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Neuroendocrine Cancers (JR Strosberg, Section Editor)

Interventional Liver-Directed Therapy for Neuroendocrine Metastases: Current Status and Future Directions

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Opinion statement

Liver-directed therapy should be considered for patients with unresectable liver metastases from neuroendocrine tumor if symptomatic or progressing despite medical management. Our experience and current literature shows that the bland embolization, chemoembolization, and radioembolization are very effective in controlling symptoms and disease burden in the liver, and that these embolization modalities are similar in terms of efficacy and radiologic response. Their safety profiles differ, however, with recent studies suggesting an increase in biliary toxicity with drug-eluting bead chemoembolization over conventional chemoembolization, and a risk of long-term hepatotoxicity with radioembolization. For this reason, we tailor the type of embolotherapy to each patient according to their clinical status, symptoms, degree of tumor burden, histologic grade, and life expectancy. We do not recommend a "one-size-fits-all" approach. Our general strategy is to use bland embolization as first-line embolotherapy, and radioembolization for patients with high-grade tumors or who have failed other embolotherapy.

Introduction

Neuroendocrine tumors (NETs) are uncommon with a prevalence of 35 per 100,000 patients [1]; the most common primary sites are gastroenteropancreatic in origin [2, 3]. Between 20 and 27% of patients have distant metastases at the time of diagnosis, commonly to the liver, and 40% will develop liver metastases during the course of their disease [3, 4].

Liver metastases from neuroendocrine tumors are not only associated with decreased overall survival but may also result in carcinoid syndrome, pain from bulk symptoms, or progressive liver failure due to tumor replacement of the hepatic parenchyma. Carcinoid syndrome may lead to long-term complications such as carcinoid heart disease, extra-cardiac fibrosis, or cognitive disorders [5, 6].

The 2019 National Comprehensive Cancer Network (NCCN) guidelines for patients with neuroendocrine liver metastases (NELMs) recommend that liver-directed therapy (LDT) be considered for unresectable liver metastases that are symptomatic despite medical management or asymptomatic but progressing despite medical management [7].

The aim of this review is to provide an overview of LDT options for patients with NELMs.

Thermal ablation

Thermal ablation uses extreme heat or cold to destroy cells. While a number of different ablation techniques have been described, the most frequently utilized modalities in the liver are microwave ablation (MWA) and radiofrequency ablation (RFA) [8, 9] which both use heat. The technique is similar for MWA and RFA and has been previously described [8, 9]; however in brief, utilizing computed tomography or ultrasound guidance, a probe is advanced percutaneously or laparoscopically into the lesion. The probe then delivers a controlled amount of energy to the lesion and adjacent tissue resulting in coagulative necrosis. The RFA and MWA are limited by tumor size, with lesions up to 3–4 cm being ideal for ablation treatment.

Thermal ablation is a frequently used technique for both primary and secondary malignancies of the liver; however, because of the tendency of NET patients to present with numerous hepatic lesions, its utility in this patient population has not been widely reported. Thermal ablation has been frequently used in conjunction with surgery to treat the entire tumor burden when surgical resection of all tumors was not possible; however, review of this data is beyond the scope of this article.

Outcomes

Data for thermal ablation in NELMs is limited to small single center reviews [10–13]. However, a 5-year overall survival (OS) of 53% with 22% local recurrence has been reported [12]. One paper showed that 95.3% (41/43) of treated tumors showed a complete radiologic response at a mean of 2.1 years of follow-up [13]. However, this has varied significantly with another showing a complete response (CR) in 31.6% (6/19) and partial response (PR) in 36.8% (7/19) of patients [10]. The complication profile has been minimal, with most being minor. However, a death has been reported secondary to a carcinoid crisis and abscesses can occur, the latter with a higher risk in those without an intact sphincter of Oddi [10].

Summary

Thermal ablation is likely a very effective treatment for a small number of patients with NELMs, namely those with a few unresectable small (< 4 cm) hepatic tumors. Thermal ablation may also be used in conjunction with surgery when resection of all disease is not possible.

Transarterial embolization

Transarterial embolization (TAE), also known as bland embolization, is the intra-arterial delivery of bland embolic agents into the hepatic arteries supplying the tumors. Because NELMs are hypervascular tumors that derive their blood supply from the hepatic arteries, occluding the arterial supply via embolization leads to tumor ischemia and necrosis. The normal liver parenchyma is preserved since it derives most of its blood supply from the portal veins. Common embolic agents used are microspheres, polyvinyl alcohol particles, gelatin sponge particles, or ethiodized oil (Lipiodol; Guebert, Villapinte, France).

