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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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 Volumenreduktion 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 thermoablativen Verfahren behandelt. Das Überleben wurde retrospektiv mit der Kaplan-Meier-Methode analysiert. Zusätzliche Analysen wurden hinsichtlich der therapeutischen Intention (kurativ, palliativ, symptomatisch) durchgeführt. Prognosefaktoren für längeres Überleben wurden mit dem Logrank-Test und der Cox-Regressionsanalyse ermittelt. Prädiktive Faktoren hinsichtlich der Volumenreduktion durch c-TACE wurden mithilfe des gemischten Modells dargestellt.

Ergebnisse Mit c-TACE konnte eine mediane Volumenreduktion von 23,5 % erzielt werden. Eine durchschnittliche Volumenreduktion konnte bis zur sechsten c-TACE-Behandlung erzielt werden. Danach ließ der Effekt der c-TACE nach. C-TACE war besonders effektiv zu Beginn von multiplen c-TACE-Interventionen. Behandlungspausen > 90 Tage wirkten sich negativ auf die Volumenreduktion aus. Signifikante prognostische Faktoren hinsichtlich der Überlebenszeit waren die Anzahl der Leberläsionen (p = 0,0001) und die therapeutische Intention (p < 0,0001). Komplikationen traten in 20,3 % der Fälle bei LITT und in 8,6 % der Fälle bei MWA auf. Eine komplette Ablation wurde in 95,7 % (LITT) und in 93,1 % (MWA) der Fälle erzielt.

Schlussfolgerung Es wurden signifikante Faktoren für eine längere Überlebenszeit und eine größere Volumenreduktion durch c-TACE gefunden. C-TACE ist eine effektive Behandlung für die Volumenreduktion der NELM, wobei die Effektivität nach der sechsten Intervention nachlässt und Behandlungspausen länger als 90 Tage vermieden werden sollten. Mit den thermoablativen Verfahren konnte eine hohe Rate an kompletter Ablation erreicht und eine Korrelation mit verlängertem Überleben gezeigt werden.

Kernaussagen
- Anzahl der Leberläsionen und therapeutische Intention sind prognostische Faktoren für die Überlebenszeit.
- C-TACE ist besonders effektiv zu Beginn der Behandlung und längere Behandlungspausen sollten vermieden werden.
- Mit MWA und LITT konnte eine hohe Rate an vollständiger Ablation erreicht werden. Bezüglich Komplikationen konnte ein statistischer Trend hinsichtlich weniger Komplikationen bei MWA als bei LITT gezeigt werden. (p = 0,07)

Zitierweise
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ABBREVIATIONS

NELM	Neuroendocrine liver metastasis
c-TACE	Conventional transarterial chemoembolization
MWA	Microwave ablation
LITT	Laser interstitial thermotherapy
NET	Neuroendocrine tumor
RFA	Radiofrequency ablation
TAE	Transarterial embolization
VR	Volume reduction
CT	Computed tomography
MRI	Magnetic resonance imaging
OS	Overall survival time
mOS	Median overall survival
SR	Survival rate
CA	Complete ablation
NEC	Neuroendocrine carcinoma
CUP	Cancer of unknown primary

Introduction

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 NELMs showed an estimated survival of 176.3 ± 30.3 months, whereas patients with NELMs had a survival of 98.1 ± 8.1 months [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 radio 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 investigate 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.

c-TACE

A total of 813 c-TACE procedures were performed on the 130 patients. Patients who underwent only one c-TACE procedure were not included in the tumor VR analysis.

After a catheter was inserted into the common femoral artery using the Seldinger technique, an angiography examination of the abdominal arterial vasculature was performed. Then a microcatheter was positioned through the celiac trunk into the common hepatic artery. Depending on which NELM was to be treated, the microcatheter was advanced into either the right or left hepatic artery or into a segmental artery. Once the correct location was confirmed, chemotherapeutic agents and embolization material were injected into the target artery.

