Ampullary adenocarcinoma is an uncommon neoplasm that most often requires pancreatoduodenectomy, has a less than optimal cure rate, and is a cancer for which the impact of multidisciplinary care remains unclear. Although often believed to have a better prognosis than pancreatic cancer, ampullary cancer remains a highly lethal disease. Given its rarity and the typical lack of surrounding vessel invasion, a surgery-first approach has most commonly been used in treatment sequencing. The literature has yielded conflicting results regarding the use of adjuvant therapy. Neoadjuvant therapy has received little attention but offers promise with regard to pathologic downstaging, particularly when chemotherapy is combined with radiation. Genetic evaluation may help guide future therapies, and multi-institutional trials are needed to develop optimal treatment sequencing and directed at the 2 specific histologic subtypes.

Principles of Management of Patients With Ampullary Adenocarcinoma

Presented by Stephen W. Behrman, MD

ABSTRACT

Ampullary adenocarcinoma is an uncommon neoplasm that most often requires pancreatoduodenectomy, has a less than optimal cure rate, and is a cancer for which the impact of multidisciplinary care remains unclear. Although often believed to have a better prognosis than pancreatic cancer, ampullary cancer remains a highly lethal disease. Given its rarity and the typical lack of surrounding vessel invasion, a surgery-first approach has most commonly been used in treatment sequencing. The literature has yielded conflicting results regarding the use of adjuvant therapy. Neoadjuvant therapy has received little attention but offers promise with regard to pathologic downstaging, particularly when chemotherapy is combined with radiation. Genetic evaluation may help guide future therapies, and multi-institutional trials are needed to develop optimal treatment sequencing and directed at the 2 specific histologic subtypes.
several reasons, including the perceived improved prognosis compared with pancreatic cancer. Additionally, in contrast to pancreatic cancer, vascular involvement of these lesions is uncommon—they are almost always resectable lesions. Bleeding and gastrointestinal obstructions sometimes occur with ampullary carcinoma, which prompts early resection. Furthermore, the impact of adjuvant therapy on these lesions is unclear, suggesting that surgery may be the mainstay of treatment. And lastly, the rarity of these lesions impedes study of multimodality treatment sequencing.

**Adjuvant Therapy**

Despite several recent studies of adjuvant therapy to treat ampullary cancer following surgical resection, the benefits of this approach remain unclear. A 2019 study by Ecker et al found no benefit with adjuvant therapy, regardless of histologic subtype. Results of a study of the NCDB, however, showed that OS was improved with adjuvant chemoradiation therapy. Deeper analysis of the Ecker study by a European group also showed that survival was improved, but only in patients with biologically advanced disease, and was limited to the pancreaticobiliary subtype.

A single-center study by Ramaswamy et al demonstrated improved survival for patients with stage II–III ampullary cancer in both subtypes of the disease following a gemcitabine-based adjuvant therapy regimen. However, Abbas et al found that a fluorouracil-based adjuvant therapy regimen yielded a survival benefit over gemcitabine in both subtypes. Finally, a recent systemic review and meta-analysis found that adjuvant therapy decreased the mortality risk—more so in those who received chemoradiotherapy compared with chemotherapy alone. However, the benefit was limited to the pancreaticobiliary subtype.

“Although the benefit of adjuvant therapy remains inconclusive, it is most likely helpful in advanced disease and the pancreaticobiliary subtype,” said Dr. Behrman. “Results from these studies suggest that subtype-based chemotherapy may not be as important as receiving adjuvant therapy in and of itself, and that radiation therapy, although incompletely assessed, may prove advantageous in this disease.”

**Neoadjuvant Therapy**

Given the somewhat contradictory results of recent studies of adjuvant therapy in ampullary carcinoma, Dr. Behrman noted that it may be time for a paradigm shift in treatment sequencing and to consider neoadjuvant therapy as a viable option. The rationale for neoadjuvant therapy is similar to that for pancreatic adenocarcinoma, he said, due to the lethal nature of the cancers and the concern for micrometastatic disease at the time of diagnosis. Neoadjuvant therapy could select patients with early development of metastatic disease and save them an aggressive operation,” said Dr. Behrman. “There is also the opportunity for pathologic downstaging, which has led to improved outcomes in pancreas cancer. What is unknown is the impact on survival from neoadjuvant therapy in a disease that’s often clearly resectable at diagnosis,” Dr. Behrman added.

A study from MD Anderson of 56 patients with ampullary cancer who received neoadjuvant therapy showed a major pathologic response in 64% of patients. Major pathologic response, which occurred irrespective of subtype, was more common in those who received chemoradiation therapy, and resulted in significantly increased disease-specific survival.

A recent propensity score–matched analysis of the NCDB, however, found no difference in OS between patients who received neoadjuvant therapy and those who did not. However, only 30% of patients received radiation therapy in addition to chemotherapy, and there was no information regarding pathologic response to neoadjuvant therapy.

“Neoadjuvant therapy for ampullary adenocarcinoma has been used most often in advanced disease and leads to significant downstaging,” said Dr. Behrman. “Utilization of radiotherapy as part of neoadjuvant chemotherapy regimens also seems to be a key component and warrants further investigation.”

**Genetics of Ampullary Carcinoma**

Although preliminary work has explored germline and somatic alterations of the disease, the genetics of ampullary carcinoma remain incompletely assessed. According to Dr. Behrman, it is unclear whether genetic alterations vary by histologic subtype, but there is potential for alteration in chemotherapeutic regimens, and there may be more significant actionable mutations than in pancreatic cancer.

The largest genetic assessment study to date in ampullary cancer was conducted by investigators at Memorial Sloan Kettering and included 45 patients who underwent somatic testing and 23 who underwent germline testing. They found that 18% of patients had a germline mutation (ie, BRCA2, ATM, MUTYH) with implications for chemotherapeutic treatment. A wide spectrum of somatic alterations was also identified, said Dr. Behrman, who noted that many (ie, ERBB2 amplification, DNA mismatch repair) were potential candidates for immunotherapy.

“There’s clearly much to learn about the genetic alterations associated with ampullary carcinoma, but current data suggest a larger opportunity for treatment by both chemotherapy and immunotherapy in these patients, and may help direct counseling of family members,” said Dr. Behrman.

**2022 NCCN Guidelines**

The first version of the NCCN Guidelines for Ampullary Adenocarcinoma was released in March 2022. Dr. Behrman emphasized the recommendation of histologic subtyping if possible.

“Future work with this periampullary neoplasm is critical in terms of defining effective chemotherapy
regimens specific to histologic subtype, said Dr. Behrman. The chemotherapeutic platforms suggested in the NCCN Guidelines are based on the specific subtype of the disease in surgery and require prospective evaluation.

Genetic evaluation is also recommended in this patient population, and the guidelines suggest neoadjuvant therapy as an option, especially in patients with high-risk disease. If a neoadjuvant regimen is utilized, said Dr. Behrman, it is important to include a tumor regression score as part of the pathologic analysis.

“The most important aspect of the NCCN Guidelines is that they offer a platform to help guide patients and clinicians in the treatment of this disease, and they certainly provide a platform for future research endeavors and potential clinical trials,” Dr. Behrman concluded.

Disclosures: Dr. Behrman has disclosed no relevant financial relationships.
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