Editorial

Surgical management of metastatic neuroendocrine tumors: beyond the realm of evidence-based medicine

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How strong is the evidence supporting surgery for patients with metastatic neuroendocrine tumors (NETs)? This is the chief question from Dr. Williams' comprehensive and balanced literature analysis on the surgical treatment of metastatic pancreatic NETs (1). No matter how many non-randomized studies demonstrate a survival advantage for patients undergoing cytoreductive hepatic surgery or resection of the primary pancreatic tumor, the methodological biases remain constant (2-9). Patients undergoing surgery tend to be younger and healthier, and their tumors tend to be lower grade, less aggressive, and fewer in number than patients undergoing other systemic or liver-directed therapies. In other words, the survival advantage begins when the patient is selected as a surgical candidate and before the scalpel even touches the skin. Although multivariate analyses can control for some confounding variables, it is impossible to control for all. Even a simple concept such as tumor burden is challenging to standardize: a patient with a few large tumors confined to a single hepatic lobe may have a vastly different prognosis than a patient with a similar burden of miliary tumors scattered throughout the liver (2).

Attempts to set minimal thresholds for surgical debulking are also fraught with methodological challenges (3,9). Small retrospective studies are highly underpowered to detect differences in overall survival between patients undergoing 70%, 80%, or 90% debulking (4-8,10). Merely deciding to operate (by a surgeon who has performed an appropriate presurgical evaluation) is associated with a favorable prognosis. The rare circumstance where the surgeon is unable to resect the bulk of the disease typically indicates substantially more metastases than estimated preoperatively or large unresectable tumors, both of which are associated with a poor prognosis.

Unfortunately, we cannot foresee the development of high-quality randomized trials capable of providing robust evidence to support surgical cytoreduction. Randomized surgical trials evaluating overall survival as the primary endpoint require large sample sizes. The main surrogate endpoint, progression-free survival, is not quite suitable for cytoreductive surgeries, which eradicate some tumors and leave others behind. Perhaps most importantly, patients are generally reluctant to accept a random surgical or non-surgical treatment selection.

Liver transplantation offers the possibility of a cure for rare patients with metastatic disease confined to the liver (11). However, to achieve high recurrence-free survival rates, patients must be carefully selected to have a relatively low number of tumors, low grade of disease, and stable disease at baseline (12-15). Small bowel NETs are associated with lower rates of recurrence post-transplantation compared to pancreatic NETs (13). Not surprisingly, patients with the best post-transplant outcomes would also fare well with

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non-transplant treatments. While liver transplantation undoubtedly benefits some patients, it can be hard to identify the optimal candidates. As with surgical cytoreduction, randomized transplantation trials are highly impractical.

Given the unavoidable weakness of the data, can surgical approaches to metastatic NETs continue to be justified in an age of evidence-based practice? In our opinion, the answer is yes. To paraphrase a saying: absence of evidence of benefit is not evidence of absence of benefit. Although we are unable to prove that surgery in appropriately selected patients improves survival, it is very likely that removal of the bulk of tumors in patients with unaggressive cancer improves long-term outcomes and delays the need to prescribe potentially risky systemic treatments. We, therefore, must continue to evaluate patients in a multidisciplinary fashion, weighing surgical, interventional, and systemic treatments, and making complex decisions based on a multiplicity of factors. An individualized approach to patient care embodies the art of medicine, which continues to thrive where the light of evidence cannot reach.

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