Liver metastases of neuroendocrine tumors: Conventional transarterial chemoembolization and thermal ablation

Lebermetastasen von neuroendokrinen Tumoren: konventionelle transarterielle Chemoembolisation und thermische Ablation

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Key words
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ABSTRACT

Purpose To identify prognostic factors for patients with neuroendocrine liver metastases (NELM) undergoing conventional transarterial chemoembolization (c-TACE), microwave ablation (MWA), or laser interstitial thermotherapy (LITT) and to determine the most effective therapy regarding volume reduction of NELM and survival.

Materials and Methods Between 1996 and 2020, 130 patients (82 men, 48 women) were treated with c-TACE, and 40 patients were additionally treated with thermal ablation. Survival was retrospectively analyzed using the Kaplan-Meier-method. Additional analyses were performed depending on the therapeutic intention (curative, palliative, symptomatic). Prognostic factors were derived using Cox regression. To find predictive factors for volume reduction in response to c-TACE, a mixed-effects model was used.

Results With c-TACE, an overall median volume reduction of 23.5 % was achieved. An average decrease in tumor volume was shown until the 6th c-TACE treatment, then the effect stopped. C-TACE interventions were most effective at the beginning of c-TACE therapy, and treatment breaks longer than 90 days negatively influenced the outcome. Significant prognostic factors for survival were number of liver lesions (p = 0.0001) and type of therapeutic intention (p < 0.0001). Minor complications and one major complication occurred in 20.3 % of LITT and only in 8.6 % of MWA interventions. Complete ablation was observed in 95.7 % (LITT) and 93.1 % (MWA) of interventions.

Conclusion New prognostic factors were found for survival and volume reduction. Efficacy of c-TACE decreases after the 6th intervention and treatment breaks longer than 90 days should be avoided. With thermal ablation, a high rate of complete ablation was achieved, and survival improved.

Key points:
- Number of liver lesions and therapeutic intention are prognostic factors for survival.
- Regarding volume reduction, c-TACE is most effective at the beginning of treatment and longer treatment breaks should be avoided.
- With MWA and LITT, a high rate of complete ablation was achieved. MWA trends toward fewer complications than LITT in the treatment of NELM (p = 0.07).

ZUSAMMENFASSUNG

Ziel war es, neue prognostische Faktoren für Patienten mit neuroendokrinen Lebermetastasen, die eine radiologisch interventionelle Therapie bekamen, zu identifizieren. Zusätzlich sollte die effektivste Therapie hinsichtlich der Überlebenszeit und der Volumenreduction ermittelt werden. Ausgewertet wurden dabei die konventionelle transarterielle Chemoembolisation (c-TACE), die Mikrowellenablation (MWA) und die laserinduzierte Thermotherapie (LITT).

Material und Methoden Zwischen 1996 und 2020 wurden insgesamt 130 Patienten (82 Männer, 48 Frauen) mit c-TACE behandelt. 41 Patienten wurden zusätzlich mit thermoablative Verfahren behandelt. Das Überleben wurde retrospektiv...
Interventional Radiology

