PANCREAS NEWS

Periampullary Carcinoma: Some Important News in Histopathology

Generoso Uomo

Internal Medicine Department, Unit 3, Cardarelli Hospital. Naples, Italy

Incidence of periampullary carcinoma is low, approximately 0.5-2% of all gastrointestinal malignancies and 20% of all tumours of the extrahepatic biliary tree [1, 2, 3]. Peri-ampullary carcinoma arises around the confluence of the common bile duct with the main pancreatic duct and therefore may have a different anatomical origin: at the level of the pancreatic head (60% of the resected specimens), ampulla of Vater (20%), distal common bile duct (10%) and duodenum (10%) [4]. In clinical practice, all these kind of periampullary carcinoma are joined by the occurrence that they have a higher frequency of resectability compared to the pancreatic head cancers, which represent as much as 90% of the tumours (both resectable and unresectable) of the periampullary area. The clinical picture of periampullary carcinoma is mainly related in the vast majority of patients to an early occurrence of jaundice, thus contributing to the early detection and a higher resection rate. The macroscopic appearance of periampullary carcinoma includes: a) intramural tumours – inside the ampulla, without any protrusion inside the duodenum; b) extramural tumours – polypoid tumours protruding through the ampullary orifice into the duodenum, c) ulcerative cancers of the ampulla, which is associated with the worst prognosis [5]. According to the microscopic classification, there are two main histological types of periampullary carcinoma: the "intestinal type" (similar to tubular carcinoma of the stomach or the colon and the "pancreatobiliary type" (characterized by papillary projections with scant fibrous cores) [6] Immunohistochemical staining pattern of apomucins and cyto-keratins is different for the two periampullary carcinoma histological types: positivity for MUC2, CK20, CDX2 and CD10 is typical of the periampullary carcinoma-intestinal type whereas positivity for MUC1 and CK7 is predominant in pancreaticobiliary adeno-carcinomas. Due to the rarity of this malignancy, the paucity of specific papers and the absence of prospective trials no relevant data have been available for the scientific community till the last few years. Quite recently, some articles focused on diagnostic assessment [7, 8, 9] and treatment modalities [10, 11, 12, 13, 14] have been published thus filling a lot of gaps. On this concern, some very interesting features come from recent advances in periampullary carcinoma pathology.

Key words Ampulla of Vater; Common Bile Duct Neoplasms; Duodenal Neoplasms; Histology; Pancreatic Neoplasms; Pathology

Abbreviations AJCC: American Joint Committee on Cancer; PTEN: phosphatase and tensin homolog

Correspondence Generoso Uomo
Internal Medicine Department, Unit 3; Cardarelli Hospital; Via Cardarelli, 9; 80131 Naples; Italy
Phone: +39-081.747.201; Fax: +39-081.747.2117
E-mail: gene.uomo@gmail.com

Bronsert *et al*. [15] assessed the histological subtype and immunohistochemical staining pattern for CK7, CK20 and CDX2 in 198 cases of pancreatic ductal, distal bile duct, ampullary and duodenal adenocarcinoma with clinical follow-up and survival analysis. The authors showed that intestinal subtype was associated with better survival in ampullary, pancreatic ductal and duodenal adenocarcinoma at univariate analysis. The intestinal type of pancreatic ductal adenocarcinoma was not associated with intra-ductal papillary mucinous neoplasm and could not be reliably diagnosed by immunohistochemical staining pattern alone. Intestinal differentiation and lymph node ratio, but not tumour location, were independent predictors of survival when all significant predictor variables from univariate analysis (grade, TNM stage, presence of precursor lesions, surgical margin status, perineural, vascular and lymphatic vessel invasion, CK7 and CDX2 staining pattern) were included in a Cox proportional hazards model. Therefore, these results seem to confirm that differentiation is more

important than tumour location for prognostic stratification in periampullary carcinoma. Some genetic molecular features recently published [16] seem to point out the same way. The starting hypothesis of this research was that periampullary carcinoma could have differential expression of microRNA, which may differentiate the tumour histological subtypes. The study protocol comprises examination of samples from periampullary carcinoma patients undergoing Whipple's pancreaticoduodenectomy and control samples (obtained from adjacent normal pancreas, common bile duct, duodenum and ampulla) for microRNA microarray profiling. Comparison of periampullary carcinoma tissue samples with controls revealed 29 common and differentially expressed microRNAs (20 upregulated and 9 downregulated) with a higher statistical significance (P<0.001). A subset of 16 microRNAs (15 overexpressed and 1 underexpressed) differed in expression levels between pancreatobiliary and intestinal subtypes. Differential expression profiles of microRNAs specific to TNM staging was also observed in periampullary carcinoma subtypes. Authors' conclusion was that differentially expressed common microRNA signatures identified in periampullary carcinoma subgroups may have a role in pathogenesis of periampullary carcinoma and miR-375, miR-31 and miR-196a expression patterns may differentiate periampullary carcinoma subtypes.

Another interesting contribution [17] focused on, in patients with periampullary carcinoma, the expression of phosphatase and tensin homolog (PTEN), one of the most frequently inactivated tumour suppressor genes in sporadic cancers. The study was retrospective on tissue microarrays from 92 patients who underwent pancreatico-duodenectomy. PTEN expression was evaluated by immunohistochemistry, scored semi-quantitatively (based on staining intensity and percentage positive tumour cells), and correlated with clinico-pathological features and survival. Of 92 cases, 23 (25.0%) were PTEN negative. Loss of PTEN expression correlated with lymph node metastasis (P=0.004), advanced American Joint Committee on Cancer (AJCC) stage (P=0.02), and higher frequency of recurrence (P=0.03). Patients with PTEN-negative tumours had shorter disease-free survival (mean: 89.0±20.8 months) and overall survival (mean: 93.1±19.1 months) than those with PTEN-positive tumours (disease-free survival, mean: 161.4±11.7 months, P=0.01; overall survival, mean: 175.4±11.0 months, P=0.001). In multivariate analyses, PTEN expression was a prognostic factor for both disease-free and overall survival, independent of AJCC stage, lymph node status, pathologic tumour stage, and differentiation. These results suggest that loss of PTEN expression is associated with poor disease-free survival and overall survival in patients with periampullary carcinoma after curative surgery and that PTEN expression may be used as a prognostic marker for patients with resected cancers.

Another article coming from Korea [18] addressed the topic of the epithelial-mesenchymal transition-related proteins in periampullary carcinoma by using immunohistochemical staining for E-cadherin, b-catenin, and S100A4 expression in intestinal and nonintestinal type of 105 samples from patients with periampullary carcinoma and analysed their relationships with clinicopathological variables and survival. The study includes 65 intestinal type, 35 pancreatobiliary type, and 5 other types of periampullary carcinoma. The severity of epithelial-mesenchymal transition changes differed between the periampullary carcinoma subtypes; membranous loss of E-cadherin and b-catenin was observed in nonintestinal type tumours, whereas aberrant non-membranous b-catenin expression was observed in intestinal type tumours. Epithelial-mesenchymal transition-related changes were more pronounced in the invasive tumour margin than in the tumour centre, and resulted related to tumour aggressiveness. Among the clinicopathological parameters, a desmoplastic reaction was related to overall survival, and the reaction was more severe in nonintestinal type than in intestinal type of periampullary carcinoma.

Knowledge of not knowing is the best thing; to fake to know when it is not known is a disease ... (Lao Tsu)

Conflict of interest The author has no potential conflict of interests

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