**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 53980

**Manuscript Type:** OPINION REVIEW

**Liver-directed therapies for liver metastases from neuroendocrine neoplasms: Can laser ablation play any role?**

Sartori S *et al*. LA in NEN

Sergio Sartori, Lara Bianchi, Francesca Di Vece, Paola Tombesi

**Sergio Sartori, Lara Bianchi, Francesca Di Vece, Paola Tombesi,** Department of Internal Medicine, Section of Interventional Ultrasound, St. Anna Hospital, Ferrara 44100, Italy

**Author contributions:** Sartori S and Tombesi P wrote the paper; Bianchi Land Di Vece F reviewed the literature and collected the data.

**Corresponding author:** **Sergio Sartori, MD, Chief Doctor, Director,** Department of Internal Medicine, Section of Interventional Ultrasound, St. Anna Hospital, Via A. Moro 8, Ferrara 44100, Italy. srs@unife.it

**Received:** January 2, 2020

**Revised:** June12, 2020

**Accepted:** June 16, 2020

**Published online:** June 21, 2020

**Abstract**

Aggressive cytoreduction can prolong survival in patients with unresectable liver metastases (LM) from neuroendocrine neoplasms (NEN), and minimally invasive, liver-directed therapies are gaining increasing interest**.** Catheter-based treatments are used in disseminated disease, whereas **a**blation techniques are usually indicated when the number of LM is limited. Although radiofrequency ablation (RFA) is by far the most used ablative technique, the goal of this opinion review is to explore the potential role of laser ablation (LA) in the treatment of LM from NEN**.** LA uses thinner needles than RFA**,** and this is an advantage when the tumors are in at-risk locations**.** Moreover,the multi-fiber technique enables the use of one to four laser fibers at once, and each fiber provides an almost spherical thermal lesion of 12-15 mm in diameter**.** Such a characteristic enables to tailor the size of each thermal lesion to the size of each tumor, sparing the liver parenchyma more than any other liver-directed therapy, and allowing for repeated treatments with low risk of liver failure. A recent retrospective study reporting the largest series of LM treated with LA documents both safety and effectiveness of LA, that can play a useful role in the multimodality approach to LM from NEN.

**Key words:** Neuroendocrine neoplasms; Liver metastases; Liver-directed therapies; Ablation techniques; Laser ablation; Radiofrequency ablation

**Citation:** Sartori S, Bianchi L, Di Vece F, Tombesi P. Liver-directed therapies for liver metastases from neuroendocrine neoplasms: Can laser ablation play any role? *World J Gastroenterol* 2020; 26(23): 3118-3125

**URL:** https://www.wjgnet.com/1007-9327/full/v26/i23/3118.htm

**DOI:** https://dx.doi.org/10.3748/wjg.v26.i23.3118

**Core tip:** Laser ablation (LA) can be useful in the treatment of liver metastases (LM) from neuroendocrine neoplasms (NEN). The multi-fiber technique enables the use of one to four fibers at once, achieving ablation areas from one to 4-5 cm in diameter, and tailoring the size of each thermal lesion to that of each tumor, sparing the liver parenchyma more than any other liver-directed therapy. A recent retrospective study reporting the largest series of LM treated with LA documents both safety and effectiveness of LA, that can be added to the armory of the multimodality approach to LM from NEN.

**INTRODUCTION**

Neuroendocrine neoplasms (NEN) encompass a heterogeneous group of neoplasms with variable biological behavior, and wide range of aggressiveness[1-3]. The incidence of NEN is increasing, and to date it is about 5.86/100000 per year[4]. NEN include both functioning tumors, which may secrete different peptide hormones, and non-functioning tumors. From a histologic and prognostic perspective, NEN are currently divided into low-grade indolent tumors and high-grade aggressive carcinomas[5]. However, histologically low-grade tumors may sometimes have aggressive behavior[6]. Twelve percent to 22% of patients with NEN have liver metastases (LM) at presentation[6], and 40% of patients will develop LM during the course of their disease[7]. LM are unanimously considered to significantly reduce 5-year survival rates, that range from 24% to 40 %[7-10]. The overall prognosis of patients with NEN differs widely according to the extent of disease, histological grade and site of the primary tumor. The 5-year survival rate can range from 60% to 90% in patients with localized NEN following surgery, whereas it barely reaches 40% in patients with distant metastases[2-4,6,7]. Treatment decision making is usually based on the clinical status of the patient, local availability of different therapeutic options, histological characteristics of the tumor, and tumor burden. Therefore, it requires a tailored approach that should be shared by a multidisciplinary team including at least medical and radiation oncologists, surgeon, pathologist, endocrinologist, and interventional radiologist. The primary treatment goal should be curative, and radical surgical resection is considered the only curative option, but it can be offered to a minority of patients[7,11-13]. Indeed, LM are often present at diagnosis, or occur during the disease, also in slow-growing tumors[8]. Moreover, LM have a high rate of recurrence after surgical resection, reaching up to 70%-94% at 5 years[7,12-15]. Chemotherapy is poorly effective, especially in well-differentiated tumors[13,16,17] . Systemic treatments, such as somatostatin analogues, targeted therapies, and peptide receptor radionuclide therapy, have been demonstrated to be effective in disease stabilization, but they have a limited role in obtaining significant radiological response[8,13,18]. In the setting of advanced NEN and indolent disease, or disease stabilized by systemic treatments, an aggressive cytoreduction with liver-directed therapies can achieve objective radiological response, prolonged survival, and hormonal symptom control[7,13,15-17,19]. Surgical resection is worldwide considered the first option to treat LM, but de-bulking interventions can be offered to a very limited number of patients[7,9,13]. Recently, the threshold of liver de-bulking has been lowered from 90% to 70% of tumor burden to increase the number of eligible patients, while still achieving good survival rates[20,21]. However, eligible patients remain under the threshold of 25% even with these expanded criteria[7,14,20,21].