With an incidence of 5–7 cases per 100,000, gastropancreatic neuroendocrine neoplasms show the second highest prevalence among gastrointestinal cancers today [1]. Neuroendocrine liver metastases (NELMs) occur in 28–75% of patients with neuroendocrine tumors (NETs) [2] and NELMs severely reduce life expectancy. For example, patients with NETs of the small intestine without endocrine tumors (NETs) [2] and NELMs severely reduce life expectancy. For example, patients with NETs [3]. Various procedures are available for the treatment of NELMs. The best curative method in terms of survival is liver resection, but according to the latest ENETS guidelines, only 20–57% of patients can be treated this way [4]. Since symptoms in neuroendocrine tumors often appear very late and nonspecifically, a disseminated stage of disease is often already present, which reduces the chance of surgical treatment [5]. Therefore, other therapy methods for non-resectable liver metastases play an important role. These therapeutic procedures include drug therapy, nuclear medicine approaches (such as peptide receptor therapy, selective intra-arterial radiotherapy [SIRT or TARE]), and interventional radiological therapies. These interventional radiological therapies can be further divided into local ablations (microwave ablation [MWA], radiofrequency ablation [RFA], laser interstitial thermotherapy [LITT]) and transarterial therapies (conventional transarterial chemoembolization [c-TACE], transarterial embolization [TAE]) [6]. Following the guidelines of the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), local ablation is recommended for unresectable liver metastases with an oligometastasis (≤5 metastases) with a diameter of ≤5 cm. Embolization therapy (TAE/TACE) of the liver can be performed in symptomatic NETs, with the presence of multiple unresectable liver metastases, but also in case of asymptomatic NELMs with hepatic progression [7].

Numerous studies have shown that these interventional therapies have significantly improved the survival and well-being of patients [3, 6, 7]. Most data published to date relates to RFA [6], while there are only a few publications on MWA and LITT [7]. In addition, there are few studies that examine the application of interventional therapies in more detail. It is important to investi-
gate whether there are factors that influence the success of c-TACE therapy in terms of volume reduction (VR) and how VR of the lesions varies over the course of c-TACE therapy. The aim of this study was to retrospectively identify prognostic factors for patients with NELMs undergoing interventional therapies and to determine the most effective therapy in terms of VR and survival.

Materials and Methods
This retrospective cohort study was approved by the institutional review board (IRB) with a waiver for written informed consent.

Patient selection
130 patients (82 men, 48 women) who received NELM treatment between 1996 and 2020 were retrospectively evaluated. The mean age was 59.0 years (range 24.6–87.0 years) (Table 1). The number of liver lesions per patient ranged from 1 to > 100 lesions. The diameter of the lesions ranged from 0.2–17 cm. Ablations were performed in oligometastatic (≤5 metastases) patients with lesions with a diameter of ≤5 cm. 40 patients (24 LITT, 19 MWA, 3 LITT and MWA) were treated with a thermoablative procedure. In the 24 LITT patients, a total of 82 lesions were treated in 69 interventions. In the 19 MWA patients, 63 lesions were treated in 62 interventions.

c-TACE was performed in patients with symptomatic NELMs or with the presence of multiple unresectable NELMs. c-TACE was also performed in the neoadjuvant context: In patients who had >5 lesions, the use of c-TACE could reduce the number of lesions to ≤5. Thus, these patients could now undergo thermal ablation. All patients were discussed in a multidisciplinary tumor board. All included patients were not amenable to surgery or refused surgery.

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics.</th>
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<td>Parameters</td>
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<td>Treatment</td>
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<td>• Only c-TACE</td>
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<td>• c-TACE and only MWA</td>
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<td>• Hindgut</td>
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<td>• Pancreas</td>
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<td>• Lung</td>
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<td>• Other</td>
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<td>Number of c-TACE interventions, n</td>
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<td>Days between c-TACE interventions (mean/median)</td>
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<td>Liver lesions, n</td>
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<td>• 3–9</td>
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<tr>
<td>• &gt;10</td>
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<td>• No retrospective documentation</td>
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MWA
MWA was performed using a CT–guided percutaneous approach under analgo-sedation. The first MWA was carried out in October 2009. The systems used for ablation were Covidien (Medtronic, Minneapolis, USA), Amica (Amica Hospital Service, Aprilia, Italy), and Microsulis (Microsulis Medical Limited, Waterlooville, UK).

LITT
LITT was performed from 1996 to 2009. Due to the high material and personnel expenditure, the procedure was then replaced by MWA. First, metastases were localized with a CT examination and the laser application set was introduced using local anesthesia. Then the patients were transferred to an MRI scanner where the actual ablation took place. LITT was performed using a Nd:YAG-laser (Dornier MedLas 5060 and S100) with a bare fiber (400μm).
The laser application kit (SOMATEX, Berlin, Germany) consisted of a cannulation needle, guide wire, a sheath system, and a special protective catheter [6].

