Interventional Oncology

Laser-induced thermoablation and regional chemotherapy of liver metastases

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Summary

Interventional oncology is an evolving subspeciality in the field of radiology. LITT is a new promising method of tumor ablation. It is mainly performed in hepatic metastases mostly from colorectal cancer. Regional chemotherapy is also an established method in the palliative management of hepatoma; however, its application in liver metastases is not universally accepted. Both modalities can be applied in a combined approach. Local tumor control and survival rates are promising. We will describe here the technique of laser ablation and review results of LITT and combined LITT and chemoemolization as well as our expectations for its future role.

Key words: laser – thermotherapy – liver – metastases – LITT - regional chemotherapy - TACE

Key issues

- LITT is a new promising method of tumor ablation
- The process is minimally invasive and can be performed as outpatient procedure under local anesthesia
- Local control and survival data are comparable to surgery
- Morbidity and mortality are low and significant complications are rare
- LITT can be applied as the sole line of treatment or in coordination with surgical resection and regional chemotherapy
- A combination of regional chemoembolization and LITT improves tumor control and survival
- The indications of LITT can develop and extend in the near future to involve more patients who were previously only surgically treatable

Introduction

Metastasis is the most common neoplasm in adult liver, and the liver is the second most common site for metastatic spread, after the lymph nodes. Liver metastases can be found in up to 80% of colorectal cancer patients; in 25-50% it is encountered at primary presentation [1]. Surgical resection is the standard curative treatment for selected patients with resectable liver metastases (usually less than 4, and localized to one liver lobe), as it consistently provides long-term disease-free survival in a substantial number of patients [2, 3].

The high tendency of recurrent liver metastases following successful resection of metastases has spurred the search for therapeutic alternatives, the goal of which is achieving survival rates similar to those in surgery with the advantage of being at the same time less invasive, applicable on an outpatient basis under local anesthesia, less expensive, and with a lower complication rate [3-7].

Minimally invasive treatment techniques are based on two approaches: transarterial and percutaneous. Transarterial treatment is applied through the hepatic arterial supply of the tumor which can be done in the form of chemoperfusion, transarterial chemoembolization (TACE) and transarterial embolization (TAE). Several local percutaneous ablative therapies have proved their effectiveness for the treatment of primary liver carcinoma such as percutaneous ethanol injection, radiofrequency ablation (RFA), and microwave or ultrasound ablation. However, effective local treatment is far more difficult for liver metastases [3].

On the following pages we will discuss the clinical indications, technique and results of LITT for the treatment of liver metastases, and we will emphasize the increased efficacy achieved by the combination of regional chemotherapy and LITT.

Principle and technique

Laser-induced interstitial thermotherapy (LITT) is among the relatively new percutaneous ablation techniques which proved effective. Laser coagulation is accomplished using neodymium–yttrium aluminium garnet laser light (Dornier mediLas 5060, Dornier mediLas 5100; Dornier Medizintechnik, Germering, Germany) with a wavelength of 1,064 nm. The light is delivered through 400-mm-long fibres terminated by a specially developed diffuser which emits laser light to an effective distance of 12–15 mm.

The laser application kit (SOMATEX, Berlin, Germany) consists of a cannulation needle, a guide wire, a sheath system, and a special protective catheter closed at the distal end. Power applicators are 9 F in diameter and internally cooled with a room-temperature sodium chloride solution that circulates within a double-lumen catheter. Cooling the surface of the laser applicator improves the radial temperature distribution shifting the maximum possible amount of heat energy into deeper tissue layers and at the same time avoiding carbonization allowing the use of higher laser power, up to 35 watts. These parameters result in a more homogeneous tissue penetration of laser radiation. The laser systems are fully compatible with magnetic resonance imaging (MRI) units [4].