Minimally invasive, liver-directed therapies can be used either as a primary approach in patients who are not surgical candidates, or as an adjunct to surgery and/or systemic therapies in a multimodality approach[8,13,18]. Although their impact on overall survival is still debated, liver-directed therapies have been proven to be safe and effective in both local disease control and symptom control[7-10,18]. Ablation techniques are usually indicated in patients with a limited number of small LM, whereas catheter-based treatments are mostly used in patients with disseminated and progressive disease.

**CATHETER-BASED TREATMENTS**

The rationale for transarterial embolization (TAE) is based on the observation that LM from NEN frequently show preferential arterial blood supply and arterial hypervascularity. The arterial occlusion induces ischemia and necrosis of the tumors, which can be enhanced by intra-arterial administration of bland chemotherapeutic agents [transarterial chemoembolization (TACE), or chemotherapeutic drugs eluting beads (DEB-TACE)], or yttrium-90 microspheres [transarterial radioembolization (TARE)]. Many studies reported that these treatments are effective in reducing tumor growth, and in controlling both hormone-related symptoms and tumor size-related symptoms[22-25]. Moreover, these procedures can be repeatedly performed until satisfactory disease control is achieved, or in case of recurrence. The 5-year overall survival rates from several studies using TACE were 50%-83%, with similar results reported for TAE (40%-67%)[8,18,22,25]. The clinical side-effects of the procedures include fever, leukocytosis, abdominal pain and elevated liver enzyme levels. More severe complications include pleural effusion, bowel ischemia, hepatic infarction, liver abscess; radiation-induced liver disease was also reported in < 2% of patients treated with TARE[23,25]. However, the occurrence of severe side-effects is quite uncommon. Interestingly, in a study by Ho *et al*[8] survival was not adversely affected by the presence of unresected primary tumor, a clinical response was observed in 78% of symptomatic patients, and the mean progression-free survival time was 18.5 mo including also patients with extrahepatic disease. Based on these results, the authors suggested that the presence of extrahepatic metastases or unresected primary tumor should not limit the use of TAE and TACE. In another more recent study, clinical response was observed in 95% of the patients treated with various hepatic intra-arterial therapies[26]. Data about TARE in the treatment of LM from NEN are still limited, but response rates of 70%-90% have been reported[27]. TARE preferentially delivers a high dose of radiation to the tumor, while sparing much of the normal liver. Some authors reported that TARE can treat the most tumor burden with the least side effects[18]. In particular, large and bulky tumor burden with relatively well-preserved liver function may represent the best target form TARE. In patients with both a large lesion in the right lobe of the liver, and smaller lesions in the left lobe, a combined approach with TARE for the dominant right lobe metastasis, and TACE for the small lesions in the left lobe, has been proposed to obtain better results with lower risk of complications[18]. Moreover, a recent systematic review of literature suggested that TARE can also be effective for patients who previously underwent unsuccessful TAE or TACE[28]. However, although TARE seems to offer the advantage of minimal side effects in the early post-treatment period, data on long-term toxicity including radiation-induced liver disease are still quite limited[28,29]. Furthermore, a propensity score analysis suggested significant survival benefits for patients treated with TACE as compared to DEB-TACE and TARE[29]. Consequently, waiting for further and conclusive safety data on long-term tolerability of TARE, at present TACE should be considered the primary intra-arterial option for patients with multiple, unresectable LM from NEN, reserving TARE to patients with contraindications to TACE, or non-responders to TACE[29].

