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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Percutaneous Laser Ablation of Liver Metastases from Neuroendocrine Neoplasm. A Retrospective Study for Safety and Effectiveness

Sergio Sartori[1] · **Paola Tombesi**[1] · **Francesca Di Vece**[1] · **Lara Bianchi**[1] · **Rosaria Ambrosio**[2]

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Abstract

Purpose To retrospectively assess safety and efficacy of laser ablation (LA) of multiple liver metastases (LM) from neuroendocrine neoplasms (NEN).

Methods Twenty-one patients with NEN and at least 3 LM $\leq$ 4 cm in diameter underwent ultrasonography-guided LA. Up to seven LM were ablated in a single session; if the number of LM exceeded seven, the remaining LM were ablated in further LA sessions with a time interval of 3–4 weeks. LA was performed according to the multifiber technique. The patients underwent contrast-enhanced CT 1 month after LA, and were subsequently monitored every 3 months for the first 2 years and then every 6 months.

Results In total, 189 LM were treated in 21 patients (mean 9 $\pm$ 8.2, median 6) in 41 LA sessions (range 1–5). The diameter of LM ranged from 5 to 35 mm (median 19 mm, mean 17.9 $\pm$ 6.4 mm). One grade 4 complication occurred (0.53%): a bowel perforation managed by surgery. Technical efficacy was 100%, primary efficacy rate 94.7%, and secondary efficacy rate 100%. Complete relief of hormone-related symptoms was obtained in all the 13 symptomatic patients. Median follow-up was 39 months (range 12–99). 1-, 2-, 3-, and 5-year survival rates were 95%, 86%, 66%, and 40%, respectively. Overall survival resulted higher for patients with Ki-67 expression $\leq$ 7% than for those with Ki-67 > 7% (p = 0.0347).

Conclusions LA is a promising and safe technique to treat LM from NEN. A longer follow-up should provide definitive information on the long-term efficacy of this liver-directed therapy.

Level of Evidence Retrospective study, local non-random sample, level 3.

Keywords Neuroendocrine tumors · Liver neoplasms · Ablation techniques · Laser therapy

✉ Sergio Sartori
srs@unife.it

1 Section of Interventional Ultrasound, St. Anna Hospital, Via A. Moro 8, 44100 Ferrara, Italy

2 Endocrinology Unit, St. Anna Hospital, Ferrara, Italy

Introduction

Neuroendocrine neoplasms (NEN) encompass a variety of cell types with variable clinical course [1, 2]. Liver metastases (LM) are frequently present at initial diagnosis, or occur in the course of the disease, and have a major impact on survival with 5-year survival rates ranging from 24 to 40% [2–5]. Systemic treatments often achieve disease stabilization, but they rarely achieve objective radiological response [1, 2, 4, 6]. Aggressive cytoreduction can positively impact on either radiological response or survival and hormonal symptom control [5–9]. Liver resection is the best option to treat LM [4, 6–10], but it can only be offered to 9–25% of patients [5, 6, 10, 11]. Moreover, most patients experience recurrence of LM 2–5 years after surgery [3, 5, 11], and require further treatments. For patients who are not surgical candidates, or have recurrence after surgery, or require a multimodality approach, catheter-based treatments and thermal ablation can be used as a primary approach or as an adjunct to surgery [1–6].

Ablation techniques deliver thermal energy, either cooling or heating the tissues. Radiofrequency ablation (RFA), microwave ablation (MWA), and laser ablation (LA) enable to raise the tissue temperature up to 100 °C, producing coagulative necrosis. RFA is the most used ablation modality worldwide, and its efficacy and safety have largely been proved [12, 13]. Last-generation MWA systems offer some advantages compared with RFA, and can obtain larger ablation volumes than RFA [14, 15]. LA has been less investigated than RFA and MWA, but the available data suggest the same efficacy [16, 17]. The multifiber laser technique [18, 19] enables the use of up to four fibers at once, and uses thinner needles than RFA and MWA, making LA suitable to treat lesions in at-risk or difficult locations, for instance when blood vessels have to be passed through to reach the target [12, 13]. To date, RFA is the most used thermal technique to ablate NEN LM [3, 4, 20–27], whereas the experiences with MWA [28] and LA [29, 30] are sporadic and limited to case reports or small series.

In this retrospective study, we report our experience with LA in patients with multiple LM from NEN.

