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Mutational analysis by next generation sequencing in patients with biliary and pancreatic adenocarcinoma

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Purpose/Objective: In this retrospective study, next-generation exomic sequencing (NGS) was utilized in biliary and pancreatic adenocarcinoma samples to identify potential novel therapeutic targets that are not routinely assayed in the clinical setting.

Materials and Methods: Patients with confirmed pancreatic adenocarcinoma or cholangiocarcinoma were selected based on availability of tissues. A total of 236 somatic genes were surveyed in this review, including 3,230 exons and 47 introns at >900x mapping coverage. NGS reports were generated from 2011 to 2013 and reviewed retrospectively. Statistical analysis was performed using univariate analysis and Kaplan-Meier survival estimates.

Results: Seventeen (95%) of cases harbored at least one potentially actionable mutation, including BRCA (10.5%), CDKN2 (26.3%), FGFR (15.8%), KRAS (42.1%), MLL (26.3%), NRAS (5.3%), PIK3CA (10.5%), and TP53 (42.1%). Notably, KRAS mutations were found at a higher frequency in pancreatic adenocarcinomas in comparison to cholangiocarcinomas (87.5% vs 9.1%). Overall, the most frequent genomic alterations were found within KRAS (42.1%), TP53 (42.1%), CDKN2 (26.3%), and MLL (26.3%). All patients with SMAD alterations were also found to have concurrent KRAS mutations, which is consistent with reported literature. KRAS mutations most commonly involved codon 12, while the locations of SMAD and Tp53 mutations were heterogeneous. In addition, concurrent mutations were found within genes that have been shown to potentially modulate or interact with KRAS-mediated signaling pathways, including CCND3, CDKN2A/B, and RB1. Alterations of BCOR, CCND3, CRKL, NF1, STK11, and TSC1 were rare events (<6%). Furthermore, 95% of patients had multiple, novel mutations that have not been associated with pancreatic or biliary adenocarcinoma. The majority (63.2%) of patients had greater than five mutations identified. Median survival and 5-yr OS in pancreatic adenocarcinoma were 30.1 months and 41%, respectively. 5-yr OS in cholangiocarcinoma cases was substantially higher (85.7%), and 27.2% of these patients received EBRT as a component of their treatment. For either subset of patients, there was no significant correlation between number of mutations and OS. Overall, 63% of patients were found to have mutations associated with targeted therapies. One quarter of these patients possessed multiple, concurrent molecular targets for which FDA-approved chemotherapeutic agents are currently available. **Conclusions:** Novel mutations were identified in the majority of patients, including mutations within a number of genes which have the potential to influence KRAS-mediated signaling, as well as other prominent signaling pathways. These results could potentially serve to identify targets for novel chemotherapeutic agents and to guide personalized, combinatorial therapy in appropriately selected patients.

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Comparative study failure model esophageal carcinoma with elective nodal regional and involved field irradiation

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Purpose/Objective: The aim of this study is to compare the failure model between esophageal carcinoma patients receiving elective nodal prophylactic irradiation and involved-field irradiation, and to explore the reason of failure and influence factors of local recurrence.

Materials and Methods: From January 2006 to December 2012, 245 patients of esophageal carcinoma receiving definitive radiation therapy in our hospital were respectively analyzed. One hundred and twenty-six patients received elective nodal prophylactic irradiation (ENI), and the other 119 patients received involved-field irradiation (IFI). Failure patterns were analyzed after treatment and long-term follow up. Local regional failure included esophagus lesion remaining or relapse and regional lymph nodes recurrence. Distance metastases included distant organ metastases and distant lymph node metastases. Multivariate analysis was performed by the Cox proportional hazard model. **Results:** The 1, 3 and 5 years loco-regional control rates of ENI group and IFI group were 72.5%, 52.8%, 50.6% and 58.4%, 35.8%, 21.9% ($\chi^2=7.881, P=0.005$) respectively. The 1, 3, and 5 years overall survival rates of the ENI group and IFI group were 74.3%, 44.2%, 24.5% and 68.9%, 27.6%, 15.9% ($\chi^2=1.903, P=0.168$). In Cox multivariate analysis, clinical T stage, tumor location, different radiotherapy region were independent factors for the loco-regional control of all patients. One hundred and sixty-three patients developed failure after treatment and follow-up. Simple loco-regional failure was observed in 92 patients, alone distant metastases was observed in 36 patients, and both regional failure and distant metastases was observed in 35 patients. The 1, 3, and 5 years total failure rates of ENI group and IFI group was 35.4%, 62.5%, 69.0% and 46.5%, 71.5%, 81.5% respectively ($\chi^2=4.402, P=0.036$). The 1, 3, and 5 years loco-regional failure rates of ENI and IFI group were 29.9%, 48.4%, 50.0% and 39.6%, 62.1%, 71.4% respectively ($\chi^2=8.638, P=0.003$). **Conclusions:** The elective nodal prophylactic irradiation of esophageal carcinoma with receiving definitive treatment could reduce loco-regional failures and improve local control. Maybe in order to improve the long-term survival.

