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HIGHLIGHT ARTICLE

Ampullary and Periampullary Tumors: Translational Efforts to Meet a Challenge in Diagnosis and Treatment

Highlights from the "2011 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 20-22, 2011

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Summary

Ampullary adenocarcinoma is a rare diagnosis and often managed as carcinomas of pancreatobiliary origin. However, there is accumulating evidence unveiling attributes of ampullary carcinomas that are distinct from that of pancreas or biliary cancers. Growing translational efforts in understanding this rare disease are exemplified by Abstracts #161 and #204 presented at the 2011 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium.

What Did We Know Before 2011 ASCO GI Cancers Symposium?

Periampullary cancers are described as carcinomas arising from structures near the ampulla of Vater (pancreas, common bile duct, duodenum, or the ampulla of Vater itself). Primary ampullary carcinoma or ampullary carcinoma refers to cancers originated from ampulla of Vater itself and is often challenging to distinguish from other periampullary carcinomas. Primary ampullary carcinomas are uncommon tumors (6 cases per million populations) and known to be associated with better overall prognosis than periampullary cancers arising from pancreatobiliary structures [1, 2, 3, 4].

Current practice pattern for primary ampullary carcinoma is to treat with active agents in pancreatobiliary cancers based on the fact that primary ampullary carcinoma patients are frequently included in trials for pancreas and/or biliary tract cancers and that there are no high quality data addressing treatment of this rare entity. However, there are growing evidence suggesting that clinicopathophysiology of primary ampullary carcinoma is closer to intestinal cancer than pancreatobiliary cancer. Histology, genetic association, and clinical outcomes have suggested primary ampullary carcinoma's similarity to carcinoma of intestinal origin rather than to cancers of pancreas or biliary tract [5, 6, 7].

Surgery (pancreaticoduodenectomy) remains the only treatment modality that offers chance for a cure. While surgical outcomes have been improving over the years (rate of potentially curative resection/R0 resection of up to 90% and less than 5% mortality rate), a significant number of patients (more than 50%) still die from disease recurrence indicating the need for effective adjuvant therapy [8]. However, there is limited evidence to support routine use of adjuvant therapy in completely resected primary ampullary carcinomas [9, 10, 11, 12]. There is no prospective trial with optimal design or adequate sample size to examine the role of adjuvant therapy in this setting. Currently available adjuvant therapy in resected ampullary cancer is based largely on the data extrapolated from pancreas cancer space or retrospective data. In this context, frequently used treatments are gemcitabine single agent (1,000 mg/m^2 on days 1, 8, and 15 every 4 weeks for 6 months) used in European Charité Onkologie (CONKO) trial or chemoradiation therapy based on Radiation Therapy Oncology Group (RTOG) 9704 (gemcitabine 1,000 mg/m^2 weekly for three weeks, followed by chemoradiation with concurrent infusional 5-FU (250mg/m^2 daily), then followed by gemcitabine alone (1,000 mg/m^2 on days 1, 8, and 15 every 4 weeks for three months) [13, 14]. Given the "dearth of evidence", it is most appropriate to refer these patients for consideration of clinical trials when it is feasible.

Key words Ampulla of Vater; Cholangiocarcinoma; Common Bile Duct Neoplasms; Drug Therapy; Gene Expression Profiling; Pancreatic Neoplasms

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In advanced setting, a generally accepted standard of therapy is gemcitabine and cisplatin combination regimen (six cycles of cisplatin 15 mg/m^2 followed by gemcitabine 1,000 mg/m^2 on days 1, 8, every 21 days) based on "The Advanced Biliary Cancer (ABC)" study of biliary carcinoma that included patients with primary ampullary carcinomas. Given a small number of patients with primary ampullary carcinoma in the study (n=20) and lack of other randomized study, optimal treatment for these patients is still debatable [15]. Similar to adjuvant setting, it is most appropriate to consider clinical trials when it is possible.

What Did We Learn at the 2011 ASCO GI Cancers Symposium?

Use of gene expression analysis of periampullary carcinomas to identify biliary-like and intestinal-like subgroups of ampullary and duodenal carcinomas (Abstract #161) [16]

Overman *et al*. examined untreated periampullary carcinoma samples (n=32) to delineate them by differences in histology (pancreas, biliary tract, intestinal, and mixed), *MSI*, *CDX-2*, *KRAS* and *PI3K* mutations. Based on the analysis of key attributes including gene expression profile, authors were able to classify ampullary carcinomas to three subgroups: pancreatic, biliary-like, and intestinal-like. Authors then correlated this classification with clinical outcome and reported a statistically significant difference in relapse free survival (P=0.03) and overall survival (P=0.04) favoring the intestinal-like subgroup over biliary-like subgroup. The study also noted a similarity between duodenal and ampullary carcinomas with respect to pathological attributes including the key gene expression profile [16]. Despite the limitations such as small sample size, authors report intriguing data corroborating existing hypothesis that ampullary carcinomas share common attributes with intestinal carcinomas that they do with pancreatobiliary cancers.

Comparison of ampullary adenocarcinomas and duodenal adenocarcinomas with regard to clinical outcomes and responsiveness to fluoropyrimidine-based chemotherapy (Abstract #204) [17]

Building upon the findings of Abstract #161 [16], Overman *et al*. examined similarity in clinical outcomes among patients with periampullary carcinomas. Using 20-year data set at M.D. Anderson Cancer Center from early 1990s, investigators identified 46 patients with resected ampullary carcinomas with M.D. Anderson Cancer Center confirmed pathology, distant metastatic recurrence, and systemic chemotherapy with either gemcitabine or 5-FU base chemotherapy as the first line therapy. This study reports that 5-year overall survival (stratified by T and N stages) of patients with ampullary carcinoma was similar to that of patients with duodenal cancer while showing a clear difference from that of pancreatobiliary carcinoma patients. Ampullary carcinoma patients who were treated with 5-FU based therapy showed statistically significant improvement in clinical outcomes, superior median time to progression and a trend toward a better median overall survival (16 months *vs*. 12.7 months; P=0.14). While the sample size is small and there is a limitation in retrospectively comparing two chemotherapies, the presented data is provocative in suggesting that more refined classification may have a significant treatment implication.

Discussion

Abstracts by Overman *et al*. add to the growing body of evidence that ampullary carcinoma is a pathophysiologically diverse entity. They also suggest clinical implications of this diversity manifested as varying prognosis and treatment outcome. Authors expose the limitations of grouping all ampullary or periampullary carcinomas in trials and practices based primarily on anatomical differences in making treatment decisions.

Overman *et al*.'s effort is in line with developing interests by researchers to go beyond anatomy and to reflect histopathological differences in describing and classifying periampullary carcinomas. Since ampulla of Vater encompasses two distinct types of mucosa (intestinal and pancreatobiliary), cancers can originate from either of two histological mucosa hence grouping them as such. These two subgroups were known to possess rather distinct immunostain patterns that allow investigators to differentiate the two in more concrete and consistent manners than traditional anatomy based approach [18, 19]. Studies also suggested that patients with intestinal types tend to have better prognosis than those with pancreatobiliary types [20].

This year's abstracts go beyond histology and incorporate a gene expression profiling technique that resulted in more comprehensive classification of ampullary carcinomas. Clinicians ought to recognize that "not all ampullary carcinomas are alike" and optimal treatment for them may significantly vary based on various attributes, including gene expression profile of their tumors. Given the rarity of this disease and poor clinical outcomes of patients even after a complete resection, more concerted efforts should be made to validate these findings and make them available for practicing clinicians.

Conflict of interest The authors have no potential conflict of interest

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