Materials and Methods

The records of twenty-one patients (12 males and 9 females, age range 31–82 years) with LM from NEN, who were treated with ultrasonography (US)-guided LA from December 2004 to November 2017, were retrospectively reviewed. Institutional review board approval was obtained and patients' informed consent was waived. Inclusion criteria were the following: patients judged unsuitable for surgery by the multidisciplinary team of our hospital owing to the number and/or location of LM, or comorbidity; three or more than three LM with long-axis diameter $\leq$ 4 cm; location of all LM suitable to be confidently reached for thermal ablation; informed consent of the patients to undergo the procedure. Exclusion criteria were the following: LM with exophytic or strictly subcapsular location; distance of LM less than 5 mm from the gallbladder or main bile duct; platelet count $<$ 50,000/µL; international normalized ratio $>$ 1.5.

All the patients had previously undergone surgical removal of the primary tumor, and Ki-67 was assayed on the surgical specimens by immunohistochemistry by using CONFIRM anti-Ki-67 rabbit monoclonal antibody (Hoffmann-La Roche, Basel, Switzerland). Fifteen patients had carcinoid (9 from the small bowel, 2 from the colon, 2 from the pancreas, 2 from the lung), 3 pancreatic insulinoma, 2 pancreatic gastrinoma, and one adrenal gland carcinoma. Thirteen patients had hormone-related symptoms. The number of LM per patient ranged from 3 to 22. Up to seven LM were ablated in a single LA session; if the number of LM exceeded seven, the remaining LM were ablated in further LA sessions with a time interval of 3–4 weeks each other. If new LM occurred after all initial LM were ablated, they underwent LA when their long-axis diameter was $\leq$ 4 cm and their location did not fit the exclusion criteria of the study.

Ablation Procedure

LA was performed on an inpatient basis by using a commercially available system (BS-1064, DEKA M.E.L.A., Florence, Italy, until 2009; Echolaser, Elesta Srl, Florence, Italy, from 2010). The laser source was Nd:YAG for BS-1064 and a semiconductor diode for Echolaser, both of them with a wavelength of 1064 nm and a multi-source device enabling the use of up to four 300-µm fibers at once. LA procedures were performed by two physicians with more than 5 years of experience in US-guided ablation of liver and kidney tumors. All patients received a premedication with 500 µg of short-acting subcutaneous octreotide 1 h before the procedure. After local anesthesia with lignocaine 1% 10 mL and conscious sedation with intravenous midazolam and remifentanil, the laser fibers were introduced into the tumor under US guidance through 21-gauge Chiba needles. One fiber was used for lesions up to 7 mm in diameter, two fibers spaced 12 mm were used for lesions between 7 and 14 mm, three fibers spaced 12–18 mm apart for lesions between 15 and 20 mm, and four fibers spaced 12–18 mm apart arranged in a square configuration for lesions between 21 and 35 mm; the pull-back technique [18, 19] was used if the anteroposterior diameter of the nodules exceeded 12 mm. The laser machine was set at a power of 5 W, and 1800 J per fiber was delivered in 6 min; further 1800 J was delivered if the pull-back technique was used. The completeness of the ablation was assessed by contrast-enhanced US (CEUS) performed about 10 min after the end of the procedure. If no enhancing zone with diameters equal to or greater than those of the treated tumor was depicted, the treatment was considered complete (Fig. 1A, B). If residual enhancing foci of tumoral tissue were identified (Fig. 2A), further one or two laser fibers were inserted into the viable foci under CEUS guidance (Fig. 2B), and further 1800 J per fiber was delivered to complete the treatment (Fig. 2C).

Follow-Up

All patients were followed up until death or the time the data were censored (April 30, 2019). They underwent contrast-enhanced computed tomography (CECT) 1 month after LA, and were subsequently monitored with alternating CECT and CEUS every 3 months for the first 2 years

