European Journal of Radiology 83 (2014) 1804–1810

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Neoadjuvant TACE before laser induced thermotherapy (LITT) in the treatment of non-colorectal non-breast cancer liver metastases: Feasibility and survival rates

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ARTICLE INFO

Article history:
Received 2 January 2014
Received in revised form 5 June 2014
Accepted 26 June 2014

Keywords:
Liver metastases
Neoadjuvant treatment
Transarterial chemoembolization

ABSTRACT

Purpose: To evaluate safety, feasibility and overall survival rates for transarterial chemoembolization (TACE) alone or combined with MR-guided laser-induced-thermotherapy (LITT) in liver metastases of non-colorectal and non-breast cancer origin.

Methods and materials: Included were patients with unresectable non-colorectal non-breast cancer liver metastases with progression under systemic chemotherapy. Excluded were patients with Karnofsky score ≤70, respiratory, renal and cardiovascular failure, and general TACE contraindications. TACE using Mitomycin alone, Mitomycin–Gemcitabine or Mitomycin–Gemcitabine–Cisplatin was performed to all patients. After TACE 146 metastases were ablated with MR-guided LITT. To be eligible for LITT metastases should be <5 cm in size and ≤5 in number. Tumor response was evaluated using MRI according to RECIST. Survival was evaluated using Kaplan–Meier analysis.

Results: A total of 110 patients (mean age 59.2 years) with 371 metastases received TACE (mean 5.4 sessions/patient, $n = 110$) with 76 (69%) receiving LITT (mean 1.6 session/patient) afterwards. TACE resulted in a mean decrease of mean maximum diameter of 52% ± 26.6 and volume change of −68.5% ± 22.9 in the 25 patients (23%) with partial response. Stable disease ($n = 59$, 54%). Progressive disease ($n = 26$, 23%). The RECIST outcome after LITT showed complete response ($n = 13$, 17%), partial response ($n = 1$, 1%), stable situation ($n = 41$, 54%) and progressive disease ($n = 21$, 28%). The mean time to progression (TTP) was 8.6 months. Median survival of all patients was 21.1 months.

Conclusion: TACE with different protocols alone and in combination with LITT is a feasible palliative treatment option resulting in a median survival of 21.1 months for unresectable liver metastases of non-colorectal and non-breast cancer origin.

1. Introduction

Metastases are the most common type of liver tumors, originating from various primary cancer sites [1]. The most frequent origins are colorectal and breast cancer, whereas metastases from gastric cancer, ovarian carcinoma, endometrial carcinoma or melanoma are less frequent and go along with a poor prognosis [2].

For resectable liver metastases the treatment of choice is surgery, however in patients unsuitable for resection due to general health status, certain histopathological types of metastases, location, number of lesions and insufficient residual functional liver parenchyma post-operatively, minimally invasive techniques are potential alternatives [3,4]. Possible treatments include the transarterial chemoembolization (TACE), radiofrequency ablation, laser-induced thermotherapy and cryotherapie.

Multiple studies have shown that TACE is a suitable treatment for downsizing liver metastases with a mean reduction of size up to 35% [5,6]. However, there is a possibility of viable tumor cells that may remain after TACE treatment, making an ablative technique necessary. Since laser ablation and RF are only suitable for metastases not exceeding a maximum of 5 cm in diameter and

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http://dx.doi.org/10.1016/j.ejrad.2014.06.029
0720-048X/

lesion number of 5, the combination with TACE could widen the therapeutic spectrum of thermal ablation to larger lesions that have been previously downsized. Furthermore LITT has proven its reliability for local tumor control and with low incidence of side effects [7,8]. Just a few studies have yet been published for the use of TACE in combination with LITT for the treatment of liver metastases of various non-colorectal and non-breast cancer origins [6].

In this study, we analyzed unresectable liver metastases that originated from primaries, that spread to the liver less frequently like the gastric carcinoma, ovarian carcinoma, non-small-cell lung carcinoma (NSCLC), melanoma and carcinoid tumors.

The purpose of our study was to evaluate the safety, feasibility and overall survival rates for a treatment protocol of TACE in combination with MR-guided laser-induced thermotherapy (LITT) in liver metastases of various non-colorectal non-breast cancer origins and especially the potential for downsizing via TACE.

2. Methods and materials

The retrospective study protocol was approved by our ethics committee and informed consent for all procedures was obtained from all our patients.

2.1. Indications

Inclusion criteria for the study were unresectable non-colorectal and non-breast cancer liver metastases. Only patients with progression under standard systemic chemotherapy, evaluated at contrast and non-contrast enhanced MRI, were included. There was no foreseen number or size of metastases for TACE treatment but the tumor load should not be more than 70% of the liver.

The purpose of TACE treatment was neoadjuvant or palliative. The neoadjuvant treatment was performed to reduce the number of lesions and to downsize lesions bigger than 5.0 cm in diameter, making them suitable for laser ablation. The palliative treatment was not performed with the intention to cure the disease, but to prolong survival and preserve life quality.