PO-0698

Clinical outcomes of 4D CBCT-guided stereotactic body radiotherapy for inoperable hepatocellular carcinomas

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Purpose/Objective: To report the clinical outcomes of patients with inoperable hepatocellular carcinoma (HCC) receiving 4D cone-beam CT (4D CBCT) guided stereotactic body radiotherapy (SBRT) using lipiodol as tumor surrogate. **Materials and Methods:** From Jan-2012 to Dec-2013, thirty

patients with inoperable HCC (N=30) received single trans-arterial chemoembolization (TACE) followed by volumetric-modulated arc radiotherapy (VMAT)-based SBRT applying the van Herk margin recipe with mid-ventilation concept. Doses of SBRT were individualized according to normal tissue constraints. Tumor localization was performed by 4D CBCT using lipiodol as surrogate. Tumor responses were assessed by CT images using RECIST criteria every 3 months in the first year. In-field recurrence was defined as recurrence within the high-dose region (80% isodose volume). Overall survival, progression-free survival and local control rates were evaluated by the Kaplan-Meier method. Toxicities were graded according to CTCAE version 4.

Results: Median follow-up time was 12 months (range: 4.2-30.6 months). Patients' characteristics were as follows: Median age (61 years, range: 28-87); Male/ female (n= 28/2); Child-Pugh class A/B (n= 28/2); ECOG 0-1/2 (n=21/9); BCLC stage A/B/C (n= 2/14/14); TNM stage I/II/III/IV (n=10/0/17/3); Solitary/ Multifocal (n=20/10); Portal vein thrombosis (n=8). Median size of tumor was 12.7cm (range: 4.4-19.7cm) and Median GTV size was 937cc (range: 81-3218cc). Median dose (2Gy equivalent, a/b=3) was 75Gy (range: 56-140Gy). Overall objective response rate was 67% (CR: n=1, PR: n=19). The 1-year in-field control, overall survival (OS) and progression-free survival (PFS) rate was 86%, 65% and 42% respectively. Median survival not yet reached. Treatments were well tolerated. No grade 4-5 toxicities were observed. Most common grade 3 toxicities were elevation of liver enzymes (n=6, 20%) and thrombocytopenia (n=1, 3%). No patient developed radiation-induced liver disease (RILD).

Conclusions: 4DCBCT guided SBRT using lipiodol as surrogate for tumor localization is feasible for inoperable HCC patients. It is safe, well tolerated and achieves high in-field control rate.

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Pleural and pericardial effusion after neo-adjuvant chemoradiotherapy followed by surgery for esophageal cancer

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Purpose/Objective: Neo-adjuvant chemoradiotherapy (neo-CRT) followed by surgery is currently the standard curative treatment for esophageal cancer. Both modalities may cause serious toxicity and morbidity. The aim of this study was to evaluate the incidence of pleural and pericardial effusion after neo-CRT followed by surgery and to investigate the impact on quality of life (QoL).

Materials and Methods: Patients, that were included in a prospective trial to evaluate the impact of PET/CT for radiotherapy planning, underwent routine CT scanning during follow up in order to evaluate tumour recurrences. All these follow up CT's were blindly reviewed by a radiologist for signs of pleural and/or pericardial effusion. The degree of

these toxicities was categorized as minor, moderate or severe. QoL questionnaires (EORTC QLQ-C30) were part of this follow up as well and were used to evaluate the impact of pleural and/or pericardial effusion. To investigate the relationship between pleural or pericardial effusion and the different domains of QoL a ANOVA was used. Results: Seventy-one patients were treated with neo-CRT and underwent routine CT scanning during follow up in absence of known recurrence and insufficient physical condition. The disease free survival (DFS) was 79%, 59% and 52% at 6, 12 and 18 months after neo-CRT. At that time, 50, 42 and 35 patients underwent follow up CT's. Pleural effusion occurred in 25 patients (50%) at 6 months and reduced over time; 33% at 12 months and 31% at 18 months. The degree was minor, moderate and severe in 11, 10 and 4 patients at 6 months. At 18 months severe pleural effusion was still present in 3 patients (9%). Pericardial effusion was seen in only 3 patients (6%) and completely reduced over time; 2.4% at 12 months and 0% at 18 months. Both pleural and pericardial effusion seemed of non-malignant origin, except for one patient with progressive malignant pleural effusion. Pleural effusion had a significant impact on physical functioning (p=0.001) and significantly enhanced dyspnoea (p=0.02). The mean score for physical functioning was 69 (SD: 26.3) in patients with pleural effusion vs. 82 (SD: 14.3) in absence of pleural effusion. Furthermore, pericardial effusion was significantly related to decreased global health status (39 vs. 75, p

Table 1.

| Toxicity and QoL scales | Mean scores | | |
|-----------------------------|-----------------|------------------|------------------|
| | No | Yes | p-value |
| Pleural effusion | | | |
| Global health status | 75 (15.2) | 75 (17.2) | ns |
| Physical functioning | 82 (14.3) | 69 (26.3) | <0.01 |
| Dyspnoea | 25 (26.3) | 38 (31.6) | 0.02 |
| Pericardial effusion | | | |
| Global health status | 75 (15.8) | 39 (4.8) | <0.01 |
| Physical functioning | 78 (19.0) | 15 (3.9) | <0.01 |
| Dyspnoea | 28 (26.7) | 100 (0.0) | <0.01 |
| Overall | | | |
| | 6 months | 12 months | 18 months |
| Global health status | 69 (18.0) | 78 (14.2) | 77 (13.9) |
| Physical functioning | 71 (24.0) | 81 (18.9) | 85 (14.2) |
| Dyspnoea | 38 (31.6) | 24 (24.0) | 25 (27.7) |

Conclusions: Pleural effusion is frequently observed after neo-CRT followed by surgical resection and improved over time and persisted up to 18 months pleural in 31% of the patients. Pericardial effusion is less common. Both pleural and pericardial effusions have a significant impact on QoL in terms of decreased physical functioning and increased dyspnoea.

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Fluoromisonidazole-PET/CT in pancreatic cancer: moving towards hypoxic biological target volume definition

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