Imaging
To evaluate c-TACE interventions, a 1.5 Tesla MRI scanner and a 256 row CT scanner were used. Before the first c-TACE procedure, a non-enhanced and a contrast-enhanced MRI examination was performed. In all subsequent c-TACE interventions, a preinterventional MRI examination without contrast enhancement was performed. After each c-TACE, a CT scan was performed to assess the retention of lipiodol and to detect misdirected lipiodol. To evaluate and control MWA and LITT, patients received an MRI scan before and after the intervention. For follow-up, MRI scans were performed every 3 months in the first year and every 6 months thereafter.

The volume of the reference lesions was determined by the sum of the area of the lesions in the individual layers multiplied by the layer thickness. The ablation margin was considered sufficient if the ablation zone exceeded the NELM by at least 5 mm.

Statistical analysis
Descriptive statistics were performed with BIAS, survival analysis with MedCalc. The mixed-effects model for VR analysis was calculated with R.

For survival analysis and to determine predictors of death, patients were divided into different cohorts according to the following parameters: sex, age at the beginning of treatment (20–39, 40–59, ≥60 years), therapeutic intention (curative, palliative, symptomatic), number of liver lesions (1–2, 3–9, ≥10), and location of the primary (foregut, midgut, hindgut, pancreas, lung, and other origin) (Fig. 1).

Fig. 1 Patient selection and analyses performed.

Abb. 1 Patientenauswahl und durchgeführte Analysen.
The classification considering the therapeutic intention was based on the following criteria: The aim of the curative treatment was the complete eradication of liver metastases in patients who had no other extraparenchymal metastases. Patients categorized as palliative had extraparenchymal metastases or a high tumor burden in the liver. The goal of palliative treatment was to prolong their survival and achieve a stable disease. Patients were categorized as symptomatic if they showed symptoms which was usually associated with a massive intrahepatic tumor load (>50 % of the liver).

The parameter “therapeutic intention” was additionally investigated in more detail. It was analyzed how many patients, depending on their therapeutic category, had a response to c-TACE and whether the therapeutic intention would change over the course. Response to c-TACE meant that the treatment criteria for local ablation (oligometastasis, diameter ≤ 5 cm) were achieved with c-TACE therapy.

Additionally, survival depending on therapy was analyzed. All survival analyses were done using the Kaplan-Meier method, the logrank test, and Cox regression analysis. Four patients who only visited our radiological institute once were excluded from survival analysis.

Overall survival time (OS) was determined from the time of first interventional treatment until death or last follow-up. Patients alive at the time of the last follow-up were censored.

Because of the simultaneous analysis of locoregional ablations and c-TACE, different numbers of lesions were evaluated in patients. Therefore, a mixed-effects model was used for the evaluation of c-TACE volume reduction: The investigated parameters were the drugs used for c-TACE (gemcitabine, irinotecan, other drugs), the site of the primary (foregut, midgut, hindgut, pancreas, lung, other), the therapeutic intention (curative, palliative, symptomatic), whether there was a break of treatment longer than 90 days between two c-TACE procedures, and whether the liver had been treated with c-TACE before treating the reference lesion. The last parameter was assessed because in some cases lesions occurred in the later course of c-TACE therapy, for example, after the 5th c-TACE intervention, or were not treated before because the liver segment containing the reference lesion was not treated during the prior interventions. Accordingly, patients were divided into three groups depending on how many c-TACE procedures had been performed prior to the treatment of the reference lesion: 1–4, 5–9 or ≥ 10 c-TACE procedures.

For the assessment of thermoablative procedures regarding complications and complete ablation, descriptive statistics, Chi²-test, and Fisher’s exact test were used. Complications were divided according to the CIRSE classification system [8].