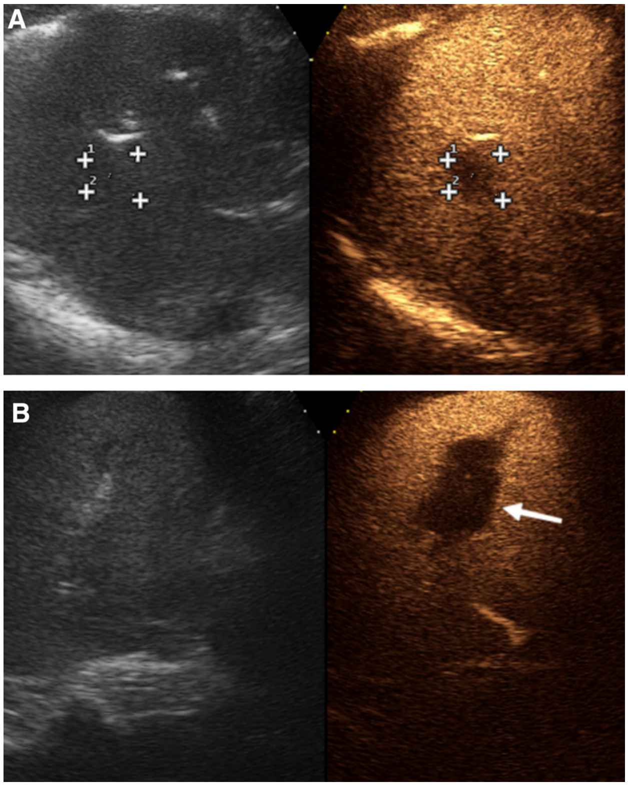

Fig. 1 **A** Intercostal CEUS scan of the right liver lobe showing a 22 × 20 mm hypoechoic LM (cross-shaped markers). **B** Intercostal CEUS scan performed ten minutes after LA showing an ablation area completely covering the LM (arrow)

and then every 6 months. If liver recurrences were observed, they were treated with LA when their long-axis diameter did not exceed 4 cm and their location did not fit the exclusion criteria of the study. Otherwise, the patients underwent TACE, surgery, radionuclide metabolic therapy, systemic chemotherapy, or combination of the most suitable treatments, based on the judgment of the multidisciplinary team for the diagnosis and treatment of NEN of our hospital, and according to number, size, and location of the new LM.

Technical success, technical efficacy, primary and secondary efficacy rate, and local tumor progression (LTP) were defined according to the recommendations of the International Working Group on the Image-guided Tumor Ablation [31]. Technical success addressed whether the tumor was treated according to protocol and was covered completely by the ablation zone. Technical efficacy was defined as a non-enhancing area with diameters equal to or greater than those of the treated tumors, assessed by CECT performed 1 month after LA. Primary efficacy rate was defined as the percentage of tumors successfully eradicated following the planned sessions of LA. LTP was defined as the appearance of tumor foci at the edge of the ablation zone, after follow-up imaging documented complete ablation. The viable foci underwent LA under CEUS guidance by using from one to four laser fibers according to their size; these treatments were not included in the overall calculation of LA sessions. Secondary efficacy rate was defined as the percentage of tumors that were successfully ablated after identification of LTP. Hepatic progression (HP) and extrahepatic progression (EP) were defined as the appearance of new tumors in other areas of the liver and in distant organs, respectively. Complications were classified according to the CIRSE classification system for complications reporting [32].

Statistical Analysis

Overall survival was estimated by using the Kaplan–Meier method and was calculated from the date of the first LA session to patients death or April 30, 2019. The log-rank test was used to evaluate the prognostic role of Ki-67 expression, dividing the population into two groups: patients with Ki-67 $\leq$ 7% and patients with Ki-67 $>$ 7%. A p value of 0.05 was assumed as statistically significant. All analyses were performed by using a statistical software program (STATA 13.0 for Windows; Stata Corp., College Station, TX, USA).

Results

Patients and tumors characteristics are detailed in Table 1.

One hundred twenty-five LM were initially present and were treated in 26 LA sessions. Other sixty-four LM occurred 7–68 months after LA; they were ablated in 15 sessions and were included in the data analysis. On the whole, 189 LM underwent LA in 21 patients (mean per patient 9 ± 8.2, median 6) in 41 LA sessions (range 1–5). The long-axis diameter of LM ranged from 5 to 35 mm (median 19 mm, mean 17.9 ± 6.4 mm). One grade 4 complication was observed (0.53%): a bowel perforation that occurred despite an apparently successful hydrodissection, and was successfully managed by surgery. Three patients experienced mild pain in the afternoon after LA; the pain was well controlled by 500–1000 mg of intravenous paracetamol, and no prolonged hospital stay was required.