**ABLATION TECHNIQUES**

Ablation techniques have gained increasing interest either when used alone or in association with resection in presence of a relatively low number of small LM. For tumors ≤ 4 cm in diameter and up to 7-8 in number, thermal ablation used alone or in a multimodality approach can achieve 5-year survival rates ranging from 54% to 84%[7,10,13,20,30-32]. Although surgical resection is the aggressive approach of choice, morbidity and mortality rates are still 30% and 1%-2%, respectively[7,13]. Moreover, repeated treatments are frequently needed during the course of the disease, because 5-year recurrence rates after all liver-directed interventions are very high, ranging from 80% to 95% with a median time to recurrence of 21 mo[7,12,14,15,20]. Therefore, the therapeutic decision making should be aimed at choosing a treatment that is not only effective, but also parenchymal-sparing as much as possible[7,15]. Ablation techniques deliver thermal energy, either cooling or heating the tissues. Similar to the treatment of LM from other tumors, radiofrequency ablation (RFA) is by far the most used technique to ablate LM from NEN, with 5-year survival rates up to 53% also when it is used alone[10,31-40]. Conversely, until the very last years the experiences with cryoablation, microwave ablation and laser ablation in the treatment of LM from NEN are quite sporadic and limited to case reports or small series[41-44]. However, laser ablation (LA) presents some technical characteristics that may make it an interesting alternative to RFA. LA uses laser devices that convert electrical into light energy, which determines tissue heating and cellular death by coagulative necrosis. Light is delivered via 300-μm flexible bare tip fibers that are introduced into the tumor through 21-gauge needles. The diameter of the needles is considerably thinner than that of RFA electrodes, and this characteristic can represent an advantage when the tumors are in at-risk locations[33,34]. Indeed, LA has recently been reported to be safe and effective in the treatment of small renal tumors in patients at increased bleeding risk[45], and in tumors located in the portacaval space[46]. Furthermore, the multi-fiber technique enables the use of one to four fibers at once, and each fiber provides an almost spherical thermal lesion of 12-15 mm in diameter[47,48]. By also using, when necessary, the pull-back technique, it is possible to achieve ablation areas from one to 4-5 cm in diameter. Therefore, LA can enable to treat tumors ranging from 5-6 mm to 3 cm in diameter obtaining an acceptable safety margin[47,48]. LM from NEN are variable in size, and frequently require repeated treatments because they are often multiple, and recurrence rates are very high[7,12,14,15,20]. In such settings, the need of sparing the normal liver parenchyma is mandatory. The possibility of placing from one to four laser fibers into the tumors enables to tailor the size of each thermal lesion to the size of each nodule, sparing the liver parenchyma more than any other liver-directed therapy, and allowing for multiple and repeated treatments over time with low risk of liver failure[33,34.44,47,48]. A total of twenty-eight LM have been reported to be successfully ablated in a patient with insulin-secreting NEN, and the patient was still alive and disease-free, with normal liver function, at the time the case-report was published[49]. Furthermore, a pilot study reported interesting results in the treatment of large LM from NEN by using LA followed by TACE. Complete response was obtained in lesions of 6.4 cm and 7 cm in diameter, and partial response with an estimated volume of ablated tumor tissue of approximately 80% was obtained in a lesion of 12 cm in diameter[50]. Although the number of large lesions treated was quite low, these results suggest that LA combined with TACE might be used to reduce the tumor burden in presence of large, non-surgical LM. In another prior study, the combined treatment was also reported to obtain good results by using TACE as a first procedure to downsizing the initial tumor burden as much as possible, and successively treating any residual vital tissue by LA[51].

**IS THERE ANY ROLE FOR LASER ABLATION IN THE TREATMENT OF LM FROM NEN?**

A very recent retrospective study reinforces the potential role of LA in the treatment of small LM from NEN, reporting the largest series of LM that were ablated by using this technique[52]. Twenty-one patients with a total of 189 LM with median long-axis diameter of 19 mm underwent ultrasound (US)-guided LA in 41 ablation sessions. Patients and tumors characteristics are detailed in Table 1. LA was performed by using the multifiber technique and the pull-back technique, as described elsewhere[52]. After the end of the procedure, contrast-enhanced US (CEUS) was performed, and ablation was judged complete when no enhancing focus was observed in the treated tumor. When some enhancing foci were identified, the treatment was completed under CEUS guidance. The outcomes of the treatment were defined according to the recommendations of the International Working Group on the Image-guided Tumor Ablation[53]. Complications were classified according to the Cardiovascular and Interventional Society of Europe classification system for complications reporting[54]: Just one grade 4 (0.53%) and three grade 1 complications were observed.