Results

Survival analysis
The median overall survival (mOS) of all 126 patients that could be evaluated for survival was 38.4 months (95 %CI 22.8–55.1). The 1, 2, 3 and 5-year survival rates (SR) were 75 %, 58 %, 51 %, and 36 %, respectively. Regarding survival depending on therapy, patients who only underwent c-TACE showed an mOS of 19.6 months (95 %CI 13.8–35.5), a one-year SR of 65 %, and a five-year SR of 31 %. Patients who received subsequent MWA had an mOS of 37.2 months (95 %CI 29.4–54.4), a one-year SR of 93 %, and a five-year SR of 32 %. Patients who received subsequent LITT showed an mOS of 54.1 months (95 %CI 34.3–93.9), a one-year SR of 100 %, and a five-year SR of 40 %. However, no statistically significant difference in survival between MWA, LITT, and c-TACE was found (p = 0.0703). (Table 2)

Statistically significant differences in survival were found for the parameters: number of liver lesions and therapeutic intention. The group of ≥ 10 liver lesions differed significantly from 1–2 liver lesions (p = 0.0019, HR = 0.27, 95 %CI 0.12–0.62) and from 3–9 liver lesions (p = 0.0008, HR = 0.35, 95 %CI 0.19–0.65). Regarding the therapeutic intention, all groups differed significantly from each other (Fig. 2). The curative group had a significantly longer survival than the palliative group (p = 0.0387, HR = 2.35, 95 %CI 1.0452–5.2768) and the symptomatic group (p < 0.0001, HR = 6.27, 95 %CI 2.70–14.50). The palliative group had a significantly longer survival than the symptomatic group (p < 0.0001, HR = 2.67, 95 %CI 1.69–4.22).

No statistical significance (p > 0.05) was identified regarding the parameters: sex (p = 0.393), location of the primary (p = 0.397), and age (p = 0.491).

Course of disease depending on therapeutic intention
In the curative cohort, response to c-TACE was achieved in 90.9 % of patients (10/11). In the palliative cohort, response was reached in 43.6 % of patients (31/71). Nevertheless, 7 of 11 (63.6 %) initially curative patients ended up in the palliative group, while 13 of 71 (18.3 %) initially palliative patients were finally given curative therapy. All patients classified as symptomatic remained in this group for the entire course of therapy (Table 3).

Evaluation of tumor volume reduction – c-TACE
VR of the reference lesions was achieved in 65 % of patients. The median VR was 23.5 % (Fig. 3). With respect to whether the liver was already treated with c-TACE before the treatment of the reference lesion, a statistically significant correlation was determined in the mixed-effects model. The group “≥ 10 c-TACE procedures” differed significantly from the group “1–4 c-TACE procedures” (p = 0.026, OR = 4.689, 95 %CI 1.20–18.25). For the group of 1–4 c-TACE procedures, VR was demonstrated in 69 % of reference lesions, whereas for the group of ≥ 10 c-TACE procedures, VR was achieved in only 35 %. Treatment interruptions of longer than 90 days (e.g., due to a wait-and-see therapy strategy, intermediate remission, or scheduling reasons on the part of the patient) were also associated with a negative outcome regarding VR (p = 0.052, OR = 3.150, 95 %CI 0.990–10.018). No significant association was shown for the therapeutic intention, location of primary, and drugs used in c-TACE.

In addition, it was investigated whether the effect of the individual c-TACE interventions changed during the course of c-TACE therapy. The number of c-TACE interventions per patient ranged from 1–26 interventions. Despite c-TACE therapy, patients on average showed intrahepatic disease progression after the 6th intervention (Table 4). Therefore, from the 7th intervention...
onwards the proportion of interventions, in which a VR was achieved through c-TACE therapy, was always smaller than or equal to the proportion of volume increase. For example, 18 lesions that were treated with ≥7 c-TACE procedures were evaluated in this study. After the seventh c-TACE intervention, increased lesion volume was detected in 56% of lesions (n = 10). A VR was detected in only 44% of the lesions (n = 8). Also, after the 8th to 10th c-TACE intervention, a larger lesion volume was detected in the majority of lesions after c-TACE than before c-TACE. In contrast, after the first 6 c-TACE procedures, a VR was detected in the majority of cases (Table 4).