The TAE procedure is performed via the femoral or radial artery, and often with conscious sedation. In patients with known carcinoid symptoms, subcutaneous or intravenous infusion of octreotide is commonly administered during the periprocedural period to prevent a carcinoid flare. For patients with bilobar disease, one lobe is treated at a time in staged fashion, generally at least 4 weeks apart. Treatment sessions may be repeated if clinically indicated. The main contraindications are decompensated liver disease, portal vein thrombosis (PVT), active infection, severe iodinated contrast allergy, short life expectancy, and poor performance status.

Symptom control

Studies evaluating symptomatic improvement after TAE have been very positive. Common symptoms included were flushing, diarrhea, and abdominal pain. The symptom response rate varies between 80 to 91% [14–17]. Osborne et al. noted 59% had complete response and 32% had partial response in their series of 59 patients, while Carrasco et al. described the symptom response as excellent in 70% and moderate in 30% in their series of 25 patients. The mean duration of response has been reported at 20 to 22 months [14, 15].

Radiologic response

Radiologic response has been evaluated in several series [16, 18, 19] using Response Evaluation Criteria in Solid Tumors (RECIST) or modified RECIST (mRECIST). Complete response is uncommon, given the widespread multifocal nature of NELMs in most patients when referred for embolization. Zener et al. reported in their cohort of 160 patients a CR of 13%, PR of 40%, and stable disease (SD) 24%. Twenty-three of the 84 patients evaluated by Strosberg et al. had a follow-up imaging; 48% had PR and 52% had SD. Disease control rate (DCR) is considered as the sum of CR, PR, and SD. The reported DCR varies between 77 and 100% [16, 18, 19].

Survival

Hepatic progression-free survival (HPFS) and OS have been reported [16–19, 20•].Most studies have evaluated survival in a heterogeneous patient cohort with varying tumor grades, tumor histology, primary tumor site, prior treatment, and disease burden. The latter invariably includes patients with extrahepatic metastases.

Median HPFS varies between 15 and 36 months [16, 19, 20•]. Chen et al. found a significantly shorter HPFS with higher tumor grade and higher tumor burden (> 50% liver volume).

Regarding OS, Pitt et al. reported a median OS of 25.7 months (range 1.3–177) in 51 patients and Osborne et al. a mean OS of 24 months in 59 patients, but these patients were not stratified by tumor grade.

When stratified by tumor grade, the Zener study evaluated 160 patients and found 1-, 3-, and 5-year OS to be 87%, 59%, and 48% for well- to moderately differentiated tumors versus 51%, 17%, and 17% for poorly to undifferentiated tumors, with these differences being statistically significant. The Strosberg study evaluated 84 patients and reported median OS of 44 months (95% confidence interval [CI] 33–55) for carcinoid tumors, 31 months (95% CI 21–42) for pancreatic NETs, and 15 months (95% CI 0–39) for poorly differentiated tumors, with these differences also being statistically significant. Maire et al. reported both 1 and 2 year OS to be 100% in their 14 patients with well-differentiated midgut NETs.

Toxicity

TAE is generally well tolerated with the main side effect of post-embolization syndrome (PES), consisting of varying degrees of pain, nausea with or without vomiting, fever, fatigue, and transient increase in liver enzymes [16, 18, 20•, 21]. It is self-limiting and managed conservatively with analgesia and antiemetics. Severe PES may be seen in 9 to 15% of patients [18, 20•] and may require prolonged hospital stay.

Carcinoid flare or carcinoid crisis, with hypotension or hypertension, may occur when treating hormonally active tumors [6]. Reported rates vary from 2 to 11% [16, 18, 22] and likely depend on the regimen of periprocedural octreotide coverage that has been inconsistently reported.

Liver abscess may rarely occur, with rates reported from 0.05 to 3% [15, 17, 18, 22], and rates can be minimized with periprocedural antibiotic coverage which is particularly important in the setting of a violated sphincter of Oddi.