One-month contrast-enhanced computed tomography showed complete ablation of all LM, and technical efficacy was 100%. Local tumor progression occurred in 10/189 LM; all of them were successfully ablated, and primary and secondary efficacy rate were 94.7% and 100%, respectively. After a median follow-up (FU) of 39 mo (range 12-99 mo, mean 45.4 ± 24), 10 patients were still alive 10 to 99 mo after LA, and 6 of them were disease-free; seven patients died owing to disease progression, whereas 4 patients died owing to causes other than NEN. All of them were disease-free at the time of death. 1-, 2-, 3-, and 5-year survival rates were 95%, 86%, 66%, and 40%, respectively. Overall survival resulted significantly higher for patients with Ki-67 expression ≤ 7% than for those with Ki-67 > 7%[52]. These results compared well with those previously reported for RFA, as well as 1-, 2-, and 3-year survival rates[10,31,35,38-40]. When the data of the study were censored, the median FU was not long enough to enable to adequately evaluate 5-year survival, especially considering that four alive and disease-free subjects had a FU shorter than 3 years. Nevertheless, 1-, 2-, and 3-year survival rates were similar to those of RFA, and primary and secondary efficacy rates were even better than RFA. Therefore, it is not too big a leap to infer that also the long-term outcome might result comparable to that of RFA after an adequately long FU. Based on their results, the authors concluded that LA is a safe and effective alternative to RFA, in particular when multiple LM variable in size have to be treated and blood vessels have to be passed through to reach the lesions[52].

**CONCLUSION**

Although this study was retrospective and enrolled a relatively low number of patients, in our opinion it provides interesting information and suggests that a further weapon can be added to the armory of the liver-directed therapies. The relative rarity of NEN and their heterogeneity make quite hard to plan prospective studies enrolling a sufficiently high number of patients: Indeed, and all the trials published in literature on the ablation therapies of LM from NEN are retrospective[9,10,30,31,35-40,42-44]. Furthermore, the study reports the largest series of LM that underwent LA, and only two trials evaluating the efficacy of RFA used alone involved larger series of LM from NEN[31,38]. The role played by each single liver-directed therapy in the long-term outcome of patients with advanced NEN can not be reliably assessed, as they often undergo sequential and multimodality therapies[6]. Nevertheless, the results of the study were very promising. LA, used alone or in combination with surgery, catheter-based treatments, and systemic therapies, should be taken into account in the multimodality tailored approach to the patients with LM from NEN. However, further studies involving larger series of patients followed for a longer time are needed to better evaluate the long-term efficacy of this liver-directed therapy.

**REFERENCES**

1 **Lawrence B**, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011; **40**: 1-18, vii [PMID: 21349409 DOI: 10.1016/j.ecl.2010.12.005]

2 **Mocellin S**, Nitti D. Gastrointestinal carcinoid: epidemiological and survival evidence from a large population-based study (n = 25 531). *Ann Oncol* 2013; **24**: 3040-3044 [PMID: 24050954 DOI: 10.1093/annonc/mdt377]

3 **Kulke MH**, Siu LL, Tepper JE, Fisher G, Jaffe D, Haller DG, Ellis LM, Benedetti JK, Bergsland EK, Hobday TJ, Van Cutsem E, Pingpank J, Oberg K, Cohen SJ, Posner MC, Yao JC. Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. *J Clin Oncol* 2011; **29**: 934-943 [PMID: 21263089 DOI: 10.1200/JCO.2010.33.2056]

4 **Yao JC**, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; **26**: 3063-3072 [PMID: 18565894 DOI: 10.1200/JCO.2007.15.4377]

5 **Chandrasekharappa SC**, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR, Debelenko LV, Zhuang Z, Lubensky IA, Liotta LA, Crabtree JS, Wang Y, Roe BA, Weisemann J, Boguski MS, Agarwal SK, Kester MB, Kim YS, Heppner C, Dong Q, Spiegel AM, Burns AL, Marx SJ. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* 1997; **276**: 404-407 [PMID: 9103196 DOI: 10.1126/science.276.5311.404]

6 **Edge S,** Byrd DR, Compton CC, Fritz AG, Greene F, Trotti A. AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual. 7th ed. New York: Springer-Verlag, 2010

7 **Fairweather M**, Swanson R, Wang J, Brais LK, Dutton T, Kulke MH, Clancy TE. Management of Neuroendocrine Tumor Liver Metastases: Long-Term Outcomes and Prognostic Factors from a Large Prospective Database. *Ann Surg Oncol* 2017; **24**: 2319-2325 [PMID: 28303430 DOI: 10.1245/s10434-017-5839-x]

8 **Ho AS**, Picus J, Darcy MD, Tan B, Gould JE, Pilgram TK, Brown DB. Long-term outcome after chemoembolization and embolization of hepatic metastatic lesions from neuroendocrine tumors. *AJR Am J Roentgenol* 2007; **188**: 1201-1207 [PMID: 17449759 DOI: 10.2214/AJR.06.0933]

9 **Elias D**, Goéré D, Leroux G, Dromain C, Leboulleux S, de Baere T, Ducreux M, Baudin E. Combined liver surgery and RFA for patients with gastroenteropancreatic endocrine tumors presenting with more than 15 metastases to the liver. *Eur J Surg Oncol* 2009; **35**: 1092-1097 [PMID: 19464140 DOI: 10.1016/j.ejso.2009.02.017]

