Editorial

The future of adjuvant therapy in ampullary cancer: should we offer it to our patients?

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Ampullary carcinoma is a relatively rare and heterogenous neoplasm accounting for 0.2% of all gastrointestinal tract malignancies. The data from National Cancer Institute's Surveillance, Epidemiology, and End Results Program have shown an increase in incidence of ampullary cancer over the last decade (1). Currently, prospective clinical trials to determine optimal post-surgical therapeutic options for ampullary cancer is lacking. Patients with ampullary cancers are usually grouped with other peri-ampullary neoplasms such as pancreatic head adenocarcinoma, biliary tract and duodenal neoplasms in clinical trials. However, it is critical to understand that the biology of the tumors that are grouped into "peri-ampullary neoplasms" differ, which is evident by the differences in mucinous secretions (2), rate of resectability, and survival rates (3). Moreover, Carter *et al*., classified the ampullary cancers into two major subtypes: duodenal (or intestinal) and pancreato-biliary counterparts depending upon the histology and aggressiveness of the disease (4). Regardless of the specific histologic subtype of ampullary cancer, multiple studies have demonstrated higher resection rates for ampullary cancers as compared to that of pancreatic or biliary tract cancers (3). However, the role of adjuvant therapy in ampullary carcinoma is not well established as the data is obtained either from therapeutic protocols employed to evaluate other peri-ampullary cancers or retrospective studies (5). Despite the controversy of the role of adjuvant therapy, there has been trend towards higher utilization of adjuvant therapy by clinicians in the United States , an increase from 9% to 32% in the years 2004-05 and 2012-13, respectively (6).

Recently, Ecker *et al*., attempted to evaluate the role of adjuvant therapy in ampullary cancer by pooling up the data from 12 institutes across the United States (n=357) (7). The role of adjuvant therapy was evaluated in terms of chemotherapy agent used (5-fluorouracil-based and gemcitabine-based), stage of disease at diagnosis, and intestinal and pancreato-biliary subtypes. A total of 56% (200 of 357) of the study cohort received adjuvant therapy including chemotherapy (74%), radiation therapy (10%), combination chemoradiation therapy (16%). Interestingly, the authors did not find any overall survival (OS) advantage with the use of post-surgical adjuvant chemotherapy on multivariate analysis of unmatched cohorts (P=0.68). Absence of benefit of adjuvant therapy was resonated on histological subtype analyses as well- intestinal subtype: hazard ratio (HR): 1.21, (95% CI: 0.67–2.16, P=0.53); pancreato-biliary subtype: HR: 1.35, (95% CI: 0.66–2.76, P=0.41). The authors concluded that post-surgical adjuvant therapy has no role in improving OS in patients with ampullary cancer, irrespective of the stage at diagnosis, grade, resection margin status, lymph node positivity, and histologic subtype thereby questioning the adjuvant therapy use in clinical practice. In this study, authors tried to address

immortal time bias by excluding patients who died within 90 days of surgical resection. Propensity matched analysis was used to compare respective groups in the cohort. This is one of the largest series to date of resected ampullary cancer which includes granular information on patients' characteristics and type of chemotherapy.

The study results are to be interpreted with caution. First, it is hard to draw a firm conclusion based on the retrospective nature of the study design and relatively small sample size of the study cohort, especially in each subset. Several retrospective studies of similar or larger sample size have yielded controversial results to-date. For instance, a recent Mayo Clinic series has demonstrated the benefit of adjuvant chemotherapy in advanced stage (stage IIB or above) ampullary cancer (5). The study has demonstrated the decrease in risk of death by 55% in advanced disease patients who received adjuvant therapy [HR: 0.45, (95% CI: 0.22–0.93), P=0.03]. This corroborated to a survival benefit of almost 12 months. Similar encouraging results were seen in another retrospective series that gathered data from a national database including 4,190 patients with ampullary cancer (6). Adjuvant therapy was administered in 21% (870/4,190) of the patients. The study reported the reduction in risk of death by 18% [HR: 0.82, (95% CI: 0.71–0.95)], which was more pronounced in larger tumors and advanced stage at diagnosis. None of these studies, including the latest multi-institutional analysis by Ecker *et al*., included information on the duration and tolerance of therapy. This information is critical to assess the benefits of any therapy, especially when we try adopt study results into clinical practice.

It is known that majority of the patients with ampullary cancer die of disease recurrence after the curative intent surgical resection. Based on the study results presented by Ecker *et al*., it is hard to draw any conclusions on the role of adjuvant therapy on disease-free survival (DFS) or OS. In this study, there was no standard therapy with different chemotherapeutic regimens being used making it difficult to assess the role of adjuvant therapy in the relatively small sample size. In the subgroup analysis of ampullary cancer patients in ESPAC-3 trial, OS benefit was observed only in gemcitabine arm and not in 5-fluorouracil arm (8).

Therapies targeting the genetic aberrations and molecular pathways (precision and personalized medicine) has gained traction in other gastrointestinal malignancies such as cholangiocarcinoma (FGFR2 fusions, BRCA, NTRK, IDH1/2 mutations), pancreatic (BRCA, PALB2) and colon cancer (BRAF). Though these genetic aberrations are implicated only in a small percentage of tumors in these cancer types, use of specific targeted agents has shown promising results. Recently, Wong *et al*. identified pathogenic germ line genetic mutations in 18% (8 out of 44) of the ampullary tumors analyzed (BRCA2, ATM, RAD50, and MUTYH), whereas 36% (16 of 44) had somatic mutations (KRAS, EGFR, PIK3CA, etc.) (9). All these factors underscore the urgent need for better characterization of the molecular markers and target pathways that help in expanding the concept of precision oncology and personalized medicine in the patients with ampullary cancer. However, clinical trial accrual is a proven challenge given the rarity of cancer, which we may overcome by multi-institutional and international collaborations so that these patients are grouped into small number of clinical trials.

The question that arises is whether we should offer or advocate post-surgical adjuvant therapy to our patients with ampullary carcinoma? Generally speaking, a single retrospective study (for instance, the current study by Ecker *et al*.) is unlikely change the clinical practice especially in the presence of conflicting data. In fact, prospective randomized clinical trials that evaluated the role of adjuvant therapy in ampullary cancer showed contrast results. In the Japanese trial, on sub-group analysis of 48 ampullary cancer patients, receipt of post-surgical adjuvant therapy with the combination therapy of 5-fluorouracil and mitomycin-C did not result in OS benefit (10). On the contrary, a subgroup analysis of ampullary cancer patients (n=297) in the European Study Group for Pancreatic Cancer (ESPAC)-3 trial demonstrated a median OS benefit of 30 months with gemcitabine as adjuvant therapy (71 *vs*. 41 months), after adjusting for prognostic variables (8). However, no benefit was reported in 5-fluorouracil arm.

Going forward, when we have controversial data from multiple studies, having a multi-disciplinary team of experts that constitutes radiologists, pathologists, gastroenterologists, medical and surgical oncologists could help in shared decision making, especially in the patients with poor prognostic features such as positive surgical margins, invasion of lymph nodes, pancreatic subtype, advanced stage or poor histological grade. The controversy about the benefits of adjuvant therapy in ampullary cancer should be discussed with the patient and their goals of care are to be taken into consideration to deliver highest quality care to our patients. In the patients who have good baseline functional status and who are willing to proceed with adjuvant therapy, clinical trial participation

should be highly encouraged. A better understanding on molecular pathogenesis and genetic aberrations implicated in ampullary cancer will hopefully open doors for precision oncology, especially in the adjuvant setting.

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Footnote

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