HIGHLIGHT ARTICLE

Biological Identification of Ampullary Adenocarcinomas

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ABSTRACT

Ampullary adenocarcinomas have unique biologic and clinical features that result in its improved prognosis versus adenocarcinomas that arise from the distal bile ducts and pancreas. However the histological differentiation and identification of these tumors is not easily accomplished. Two abstracts at this year's ASCO Annual Meeting describe attempts to identify unique methods for distinguishing these tumors. Abstract 4141 described a 92 gene RT-PCR assay that was used for molecular classification of patients with ampullary adenocarcinomas while abstract e15175 looked at mutational status of K-ras in patients with these tumors. The results of their abstracts will be discussed.

Introduction

Ampullary adenocarcinomas arise from the Ampulla of Vater and account for a small percentage of all gastrointestinal malignancies with rates estimated to be in the range of 0.5% [1]. This subtype of cancer maybe associated with a better prognosis as compared with adenocarcinomas arising from the distal bile ducts or pancreas. The standard treatment for these tumors remains surgical with pancreaticoduodenectomy being the most common procedure. Complete resection can translate into long term survival in approximately 50% of patients as compared to long term survival of approximately 25% in those with pancreaticobiliary cancers [2]. One of the challenges in treating these tumors arises during diagnosis and depends upon the pathologist's ability to distinguish one subtype from the other given current technology. Two abstracts at this year's American Society of Clinical Oncology (ASCO) Annual Meeting look at alternate methods for identifying and categorizing these tumors.

What Did We Know Before ASCO 2014?

The origin of ampullary adenocarcinomas can be difficult to distinguish. Two distinct pathological subtypes have been identified–one that arises from the intestinal epithelium or one that arises from the pancreaticobiliary epithelium [3]. Some studies have shown that ampullary adenocarcinomas arising from intestinal epithelial sources confer a better prognosis and selection of these patients for pancreaticoduodenectomy is the first step for long term survival [4-6]. Data suggests that biological differences in these tumors lead to a better prognosis. Attempts to identify specific molecular features of these tumors have been undertaken in order to further categorize and clarify this picture. The availability of a test that can easily differentiate between these two subtypes of ampullary adenocarcinomas is not currently available and their identification relies solely on pathological findings. Because of the difficulties in making the diagnosis and identifying these patients, practitioners may not have all the relevant clinical information necessary to make decisions with regard to how aggressive they should be with treatments or surgery. At this year's ASCO Annual Meeting two abstracts (4141 and e15175) were presented that sought to clarify this picture.

What Did We Learn at ASCO 2014?

Molecular Classification of Ampullary Adenocarcinomas

Schueneman and his group looked at the use of a 92 gene, reverse transcription - polymerase chain reaction (RT-PCR) assay and histomolecular phenotypes to try and stratify patients [7]. This prospectively defined, blinded study looked at ampullary adenocarcinoma tissue samples (n=77). Fifty-four samples met QC criteria and were analyzed. The reference diagnosis, established prior to blinding, was completed by an independent histopathological review. When used for tumor subtyping, the sensitivity of the 92 gene RT-PCR assay and histomolecular classification for the intestinal subtype were similar; however the sensitivity of the 92 gene RT-PCR assay when used for identifying the pancreaticobiliary subtype was greater than when used for the histomolecular phenotype (P=0.045). The 92 gene RT-PCR assay identified samples which were prognostic for relapse free survival (RFS) and overall survival (OS) however the histomolecular phenotyping did not. Finally when the samples were stratified based on lymph node status, the 92 gene RT-PCR assay defined three distinct

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prognostic groups for ampullary subtypes (P=0.04) while the histomolecular phenotype did not (P=0.39). This work may provide a foundation for future studies with this and other gene assays to try and identify ampullary adenocarcinoma subsets that may have prognostic and therapeutic implications.