10 **Gillams A**, Cassoni A, Conway G, Lees W. Radiofrequency ablation of neuroendocrine liver metastases: the Middlesex experience. *Abdom Imaging* 2005; **30**: 435-441 [PMID: 15759207 DOI: 10.1007/s00261-004-0258-4]

11 **Sarmiento JM**, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg* 2003; **197**: 29-37 [PMID: 12831921 DOI: 10.1016/S1072-7515(03)00230-8]

12 **Mayo SC**, de Jong MC, Pulitano C, Clary BM, Reddy SK, Gamblin TC, Celinksi SA, Kooby DA, Staley CA, Stokes JB, Chu CK, Ferrero A, Schulick RD, Choti MA, Mentha G, Strub J, Bauer TW, Adams RB, Aldrighetti L, Capussotti L, Pawlik TM. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann Surg Oncol* 2010; **17**: 3129-3136 [PMID: 20585879 DOI: 10.1245/s10434-010-1154-5]

13 **Cavalcoli F**, Rausa E, Conte D, Nicolini AF, Massironi S. Is there still a role for the hepatic locoregional treatment of metastatic neuroendocrine tumors in the era of systemic targeted therapies? *World J Gastroenterol* 2017; **23**: 2640-2650 [PMID: 28487601 DOI: 10.3748/wjg.v23.i15.2640]

14 **Maxwell JE**, Sherman SK, O'Dorisio TM, Bellizzi AM, Howe JR. Liver-directed surgery of neuroendocrine metastases: What is the optimal strategy? *Surgery* 2016; **159**: 320-333 [PMID: 26454679 DOI: 10.1016/j.surg.2015.05.040]

15 **Howe JR**, Cardona K, Fraker DL, Kebebew E, Untch BR, Wang YZ, Law CH, Liu EH, Kim MK, Menda Y, Morse BG, Bergsland EK, Strosberg JR, Nakakura EK, Pommier RF. The Surgical Management of Small Bowel Neuroendocrine Tumors: Consensus Guidelines of the North American Neuroendocrine Tumor Society. *Pancreas* 2017; **46**: 715-731 [PMID: 28609357 DOI: 10.1097/MPA.0000000000000846]

16 **Öberg K**, Knigge U, Kwekkeboom D, Perren A; ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; **23 Suppl 7**: vii124-vii130 [PMID: 22997445 DOI: 10.1093/annonc/mds295]

17 **Kunz PL**, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, Chen H, Jensen RT, Kim MK, Klimstra DS, Kulke MH, Liu EH, Metz DC, Phan AT, Sippel RS, Strosberg JR, Yao JC; North American Neuroendocrine Tumor Society. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas* 2013; **42**: 557-577 [PMID: 23591432 DOI: 10.1097/MPA.0b013e31828e34a4]

18 **Kolbeck KJ**, Farsad K. Catheter-based treatments for hepatic metastases from neuroendocrine tumors. *AJR Am J Roentgenol* 2014; **203**: 717-724 [PMID: 25247935 DOI: 10.2214/AJR.14.12983]

19 **Kulke MH**, Benson AB 3rd, Bergsland E, Berlin JD, Blaszkowsky LS, Choti MA, Clark OH, Doherty GM, Eason J, Emerson L, Engstrom PF, Goldner WS, Heslin MJ, Kandeel F, Kunz PL, Kuvshinoff BW 2nd, Moley JF, Pillarisetty VG, Saltz L, Schteingart DE, Shah MH, Shibata S, Strosberg JR, Vauthey JN, White R, Yao JC, Freedman-Cass DA, Dwyer MA; National Comprehensive Cancer Networks. Neuroendocrine tumors. *J Natl Compr Canc Netw* 2012; **10**: 724-764 [PMID: 22679117 DOI: 10.6004/jnccn.2012.0075]

20 **Chambers AJ**, Pasieka JL, Dixon E, Rorstad O. The palliative benefit of aggressive surgical intervention for both hepatic and mesenteric metastases from neuroendocrine tumors. *Surgery* 2008; **144**: 645-651; discussion 651-653 [PMID: 18847650 DOI: 10.1016/j.surg.2008.06.008]

21 **Graff-Baker AN**, Sauer DA, Pommier SJ, Pommier RF. Expanded criteria for carcinoid liver debulking: Maintaining survival and increasing the number of eligible patients. *Surgery* 2014; **156**: 1369-1376; discussion 1376-1377 [PMID: 25456912 DOI: 10.1016/j.surg.2014.08.009]

22 **Vogl TJ**, Naguib NN, Zangos S, Eichler K, Hedayati A, Nour-Eldin NE. Liver metastases of neuroendocrine carcinomas: interventional treatment via transarterial embolization, chemoembolization and thermal ablation. *Eur J Radiol* 2009; **72**: 517-528 [PMID: 18829195 DOI: 10.1016/j.ejrad.2008.08.008]