Technical success was obtained in all LA procedures, and 1-month CECT documented complete ablation of 189/189 LM, with a technical efficacy of 100%. LTP was observed five to 11 months after LA in 10/189 cases, with a primary efficacy rate of 94.7%. All local recurrences were successfully treated with LA, and secondary efficacy rate was 100%. Complete relief of hormone-related symptoms was obtained in all the 13 symptomatic patients.

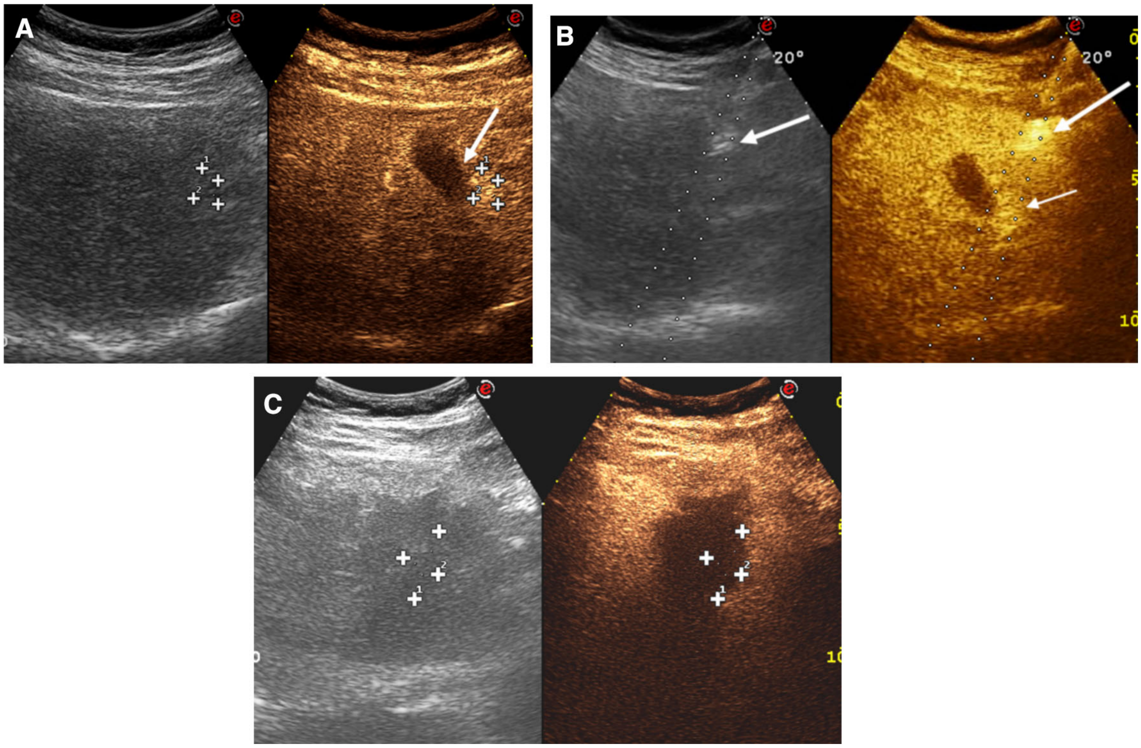

Fig. 2 **A** Subcostal CEUS scan of the right liver lobe performed 10 min after LA, showing incomplete ablation with a 11 × 9 mm enhancing focus of residual tumoral tissue (cross-shaped markers) strictly close to the ablation area (arrow). **B** Subcostal CEUS scan showing the tip of the needle (large arrow) directed toward the enhancing focus of tumoral tissue (thin arrow, right side of the split screen). **C** Subcostal CEUS scan performed 10 min after CEUS-guided LA showing complete coverage of the residual tumor (cross-shaped markers)

Nine patients (42.8%) developed subsequently extensive HP unsuitable to LA; five of them and other two patients developed also EP. All these patients underwent (or are undergoing if they are still alive) TACE when appropriate, radionuclide metabolic therapy, systemic therapy, combination treatments, or best supportive care.

The median follow-up, calculated from the first LA session to death or April 30, 2019, was 39 months (range 12–99, mean 45.4 ± 24). Eleven patients died 12–83 months after the first LA session: seven owing to disease progression and four owing to causes other than NEN. At present, ten patients are still alive 10–99 months after the first LA session: Four have EP, and six are disease-free (see Table 1).

