Tumors of neuroendocrine origin arising from the pancreas, luminal gastrointestinal tract, and other tissues differ greatly in their malignant potential. However, relative to malignancies arising from the same organ, the natural history of neuroendocrine tumors (NETs) is comparatively indolent. The management of patients with localized NETs has been extensively studied, with current recommendations summarized in the consensus guidelines published in 2011 by the National Comprehensive Cancer Network (NCCN).[1] Huang et al., of Stanford University, provide a thorough review of the management of patients with NETs, drawing on their extensive clinical and research experience with this disease. Importantly, the authors organize the discussion by histology and primary organ—both of which reflect the diverse biology of the disease, resulting in differences in malignant potential and ultimately in long-term survival.

While there is little debate about the necessity of surgical management in patients with localized NETs, the role of surgery in patients with metastatic disease remains controversial. As noted by Huang et al. and others, NETs commonly metastasize to the liver, with upwards of 44% of patients developing neuroendocrine tumor liver metastasis (NELM) over the course of their disease.[2,3] Patients with NELM often develop hormonal symptoms related to their hepatic disease burden, leading to both a decreased quality of life and ultimately to poorer long-term survival.[2,4-9] Liver-directed therapy (ie, hepatic resection, ablation, or intra-arterial therapy [IAT]) for patients with NELM remains controversial, with some centers advocating one approach and some centers favoring another. In the current era, however, hepatic resection of NELM offers the only chance at long-term survival. While Huang et al note that 5-year survival may decrease to 30% in the setting of hepatic metastasis, more recent data from our own group suggest a more favorable long-term survival. Specifically, we recently reported the results of two separate international multi-institutional studies examining the role of surgical management (resection and ablation)[6] and comparing IAT to surgery[10] for patients with NELM. In these studies, we noted that surgical management resulted in a median survival of 125 months, with overall 5- and 10-year survivals of 74% and 51%. While long-term survival was excellent, disease recurrence was almost universal (94%) at 5 years.[6] We found that patients with hormonally functional NETs who had an R0/R1 resection benefited the most from surgery ($P = .01$). On multivariate analyses, synchronous disease (hazard ratio (HR) = 1.9), nonfunctional NET hormonal status (HR = 2.0), and extrahepatic disease (HR = 3.0) remained predictive of worse survival (all $P < .05$). Of note, however, was our finding that there was no difference in the incidence of disease recurrence between patients resected with negative margins and those resected with positive surgical margins. Other investigators have shown that numerous subcentimeter hepatic foci of NET metastatic disease are frequently present in the liver specimens of patients with NELM that were not appreciated on preoperative imaging—suggesting that even after a "complete" resection, subclinical disease may often be left behind.[11] As such, disease recurrence may not be the most appropriate term for patients who develop clinically detectable disease following hepatic resection for NELM; rather, disease progression may be a more apt biological description, even in the setting of a prior "complete" resection.

Given the nearly universal disease progression after complete surgical resection of NELM, many centers have suggested that IAT (including transarterial chemoembolization, bland transarterial embolization, drug-eluting beads, or yttrium-90) may be a better option as a primary therapy for NELM than hepatic resection. The intuitive appeal of IAT is based on the fact that the blood supply for NELM is derived almost exclusively from the hepatic arteries, thereby providing direct access to the metastatic lesions. In a study of over 700 patients with NELM, we examined patients who were managed primarily with surgery ($n = 339$) vs those who were managed with IAT ($n = 414$). The
median survival and 5-year survival of patients treated with surgery were 123 months and 74%, compared with 34 months and 30% for those managed with IAT (P < .001); however, the baseline clinicopathologic characteristics of the patients were vastly different. To account for these differences, we employed a propensity-adjusted analysis.[10] In the propensity-adjusted multivariate Cox model, asymptomatic disease (HR = 2.6) was strongly associated with a worse outcome (P = .001). Although surgical management provided a survival benefit over IAT among symptomatic patients with > 25% hepatic tumor involvement, there was no difference in long-term outcome post-surgery vs post-IAT among asymptomatic patients (P = .78). Thus, asymptomatic patients with a large (> 25%) burden of liver disease benefited least from surgical management, and IAT may be a more appropriate treatment strategy in this setting. Surgical management of NELM should therefore in general be reserved for patients with low-volume disease and/or those with symptomatic high-volume disease.