23 **Memon K**, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Sato KT, Gupta R, Nikolaidis P, Miller FH, Yaghmai V, Gates VL, Atassi B, Newman S, Omary RA, Benson AB 3rd, Salem R. Radioembolization for neuroendocrine liver metastases: safety, imaging, and long-term outcomes. *Int J Radiat Oncol Biol Phys* 2012; **83**: 887-894 [PMID: 22137020 DOI: 10.1016/j.ijrobp.2011.07.041]

24 **Pavel M**, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, Anlauf M, Wiedenmann B, Salazar R; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2012; **95**: 157-176 [PMID: 22262022 DOI: 10.1159/000335597]

25 **Memon K**, Lewandowski RJ, Riaz A, Salem R. Chemoembolization and radioembolization for metastatic disease to the liver: available data and future studies. *Curr Treat Options Oncol* 2012; **13**: 403-415 [PMID: 22773276 DOI: 10.1007/s11864-012-0200-x]

26 **Grozinsky-Glasberg S**, Kaltsas G, Kaltsatou M, Lev-Cohain N, Klimov A, Vergadis V, Uri I, Bloom AI, Gross DJ. Hepatic intra-arterial therapies in metastatic neuroendocrine tumors: lessons from clinical practice. *Endocrine* 2018; **60**: 499-509 [PMID: 29383678 DOI: 10.1007/s12020-018-1537-0]

27 **Landry CS**, Scoggins CR, McMasters KM, Martin RC 2nd. Management of hepatic metastasis of gastrointestinal carcinoid tumors. *J Surg Oncol* 2008; **97**: 253-258 [PMID: 18264984 DOI: 10.1002/jso.20957]

28 **Jia Z**, Wang W. Yttrium-90 radioembolization for unresectable metastatic neuroendocrine liver tumor: A systematic review. *Eur J Radiol* 2018; **100**: 23-29 [PMID: 29496075 DOI: 10.1016/j.ejrad.2018.01.012]

29 **Do Minh D**, Chapiro J, Gorodetski B, Huang Q, Liu C, Smolka S, Savic LJ, Wainstejn D, Lin M, Schlachter T, Gebauer B, Geschwind JF. Intra-arterial therapy of neuroendocrine tumour liver metastases: comparing conventional TACE, drug-eluting beads TACE and yttrium-90 radioembolisation as treatment options using a propensity score analysis model. *Eur Radiol* 2017; **27**: 4995-5005 [PMID: 28677067 DOI: 10.1007/s00330-017-4856-2]

30 **Taner T**, Atwell TD, Zhang L, Oberg TN, Harmsen WS, Slettedahl SW, Kendrick ML, Nagorney DM, Que FG. Adjunctive radiofrequency ablation of metastatic neuroendocrine cancer to the liver complements surgical resection. *HPB (Oxford)* 2013; **15**: 190-195 [PMID: 23374359 DOI: 10.1111/j.1477-2574.2012.00528.x]

31 **Mazzaglia PJ**, Berber E, Milas M, Siperstein AE. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. *Surgery* 2007; **142**: 10-19 [PMID: 17629995 DOI: 10.1016/j.surg.2007.01.036]

32 **Mohan H**, Nicholson P, Winter DC, O'Shea D, O'Toole D, Geoghegan J, Maguire D, Hoti E, Traynor O, Cantwell CP. Radiofrequency ablation for neuroendocrine liver metastases: a systematic review. *J Vasc Interv Radiol* 2015; **26**: 935-942.e1 [PMID: 25840836 DOI: 10.1016/j.jvir.2014.12.009]

33 **Tombesi P,** Di Vece F, Sartori S. Radiofrequency, microwave, and laser ablation of liver tumors:time to move toward a tailored ablation technique? *Hepatoma Res* 2015; **1**: 52-57 [DOI: 10.4103/2394-5079.155697]

34 **Sartori S**, Di Vece F, Ermili F, Tombesi P. Laser ablation of liver tumors: An ancillary technique, or an alternative to radiofrequency and microwave? *World J Radiol* 2017; **9**: 91-96 [PMID: 28396723 DOI: 10.4329/wjr.v9.i3.91]

35 **Akyildiz HY**, Mitchell J, Milas M, Siperstein A, Berber E. Laparoscopic radiofrequency thermal ablation of neuroendocrine hepatic metastases: long-term follow-up. *Surgery* 2010; **148**: 1288-93; discussion 1293 [PMID: 21134563 DOI: 10.1016/j.surg.2010.09.014]

36 **Wessels FJ**, Schell SR. Radiofrequency ablation treatment of refractory carcinoid hepatic metastases. *J Surg Res* 2001; **95**: 8-12 [PMID: 11120628 DOI: 10.1006/jsre.2000.5988]

37 **Henn AR**, Levine EA, McNulty W, Zagoria RJ. Percutaneous radiofrequency ablation of hepatic metastases for symptomatic relief of neuroendocrine syndromes. *AJR Am J Roentgenol* 2003; **181**: 1005-1010 [PMID: 14500219 DOI: 10.2214/ajr.181.4.1811005]