1-, 2-, 3-, and 5-year survival rates after the first LA session were 95%, 86%, 66%, and 40%, respectively (Fig. 3). Overall survival was significantly higher for patients with Ki-67 expression $\leq$ 7% than for those with Ki-67 > 7% ($p = 0.0347$) (Fig. 4).

Discussion

The relative rarity of NEN and their heterogeneity make nearly impossible to conduct randomized prospective trials to determine the optimal treatment [2, 5, 6]. Therefore, the level of evidence of the various approaches is low, and all current recommendations are based on retrospective studies. Although LM are present in 35–60% of cases at the time of diagnosis [7], long-term survival is common and can be improved by an aggressive approach [3, 5–9]. Chemotherapy achieves poor results in the treatment of LM, especially in well-differentiated tumors [6, 8, 9]. Systemic treatments such as somatostatin analogues, peptide receptor radionuclide therapy, or targeted therapies infrequently achieve any significant objective response, but can obtain disease stabilization [6, 8, 9]. In the setting of relatively indolent disease progression, or disease stabilized by systemic treatments, liver-directed therapies can lead to good long-term outcomes [1, 5, 7–9]. Liver debulking interventions were previously recommended when at least 90% of tumor burden could be removed [33, 34], with 5-year survival rates over 60% [34, 35]. However, fewer than 20% of patients were eligible for this approach [7]. Recently, eligibility criteria have been expanded to a

Table 1 Patients and tumor characteristics and outcome

Age/sex	Primary tumor	Ki-67 (%)	LM before 1st LA	Total LM treated	Diameter range (mm)	No. of LA sessions	Date 1st LA session	HP	Date of death	Cause of death
78/M	Pancreas	6–7	3	3	14–24	1	12/02/04	No	10/12/11	Larynx cancer
31/F	Sm. bowel	7–8	6	6	7–26	1	12/14/06	Yes	03/07/10	HP + EP
75/F	Colon	< 1	3	3	9–21	1	09/20/07	No	04/18/12	Stroke
74/M	Sm. bowel	< 1	6	13	5–25	3	01/20/08	No	03/22/11	Colon cancer
72/M	Pancreas	20	7	7	12–28	1	05/26/10	Yes	05/30/11	HP + EP
47/F	Sm. bowel	< 1	3	3	12–24	1	06/30/10	No	04/12/12	EP
28/F	Pancreas	2–3	22	37	5–21	5	01/20/11	No	Alive	–
72/M	Sm. bowel	2	6	18	5–35	5	06/09/11	Yes	06/23/14	HP + EP
65/M	Sm. bowel	< 1	3	3	12–31	1	01/26/12	No	Alive	–
58/F	Pancreas	> 30	3	3	11–24	1	02/16/12	Yes	04/28/14	HP + EP
72/F	Lung	4	9	23	6–26	4	03/28/12	No	06/12/15	EP
60/F	Pancreas	5	8	11	6–30	2	03/13/13	Yes	Alive	–
67/M	Sm. bowel	5	8	12	5–20	3	05/23/13	No	12/28/15	Endocarditis
73/M	Colon	< 2	6	8	6–23	2	05/23/13	Yes	Alive	–
78/M	Sm. bowel	> 30	6	11	9–25	2	08/07/14	Yes	12/18/17	HP + EP
64/M	Pancreas	2	5	5	8–26	1	08/21/14	Yes	Alive	–
82/M	Lung	6–7	6	8	9–28	2	03/05/15	No	Alive	–
70/M	Pancreas	10	3	3	10–25	1	03/09/17	No	Alive	–
43/F	Sm. bowel	< 2	4	4	8–22	1	04/06/17	No	Alive	–
47/F	Adrenal	< 1	4	4	6–24	1	04/20/17	No	Alive	–
80/M	Sm. bowel	30	4	4	11–28	1	11/06/17	Yes	Alive	–

LA laser ablation, *LM* liver metastases, *HP* hepatic progression at April 2019, *EP* extrahepatic progression