MWA

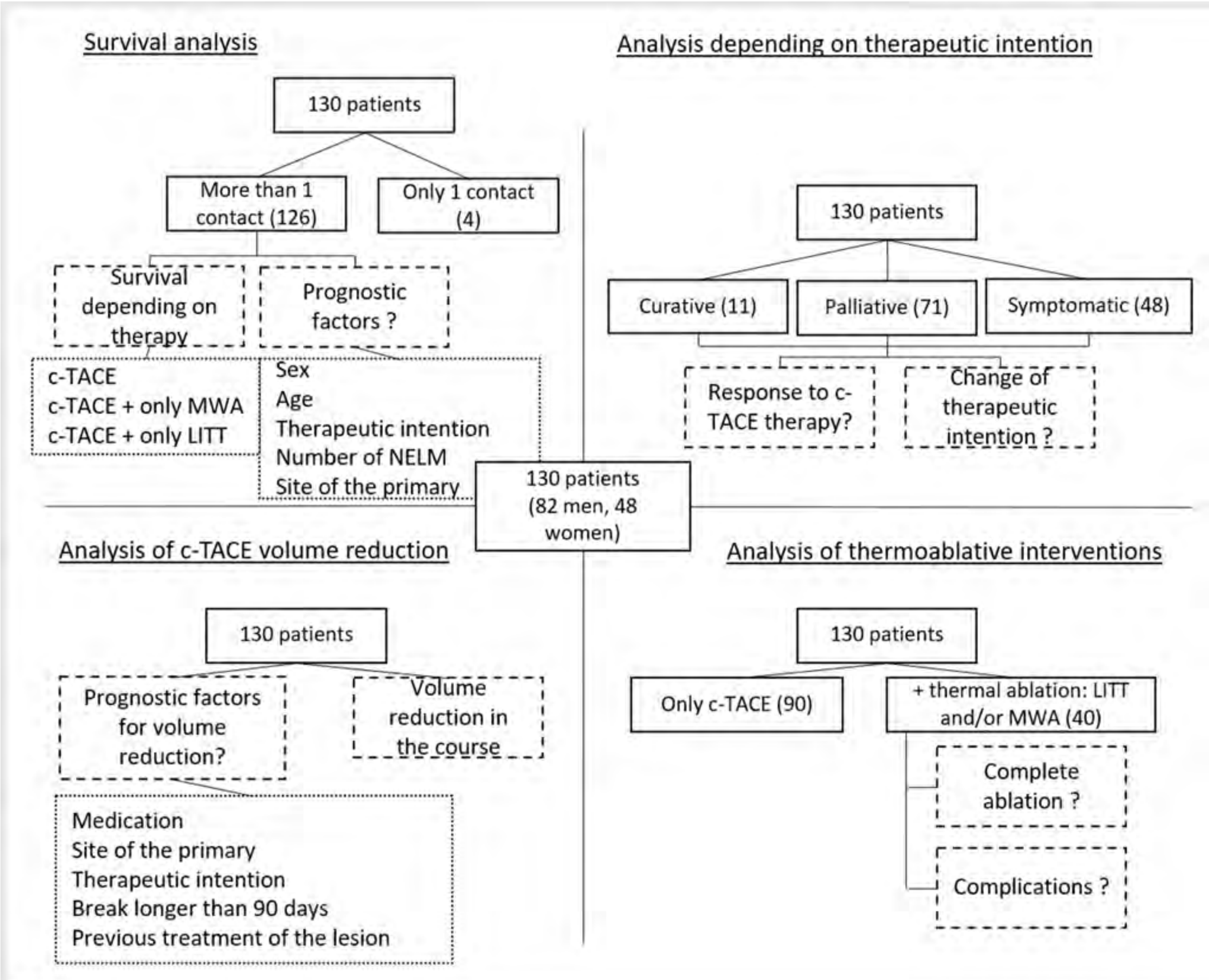
MWA was performed using a CT–guided percutaneous approach under analgo-sedation. The first MWA was carried out in October 2009. The systems used for ablation were Covidien (Medtronic, Minneapolis, USA), Amica (Amica Hospital Service, Aprilia, Italy), and Microsulis (Microsulis Medical Limited, Waterlooville, UK).

▶ **Table 1** Baseline characteristics.

Parameters	n = 130 patients
Mean age/range	59.0 years/24.6–87.0 years
Gender, male/female	82/48
Treatment	
▪ Only c-TACE	89
▪ c-TACE and only MWA	16
▪ c-TACE and only LITT	20
▪ c-TACE and mixed thermal ablation	5
Primary tumor	
▪ Foregut	6
▪ Midgut	28
▪ Hindgut	8
▪ Pancreas	37
▪ Lung	9
▪ Other	42
Number of c-TACE interventions, n	
▪ 1	25
▪ 2	8
▪ 3	22
▪ 4	14
▪ 5	5
▪ 6	9
▪ 7	4
▪ 8	7
▪ 9	3
▪ 10	5
▪ 11–26	23
▪ Mean	6.25
▪ Median	4
Days between c-TACE interventions (mean/median)	83.7/35
Liver lesions, n	
▪ 1–2	12
▪ 3–9	28
▪ >= 10	88
▪ No retrospective documentation	2

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 5100) with a bare fiber (400µm).



