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**PANCREATICODUODENAL RESECTION FOR CARCINOMA HEAD OF PANCREAS – THE INFLUENCE OF MARGIN STATUS ON SURVIVAL**

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**Aim:** To evaluate the influence of margin status on survival following resection for carcinoma head of pancreas (CaHOP).

**Methods:** A retrospective analysis of prospectively maintained database of patients undergoing a Pancreatecroduodenal resection (PDR) for CaHOP. 547 patients underwent a PDR at a tertiary care center from Jan 2001 till Dec 2013. Of these, 24 patients (4.4%) operated for CaHOP form the study material. Margins were defined as macroscopically positive (R2), microscopically positive (R1), negative margins (R0) and close margins which were less than 1mm (Rc).

**Results:** 13/24 (54.2%) patients were R0, 6/24 (25%) were R1, 3/24 (12.5%) were Rc. 2 (8.3%) patients had positive margins on intra-operative frozen section and underwent a total pancreatecroduodenectomy (TPD). 1 (4.2%) patient expired postoperatively following a classical PD. The post-operative morbidity included post pancreatoduodenectomy hemorrhage (PPH)(n=3, 12.5%), pancreaticojejunostomy (PJ) leak (n=5, 22.7%), bile leak (n=2, 8.3%) and DGE (n=4, 16.7%). The overall survival of these patients was 15.3 months. The survival following R0 resection was 15.5 months, 13.9 months for R1 and Rc resection and 20 months for TPD. Patients undergoing TPD for positive intraoperative margin on frozen section had better survival than those with R1 or close surgical (Rc) margins (20 months vs 13.9 months) though there was no statistically significant difference based on margin status of the patients because of small group size.

**Conclusion:** R1 and Rc resections fare similarly. TPD for positive intraoperative margins provides better overall survival though there was no statistically significant difference.

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EP02C-092

**A GENOME-WIDE SCREEN FOR INHERITED GENETIC VARIANTS THAT AFFECT SURVIVAL AND THERAPY OF RESECTABLE PANCREATIC DUCTAL ADENOCARCINOMA**

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**Introduction:** Although pancreatic ductal adenocarcinoma (PDAC) is an aggressive tumour, it displays a wide range of biology. However, at present, there are no reliable tests to predict patients’ cancer-specific outcomes and personalise therapy. Therefore, we aim to identify such biomarkers that can serve to individualise treatment of resectable PDAC by performing a genome-wide survival screen for single nucleotide polymorphisms (SNPs) that reside in druggable and functional coding genomic regions.

**Methods:** Two prospective independent training/validation datasets with a total of 331 consecutive patients who underwent pancreatic resection for PDAC were utilised, including a multicentre European cohort (Switzerland and Germany) and The Cancer Genome Atlas (TCGA) database. The genotypes were determined with SNP microarrays. Cox multivariate analysis was used to screen for SNPs that associate with allelic differences in tumour-related survival. OncoKB, PolyPhen-2 and Provean algorithms were utilised to search for SNPs in genes

(i) with reported therapeutic implications, and

(ii) that change the protein structure and function.

**Results:** We identify and validate SNPs, such as PTEN (SNPrs644205 A/G), that robustly associate with allelic differences in tumour-related survival in both study cohorts (up-to p=0.0004; HR=2.64). We report on the alterations of the protein sequence and the regulatory changes introduced by the identified SNPs, and describe the resulting potential therapeutic implications.

**Conclusion:** The identified polymorphisms can serve as non-invasive, potentially predictive biomarkers readily available at the time of PDAC diagnosis. These SNPs could help guide personalise therapeutic strategies, such as the treatment with PI3K inhibitors of patients who carry the A-allele of PTEN SNPrs644205.

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EP02C-093

**SMAD4 LOSS: A PREDICTOR OF WORSE TUMOR DIFFERENTIATION, EARLY METASTASIS AND SHORTER SURVIVAL IN PANCREATIC DUCTAL ADENOCARCINOMA**

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**Background:** Among the various biomarkers available in pancreatic cancer, this study aimed to analyzes whether the expression patterns of SMAD4 are correlated with metastatic potential and are predictive of clinical outcome and survival in patients with pancreatic cancer.

**Methods:** This is a prospective study conducted from March 2014 till February 2017, includes patients of pancreatic ductal adenocarcinoma who underwent surgical excision or tru-cut biopsy.
**Results:** Among forty-five patients, 33 had loss while 12 had intact SMAD4. Loss of SMAD4 carries a 1.3 times increased risk of vascular and 1.6 times risk of nodal spread. Deletion of SMAD4 was associated with poor differentiation (p=0.04, OR=5.6, CI=0.9-34.4), and increased the risk of perineural invasion by two times (OR=2.1, CI=0.1-34.8).

Thirty-three, eighteen, and five patients survived at the end of 6, 12 and 24 months respectively. Analysis revealed statistically significant association between SMAD4 loss and survival at six months (p=0.04), 12 months (p=0.01) and 24 months (p=0.007). Among the operated patients (n=19), eleven patients developed recurrence during follow-up, period. all had loss of SMAD4 (p=0.03).

The hazard ratios for poor tumor differentiation and SMAD4 loss were 5.8 (95% CI=1.2-28.4, p=0.02) and 6.7 (HR=6.7, 95% CI=1.9-23.3, p=0.002) respectively. The SMAD4 intact and loss group had median survival of 19.5+ months (95% CI=15.4-23.7) and 9.3+1.0 months (95% CI=7.3-11.4) respectively, confers a survival advantage of 10 months (p=0.002, CI=-4.1 to -0.9).

**Conclusion:** Loss of SMAD4 is strongly associated with poor tumor differentiation with risk of metastasis at presentation. The overall survival is significantly influenced by the loss of SMAD4 and poor tumor differentiation.

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**CIRCULATORY TUMOR CELLS OF PORTAL VENOUS SYSTEM IN CASE OF PANCREATIC CANCER AS A PREDICTIVE AND PROGNOSTIC INDICATOR OF METASTATIC PROGRESSION AND OVERALL SURVIVAL**

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**Background:** Pancreatic cancer (PC) is one of most common, aggressive and potentially lethal oncological disease. PC builds up ~3% of oncological burden and is a cause of mortality in 7% of cancer cases. Standard diagnostics of PC is CT, although in the last years endoscopic ultrasonography (EUS) is a helpful tool in management of small and borderline tumors. In situation of borderline cases more information should be acquired before the appropriate treatment is chosen. Nowadays "liquid biopsy" of the venous system can assist in circulatory tumor cell (CTC) verification in case of PC. The prognostic value of CTC is still investigated. Central blood samples are proved to be more informative and specific than peripheral.

**Methods:** In a single-center cohort study 16 patients with suspected PC were evaluated. In all cases CT scan was done. Open laparotomy with or without pancreaticoduodenal resection was performed in 14 patients with acquisition of liquid biopsy from portal system. EUS guided transhepatic needle aspiration of portal vein was performed in 2 cases. Peripheral blood samples were obtained in both groups, sizes of the both samples were 10 mL.

**Results:** In 10 cases ductal adenocarcinoma was found in histological or cytological examination. In 3 cases neuroendocrine tumor was found. In another 3 cases pancreas cystadenoma was confirmed. Central and peripheral blood samples of 10 ductal adenocarcinoma cases were further analysed by InCell and NGS methods. In all cases positive liquid biopsy was verified. 9 out of 10 patients have died in 6 months after the surgery.