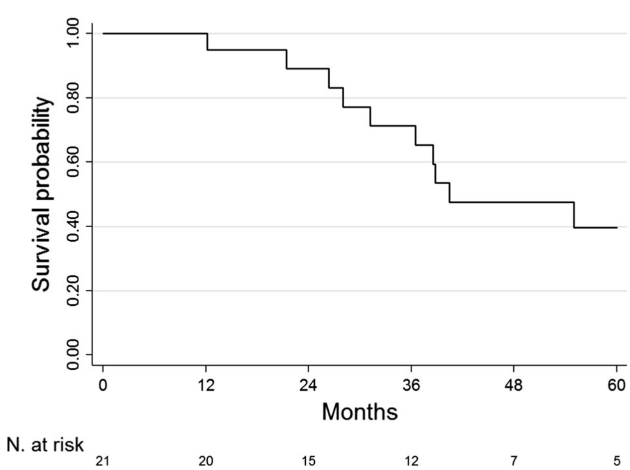

Fig. 3 Overall survival curve for all patients from the first LA session to death or April 30, 2019

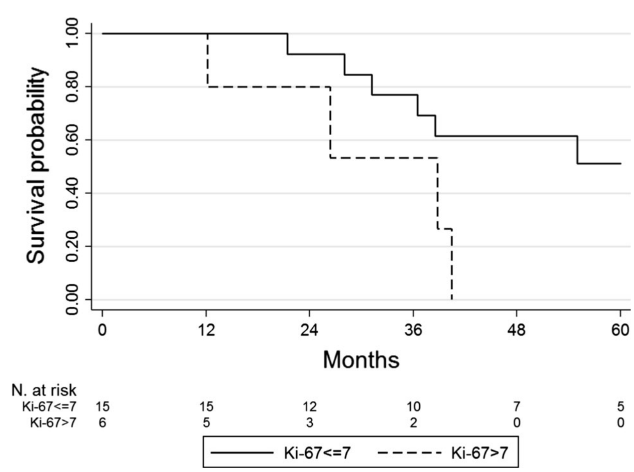

Fig. 4 Overall survival curves for patients with Ki-67 ≤ 7% and > 7%

70% de-bulking threshold, increasing the number of eligible patients, while still achieving comparable survival rates [36, 37]. Liver resection is the treatment of choice in selected patients, with either curative or de-bulking intent [3, 5, 7–11]. However, the percentage of eligible patients remains low and does not exceed 25% even with the expanded criteria [5, 35–37]. Moreover, extended resections involving multiple LM must be weighted against the associated morbidity and mortality rates that can be as high as 30% and 1–2%, respectively [5, 6]. Furthermore, 5-year recurrence rates range from 80 to 95% with a median time to recurrence of 21 months, requiring repeated treatments [5, 7, 11, 35, 36]. Therefore, parenchymal-sparing procedures are increasingly recommended to reduce the number of patients who ultimately die of liver failure [5, 7]. In this regard, catheter-based treatments are currently used to treat NEN LM (1, 2, 5, 6), and radioembolization with ^{90}Y resin microspheres has recently been reported to achieve promising results [38]. However, ablation procedures also represent an interesting option either as a primary approach or as an adjunct to surgical resection, because they allow for sparing liver parenchyma more than all other liver-directed therapies [4–7]. As with all the other liver-directed therapies, there are no randomized trials comparing thermal ablation with other treatments in patients with NEN LM, and it is likely that such trials will never be conducted. Nevertheless, although the level of evidence is unavoidably low and the reports about its impact on the long-term outcome mostly derive from retrospective studies, the available data are encouraging. For tumors up to 4 cm in diameter and less than 7–8 in number, 5-year survival rates from 54 to 84% have been reported for thermal ablation used alone or in a multimodality approach [5, 6, 22, 24, 36, 39].