38 **Berber E**, Flesher N, Siperstein AE. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases. *World J Surg* 2002; **26**: 985-990 [PMID: 12016479 DOI: 10.1007/s00268-002-6629-5]

39 **Hellman P**, Ladjevardi S, Skogseid B, Akerström G, Elvin A. Radiofrequency tissue ablation using cooled tip for liver metastases of endocrine tumors. *World J Surg* 2002; **26**: 1052-1056 [PMID: 12016482 DOI: 10.1007/s00268-002-6663-3]

40 **Elvin A**, Skogseid B, Hellman P. Radiofrequency ablation of neuroendocrine liver metastases. *Abdom Imaging* 2005; **30**: 427-434 [PMID: 15791486 DOI: 10.1007/s00261-004-0257-5]

41 **Seifert JK**, Cozzi PJ, Morris DL. Cryotherapy for neuroendocrine liver metastases. *Semin Surg Oncol* 1998; **14**: 175-183 [PMID: 9492888 DOI: 10.1002/(SICI)1098-2388(199803)14:2<175::AID-SSU10>3.0.CO;2-2]

42 **Wang W,** Seeruttun SR, Fang C, Zhou Z. Comprehensive treatment of a functional pancreatic neuroendocrine tumor with multifocal liver metastases. *Chin J Cancer Res* 2014; **26**: 501-506 [PMID: 25232226 DOI: 10.3978/j.issn.1000-9604.2014.08.16]

43 **Perälä J**, Klemola R, Kallio R, Li C, Vihriälä I, Salmela PI, Tervonen O, Sequeiros RB. MRI-guided laser ablation of neuroendocrine tumor hepatic metastases. *Acta Radiol Short Rep* 2014; **3**: 2047981613499753 [PMID: 24778794 DOI: 10.1177/2047981613499753]

44 **Tombesi P**, Di Vece F, Sartori S. Laser ablation for hepatic metastases from neuroendocrine tumors. *AJR Am J Roentgenol* 2015; **204**: W732 [PMID: 26001265 DOI: 10.2214/AJR.14.14242]

45 **Sartori S**, Mauri G, Tombesi P, Di Vece F, Bianchi L, Pacella CM. Ultrasound-guided percutaneous laser ablation is safe and effective in the treatment of small renal tumors in patients at increased bleeding risk. *Int J Hyperthermia* 2018; **35**: 19-25 [PMID: 29749271 DOI: 10.1080/02656736.2018.1468038]

46 **Chai W**, Zhao Q, Kong D, Jiang T. Percutaneous Laser Ablation of Hepatic Tumors Located in the Portacaval Space: Preliminary Results. *Lasers Surg Med* 2019; **51**: 866-873 [PMID: 31286541 DOI: 10.1002/lsm.23123]

47 **Pacella CM**, Bizzarri G, Magnolfi F, Cecconi P, Caspani B, Anelli V, Bianchini A, Valle D, Pacella S, Manenti G, Rossi Z. Laser thermal ablation in the treatment of small hepatocellular carcinoma: results in 74 patients. *Radiology* 2001; **221**: 712-720 [PMID: 11719667 DOI: 10.1148/radiol.2213001501]

48 **Di Costanzo GG**, D'Adamo G, Tortora R, Zanfardino F, Mattera S, Francica G, Pacella CM. A novel needle guide system to perform percutaneous laser ablation of liver tumors using the multifiber technique. *Acta Radiol* 2013; **54**: 876-881 [PMID: 23761559 DOI: 10.1177/0284185113489825]

49 **Sartori S,** Di Vece F, Bianchi L, Tombesi P. Percutaneous laser thermal ablation in a patient with 22 liver metastases from pancreatic neuroendocrine tumor. A case report. *EMJ Hepatol* 2018; **6**: 95-99

50 **Pacella CM,** Nasoni S, Grimaldi F, Di Stasio E, Misischi I, Bianchetti S. Laser ablation with or without chemoembolization for unresectable neuroendocrine liver metastases: a pilot study. *Int J Endo Oncol* 2016; **3**: 97-107 [DOI: 10.2217/ije.15.34]

51 **Vogl TJ**, Gruber T, Naguib NN, Hammerstingl R, Nour-Eldin NE. Liver metastases of neuroendocrine tumors: treatment with hepatic transarterial chemotherapy using two therapeutic protocols. *AJR Am J Roentgenol* 2009; **193**: 941-947 [PMID: 19770314 DOI: 10.2214/AJR.08.1879]

52 **Sartori S**, Tombesi P, Di Vece F, Bianchi L, Ambrosio R. Percutaneous Laser Ablation of Liver Metastases from Neuroendocrine Neoplasm. A Retrospective Study for Safety and Effectiveness. *Cardiovasc Intervent Radiol* 2019; **42**: 1571-1578 [PMID: 31410534 DOI: 10.1007/s00270-019-02308-4]