Laser applicator systems can be placed at the desired position under computed tomographic (CT) fluoroscopy guidance. The multi-application technique involves the treatment of one lesion with multiple (up to 5) laser applicators simultaneously (fig 1). It is also possible to treat more than one lesion in the same session. Then the patients are transferred to a 0.5-T closed MRI unit. Laser ablation is performed under near real-time MR using T1-weighted gradient-echo sequence (140/12, flip angle of 80°, matrix of 128 x 256, five 8-mm sections, acquisition time of 15 seconds) in transverse section and parallel to the laser applicators repeated every minute for monitoring of thermal ablation. Following the first laser cycle, the laser fibre can be

retracted by a distance of 2 cm and a second laser cycle can be performed to enlarge the area of coagulation necrosis. Necrosis manifests as progressively deepening T1 hypointensity (fig 1). After the procedure, the puncture tract is closed with fibrin glue (Tissucol Duo S; Baxter, Unterschleissheim, Germany) [4].

Alternatively, the puncture, applicator positioning and laser ablation monitoring can all be performed in an open 0.2T MRI unit.

The entire LITT treatment can be tolerated under local anesthesia using 20–30 mL of 1% Lidocaine (Astra Zeneca, Wedel, Germany) and analgesics (Pethidine [10–80 mg], Aventis, Frankfurt, Germany, and/or Piritramid [5–15 mg], Janssen, Beerse, Belgium) and sedation (Midazolam [2–10 mg]; Merkle, Blaubeuren, Germany). The mean duration of ablation is 20 minutes (range: 2–55 minutes). Besides, pulling-back and repositioning the laser fibre is calculated on the basis of signal change because the heat deposition in the tissue cannot be predicted, which means that a certain amount of energy can result in different volumes of coagulation necrosis in different settings [4].

Indications and contraindications

The indications for percutaneous ablation of liver metastases using LITT are recurrent metastases after partial hepatectomy or segmentectomy, bilobar metastases, locally unresectable lesions, general contraindications for surgery, or refusal of surgery [3, 8]. LITT is not feasible in patients with more than 5 lesions, lesions larger than 5 cm in greatest diameter, or extrahepatic metastases [3]. Some other possible contraindications are poor coagulability, liver insufficiency and contraindications for MRI [8]

Results

We searched Pubmed using “laser”, “liver”, “metastases”, “chemoembolization”, “TACE” and “LITT” as search criteria to locate all patient studies using LITT for liver metastases. We used the “Related articles” option to obtain more relevant articles.

The largest published patient series with LITT involved 5,105 lesions in 1,650 consecutive patients. The local tumor control rate in the 3-month follow-up control was 99.2%. After 6 months a local tumor control rate of 98.2% was seen. There were no statistically significant differences between the local control rates of the various primary tumors. The same holds for the various positions of the lesions with regard to the segmental topography of the liver. The mean survival was 41.8 months in patients with unresectable colorectal liver metastases and 51 months in patients with breast cancer [5].

The overall rate of complications and side effects was 7.5%. The rate of clinically relevant complications was 1.3%. The most common side effects of LITT treatment are reactive pleural effusion, intrahepatic abscess, pleural empyema, subcapsular hematoma (fig 2), intrahepatic and intrabdominal bleeding. Less significant complications include local infection and bile duct injury [4, 5, 9].

As an update to this study, the results in 603 patients with colorectal metastases with 1,801 lesions were equally good. The mean survival rate for all patients, with a calculation started on the date of diagnosis of the metastasis, was 4.4 years. One-year survival was 94%, 2-year survival; 77%, 3-year survival; 56%, 5-year survival; 37%). Median survival was 3.5 years [3].

Several factors may influence the size and morphology of the areas of induced necrosis, including tumor geometry and adjacent structures such as arteries, portal and hepatic veins, and the biliary tree as well as tumor relation to the liver capsule.

Central lesions pose the problem of a difficult access and larger surrounding vessels causing more heat loss. In the study by Mensel et al to evaluate LITT effectiveness in

central lesions 23 patients with 28 central malignant liver tumors including 27 metastases and one hepatoma were included. Complete ablation was achieved after the 1st treatment session in 71.4%. The rate of effectiveness during follow-up was 78.6%, 71.4% and 64.3% after 3, 6 and 9 months, respectively. The 1-, 2-, 3- and 4-year survival rates were 90%, 72%, 60% and 40%, respectively. The median survival was 46 months. Major complications occurred in one patient (hemorrhagic pleural effusion), while minor complications occurred in 10 patients. There were no mortalities related to the procedure [9]. In accordance with these findings the success rate of LITT in our studies was not influenced by the location of the lesion [3, 4].

