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P-142 Early gastric cancer: Identification of molecular markers able to distinguish penetrating lesions with different prognosis


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Background: Early Gastric Cancer (EGC) represents 25% of the gastric cancers surgically treated and is usually characterized by a good prognosis (5-year survival > 90%). However, some patients show a significantly worse prognosis. In particular, among penetrating EGCs classified according to Kadoma’s criteria, Pen A tumors are characterized by extensive submucosal invasion, lymph node metastases, and worse prognosis, whereas Pen B tumors seem to be associated with a better prognosis.

The aim of the study was to characterize the differences between Pen A, Pen B and locally advanced gastric cancers (T3N0) in order to identify biomarkers involved in aggressiveness and clinical outcome of such tumors.

Methods: Formalin-fixed paraffin-embedded (FFPE) tissues were obtained from 87 patients (33 Pen A, 34 Pen B, and 20 T3N0 tumors), matched for age, gender and lymph nodes status. Mucins analysis (MUC2, MUC6, MUC1AC) was performed by immunohistochemistry; copy number variation (CNV) analysis by multiple ligation-dependent probe amplification (MLPA); TP53 mutational status by Sanger sequencing; TP53 loss of heterozygosity (LOH) and microsatellite instability (MSI) evaluations by fragment analysis.

Results: MUC6 expression significantly distinguished Pen A and Pen B tumors, being overexpressed in 33.3% and 2.9% of the two subgroups, respectively (p = 0.014). CNV evaluation of PIK3CA, EGFR, CDK4, MET, GATA4, FGFR1, MYC, PTPA4A, FGFR2, CCND1, KRAS, KLF5, ERBB2, TOP2A, GATA4, and CCNE1 genes showed that amplification was the most frequently observed alteration, but the only gene that was significantly different between tumor groups was the GATA4 gene (p = 0.002), amplified in 33.3% and 66.7% of Pen A and Pen B, respectively. The evaluation of MSI showed no significant differences between Pen A and Pen B. Finally, TP53 gene analysis showed that 34.0% of Pen tumors have a mutation in TP53 exons 5-8 and 38.5% has LOH, suggesting the early onset of alterations of this gene in gastric carcinogenesis. No differences between Pen A and Pen B tumors were observed in terms of TP53 mutation frequency and site of mutation, even if a different frequency of TP53 missense variants was detected (78% of Pen A and 67% of Pen B tumors). Preliminary data showed that TP53 mutation and LOH co-occur mainly in Pen A tumors with respect to Pen B (p = 0.001).

Conclusion: Overall, our analyses revealed that clinicopathological parameters, microsatellite status and frequency of TP53 mutations do not seem to distinguish Pen A and Pen B tumors. Alternatively, the overexpression of gastric mucin MUC6 significantly characterized Pen A tumors, as well as the amplification of the GATA4 gene was associated with Pen B tumors. The co-occurrence of TP53 mutations and LOH in EGC needs further investigations.

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P-144 Inflitranib versus gemcitabine plus cisplatin as first-line therapy in patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations: phase 3 PROOF trial


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Background: Treatment options for metastatic or unresectable cholangiocarcinoma are limited with a need to provide increased disease control, improved outcomes, and targeted therapy that is less toxic than standard chemotherapy. As the understanding of the molecular landscape of cholangiocarcinoma has increased, the fibroblast growth factor receptor (FGFR) family has been found to play an important role in cholangiocarcinoma. FGFR translocations (i.e. fusion events) represent driver mutations in cholangiocarcinoma. They are present in 13-17% of intrahepatic cholangiocarcinomas (iHC) and may predict tumor sensitivity to FGFR inhibitors. Inflitranib (BGJ398) is an ATP-competitive, FGFR1–3 selective oral tyrosine kinase inhibitor that demonstrated excellent preliminary anti-tumor activity in patients with relapsed/refractory cholangiocarcinoma with FGFR2 fusions/translocations in a phase 2 study (ClinicalTrials.gov identifier: NCT01773020).

Trial design: PROOF is a multicenter, open-label, randomized, controlled, phase 3 trial. Patients with previously untreated advanced/metastatic or inoperable cholangiocarcinoma with FGFR2 gene fusions (determined by local CLIA-certified and central laboratory) are randomized 2:1 to oral inflitranib 125 mg once daily for 21 days of a 28-day treatment cycle versus intravenous standard gemcitabine (1250 mg/m²) * cisplatin (25 mg/m²) on days 1 and 8 of a 21-day cycle. Treatment will continue until confirmed progressive disease by clinical review, intolerance, withdrawal of informed consent, or death. Patients assigned to the gemcitabine + cisplatin arm who progress can cross-over to inflitranib. The primary endpoint is overall survival (OS), free of progression and death (PFS, RECIST v1.1 by blinded central review). Secondary endpoints include overall survival, PFS (investigator determined), overall response rate, disease control rate, duration of response, and safety. Quality of life, pharmacokinetics and exploratory genetic and/or alterations/biomarkers will also be assessed. The trial will have sites in the US, EU, and APAC, including Australia. The target population size is 384 patients. Recruitment started in December 2019, and the study has an estimated primary completion date of September 2023.
Background: Oxaliplatin containing chemotherapy is known to induce HSOS, which is also expressed by its appearance as blue liver syndrome. HSOS has been reported to affect treatment outcomes. However, the assessment of its severity solely depends on laboratory findings of hepatic indices, and the quantitative evaluation of HSOS is not sufficient in clinical use. The purpose of this study is to construct a non-invasive prediction model for HSOS by applying radiomics which provides a comprehensive quantification of CT image textures.

Methods: We retrospectively analyzed 32 colorectal cancer patients treated in our hospital from November 2011 to May 2017. There were 16 males and 16 females with a mean age of 64.3 (38-81). These 32 pts consisted of two sub-groups; 16 HSOS-positive pts with abnormal hepatic indices who underwent oxaliplatin containing chemotherapy, and 16 HSOS-negative pts with normal hepatic laboratory findings who did not have any oxaliplatin chemotherapy. The whole liver was semi-automatically delineated. 38 radiomic features were extracted by LiFEx software (www.lifexsoft.org). Feature extractions were performed, first by a univariate analysis with Wilcoxon rank-sum test, followed by multivariate logistic regression analysis with a stepwise feature-reduction. ROC [receiver operating characteristic] analysis was performed to generate the radiomic signature for the assessment of HSOS.

Results: The radiomic signature demonstrated high discriminatory performance in predicting HSOS with an area under the curve (AUC) of 0.949 with a sensitivity of 93.75% and specificity of 93.75% (P< 0.001).

Conclusion: A prediction radiomic model for HSOS was generated successfully.

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