėti įtakos atokiesiems radijo dažnio abliacijos rezultatams. Be hepatoceliulinės karcinomos ir storosios žarnos vėžio metastazių kepenyse, yra ir kitokių histologinių tipų navikų, kuriems taikoma radijo dažnio abliacija. Navikų dydis taip pat yra svarbus veiksnys, nuo kurio priklauso radijo dažnio abliacijos veiksmingumas, nes kuo didesnis navikas, tuo sudėtingiau atlikti jo abliaciją. Stambios kepenų kraujagyslės, kurios nėra koaguliuojamos radijo dažnio abliacijos metu, aušina šalia esančius audinius, todėl navikų, esančių šalia šių kraujagyslių abliacija būna apsunkinta. Kadangi po radijo dažnio abliacijos kompiuterinės tomografijos vaizduose abliuoto naviko zonos išskirti negalima, o abliacijos zona būna hipodensinė ir dinaminio tyrimo metu nekaupianti kontrastinės medžiagos, hipodensinių ir hipovaskulinių navikų radijo dažnio abliacijos veiksmingumo ankstyvasis vertinimas būna sudėtingas.

Siekiant anksti numatyti galimą vietinį naviko progresavimą, mūsų tyrime nutarta praėjus vienam mėnesiui po radijo dažnio abliacijos atlikti ultragarsu kontroliuojamą punkcinę radikaliai abliuoto naviko biopsiją ir įvertinti gautus rezultatus, be to, nustatyti ir įvertinti morfologinius ir radiologinius vietinio naviko progresavimo rizikos veiksnius, kurie galėtų turėti įtakos radijo dažnio abliacijos veiksmingumui ir abliuoto naviko bei abliacijos zonos vizualizacijai kompiuterinės tomografijos ir ultragarso tyrimais.

Taigi mūsų tyrimo tikslas –

Nustatyti kompiuterinės tomografijos ir ultragarso tyrimų bei histologinio stulpelinės biopsijos medžiagos, paimtos iš abliuoto naviko, histologinio tyrimo rezultato reikšmę anksti vertinant radijo dažnio abliacijos veiksmingumą.

Tyrimo uždaviniai:

1. Įvertinti punkcinės biopsijos, atliktos praėjus vienam mėnesiui po radijo dažnio abliacijos, medžiagos histologinio tyrimo rezultatus ir palyginti juos su radiologinio stebėjimo rezultatais
2. Nustatyti vietinio naviko progresavimo po radijo dažnio abliacijos morfologinius rizikos veiksnius ir jų reikšmingumą.
3. Nustatyti vietinio naviko progresavimo po radijo dažnio abliacijos radiologinius rizikos veiksnius ir jų reikšmingumą

Ginamieji teiginiai:

1. Biopsijos medžiagos, paimtos iš abliacijos zonos praėjus vienam mėnesiui po naviko, esančio kepenyse, radijo dažnio abliacijos, histologinio tyrimo rezultatas neleidžia prognozuoti vietinio naviko progresavimo.
2. Naviko dydis ir jo lokalizacija šalia stambių kepenų kraujagyslių yra reikšmingi vietinio naviko progresavimo rizikos veiksniai.
3. Naviko histologinis tipas, naviko tankis ir kontrastinės medžiagos kaupimo pobūdis navike kompiuterinės tomografijos vaizduose bei naviko akustinis tankis, nustatomi prieš naviko, esančio kepenyse, radijo dažnio abliaciją, nėra vietinio naviko progresavimo rizikos veiksniai.

Rezultatai

Tyrime buvo analizuojami 58 radiologiškai radikaliai abliuoti navikai. Radiologinio stebėjimo metu vietinis naviko progresavimas buvo nustatytas 9 atvejais. Vietinis navikų progresavimas buvo nustatytas per 18 mėnesių: 4 navikų (44 proc.) per 6 mėnesius, 7 (78 proc.) – per 12 mėnesių ir 9 (100 proc.) – per 18 mėnesių. Vidutinis analizuotų navikų stebėjimo laikas buvo 16,3 mėnesiai (nuo 1,7 iki 38,7 mėnesių).

Praėjus vienam mėnesiui po radijo dažnio abliacijos kontroliuojant ultragarsu buvo atlikta punkcinė stulpelinė biopsija iš abliacijos zonos. Atlikus biopsijos stulpelių preparatų standartinį histologinį tyrimą, dažant hematoksilinu ir eozinu, ir nustačius navikinių ląstelių, kurių branduoliai dažėsi hematoksilinu, buvo laikoma, kad šis naviko biopsijos medžiagos histologinio tyrimo rezultatas rodo gyvybingą naviką, tai yra mėginyje nebuvo matoma visiškos naviko nekrozės. Jeigu navikinių ląstelių biopsijos stulpelių preparatuose nebuvo rasta, arba jos buvo nekrozavusios (nebuvo matoma branduolių, besidažančių hematoksilinu), buvo laikoma, kad šis naviko biopsijos medžiagos histologinio tyrimo rezultatas rodo audinių nekrozę.