Summary and future directions

TAE is very effective in treating symptoms from NELMs, and provides a high degree of disease control, with a good safety profile. Survival data, however, is varied and based on heterogeneous patient cohorts; future directions lie in stratifying survival outcomes according to patient factors such as tumor grade, intra- and extrahepatic tumor burden, primary tumor location, and tumor histology; this will allow for more refined patient selection and expectations from embolotherapy. This requires recruitment of larger numbers of patients, however, which is difficult given the overall rarity of the disease.

Transarterial chemoembolization

Transarterial chemoembolization (TACE) is the intra-arterial delivery of a chemotherapeutic (CTx) agent (or a mixture CTx agents) combined with a bland embolic agent into the hepatic arteries supplying the tumors. This provides a dual mechanism of tumor cell death: the cytotoxic effect of the chemotherapy plus the ischemic effect of the embolic agent, with the latter effect similar to TAE.

There are two forms of TACE. Firstly, the CTx agent can be mixed with Lipiodol, known as classic or conventional TACE (C-TACE). Alternatively, the CTx agent can be loaded onto small microspheres, known as drug-eluting bead chemoembolization (DEB-TACE). The common CTx agents used are doxorubicin, mitomycin, cisplatin, and streptozoticin.

The procedural details and contraindications for TACE are otherwise similar to the TAE procedure. Similarly, for patients with bilobar disease, one lobe is treated at a time in staged fashion, at least 4 weeks apart. Treatment sessions may be repeated if clinically indicated.

Symptom control

Similar to TAE, studies evaluating symptomatic improvement after TACE have been positive. The rate of symptomatic improvement ranges from 54 to 92% [17, 23–26]. Marrache et al. stratified their results into complete symptom response in 61% or patients and partial response in 30%.

Radiologic response

Radiologic response has been evaluated in numerous series [19, 23–28, 29•] using RECIST or World Health Organization (WHO) criteria. As with TAE, CR is uncommon due to the disease burden at time of referral for embolization. CR is reported between 0 and 1% [23, 25, 27, 29•], PR from 43 to 62% [23–25, 27, 28], and SD from 24 to 38% [23–25, 27]. DCR ranges from 71 to 100% [19, 23–27].

Survival

As with TAE, studies evaluating survival involve a heterogeneous population of patients with varying tumor grades, tumor histology, tumor burden, primary site, and extent of extrahepatic metastases.

Median HPFS is reported between 8.1 months and 29.7 months [20•, 24, 26]. Chen et al. noted a statistically significantly shorter HPFS with higher tumor grade and higher tumor burden.

Median OS from the time of embolization ranges between 25.5 and 61 months [17, 20•, 23–26, 28], though stratification by tumor grade was not performed in these studies. One- and 2-year survival rates have been reported between 69 and 92% [17, 19, 20•, 23] and 52 and 80% [17, 19, 20•, 23, 25, 26], respectively. Three- and 5-year survival rates have been reported at 41 to 59% [23, 27] and 19 to 50%, respectively [17, 23, 25–27].

Factors found to be associated with statistically significantly higher survival include increased age, poor performance status, higher tumor grade, higher tumor volume, presence of extrahepatic metastases, resection of primary tumor, and radiologic response [17, 20•, 24, 27, 28, 29•].

Toxicity

The toxicity profile for TACE is similar to TAE and the most common side effect is PES. Severe PES was reported at 6.7% in the Chen study. Carcinoid flare or carcinoid crisis ranges from 3 to 16% [19, 24–26], and liver abscess rates ranges from 0.2 to 6% [24–26, 28]. There has been some concern for increased toxicity from DEB-TACE compared to cTACE for NELMs according to the early safety data from a recent randomized control trial (RCT) [30]. There are also several studies demonstrating a significantly increased incidence of biliary or liver injuries using DEB-TACE compared to cTACE for NELMs, including biliary dilatation, bilomas, and liver infarcts [31–33].

Summary and future directions

Like TAE, TACE is very effective in relieving or reducing symptoms from NELMs, and provides a high degree of disease control, with low toxicity. Survival data is quite varied due to the heterogeneous patient populations studied and likely also due to different CTx agents used across studies. More meaningful survival outcomes could be achieved by stratification of survival by factors such as tumor grade, tumor histology, and tumor burden, but this requires larger patient populations.