Contraindications included a Karnofsky score $\leq$70 as expression of poor general status, respiratory and cardiovascular failure, as well as partial or complete main portal vein thrombosis. Furthermore serum total bilirubin level $\geq$3 mg/dL, limited hepatic synthesis (serum albumin level $\leq$2 mg/dL) and serum creatinine level $\geq$2 mg/dL showing renal failure resulted in exclusion.

2.2. TACE

All procedures were performed by a single radiologist with more than 15 years of experience. Through the femoral artery a 5-F pigtail catheter (Pigtail; Terumo, Tokyo, Japan) using the Seldinger technique was inserted and an angiographic survey of the abdominal vessels was performed. With angiography we checked for the localization of the hepatic arteries by using selective catheterization, followed by indirect portography to outline the portal circulation in venous phase. For the hepatic catheterization we used a 4-F cobra catheter (Cobra; Terumo, Tokyo, Japan), which was placed distal to the gastroduodenal and left gastric artery. Depending on the localization, the size and the arterial supply of the tumor, we proceeded further into segmental arteries. A Turbo-Tracker (Boston Scientific, Galway, Ireland) or Renagde 3F microcatheter (Boston Scientific, Galway, Ireland) was used, if selective or super selective catheterization was problematic. The chemotherapeutics used were Mitomycin C (Medac, Hamburg, Germany) alone with a maximum of 8 mg/m^2 in 47 patients (43%), in combination with Gemcitabine 1000 mg/m^2 (Gemzar®, Eli Lilly and Company, Indianapolis, IN) in 43 patients (39%) and a triple combination of Mitomycin, Gemcitabine and Cisplatin with a dose of 35 mg/m^2 was used in 20 patients (18%). In all patients a maximum of 10 mL lipiodol (Guerbet, Sulzbach, Germany) followed by 200–450 mg degradable starch microspheres (Embocept, Pharmacia & Upjohn, Erlangen, Germany) were injected for embolization. The embolization suspension was slowly injected under fluoroscopic control until stasis of blood flow was observed, followed by an additional angiography of the hepatic artery to ensure devascularization. The study design was scheduled to include the performance of at least 2 TACE sessions with a 4-week treatment interval. The mean number of TACE sessions per patient was 5.36 (SD $\pm$ 3.82; range 2–21). If lesions did not respond or showed progression after two sessions, no further TACE sessions were administered. Within the first 24 h after embolization a CT examination (Somatom plus, Siemens, Erlangen, Germany) was used to evaluate the lipiodol retention in the metastases as well as to detect lipiodol emboli that might have refluxed during injection. MRI studies were used immediately before every TACE session to evaluate the size of the lesions. They were performed using non-contrast sagittal and axial T1W sequences and axial T2W sequences on a 1.5-T MRI unit (Sonata and Avanto, Siemens, Erlangen, Germany).

2.3. LITT

To be eligible for LITT metastases should be <5 cm in size and $\leq$5 in number. All procedures were performed by two radiologists with more than 15 years of experience. The metastases were located under CT-imaging and the laser application set was introduced using local anesthesia. Patients were transferred to a MR imager (Elscint, Haifa, Israel or Avanto Siemens, Erlangen, Germany) thereafter where the LITT was performed using MRI with T1 gradient-echo sequences (140/12; flip angle, 80°; matrix, 128 $\times$ 256; five section; section thickness, 8 mm; intersection gap, 30°; acquisition time, 15 s) in transverse section orientation and parallel to the laser applicators. These images were repeated every minute. The laser induced thermotherapy was performed using a Nd:YAG-laser (Dornier MedLas 5060 and 5100) with a bare fiber (400-μm) which emits near-infrared light of 1046 nm wavelength at the end of the fiber. In the tumor tissue the light is converted into heat, causing coagulative necrosis, secondary degeneration and atrophy. The laser application kit (SOMATEX, Berlin, Germany) consists of a cannulation needle, guide wire, a sheath system with mandarin (10F, 20 cm in length), and a special protective catheter (9F, 43 cm in length) that is closed at its distal end. The light transparent and heat resistant protective catheter is protecting tissue from direct contact with the laser fiber and ensures the safe and easy removal of the fiber. The laser system is permanently cooled with saline to prevent carbonization of the fiber and therefore increases the possible coagulation volume. The application system is fully compatible with MR-imaging which allows an almost real time evaluation of the efficacy under treatment. Temperature changes were documented with a thermo sensitive T1-weighted sequence (TR/TE: 18/6 ms, Flip angle: 23, Matrix size: 128 x 128) to define the duration of ablation.

To evaluate the zone of necrosis as well as possible complications, immediately after LITT a multisection set of images were obtained with contrast-enhanced FLASH-2D sequences. The first follow-up MR study was performed the day after laser-induced thermotherapy. Additional follow-up studies were performed every 3 months after the intervention.

2.4. MRI-imaging

Preintervention and follow-up examinations were performed with a 1.5-T MRI system (Magnetom Symphony or Avanto, Siemens