While the mainstay of therapy for metastatic NETs remains surgical resection and debulking in applicable cases, there have also been several advances in recent years with systemic therapy. NETs have traditionally exhibited very poor responses to conventional chemotherapy, with response rates in the range of 15% to 20%. More recently, targeted agents have shown increasing activity in inhibiting disease progression. One such group of agents is the somatostatin analogues, which are widely used to control symptoms in patients with low- to intermediate-grade NETs, most notably in patients with carcinoid tumors. Somatostatin analogues act by binding to one of five somatostatin receptors that tend to be overexpressed in most gastroenteropancreatic NETs, thereby minimizing hormone release. In the PROMID study (Placebo-controlled Prospective Randomized Study of the Antiproliferative Efficacy of Octreotide LAR in Patients with Metastatic Neuroendocrine Midgut Tumors), 85 treatment-naive patients with well-differentiated (Ki-67 < 2%) metastatic midgut NETs and good performance status (Karnofsky Performance Status > 60) were randomly assigned to either placebo or octreotide LAR (Sandostatin LAR, a depot form of this somatostatin analogue), 30-mg intramuscular injection every month until tumor progression.[12] At the planned interim analysis, time-to-progression (TTP) in the octreotide LAR group was 14.3 months compared with 6.0 months in the placebo group (HR = 0.34; 95% confidence interval [CI], 0.20-0.59; P = .000072). In addition, there was stable disease in 66.7% of patients in the octreotide LAR group vs 37.2% in the placebo group after 6 months of treatment. Thus, octreotide LAR therapy is recommended in patients with advanced metastatic carcinoid, especially those with symptomatic disease.

Other targeted agents have shown promise for the treatment of advanced metastatic pancreatic NETs (PNETs). Preclinical data had suggested that inhibition of mammalian target of rapamycin (mTOR) has a significant antiproliferative effect in pancreatic neuroendocrine cell lines. The third RAD001 in Advanced Neuroendocrine Tumors trial (RADIANT-3) enrolled 410 patients with advanced, low- to intermediate-grade PNETs who had evidence of radiographic progression within the previous 12 months.[13] Patients were randomly assigned either to treatment with everolimus (RAD001; Afinitor), 10 mg daily, or to placebo, and the primary endpoint was progression-free survival (PFS). Median PFS was 11.0 months in the everolimus group and 4.6 months in the placebo group (HR = 0.35; 95% CI, 0.27-0.45; P < .001), leading to the approval of everolimus as first-line treatment of progressive PNET. A number of other receptors, including vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-alpha, and PDGFR-beta, have also been targeted in the treatment of metastatic PNETs. Specifically, sunitinib (Sutent) has been investigated in a randomized, double-blind, placebo-controlled phase III trial in patients with advanced, well-differentiated PNETs who had evidence of disease progression within the previous 12 months. In this study, 171 patients were randomly assigned either to treatment with sunitinib, 37.5 mg daily, or to placebo, with PFS as the primary endpoint.[14] Median PFS was 11.4 months in the sunitinib group, compared with 5.5 months in the placebo group (HR = 0.42; 95% CI, 0.26-0.66; P < .001)—leading to the approval of sunitinib for the treatment of progressive pancreatic PNETs.

The management of patients with NETs is challenging in both the localized and metastatic setting. Optimal care of these patient populations requires the dedicated collaboration of a multidisciplinary team of specialists, including medical oncologists, endocrinologists, gastroenterologists, pathologists, and surgeons, to achieve the best possible outcome. Huang et al have outlined the state-of-the-art care for treating primary NETs. Given that many patients will develop subsequent metastases, recent data on the role and efficacy of surgery and IAT, as well as the emergence of new targeted systemic agents, hold promise for treating patients with advanced NETs.

Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.
References:

REFERENCES


Links: