ASK THE EXPERTS

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Management of hepatic metastases from neuroendocrine cancer

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The multidisciplinary management of metastatic cancer to the liver has evolved rapidly over the last two decades. Lessons learned from the multidisciplinary approaches for patients with metastatic colorectal cancer have prompted similar treatment strategies for patients with metastatic neuroendocrine cancer (NEC). Although high-quality evidence-based data supporting hepatic resection of metastatic colorectal cancer are nonexistent, cumulative outcome data support such a therapy as the treatment of choice in selected patients. Translation of this approach to patients with metastatic NEC is attractive clinically but whether similar outcomes will support that position is far from established. NEC is heterogeneous with regard to tumor origin, histopathology, endocrine function and rate of clinical progression. The liver is the dominant site of distant metastases.

As in other patients with hepatic metastases, success of treatment is dependent on local-regional control of the primary NEC and the completeness of eradication of the hepatic metastases irrespective of the liver-directed therapy chosen. Although cytoreduction of metastatic NEC remains the primary aim of all treatment, selection of patients, and type and sequence of treatment algorithms vary widely. Indeed, there is no current consensus for optimal management [1]. The aim of this commentary is to highlight the management of metastatic NEC to the liver from a surgical perspective.

Q What is the rationale for operative management of hepatic metastases?

The clinical and biological behavior of most NECs has provided a rationale for operative management of hepatic

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metastases. First, most NECs progress indolently, which permits time for thorough operative planning with minimal risk of prohibitive disease progression. Second, the intensity of clinical endocrinopathies correlates with metastatic volume, thus, inviting tumor resection for durable response. Third, growth features of the metastases are typically expansile with infrequent venous or biliary invasion that permits more frequent parenchymal preserving resections. Fourth, hepatic parenchyma, except in patients with advanced carcinoid heart disease, typically is normal. Thus, regeneration usually proceeds rapidly and completely after resection, permitting subsequent liver-directed therapy if the disease progresses. These observations have promoted hepatic resection widely, but the potential for oncologic and symptomatic benefits must be balanced against the risk of operative mortality and morbidity.

Q What diagnostic work-up is required for patients with neuroendocrine tumors?

Hepatic metastases from NEC are recognized concurrent with the primary NEC or during follow-up. Preoperative evaluation should include: assessment of the site of the primary NEC; functional endocrine status; NEC grade; and extent of metastases, both hepatic and extrahepatic. The primary NEC is assessed by endoscopy, contrast-enhanced enterography, radiolabeled scintigraphy or dimensional imaging. Clinical functional status is confirmed by assay of serum or urinary hormonal markers. Grade of the primary NEC should be reviewed if previously resected. In patients with high grade NEC, a durable objective response to chemotherapy with expectations of an R0 resection is preferred before operative intervention. NEC grade is a major factor affecting treatment approaches. Indeed, patients with high-grade or dedifferentiated NEC are rarely candidates for hepatic resection. Biopsy of the most accessible NEC site to confirm NEC grade, whether the primary or a metastasis, is indicated before undertaking resection of hepatic metastases. Hepatic metastases are evaluated by contrast-enhanced dimensional computed tomography or MRI. Metastatic

NEC is hypervascular and detected best in the arterial imaging phase. Further staging for other occult distant metastatic disease is assessed by radiolabeled somatostatic scintigraphy. Positive scintigraphy is dependent upon the presence of somatostatin receptors on the NEC. Positive scintigraphy permits accurate initial and follow-up staging. Alternatively, PET imaging is used when somatostatin scintigraphy is negative or unavailable.

Q What factors make hepatic lesions amenable to surgical resection?

Resection of any hepatic tumor is dependent upon achieving negative margins of resection and preservation of an adequate functional hepatic remnant. In principle, selection of patients for resection dictates criteria for hepatic resection and a resected or resectable primary NEC. Whether resection of the primary NEC and hepatic metastases is undertaken concurrently or by staged resection is controversial and depends on the scope of the resections and surgical expertise. Moreover, staged hepatic resection of metastatic NEC is required in some patients. Selection criteria for liver transplantation are more stringent and imply resection of the primary NEC, absence of distant metastases and local regional disease control for 6–12 months. In practice, the number and distribution of hepatic metastases recognized preoperatively or intraoperatively often precludes R0 resection. Importantly, in contrast with other metastatic solid cancers to the liver, hepatic resection is still undertaken by many surgeons even when either R1 or R2 resections are expected. This strategy employs resection as the primary cytoreductive modality for hepatic metastases challenging the role of chemotherapy and antihormonal therapy for NEC. Ideally, neoadjuvant chemotherapy to downsize hepatic metastases would be preferable to improve the rate of R0 resections. To date, chemotherapy or antihormonal therapy is, at best, cytostatic and generally not associated with significant NEC downsizing. However, incomplete hepatic resection with or without concurrent ablation of metastatic NEC is not undertaken lightly. The aim of such resections is to maximally

address nearly all gross disease, minimizing the residual disease that would be amenable to subsequent liver-directed therapy. Implicit in such hepatic resections is that clinical efficacy of R1–2 resection is not offset by operative risk nor precludes other therapy for expected disease progression. Initially, an estimate of the volume of resected metastases (>90%) was used to quantify the extent of resection that correlated with a complete and durable endocrine response and a suggested improved survival. Currently, the operative focus is not the resected volume but the residual volume of metastatic NEC in the hepatic remnant. Duration of symptom control and survival is dependent on the extent and progression of the residual NEC. Ideally, the residual volume of metastatic NEC in the liver should be either occult to postoperative dimensional imaging or, if present, expectedly ablatable by subsequent liver-directed adjuncts. Thus, the biology of metastatic NEC and the typically normal underlying liver affords a nearly unique clinical circumstance to employ operative therapy.

Q What outcomes can be expected following resection?

Outcomes following hepatic resection with or without concurrent ablation and liver transplantation for selected patients with metastatic NEC consistently have shown prompt, durable and excellent control of endocrinopathies. Although greater overall survival compared to historical controls has been suggested, no randomized controlled study has provided confirmation. Endocrine response after hepatic resection has ranged from 80 to 95 and 100% after liver transplantation. Overall, 5-year survival after hepatic resection has ranged from 60 to 75%, and is similar after transplantation. However, disease progression is frequent regardless of the completeness of hepatic resection. Indeed, progression is evident in 50–70% of patients within 5 years. Although expectedly R0 resections should provide greater overall survival than R1–2 resections, reported differences in survival by completeness of resection, in fact, have been minimal, which likely reflects patient selection, NEC biology and volume of residual metastatic NEC

after resection. Overall survival has been similar after resection functional and non-functional NEC metastases. Any reported differences in survival likely relate to diagnostic lead time bias from the clinical endocrinopathy of functional NEC. Finally, concurrent resection of the primary NEC and hepatic metastases has been performed safely in selected patients. Operative mortality and morbidity for resection and transplantation have been acceptable. Ablation as an intraoperative and postoperative adjunct has proven effective in the control of recurrent symptoms and delays disease progression. These cumulative data support hepatic resection, transplantation and ablation for metastatic NEC as safe and efficacious for selected patients with metastatic NEC. However, actual curative potential is limited with disease progressing in most patients. The unresolved issue in interpreting the outcomes of liver-directed therapy is whether the therapy or the biology of NEC accounts for the apparent benefit of observed outcomes.

Q What role do intra-arterial therapies play & in which patients should these be considered?

Extent of metastatic NEC to the liver precludes resection in many patients. Consequently, hepatic arterial embolization, chemoembolization and radioembolization have been employed for liver dominant metastases. Each of these therapies are associated with symptomatic responses in >50% of patients, measurable or morphologic responses in approximately 60%, and progression-free survival of approximately 18 months and 5-year survival range of 40–80%. No current data have proven superiority of any of these approaches but, given the symptomatic responses and safety profiles, further study of these approaches in neoadjuvant, adjuvant and primary settings is warranted.

Q How do you see the management of neuroendocrine tumor liver metastases evolving over the next 5–10 years?

Lack of evidence-based data for the treatment of metastatic NEC to the liver should prompt collaborative multi-institutional studies to evaluate all approaches to

metastatic NEC to the liver. Although the incidence of NEC is increasing, the overall prevalence is low and the indolent growth rate dictates prolonged follow-up that is best supported by collaborative studies as concluded by the recent Consensus Conference statement. Currently, the oncologic community can better define the expected biologic behavior of these heterogeneous cancers and more accurately stage NEC by imaging. NEC-specific quality of life outcome measures have been developed to augment quantification of outcomes other than overall and progression-free survival, and treatment-related morbidity and mortality. Thus, patient selection and response criteria can be more accurately defined. Individual liver-directed therapies can be assessed but more likely comparison of sequential treatment strategies for metastatic NEC to the liver will be trialed given the frequency of disease progression and tumor biology. The opportunity for study and impact for the treatment of patients with metastatic NEC has never been greater. Perhaps future treatment strategies will provide cure rather

than chronic efforts toward disease control of patients with NEC.

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