Evaluation of tumor volume reduction – thermoablative interventions

Complete ablation (CA) after LITT was found in 68 of 71 evaluable lesions (95.7%). CA by MWA was observed in 54 out of 60 lesions (90%) (Fig. 3). For 2 of the 6 lesions that were not completely ablated, it must be noted that these 2 lesions were too large for
CA and were only supposed to be reduced in size. Excluding these two lesions, the percentage of CA is 93.1%.

No statistically significant difference was demonstrated between MWA and LITT with respect to complete ablation (Fisher’s exact test: p = 0.70).

64 of 69 LITT interventions could be evaluated regarding complications. Minor complications occurred in 12 interventions (18.8%): 8 pleural effusions (Cirse Grade 1), 1 case of edema of adjacent structures (Grade 1), 2 subcapsular hematomas (Grade 2), and 1 bilioma (Grade 2). One hepatic abscess as a major complication was reported (Grade 3). Regarding MWA, 58 of 62 interven-

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**Table 4** C-TACE volume reduction of lesions in the course of c-TACE therapy.

<table>
<thead>
<tr>
<th>c-TACE no.</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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<tbody>
<tr>
<td>Number of lesions evaluated</td>
<td>97</td>
<td>74</td>
<td>60</td>
<td>43</td>
<td>31</td>
<td>24</td>
<td>18</td>
<td>14</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>% of lesions with volume reduction</td>
<td>59</td>
<td>53</td>
<td>65</td>
<td>58</td>
<td>45</td>
<td>67</td>
<td>44</td>
<td>36</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>% of lesions with volume increase</td>
<td>39</td>
<td>46</td>
<td>33</td>
<td>40</td>
<td>55</td>
<td>29</td>
<td>56</td>
<td>64</td>
<td>50</td>
<td>57</td>
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<tr>
<td>% of lesions with constant volume</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
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</table>
tions could be evaluated for complications. Mild complications occurred in 5 cases (8.6%): 2 pleural effusions (Grade 2), 1 hemorrhage (Grade 2), 1 case of edema (Grade 1), and 1 case of air trapping (Grade 1).

With regard to complications, a statistical trend for MWA with fewer complications than LITT was shown, although no statistical significance was demonstrated (p = 0.07, Chi²-test = 3.31).

Discussion

The aim of this study was to identify prognostic factors for patients with NELMs undergoing radiological interventional therapies and to determine the most effective therapy in terms of VR and survival. Significant prognostic factors for survival were number of liver lesions and therapeutic intention. No statistical significance was identified for the parameters: sex, age, and location of the primary. In contrast, Barat et al. described that a pancreatic primary, an unknown primary site, and male gender are associated with a shortened survival [9]. Our study also showed that the therapeutic intention for symptomatic patients cannot be changed to a palliative or curative treatment option, but a change from palliative to curative intention and vice versa is quite possible. In 2016, Vogl et al. investigated the SR depending on the clinical indication (curative vs. palliative) in patients with general liver lesions treated with MWA. In this study, no significant difference was shown between the curative and the palliative group, whereas curative treatment intention was associated with a significantly longer life in our study [10]. One explanation may be that Vogl assessed only MWA patients and liver lesions of different origin.

Assessing survival depending on therapy, no statistically significant difference was found. However, the one-year SR of the c-TACE group differed considerably from the two other groups, but the 5-year SR (31%) was quite similar. The literature contains very different data on the 5-year SR of NELM patients treated with c-TACE. In a review from 2020, the 5-year SR ranged from 19% to 50% [11]. Following Mayo et al., one explanation for the different data on SR may be the great heterogeneity of the patients and the fact that different institutes treat cases of different severity [12].