Fiedler et al. evaluated the relation between lesion size and effectiveness which was 100% for metastases less than 2 cm in diameter, 71% for metastases between 2 - 3 cm, 46% for metastases between 3 and 4 cm and 30% for metastases of more than 4 cm [10].

Combined LITT and chemotherapy

Regional chemotherapy of hepatoma is widely applied but its application in liver metastases has been successfully progressing [11]. The morphological response achieved by regional chemoperfusion in colorectal liver metastases during the last 5 years ranged between 29.7% [12] and 56% [13]. Median survival with chemoperfusion ranged between 10.6 months [14] and 62.6 months [15]. Comparable results were encountered using transarterial chemoembolization (TACE). Median survival ranged between 8.5 months in uveal melanoma metastases [16] and 69 months in neuroendocrine metastases [17]. Morphological response ranged between 9% and 79% in neuroendocrine metastases [18]. These results are so variable because of the various chemotherapeutic agents, embolizing material and treatment protocols applied as well as the variable histology of different primary tumors. Hence, in TACE of liver metastases, no universally accepted scheme exists

to achieve the best results. Results of chemoperfusion and TACE are mentioned in table 1.

LITT can be applied in coordination with TACE. Chemoembolization is applied first to obtain downsizing of metastases to a size treatable by LITT. 162 patients who had unresectable liver metastases, with the largest lesion as large as 8 cm in diameter and no more than 4 lesions were treated with repeated TACE using Mitomycin for chemotherapy and Lipiodol and microspheres for embolization. The change in size during treatment was measured using magnetic resonance (MR) imaging. If the diameter of the tumor decreased to less than 5 cm, the patients were shifted to LITT within 4-6 weeks following the last TACE session. Eighty-two patients (50.6% of cases) responded to TACE, with a mean reduction in tumor size of 35%, and were treated with LITT (fig 3). Each of these patients underwent 2 to 7 TACE treatments (mean: 4.3) prior to LITT. In 47 patients, no reduction in tumor size was achieved, which led to further follow-up. In 33 patients, disease progression was found, with either an increasing size of the lesions or newly developing metastases; these results led to further TACE treatments or shifting to systemic chemotherapy. Median survival of patients who responded to this combined treatment was 26.2 months; in patients treated with only TACE, median survival was 12.8 months [19].

Comments

The role of imaging in LITT includes guidance for applicator positioning and monitoring of thermal ablation. Ultrasound (US), CT and MRI can all be used during applicator position. Three-dimensional guidance during positioning of one or more laser applicators in the lesion is more accurate using MRI but it is more time-consuming and expensive. The needle can be introduced under CT-guidance instead of MR imaging guidance. Important advantages of CT fluoroscopy are quicker image update and more precise visualization of the needle. This is, however, more

demanding in terms of time, expenses, and manpower to operate two imaging machines dedicated only for LITT patients during the treatment sessions. Performing the whole procedure in an open MRI unit overcomes these difficulties [20, 21].

MR imaging is superior to CT and ultrasonography in thermal ablation monitoring due to the higher sensitivity of the MR sequence to detect and quantify the degree of induced necrosis of the malignant tissue and surrounding parenchyma and vital structures. Fast MRI sequences as described above allow near real-time monitoring of LITT effects. MR monitoring can confirm complete ablation of the entire lesion and detect untreated residual malignant tissue. The applicator can be repositioned under MRI guidance during ablation to increase the volume of necrosis. This technique allows safe destruction of metastases and well-controlled coagulation in a safety margin surrounding the lesion. MR monitoring also minimizes destruction of surrounding hepatic parenchyma, and decreases the risk of injury of vital structures such as large vessels or the central bile ducts thus increasing the safety of the procedure. MR imaging is also efficient for detection of complications due to its high topographic accuracy, excellent soft-tissue contrast, and high spatial resolution [3].