RFA is the most experienced ablation modality and is worldwide used to ablate primary and metastatic liver tumors, including NEN LM [3, 4, 20–27]. Last-generation MWA systems are gaining increasing interest for the treatment of liver tumors, but at present the experience in the treatment of NEN LM is limited to sporadic and very small series [28]. LA has been less investigated than RFA and MWA, but it is currently used in many centers to treat HCC and LM, with results that are comparable to RFA and MWA for either HCC [17, 40] or colorectal cancer LM [41, 42]. LA has been used sporadically in patients with NEN LM [29, 30], but thanks to some characteristics it could represent a valid alternative to RFA. The possibility of placing from one to four laser fibers into the tumor makes LA a very flexible technique. Each fiber provides an almost spherical thermal lesion of 12–15 mm in diameter, and the lesion size can be increased up to 4–5 cm by using multiple fibers and the pull-back technique [18, 19]. Therefore, it is possible to tailor the size of each thermal lesion to the size of each nodule, obtaining an acceptable safety margin in tumors ranging from 5 mm to 3–4 cm in diameter, sparing the liver parenchyma as much as possible. This characteristic could represent an advantage with respect to RFA when multiple LM variable in size have to be treated, as several cool-tip RFA electrodes with exposed tip of different length should be used to spare liver parenchyma as much as possible, making the procedure very expensive. Moreover, the introducing needles are considerably thinner than RFA electrodes and MWA antennas, reducing the risk of complications, in particular when multiple needle insertions are necessary or blood vessels have to be passed through to reach the lesions [12, 13]. Our series is small, and the follow-up is still too short to allow an adequate evaluation of 5-year survival, in particular considering that four alive patients (19% of the overall series) have a follow-up shorter than 3 years. Nevertheless, the results suggest that LA can represent a safe and effective option in the treatment of NEN LM. Primary and secondary efficacy rates were 94.7% and 100%, respectively, and just one major complication occurred (0.53%). These results are at least comparable to historical series of patients treated with RFA that reported primary efficacy rates ranging from 74 to 94.4%, and major complications rates ranging from 0 to 8.2% [4, 20, 24–27]. Although no conclusion can be drawn, it could be inferred that also the long-term outcome in our series might be at least comparable to those reported for RFA, when an adequately long follow-up will be available. However, it is worth emphasizing that the effect on overall survival of all liver-directed procedures is still a matter of debate, as the actual benefit remains difficult to assess for patients who frequently undergo subsequent lines of treatment [6].

Four of our patients died for causes other than NEN 32–81 months after LA. They were disease-free at the time of death, and all of them had a Ki-67 expression $\leq$ 7%, as well as five of the six patients who are still alive and disease-free. Indeed, survival curve resulted significantly better for patients with Ki-67 expression $\leq$ 7% than for patients with Ki-67 expression > 7%. This cutoff is not too different from that reported in a recent study investigating the role of Ki-67 with regard to recurrence and survival after curative resection of pancreatic NEN, which found that a Ki-67 rate higher than 5% identified the patients at high risk for recurrence [43]. It is hardly surprising that better survival rates can be achieved for patients with less aggressive tumors, and Ki-67 is known to be a reliable prognostic factor [44]. Nevertheless, our observation suggests that wider studies investigating the outcomes of patients with NEN LM undergoing thermal ablation, and different Ki-67 expression, could lead to define a Ki-67 threshold that identifies the subgroup of patients who can mainly benefit from thermal ablation.

Our study has some limitations: First, it is a retrospective analysis involving a low number of patients. However, because NEN are rather rare, it is nearly impossible to conduct prospective trials with an adequately sized sample, and to our knowledge, all the studies on thermal ablation of NEN LM reported in the literature are retrospective [3, 4, 20–30]. To date, our study reports the largest series of patients who underwent LA of NEN LM, and the number of LM is high enough to give useful, albeit preliminary, information on safety and efficacy of the procedure. Moreover, just two studies investigating RFA of NEN LM not combined with surgery involved larger series of LM [24, 25]. Second, the primary tumors of our series were different, and the data on survival could be biased by such a heterogeneity. However, the rarity of NEN makes quite hard to recruit only patients with the same primary tumor, and to our knowledge all the previous studies on thermal ablation of NEN LM enrolled patients with different primary tumors (3.4.20-30). Finally, the follow-up is still too short to allow any comparison between LA and RFA on their long-term outcome. However, primary and secondary efficacy rates of LA appear very promising and even better than those of RFA, and 1-, 2-, and 3-year survival rates compare well with those reported for RFA. Hopefully, also the 5-year survival rate of 40% could improve and become comparable to that of RFA after an adequately long follow-up.

Conclusion

This retrospective experience suggests that LA is a promising and safe technique to treat NEN LM, and it could represent a valid alternative to RFA, in particular when LM are multiple and variable in size, or are located very close to blood vessels. Further prospective studies involving larger series of patients followed for a longer time are needed to confirm our preliminary results and to provide definitive information on the long-term efficacy of this liver-directed therapy.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent This study has obtained institutional review board approval from the IRB of St. Anna Hospital, and the need for informed consent was waived.

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