Transarterial Chemoembolization in Neuroendocrine Liver Metastasis

Ricardo D. Garcia-Monaco, MD, PhD, FSIR; Andres Alejandro Kohan, MD

From Vascular and Interventional Radiology, Department of Radiology, Hospital Italiano de Buenos Aires, Argentina.

Abstract: Neuroendocrine tumors (NET) are rare neoplasms that present in up to 40% of patients with metastasis at diagnosis, notably in the liver. Radical surgery is the treatment of choice, however it is seldom possible in patients with liver metastasis. Medical treatment and locoregional therapies are palliative treatments in patients with symptoms or progressive disease. Bland embolization, transarterial chemoembolization (TACE) and radioembolization are the most common therapeutic options in clinical practice. Conventional TACE has been performed for many years with good results and more recently DEB-TACE improved the pharmacokinetics of the delivered drug. However, a higher incidence of bile duct injury has been reported with DEB-TACE, therefore turning controversial its indication in NET metastasis in some institutions. The purpose of this paper is to shortly review the available evidence on the use of TACE in NET metastasis to the liver.

Key words: drug-eluting beads, transarterial chemoembolization, neuroendocrine tumors

Neuroendocrine tumors (NET) are rare neoplasms characterized by slow progression and an indolent biology. However, about 40% of patients with NET will develop metastasis during the course of their disease, mostly to the liver.1 Five-year mortality rate is as high as 80% in untreated patients with liver metastasis.2 Neuroendocrine tumors may have different clinical and biologic behavior (poor vs well differentiated, gastrointestinal vs pancreatic origin), therefore comparison between different treatment modalities is difficult.

Because liver metastases from NET are hypervascular, endovascular treatment is appealing. Indeed embolization, chemoembolization, and more recently radioembolization have been used as palliative treatments intended to reduce tumor burden and achieve symptom control.3,4

Transarterial chemoembolization (TACE) has been utilized for 20 years.5 It combines the benefits of embolization and locoregional chemotherapy providing a high rate of tumor and symptomatic response.5,6 It is indicated in nonsurgical candidates with progressive disease or refractory symptoms despite medical treatment (octreotide) and no contraindication to TACE. Best results are obtained in patients with less than 60% liver involvement and good clinical status (ECOG 0-1).

Published studies with conventional chemoembolization (cTACE), using a mixture of doxorubicin, lipiodol, and embolic agent, have shown symptom response as high as 73% to 100%, oncologic response between 55% and 80% and time to progression (TTP)
ranging from 8 to 42 months (Figure 1).\textsuperscript{5-7} Adverse events such as drug toxicity (grade 2 alopecia, grade 2-3 nausea and vomiting), postembolization syndrome, acute metabolic syndrome, or infection have been reported.\textsuperscript{3,7} Some of these complications were advocated to drug toxicity and probably resulted from the unfavorable pharmacokinetic profile of doxorubicin binding to lipiodol.\textsuperscript{8}

**DRUG-ELUTING BEADS IN TRANSARTERIAL CHEMOEMBOLIZATION**

In this regard, a new embolic agent that can be loaded with a chemotherapy drug seems to offer a favorable pharmacokinetic profile.\textsuperscript{9} This product, called drug eluting beads (DEB), has been shown to achieve higher intratumoral drug concentration and less drug concentration in the bloodstream than cTACE in animal studies.\textsuperscript{10} These results encouraged some authors to test the feasibility, safety, and efficacy of DEB-TACE in liver NET metastasis.\textsuperscript{11,12} De Baere et al published a preliminary report of 20 patients that showed 80% objective tumor response and disease control, with a TTP of 15 months.\textsuperscript{11} Interestingly, and as expected, drug toxicity was very low with grade 2 alopecia around 1% and only a few cases of mild nausea and vomiting.\textsuperscript{11} However, imaging and laboratory tests showed

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**Figure 1.** A 56-year-old female patient with symptomatic gastrinoma liver metastasis that progressed despite systemic chemotherapy. She received 4 sessions of conventional transarterial chemoembolization (TACE) that led to complete symptomatic remission and disease control. Computed tomography scan before TACE shows large tumor burden in both lobes (A). Computed tomography scan performed 5 years later shows excellent oncologic result (B).
a high rate of liver infarction and bile duct injuries, although most of the cases were asymptomatic.\textsuperscript{11} Gaur et al reported 18 patients with a high rate of objective response and TTP of 14 months.\textsuperscript{12} They reported two cases of biliary injury, one asymptomatic and another registered as a major complication that required specific treatment.\textsuperscript{12}

Giu et al in a retrospective study of patients with hepatocellular carcinoma or liver NET treated with cTACE or DEB-TACE found biliary injuries in 30\% of cases, most of them being asymptomatic and none requiring biliary drainage.\textsuperscript{13} The authors concluded that biliary injuries were independently associated with both DEB-TACE and NET metastasis.