Regarding VR and complications of thermoablative procedures in NELMs, data is still lacking [13]. Perrodin et al. examined MWA for 40 liver malignant lesions, including 17 NELMs [13]. Here, CA was seen in 97.5% and mild complications in 12% of cases. Martin et al. described a CA rate in 90% of cases [14]. Thus, these studies showed a similar trend for MWA for CA and complications. For LITT, Peräla described in a case report two LITT patients with NELMs [15]. One patient had minor complications. The total survival was 21 and 13 years.

In contrast to MWA and LITT, there are already many papers that have investigated the general outcome of TACE or TAE. In 2021, Clift et al. summarized the results of studies regarding TAE and TACE therapies for NELMs [16]. However, there are still only a few studies that have assessed c-TACE therapy in more detail regarding VR and how the VR of the lesions varies over the course of multiple c-TACE procedures. For patients with HCC, Breunig et al. investigated the course of TACE therapy (comprising 1–10 TACE procedures), in terms of expenses and survival [17]. Wang et al. investigated the effect of different numbers of TACE procedures on liver function in HCC patients with transjugular intraportal portosystemic shunt [18]. Thus, there are few papers that describe the course of TACE therapy in more detail, and mainly for HCC. Our study demonstrated that VR was achieved significantly more often when a lesion was treated at the beginning of multiple c-TACE procedures and that efficacy of c-TACE decreases after the 6th intervention. Furthermore, it has been shown that VR due to c-TACE is particularly effective when there is no treatment break longer than 90 days between interventions (p = 0.052). It can be assumed that patients should be closely monitored to treat lesions as early as possible in the case of reappearance.

In this study there are several limitations: NENs are a very heterogeneous tumor type with sometimes very rare entities with different therapeutic options. A precise classification of the different tumors with respect to the exact primary and grading would be very important to make the data more comparable and to derive more differentiated results. In the present study, no classification of tumors by grading (G1 vs. G2 vs. G3 vs. NEC, Ki67) was performed, as no data were available due to the retrospective nature of the study. Furthermore, it should be noted that the classification on Ki67 was introduced with the ENETS guidelines of 2006/2007, but the data of the study date back to 1996 [19]. Regarding the classification according to primary, it should be mentioned that there was a substantial number of patients with “other” NEN subtypes. Here, a more precise subanalysis was not possible, because this group was also very heterogeneous with many different primaries (kidney, adrenal gland, paraganglion, CUP, jugulotympanic paraganglion of the middle ear, etc.).

Additionally, in some cases several forms of therapy (c-TACE, MWA, LITT) were performed on the same patient, making a separate assessment of the individual therapeutic successes difficult. In conclusion: The number of liver lesions and therapeutic intention were shown to be prognostic factors for survival. It was shown that palliative patients could still be treated curatively and vice versa. A high rate of complete ablation in thermoablative procedures was achieved. LITT compared to MWA was associated with more complications. An interesting new aspect shown by this study was the fact that c-TACE is especially effective at the beginning of multiple interventions regarding NELM volume reduction. Also, longer treatment breaks should be avoided. The evaluation of the course of multiple c-TACE interventions has still been studied very little and therefore represents an interesting prospect for the future.

**Clinical Relevance of the Study**

- With increasing incidences of neuroendocrine neoplasms and insufficient scientific data, further analysis of neuroendocrine neoplasms is essential.
- For better prognostic assessment, identification of risk factors is important. In this study, the number of liver lesions and the therapeutic intention were confirmed as risk factors.
• It has been shown that the effectiveness of c-TACE therapy decreases over the course of several c-TACE interventions, thus providing an important finding for further evaluation of c-TACE therapy.

Conflict of Interest

The authors declare that they have no conflict of interest.

References