Atlikus vietinio naviko progresavimo tikimybės analizę pagal Nelson – Aalen kumuliacinės rizikos įverčių metodą, nustatyta, kad biopsijos medžiagos, paimtos iš abliacijos zonos praėjus vienam mėnesiui po naviko, esančio kepenyse, radijo dažnio abliacijos, histologinio tyrimo rezultatas nėra reikšmingas vietinio naviko progresavimo veiksnys (p (log rank) = 0,472). Šie duomenys rodo, kad biopsijos medžiagos, paimtos iš abliacijos zonos praėjus vienam mėnesiui po naviko, esančio kepenyse, radijo dažnio abliacijos, standartinis histologinis tyrimas nevisiškai atspindi ląstelių pokyčius išsivystančius po radijo dažnio abliacijos.

Išanalizavus vietinio navikų progresavimo morfologinių rizikos veiksnių įtaką, nustatyta, kad 30 mm skersmens arba didesnių navikų vietinis progresavimas nustatomas reikšmingai dažniau nei mažesnio kaip 30 mm skersmens navikų (p (log rank) = 0,045). Taip pat nustatyta, kad navikai, kurie lokalizuojasi arčiau kaip per 5 mm nuo stambių kepenų kraujagyslių, vietiškai progresuoja reikšmingai dažniau, nei navikai, esantys atokiau nuo stambių kepenų kraujagyslių (p (log rank) = 0,013). Nenustatyta, kad storosios žarnos vėžio metastazės kepenyse vietiškai progresuoja reikšmingai dažniau

nei kiti navikai (hepetoceliulinė karcinoma, krūties, kiaušidžių, inkstų, tulžies pūslės karcinomų, melanomos bei sarkomų metastazės kepenyse) (p (log rank) = 0,235).

Išanalizavus vietinio navikų progresavimo radiologinių rizikos veiksnių įtaką, nenustatyta, kad navikų tankis kompiuterinės tomografijos vaizduose sąlygoja vietinį naviko progresavimą po radijo dažnio abliacijos (p (log rank) = 0,114), navikų kontrastinės medžiagos kaupimo pobūdis, matomas kompiuterinės tomografijos vaizduose turi reikšmės vietinio navikų progresavimo dažniui (p (log rank) = 0,139), o navikų akustinis tankis turi įtakos vietiniam navikų progresavimo dažniui po radijo dažnio abliacijos (p (log rank) = 0,539).

Išvados

1. Biopsijos medžiagos, paimtos iš abliacijos zonos praėjus vienam mėnesiui po kepenyse esančio naviko radijo dažnio abliacijos, histologinio tyrimo rezultatas neleidžia prognozuoti vietinio naviko progresavimo;

2. Naviko dydis 30 mm ir didesnio skersmens yra reikšmingas vietinio naviko progresavimo po radijo dažnio abliacijos rizikos veiksnys;

3. Naviko lokalizacija arčiau kaip per 5 mm nuo didesnio nei 3 mm skersmens kepenų kraujagyslių yra reikšmingas vietinio naviko progresavimo po radijo dažnio abliacijos rizikos veiksnys;

4. Naviko histologinis tipas, jo tankis ir kontrastinės medžiagos kaupimo pobūdis, matomas kompiuterinės tomografijos vaizduose bei akustinis tankis (echogeniškumas), nustatomi prieš kepenyse esančio naviko radijo dažnio abliaciją, nėra vietinio naviko progresavimo rizikos veiksniai.

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CURRICULUM VITAE

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Education and training

Dates, title of qualification awarded	Principal subjects/occupational skills covered	Name and type of organization providing education and training
Medical Doctor, 1992-1998	Medical studies	Vilnius University, Faculty of Medicine
1998-1999	Residentship in general medicine	University Hospital of the City of Vilnius
Radiologist, 1999-2001	Residentship in radiology	Vilnius University Hospital Santariskiu Klinikos
PhD Student, 2004-2008	Interventional oncoradiology	Institute of Oncology, Vilnius University

Work experience

Dates	Occupation or position held	Name and address of employer
From 2001	Radiologist	Department of Interventional and Diagnostic Ultrasonography and Department of Diagnostic Radiology, Clinic of Consultations and Diagnostics, Institute of Oncology, Vilnius University, Lithuania

Professional development

Dates, title of qualification awarded	Principal subjects/occupational skills covered	Name and type of organisation providing education and training
April 8-13, 2002	Interventional Ultrasonography	Vilnius University, Faculty of Medicine, Educational Course
October 30 – November 5, 2005	Diagnostic Imaging	Weill Medical College of Cornell University, Salzburg Weill Cornell Seminar
February 10-15, 2006	Complex differential diagnostics in tumours of esophagus, stomach, pancreas and bile ducts	Vilnius University, Faculty of Medicine, Educational Course
April 10-15, 2006	Interventional Radiology	Kaunas University of Medicine, Educational Course
May 4-5, 2007	Image-Guided Radiofrequency Tumour Ablation	Masaryk University in Šlapanice/Brno, International Course
October 19-20, 2007	Bipolar Radiofrequency-Ablation	Innsbruck Medical University, International Workshop

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