Transarterial radioembolization

Transarterial radioembolization (TARE) is an intra-arterial brachytherapy utilizing yttrium-90 (Y90), a beta emitter, that is embedded in small microspheres and delivered into the arterial blood supply to liver tumors. The procedural technique is similar to that for TAE and TACE, with the exception that prior to treatment the patient undergoes a planning procedure, also called a mapping procedure, involving angiographic evaluation of the blood supply to the liver tumors and lung shunting, allowing for tailored radiation dose calculations [9, 34, 35]. An additional difference is that PVT is not a contraindication to TARE because the embolic effect is less and arterial flow is generally preserved. Similar to TAE and TACE, for patients with bilobar disease, one lobe is treated at a time in staged fashion at least 4 weeks apart. Unlike TAE and TACE, however, caution must be exercised with repeating treatment sessions due to hepatotoxicity risk, described below.

Symptom control

In a large retrospective study by Braat et al., 79% of patients reported symptom response; 44% had complete response and 35% had partial response [36•]. Jia and colleagues performed a systematic review of 870 patients and found 69% of patients had improvement in carcinoid symptoms [37•].

Radiologic response

In two of the largest retrospective trials, Kennedy et al. and Braat et al. reviewed 148 patients (185 treatments) and 244 patients, respectively [34, 36•]. Kennedy et al. reported 3-month radiologic response by RECIST or WHO criteria, finding an objective response rate (ORR) of 63.2% and a DCR of 65.1%. Braat et al. reported 3 and 6 months ORRs of 15.7% and 28.5%, respectively, and with a DCR of 91.3% and 91.4%, respectively, when utilizing RECIST v1.1. If mRECIST was utilized, the 3- and 6-month ORR was 42.8% and 62.9%, respectively, and with DCR of 91.3% and 91.4%, respectively. Of note, it may take as long as 11 months for the full effect of TARE to be realized using RECIST or WHO criteria [38]. These findings were further corroborated by Jia et al.; they found that the median DCR at 3 months was 86% (range 62.5–100%); however, a mixture of RECIST and WHO methods were utilized to evaluate radiologic response [37•].

Survival

Kennedy et al. reported a mean OS of 70 months, but survival was not stratified by prognostic factors such as tumor grade or primary tumor site. Braat et al. provided data based on grade using the ENETS/WHO grading system with median OS of grade 1 (G1) NET, grade 2 (G2) NET, and grade 3 (G3) NET being 3.1 (95% CI 2.6–3.7), 2.4 (95% CI 1.9–3.0), and 0.9 (95% CI 0.1–1.9) years, respectively. The authors found that G1 and G2 NET had significantly longer survival than G3 NET ($p < 0.001$). On multivariate analysis, it was found that DCR according to RECIST at 3 months was associated with significantly better OS, while G3 NET or unknown grade, ≥ 75% intrahepatic tumor load, and presence of extrahepatic disease were predictive of worse OS. Saxena et al. reviewed 48 patients undergoing TARE and similarly found that ORR by RECIST, low hepatic burden, well-differentiated tumor, and absence of extrahepatic disease were all predictive of better OS [39]. For the entire cohort in Jia and colleagues' systematic review, they found a median OS of 28 months (range 14–70 months). They analyzed survival by grade with G1, G2, and G3 median OS being 71, 56, and 28 months, respectively. Finally, they evaluated OS by primary tumor location with median OS with carcinoid, pancreatic, and unclassified patients being 56, 31, and 28 months, respectively.

Toxicity

In Jia et al.'s systematic review of 870 patients, serious complications occurred rarely with just 8/870 (0.9%; radiation gastritis $n = 4$, duodenal ulcer $n = 2$, radiation cystitis $n = 1$, and early death from liver failure $n = 1$) occurring. The most common side effects, which are transient and self-limiting, were abdominal pain (median 32.6%, range 2.7–100%), nausea/vomiting (median 32.5%, range 3.2–100%), and fatigue (median 30.4%, range 6.5–63%).

In the last year or two, concern over long-term liver toxicity has arisen in several retrospective studies [40, 41•, 42, 43]. In a retrospective review of 52 patients with > 1 year of follow-up, Tomozawa et al. found that aspartate aminotransferase (AST), Alanine Aminotransferase (ALT), and alkaline phosphatase (ALP) increased significantly ($p < 0.001$, $p < 0.001$, $p = 0.003$, respectively). However, total bilirubin, albumin, and platelet count and leukocyte count did not differ significantly. They also found new imaging changes of

cirrhosis-like morphology or portal hypertension in 29%, new onset ascites in 11.5%, cirrhosis-like morphology in 13.5%, new splenomegaly in 17.3%, and 3.8% developed varices. While not statistically significant, patients were more likely to develop all characteristics if receiving bilobar as opposed to unilobar treatment. These findings were supported by a study of 39 patients by Su et al., who found that the median time to development of imaging morphology of cirrhosis was 1.8 years. Cirrhosis-like morphology developed in 56.4%, with 41% developing ascites and 15.4% developing varices. There was no significant change in liver volume; however, the spleen did increase significantly in size and the platelet and albumin decreased significantly over time.