▶ **Fig. 1** Patient selection and analyses performed.

▶ **Abb. 1** Patientenauswahl und durchgeführte Analysen.

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**).

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 extrahepatic metastases. Patients categorized as *palliative* had extrahepatic 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, Chi^2-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**).

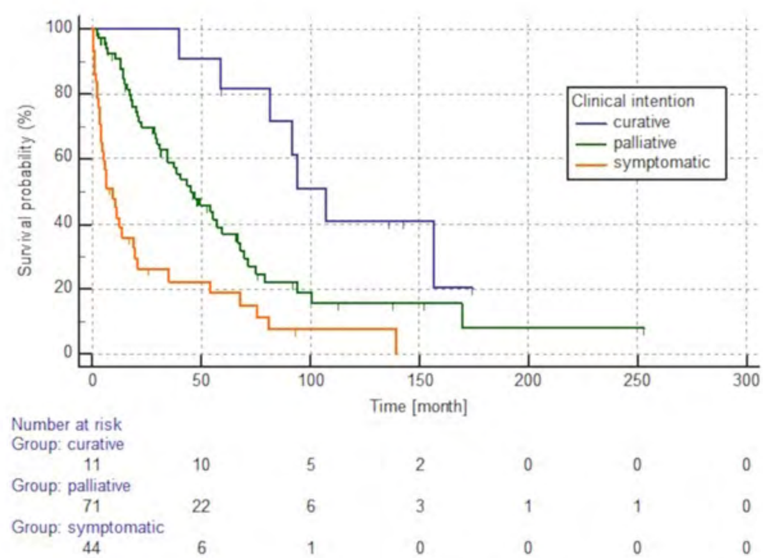
Evaluation of tumor volume reduction – c-TACE

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 6^{th} intervention (▶ **Table 4**). Therefore, from the 7^{th} intervention

▶ **Table 2** Survival depending on treatment.

	n	Mean [month]	Median [month]	1 yr-sr [%]	5 yr-sr [%]
Only c-TACE	85	42.882	19.561	65	31
c-TACE and only MWA	16	40.702	37.249	93	32
c-TACE and only LITT	20	89.291	54.082	100	40



▶ **Fig. 2** Kaplan-Meier analysis comparing the OS of the three cohorts curative, palliative, and symptomatic.

▶ **Abb. 2** Kaplan-Meier-Analyse mit Vergleich der Überlebenszeiten der drei Kohorten kurativ, palliativ und symptomatisch.

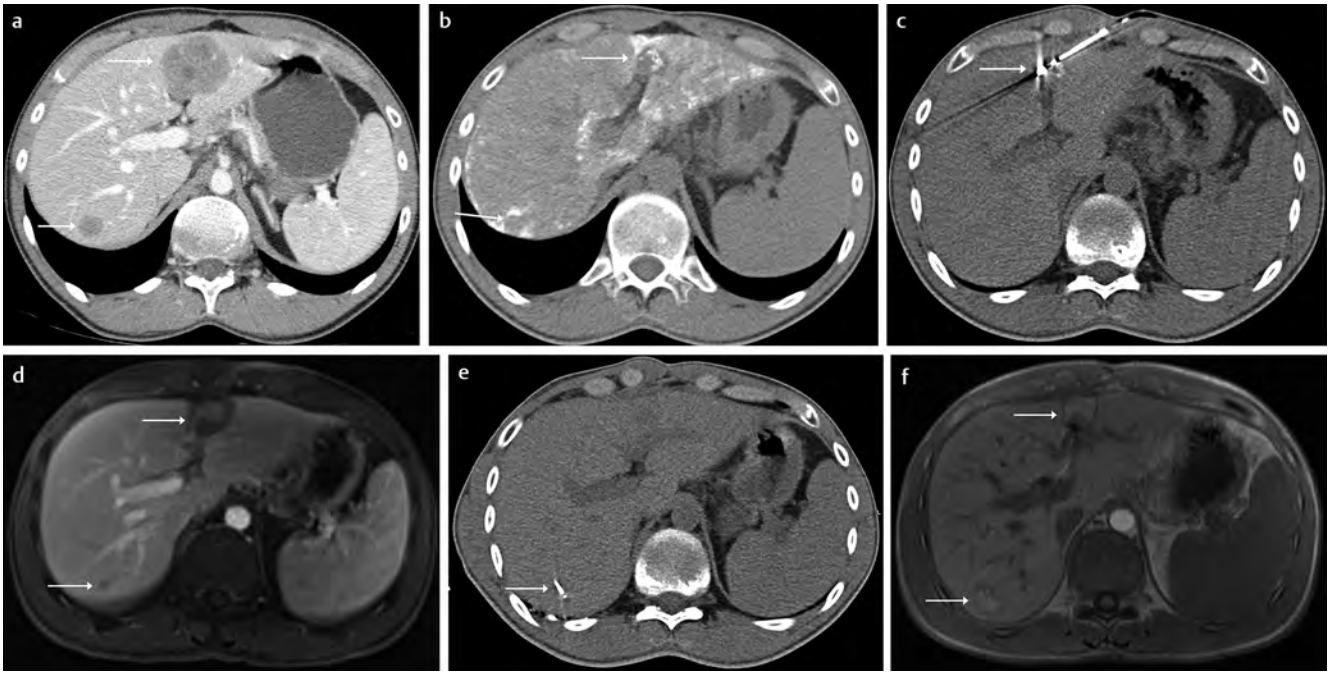
▶ **Table 3** Response to c-TACE and survival according to therapeutic intention.