Mutational Status of K-Ras in Ampullary Adenocarcinomas

Sitthideatphaiboon and colleagues sought to identify the prevalence of K-ras mutations in patients in Thailand who had been diagnosed with ampullary adenocarcinoma during the period of January 2006 through December of 2012 [8]. They identified 63 patients during this time frame who had histologically confirmed ampullary adenocarcinoma. Formalin-fixed, paraffin embedded tissue blocks were available for these patients. The tissues were analyzed via PCR amplification and pyrosequencing to look for K-ras mutations in codons 12 and 13. K-ras mutations were identified in 29 of 63 (46%) patients. The majority of the mutations (28 of 29) occurred in codon 12 (96.6%) versus 1 of 29 in codon 13 (3.6%). The authors then went on to try and correlate K-ras mutational status with the clinical characteristics and outcomes of the patients. They found that those patients with K-ras mutations had an overall poorer performance status, later stage disease, poorly or undifferentiated histologic grade, positive surgical margins and metastases to regional lymph nodes; however, none of these findings were statistically significant as compared to the wild type K-ras group. The OS of the whole cohort of patients was 38.34 months. Those patients with wild type K-ras had a median OS of 44.32 versus those with K-ras mutation who had a median OS of 29.93 months, though these findings were not statistically significant. While these findings are intriguing given the prevalence (46%) of K-ras mutations found in this Thai population an evaluation in a larger patient population may be more informative.

Discussion

Despite the numerous advances being made in the treatment of solid tumors, the data for optimal treatment of ampullary adenocarcinomas remains limited. Much of this paucity of data stems from the fact that ampullary adenocarcinomas are frequently combined and treated in clinical trials along with patients with biliary or pancreatic cancers. Two abstracts at this year's ASCO Annual meeting described efforts to help distinguish ampullary adenocarcinomas from other periampullary tumors. The use of a 92 gene RT-PCR assay showed promise in categorizing these tumors and for its prognostic classification. The mutation status of K-ras in ampullary tumors in Thai patients was also reported. A moderately high number of patients had K-ras mutations and although not statistically significant, the survival in these patients was reduced as compared to patients with wild type K-ras. Given the small numbers of patients in both these studies, the information they present should be read with caution. However they do represent exciting new areas for future research opportunities.

Conflict of Interest

The authors have no potential conflict of interest

References

1. West gaard A, Pomianowska E, Clausen OPF, Gladhaug IP. Intestinal-type and pancreatobiliary-type adenocarcinomas: How does ampullary carcinoma differ from other periampullary malignancies? Ann Surg Oncol. 2013; 20:430-9. [PMID:22956064]

2. Todoroki T, Koike N, Morishita Y, Kawamoto T, Ohkohchi N, Shoda J, Fukuda Y, et al. Patterns and predictors of failure after curative resections of carcinoma of the ampulla of Vater. Ann Surg Oncol. 2003; 10:1176-83. [PMID:14654474]

3. Kim WS, Choi DW, Choi SH, Heo JS, You DD, Lee HG. Clinical significance of pathologic subtype in curatively resected ampulla of vater cancer. J Surg Oncol 2012; 105:266-72. [PMID:21882202]

4. Howe JR, Klimstra DS, Moccia RD, Conlon KC, Brennan MF. Factors predictive of survival in ampullary carcinoma. Annal of Surg 1998; 228:87-94. [PMID:9671071]

5. Schultz NA, Werner J, Willenbrock H, Roslind A, Giese N, Horn T, Wojdemann M, et al. MicroRNA expression profiles associated with pancreatic adenocarcinoma and ampullary adenocarcinoma. Mod Pathol 2012; 25:1609-22. [PMID:22878649]

6. Chang DK, Jamieson NB, Johns AL, Scarlett CJ, Pajic M, Chou A, Pinese M, et al. Histomolecular phenotypes and outcome in adenocarcinoma of the ampullar of Vater. J Clin Oncol. 2013; 31:1348-56. [PMID:23439753]

7. Schueneman A, Wang H, Soifer HS, Schnabel CA, Wolff RA, Varadhachary MJ, Overman MJ. Molecular classification of ampullary adenocarcinoma: Comparative prognostic performance of the 92-gene assay versus histomolecular analysis. J Clin Oncol. 2014; 32:5s (suppl; abstr 4141).

8. Sitthideatphaiboon P, Teerapakpinyo C, Klailaew N, Tanasanvimon S, Vinayanuwattikun C, Parinyanitikul N, Poovorawan N, et al. Prevalence of KRAS gene mutation in ampullary cancer in Thai patients. J Clin Oncol. 2014; 32 (suppl; abstr e15175).