The ability to operate multiple application systems at the same time increases the volume of coagulation necrosis to thoroughly cover larger tumors with a safety margin. In our opinion, this is the reason for such a low local recurrence rate in comparison to that after radiofrequency ablation [2, 3].

We have to point out the importance of the fact that the interventional radiologist has to be highly aware of possible complications and adequately qualified to manage those using interventional image-guided methods such as percutaneous drainage of hemo- or pneumothorax or transarterial embolization of bleeding. Yet, she/he must also know when to refer the patient for surgical management. This ability which is acquired after long training and experience is of immense importance in performing

LITT or any interventional treatment acceptable and trustworthy for the patients. It would be absurd to learn an ablation technique without learning the right protocol to handle its consequences.

The reason why LITT is not universally adopted as a thermal ablation method might relate to being more complicated in its physics, more expensive, technically demanding. Besides, special imaging methods or more dedicated staff members are required.

Although the intention for LITT was originally palliative, its favorable survival rates are comparable with those obtained with surgical resection of liver metastases showing at the same time lower morbidity and mortality rates [3, 8, 9]. Surgery can be combined with LITT in the same treatment plan by using LITT to complement less radical operations like, for example, segmentectomy or localized resection instead of lobectomy.

These data suggest that, in the next few years, the indication for LITT and combined LITT and TACE approach can include more patients with liver metastases, including surgical candidates with no more than five metastases with a maximum diameter of 5 cm. By applying LITT rather than surgery in these patients, less healthy liver tissue would be sacrificed and more hepatic reserve salvaged. Keeping in mind the possibility of recurrence of metastases, this approach gives the patients a better prospect.

According to these results we continue to apply the combined TACE and LITT treatment protocol successfully in our institute, which represents in our opinion an optimal management protocol in interventional oncology. We hope that LITT will be applied in more centres, even in those depending on other thermal ablation methods which can also be combined with TACE in the same manner.

Expert commentary

Thermoablation is an evolving field in interventional oncology. Although the intention for LITT was originally palliative, its favorable survival rates are comparable with those obtained with surgical resection of liver metastases showing at the same time lower morbidity and mortality rates [3, 8, 9]. Surgery can be combined with LITT in the same treatment plan to reduce the resected portion while LITT is used to treat residual lesions in the spared portion. LITT also can be applied in combination with TACE. Then TACE is applied first to downsize metastases so that they can be treated by LITT [19].

Five-year view

These data suggest that, in the next few years, the indication for LITT rather than surgery can be extended to all patients with colorectal liver metastases, including surgical candidates with no more than five metastases with a maximum diameter of 5 cm. By applying LITT less healthy liver tissue would be sacrificed and more hepatic reserve salvaged. Keeping in mind the possibility of recurrence of metastases, this approach gives the patients a better prospect.

According to these results we continue to apply the combined TACE and LITT treatment protocol successfully in our institute, which represents in our opinion an optimal management protocol in interventional oncology.

Table 1

The highest results of TACE in patients with liver metastases during the last 3 years

Study	Pt no	Anticancer drug	Embolizing material	Morphological response	Median survival
Wasser 2004 (Colorectal carcinoma) [22]	21	Mitomycin	Starch (DSM)	14%	13.8 months
Muller 2003 (Colorectal carcinoma) [23]	66	Melphalan (5-FU & GM-CSF)	Lipiodol Gelfoam	76.6%	not reached (a)
Voigt 2002 (Colorectal carcinoma) [24]	10	Miotomycin Interferon (Oxaliplatin & 5-FU)	Starch (DSM)	50%	not reached (b)
Fiorentini 2004 (Neuroendocrine Tumor) [25]	10	Mitomycin Cisplatin Epirubicin	Lipiodol Gelfoam	70%	22 months
Kress 2003 (Neuroendocrine Tumor) [26]	26	Doxorobucin	Lipiodol Gelfoam PVS Absolute ethanol	9%	66 months
Agarwala 2004 (melanoma) [16]	19	Cisplatin	PVS	16%	8.5 months

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