53 **Ahmed M**, Solbiati L, Brace CL, Breen DJ, Callstrom MR, Charboneau JW, Chen MH, Choi BI, de Baère T, Dodd GD 3rd, Dupuy DE, Gervais DA, Gianfelice D, Gillams AR, Lee FT Jr, Leen E, Lencioni R, Littrup PJ, Livraghi T, Lu DS, McGahan JP, Meloni MF, Nikolic B, Pereira PL, Liang P, Rhim H, Rose SC, Salem R, Sofocleous CT, Solomon SB, Soulen MC, Tanaka M, Vogl TJ, Wood BJ, Goldberg SN; International Working Group on Image-Guided Tumor Ablation; Interventional Oncology Sans Frontières Expert Panel; Technology Assessment Committee of the Society of Interventional Radiology; Standard of Practice Committee of the Cardiovascular and Interventional Radiological Society of Europe. Image-guided tumor ablation: standardization of terminology and reporting criteria--a 10-year update. *J Vasc Interv Radiol* 2014; **25**: 1691-1705.e4 [PMID: 25442132 DOI: 10.1016/j.jvir.2014.08.027]

54 **Filippiadis DK**, Binkert C, Pellerin O, Hoffmann RT, Krajina A, Pereira PL. Cirse Quality Assurance Document and Standards for Classification of Complications: The Cirse Classification System. *Cardiovasc Intervent Radiol* 2017; **40**: 1141-1146 [PMID: 28584945 DOI: 10.1007/s00270-017-1703-4]

**Footnotes**

**Conflict-of-interest statement:** All authors declare no conflicts-of-interest related to this article

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** January 2, 2020

**First decision:** March 21, 2020

**Article in press:** June 16, 2020

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Italy

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Liu Q, Tabibian JH, Tonelli F, Yang L **S-Editor:** Dou Y **L-Editor:** A **E-Editor:** Wu YXJ

**Table 1 Main characteristics of patients and tumors of the study (modified from Sartori *et al*[52])**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patients** | **Primary tumor** | **LM before 1st LA**  | **Total LM treated** | **Diameter range (mm)** | **No. of LA sessions** | **Months of FU** | **HP** | **Outcome** | **Cause of death** |
| 1 | Pancreas | 3 | 3 | 14-24 | 1 | 82 | No | Dead | Larynx cancer |
| 2 | Sm. bowel | 6 | 6 | 7-26 | 1 | 39 | Yes | Dead | HP + EP |
| 3 | Colon | 3 | 3 | 9-21 | 1 | 55 | No | Dead | Stroke |
| 4 | Sm. bowel | 6 | 13 | 5-25 | 3 | 38 | No | Dead | Colon cancer |
| 5 | Pancreas | 7 | 7 | 12-28 | 1 | 12 | Yes | Dead | HP + EP |
| 6 | Sm. bowel | 3 | 3 | 12-24 | 1 | 21 | No | Dead | EP |
| 7 | Pancreas | 22 | 37 | 5-21 | 5 | 99 | No | Alive | -- |
| 8 | Sm. bowel | 6 | 18 | 5-35 | 5 | 36 | Yes | Dead | HP + EP |
| 9 | Sm. bowel | 3 | 3 | 12-31 | 1 | 87 | No | Alive | -- |
| 10 | Pancreas | 3 | 3 | 11-24 | 1 | 26 | Yes | Dead | HP + EP |
| 11 | Lung | 9 | 23 | 6-26 | 4 | 37 | No | Dead | EP |
| 12 | Pancreas | 8 | 11 | 6-30 | 2 | 73 | Yes | Alive | -- |
| 13 | Sm. bowel | 8 | 12 | 5-20 | 3 | 31 | No | Dead | Endocarditis |
| 14 | Colon | 6 | 8 | 6-23 | 2 | 71 | Yes | Alive | -- |
| 15 | Sm. bowel | 6 | 11 | 9-25 | 2 | 40 | Yes | Dead | HP + EP |
| 16 | Pancreas | 5 | 5 | 8-26 | 1 | 55 | Yes | Alive | -- |
| 17 | Lung | 6 | 8 | 9-28 | 2 | 49 | No | Alive | -- |
| 18 | Pancreas | 3 | 3 | 10-25 | 1 | 25 | No | Alive | -- |
| 19 | Sm. bowel | 4 | 4 | 8-22 | 1 | 24 | No | Alive | -- |
| 20 | Adrenal | 4 | 4 | 6-24 | 1 | 24 | No | Alive | -- |
| 21 | Sm. bowel | 4 | 4 | 11-28 | 1 | 22 | Yes | Alive | -- |

LA: Laser ablation; LM: Liver metastases; HP: Hepatic progression; EP: Extrahepatic progression.