Summary and future directions

TARE is very effective in the treatment of NET. As it is a fairly rare malignancy, interventional radiologists may be tempted to treat all NET in a similar fashion. We advise against this, as is underlined by the difference in survival seen with tumor grade, hepatic metastases, and primary tumor location [1, 44, 45]. We recommend caution using TARE in patients with low grade NET who have a long life expectancy due to the risk of developing long-term hepatotoxicity, but we believe TARE has a vital role to play in patients with higher grade tumors, and those who have failed previous therapies. Furthermore, the combination of TARE and systemic therapy, particularly immunologic or targeted medical therapies, has commenced and appears promising [46, 47].

Comparison of embolotherapies

Studies comparing bland to chemoembolization [17, 19, 21, 48] have found no statistically significant difference in symptom control rate [17, 21], progression-free survival (PFS) [19, 21, 48], OS [17, 19, 48], or complication rate [17, 19] between these two techniques. However, a statistically significantly better radiologic response after TAE over TACE was found in two retrospective studies [21, 48]; Fiore et al. with 30 patients found their TAE cohort showed higher rate of devascularization of treated lesions but without difference in lesion size reduction using RECIST criteria, and Gupta et al. with 123 patients found better imaging response by WHO criteria in their TAE cohort who had carcinoid tumors but not islet cell tumors. Conversely, Maire and colleagues found no difference in radiologic response by WHO criteria between TAE and TACE in their prospective RCT of 26 patients.

Other studies have compared radioembolization to chemoembolization, or radioembolization to bland and chemoembolization [20•, 29•, 49, 50]. Symptom control rate was assessed by Engelman et al. and the authors found no difference between TAE, TACE, and TARE. No difference in complication rate has been found between TAE, TACE, and TARE [50] or between TACE and TARE [29•, 49].

Radiologic response was assessed by Engleman et al., and they found no difference between TAE, TACE, and TARE; however, they did not use standardized criteria such as WHO or RECIST. On the other hand, Whitney and colleagues used mRECIST and found that TACE and TARE had similar imaging responses at 3 and 6 months, but at 12 months TACE was statistically significantly superior to TARE.

Regarding HPFS, one study found no difference between TACE and TARE [20•], and two studies found that TACE had a longer HPFS than TARE [29•, 49]. In one of the studies demonstrating longer HPFS for TACE by Do Minh and colleagues, the authors found longer HPFS for cTACE over TARE, but not DEB-TACE over TARE, or cTACE over DEB-TACE. Regarding OS, two studies showed no difference [20•, 50], while the study by Do Minh et al. found the cTACE resulted in longer OS than DEB-TACE and Y90 on propensity score analysis.

There is a definite paucity of RCT data comparing embolotherapy techniques, and we eagerly await the results of the Randomized Embolization Trial for Neuroendocrine Tumor Metastases to the Liver (RET-NET) trial [51].

Conclusion

In patients with unresectable symptomatic or progressive NELMs despite systemic treatment, the thermal ablation can be used to treat oligometastatic lesions of small size, and more diffuse multifocal disease can be treated with embolotherapy. Studies repeatedly show that when using these techniques, a high proportion of patients experience relief or reduction in carcinoid and bulk symptoms, as well as disease control in the liver. Comparative studies demonstrate that TAE, TACE, and TARE are similarly efficacious in these regards. Some patients who undergo TARE may develop long-term hepatotoxicity however, so caution should be taken using TARE in patients with low grade tumors who have a long life expectancy.

Compliance with Ethical Standards

Conflict of Interest

Donna D'Souza has received compensation from Sirtex and Medtronic for service as a consultant; Jafar Golzarian declares that he has no conflict of interest; Shamar Young has received compensation from Boston Scientific/BTG/Galil Medical for service as a consultant.

Human and Animal Rights

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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