	n	Response to c-TACE	Therapeutic intention in the course	Median OS	95 % CI for OS
Curative	11	10 (90.9 %)	Curative: 4 Palliative: 7	106.9 months	81.3–156.5
Palliative	71	31 (43.6 %)	Curative: 13 Palliative: 58	45.5 months	34.3–59.4
Symptomatic	48	0 (0 %)	Symptomatic: 48	9.4 months	4.5–19.3

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



▶ **Fig. 3** Example of c-TACE and MWA in the treatment of a 24-year-old male with two NELMs from an NET of the small intestine. In total, the patient received 8 c-TACE and 2 MWA treatments resulting in complete hepatic remission. (**a**) Two years after small intestinal resection, the patient shows the reference lesion in segment 4/2 and another lesion in segment 7. (**b**) Axial CT after eight c-TACE interventions showing a total volume reduction of 80 % of the reference lesions (upper arrow). Detection of lipiodol in the lesions (arrows). (**c**) Axial CT showing the process of MWA with the ablation antenna placed inside the reference lesion in segment 4/2 (arrow). (**d**) Axial contrast-enhanced T1-weighted MRI after first MWA. Complete ablation of the reference lesion within the necrosis zone (upper arrow) and one last persistent lesion in segment 7 (lower arrow). (**e**) Axial CT showing the process of the second MWA with the ablation antenna placed inside the lesion in segment 7 (arrow). (**f**) Axial non-enhanced T1-weighted MRI after second MWA of the last remaining lesion in segment 7 showing the necrosis zones (arrows) and resulting in complete hepatic remission.

▶ **Abb. 3** Beispiel für c-TACE und MWA bei der Behandlung eines 24-jährigen Mannes mit zwei NELM eines NET des Dünndarms. Insgesamt erhielt der Patient 8 c-TACE und 2 MWA, was zu einer vollständigen Remission der Leber führte. (**a**): Zwei Jahre nach der Dünndarmresektion zeigt der Patient die Referenzläsion in Segment 4/2 und eine weitere Läsion in Segment 7. (**b**) Axiales CT nach acht c-TACE-Eingriffen mit einer Volumenreduktion der Referenzläsion von insgesamt 80 % (oberer Pfeil). Nachweis von Lipiodol in den Läsionen (Pfeile). (**c**) Axiales CT, das den Verlauf der MWA zeigt, wobei die Ablationsantenne innerhalb der Referenzläsion im Segment 4/2 platziert ist (Pfeil). (**d**) Axiales T1-gewichtetes MRT mit Kontrastmittel nach der ersten MWA. Vollständige Ablation der Referenzläsion innerhalb der Nekrosezone (oberer Pfeil) und eine letzte persistierende Läsion im Segment 7 (unterer Pfeil). (**e**) Axiales CT, das den Verlauf der zweiten MWA zeigt, wobei die Ablationsantenne innerhalb der Läsion in Segment 7 platziert ist (Pfeil). (**f**) Axiales T1-gewichtetes MRT nach der zweiten MWA der letzten verbleibenden Läsion in Segment 7 mit Darstellung der Nekrosezonen (Pfeile) und anschließender vollständiger hepatischer Remission.

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

c-TACE no.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Number of lesions evaluated	97	74	60	43	31	24	18	14	8	7
% of lesions with volume reduction	59	53	65	58	45	67	44	36	50	43
% of lesions with volume increase	39	46	33	40	55	29	56	64	50	57
% of lesions with constant volume	2	1	2	2	0	4	0	0	0	0

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-

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 ($p = 0.07$, Chi^2-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 intrahepatic 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.

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