Potentially prognostic and predictive biomarkers in pancreatic and periampullary adenocarcinoma

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ABSTRACT

Adenocarcinomas of the periampullary region are a heterogeneous group of neoplasms, including tumours originating in the distal bile duct, pancreas, ampulla of Vater and the periampullary duodenum. Despite advances in surgery, radiotherapy, chemotherapy and targeted agents, patients still suffer from a poor prognosis. In pancreatic cancer, the overall 5-year survival is below 5%, all stages of the disease combined (approximately 20% in periampullary cancer), and the median survival is approximately 6 months. The incidence of these tumours has markedly increased and only 15–20% are resectable at presentation. In resected periampullary carcinoma, morphological type seems to provide more important prognostic information than tumour origin, with pancreatobiliary (PB-type) versus intestinal (I-type) differentiation being associated with significantly shorter survival rates.

The overall aim of this thesis is to find new prognostic and predictive biomarkers to better define clinically relevant subgroups, such that diagnostic and treatment strategies can be improved. The study cohort consists of a retrospective consecutive series of 175 patients with primary periampullary adenocarcinomas, surgically treated with pancreaticoduodenectomy at the University hospitals of Lund and Malmö, Sweden, between 2001 and 2011. Tissue microarrays were constructed from primary tumours and a subset of lymph node metastases. They were analysed immunohistochemically for expression of podocalyxin-like protein (PODXL), a cell-adhesion glycoprotein that has been found to correlate with an aggressive tumour phenotype and adverse outcome in several cancer types (Paper 1) and human epidermal growth factor receptors 1, 2 and 3 (EGFR, HER2 and HER3) (Paper 2).

Paper 1 shows that membranous expression of PODXL is significantly higher in PB-type than in I-type periampullary adenocarcinomas, and an independent factor of poor prognosis in the latter. The results further indicate a beneficial effect of adjuvant chemotherapy in I-type tumours with membranous PODXL expression, suggesting the potential utility of PODXL as a biomarker for improved treatment stratification of these patients [1].

Paper 2 demonstrates that EGFR expression is similar in PB-type and I-type tumours, whereas HER2 and HER3 expression is significantly higher in I-type tumours. High EGFR expression was found to be an unfavourable prognostic factor in gemcitabine-treated PB-type adenocarcinoma [2].
Publications