Bhagat et al reported in a small series of patients with liver NET treated with DEB-TACE, biloma formation in 7/13 cases with 4/7 requiring catheter drainage.\textsuperscript{14} They claimed that biliary injuries were more common in patients with small lesions and lower tumor burden and that the embolization technique they have been using should probably be revised to overcome the biliary complications.\textsuperscript{14}

Similar to the aforementioned authors, we found in our personal series a high rate of objective response (Figure 2) with some cases of liver or biliary injuries, most of them expressed as incidental findings with multidetector computed tomography or blood tests (elevated alkaline phosphatase).

It is important to note that in contrast to normal liver parenchyma, intrahepatic bile ducts do not have a dual blood supply and are fed exclusively from the hepatic arterial branches that form a vascular plexus (peribiliary capillary plexus) around the bile ducts (Figure 3). Therefore, ischemia of the intrahepatic bile ducts can easily occur after TACE.\textsuperscript{15} Bile duct injury changes are represented as bile duct dilatation, periportal edema, and bilomas (Figures 4 and 5), probably reflecting liver damage that occurs gradually over time.\textsuperscript{13,16}

Some authors suggested that the incidence of DEB-TACE-related bile duct injury is likely the result of inadvertent retention at the capillary peribiliary network of DEB loaded with doxorubicin causing blood flow stasis and chemical irritation of the endothelium leading to vasculitis and/or ischemia.\textsuperscript{13} This may occur as a consequence of overembolization related to a very aggressive TACE resulting in a high DEB dose and/or complete vessel occlusion.

Experienced operators are aware that the technique of DEB-TACE is rather different from cTACE, notably the embolization endpoint. Indeed, some technical recommendations have been reported for better outcomes after DEB-TACE in hepatocellular carcinoma and colorectal liver metastasis.\textsuperscript{17,18} However no recommendations for liver NET treated with DEB-TACE have been specifically addressed in the literature.

It can be speculated that a more conservative embolization endpoint and the delivery of a limited amount of DEB could avoid peribiliary plexus occlusion, therefore decreasing the complications of DEB-TACE. In a series of 35 consecutive patients with liver NET that we treated in a single institution with DEB-TACE we compared two different embolization endpoints (arterial stasis/occlusion [complete embolization] vs arterial free flow circulation with tumor devascularization [limited embolization]). We found a lower rate
of adverse events (14% vs 57%; P<.05) using the latter.\textsuperscript{19} No statistically significant difference (P=.43) was observed in the treatment response comparing the embolization endpoints.

From a practical point of view, relative risk factors for bile duct injury of TACE may be related to the use of DEB-TACE over cTACE, proximal DEB embolization, small tumors, and small tumor burden.\textsuperscript{13,14} These risk factors do not necessarily reflect a clinical complication but a higher probability to find CT or blood test biliary changes. When performing DEB-TACE, intratumoral delivery of DEB may prevent bile duct injury by avoiding overembolization that will relentlessly lead to nontarget embolization. Delivery of fewer beads in small aliquots could help achieve that goal. In this latter line of reasoning we found a tendency toward higher frequency of adverse events in patients where 2 vials were used as opposed to patients where 1 vial was used.

**Figure 2.** A 56-year-old male patient with well differentiated carcinoid liver metastases treated with DEB-TACE and followed by liver transplantation. Explanted liver shows several necrotic tumors (A). Pretransplant multidetector computed tomography in arterial phase shows tumor necrosis after DEB-TACE (B). Histopathology of the explanted liver confirms high grade of tumor necrosis (N) in contact with DCB (arrow), better depicted in the magnification photograph (C).
Figure 3. Bile duct irrigation. Figure reprinted with permission from “MDCT Findings After Hepatic Chemoembolization With DC-Beads: What the Radiologist Needs to Know.” Abdom Imaging. 2013;38(4):778-784.

DISCUSSION

One current question about TACE in liver NET that the interventional radiologist frequently raises is whether cTACE or DEB-TACE should be performed. Unfortunately “the jury is still out” on that issue. It seems clear, though, that DEB-TACE has an excellent pharmacokinetic profile resulting in minimal drug toxicity to patients. However, the use of DEB has shown to increase the risk of biliary tree injury, albeit asymptomatic in most cases.\textsuperscript{13,14} It may be that a different endpoint of DEB-TACE, such as learning curve, will overcome this drawback in the future. More rigorous data are needed to better assess the role of DEB in treatment of liver NET.

CONCLUSION

Both techniques involving TACE (conventional and DEB) offer a high objective response rate (symptomatic, humoral, morphologic) and disease control with a satisfactory durability of the response. Its role in comparison to bland embolization or radioembolization with Y90 is still controversial, but TACE is the most widely used technique in this subset of patients. Regardless of the technical option, endovascular therapies have become the treatment of choice in patients with progressive disease or symptoms refractory to medical treatment in many institutions.
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Address for correspondence: Ricardo D. Garcia-Monaco, MD, From Vascular and Interventional Radiology, Hospital Italiano de Buenos Aires, Juan D. Perón 4190, Buenos Aires C1181ACH, Argentina. Email: ricardo.garciamonaco@hospitalitaliano.org.ar


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