Serum miR-345-5p predicts pathological response to chemoradiotherapy in locally advanced rectal cancer

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Purpose or Objective: Neoadjuvant chemoradiation(nCRT) has been represented as the standard treatment for locally advanced rectal cancer(LARC). Tumor pathological responses and radiotherapeutic sensitivity alter variously. We aimed to explore the predict value of serum circulating miRNAs, which have already been certificated as potential therapeutic predictors in many cancers for the pathological responses and radiosensitivity after nCRT in LARC patients.

Material and Methods: Six fresh tumor biopsy samples of T3-4/N+ rectal cancer patients were collected before any treatments and these samples were classified as radiation sensitive and resistant groups according to the postoperative pathological analysis assessed by Mandard TRG scale(3 samples of TRG1 vs 3 samples of TRG4). The two groups were strictly matched by clinical features. miRNAs expression profile of the two groups were analyzed by microarray. Predictive value of radiotherapeutic sensitivity of the candidate miRNAs was further validated by 160 serum samples of LARC patients.

Results: 19 miRNAs were identified to have different expression profile between radiation sensitive and resistant groups by microarray analysis (p<0.05). Among these miRNAs, nine miRNAs were down-regulated and ten were up-regulated in radiation sensitive group. miR-345-5p was identified significantly correlated with radiation resistant to nCRT and appeared highly discrepant expression between the two groups (fold change>2). Low expression of miR-345-5p in serum predicted superior pathological responses and radiosensitivity after nCRT (TRG1/2) (AUC=0.69, p<0.001) and favorable LRFS (p=0.02).

Conclusion: Serum level of miR-345-5p is associated with favorable pathological responses to neoadjuvant chemoradiotherapy and local-regional control ratio in LARC patients. It presents as a promising biomarker to predict the radiotherapy sensitivity and prognosis.

PO-0718
The significance of postop CEA after preoperative CRT followed by TME in advanced rectal cancer
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Purpose or Objective: To evaluate the significance of postoperative carcinoembryonic antigen (CEA) level as a predictor for tumor recurrence and as a prognostic factor for survival in locally advanced rectal cancer patients treated with preoperative concurrent chemoradiation followed by curative surgery

Material and Methods: Total 1559 rectal cancer patients staged with cT3-4N0-2M0 received pelvic preoperative chemoradiotherapy (CRT) 50.4 Gy in 28 fractions followed by total mesorectal excision (TME). CEA levels were measured before CRT and after surgery. Clinicopathologic factors which could be associated with tumor recurrence and survival were analyzed.

Results: The cumulative probability of the tumor recurrence showed a steep increase with a cutoff value of 2.5 ng/mL for postoperative CEA, and the gradient decreased as postoperative CEA levels increased above 2.5 ng/mL. After median follow-up time of 46.7 months, patients with postoperative CEA level of >2.5 ng/mL had significantly lower relapse-free survival (75.6% vs 65.2%, p<0.001) and overall survival (88.3% vs 78.1%, p<0.001) at 5 years than patients with CEA level of<2.5 ng/mL. In the multivariate analysis, postoperative CEA level is the only significant prognostic factors of relapse free survival (HR=1.561 and 95% CI=1.221-1.996, p<0.001) and overall survival (HR=2.073 and 95% CI=1.498-2.869, p<0.001). Increased pre-CRT CEA level is not a significant prognostic factor with consideration of postoperative CEA in multivariate analysis. The postoperative CEA level above 2.5 ng/mL is a significant predictor for distant recurrence (OR=1.689 and 95% CI=1.188-2.402, p=0.004), but not for local recurrence (OR=0.776 and 95% CI=0.389-1.549, p=0.472).

Conclusion: Postoperative CEA level above 2.5 ng/mL is a predictor for tumor recurrence and a negative prognostic factor for survival in rectal cancer patients who received preoperative CRT and curative surgery. Physician can consider intense surveillance after curative resection in these patients.

PO-0719
Target delineation of anal cancer based on MR or PET - an inter-observer, inter-modality study
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Purpose or Objective: Anal cancers are treated by definitive chemoradiotherapy of the primary tumor and pelvic nodes. Although survival is high (5y 75%), locoregional recurrence occurs in 24% of patients. Patients are mostly treated with IMRT and VMAT, and therefore precise dose delivery is important. For target volume delineation typically either PET or MRI is used together with planning CT, but practice varies between institutions. In the current work, we aim to investigate the variability between imaging modalities and oncologists with respect to target volume delineation based on either PET/CT or MRI/CT information.

Material and Methods: Twenty patients with anal cancer referred to chemoradiotherapy were prospectively included. Written informed consent was obtained from all patients and the regional ethics committee approved the study. Prior to therapy, patients underwent a planning CT scan, a PET/CT scan with 18FDG and T2 and diffusion weighted MRI scans at a 3T scanner. At the treatment planning station (Varian Eclipse), all images where co-registered to the planning CT scan. Three oncologists delineated the Gross tumor volume (GTV) independently of each other twice for each patient, once with medical records and images blinded for MRI information, and once blinded for PET information. The CT image information was always available. A randomization scheme of the order of the anonymized patients was used during delineation to minimize intra-observer bias. All volumes were exported from the treatment planning system, analyzed by calculating the DICE coefficients and compared with the Wilcoxon Signed-rank test.

Results: The median volume of the GTV was respectively 27.5 cm³ and 31.0 cm³ for PET and MRI, and there was a high correlation (r=0.94) between the volumes. The DICE coefficient (minimum, median, maximum) was 0.43, 0.81, 0.93 and 0.50, 0.75, 0.89 for PET and MRI. These DICE distributions were significantly different (P=0.03). Half of the patients with low DICE (<0.7) for PET, also gave low DICE for MRI, this indicated difficulties with delineation irrespective of imaging modality. For inter-modality comparison (PET to MRI for same observer), the DICE coefficient was 0.31, 0.75, 0.92, with a significant difference in distribution relative to the inter-observer distribution.

Conclusion: PET and MRI produced similar GTV volumes for radiotherapy planning of anal cancer. However, PET has a significantly lower inter-observer variability in terms of the DICE coefficients. Still, the deviations between PET and MRI were not substantial and may not translate into clinically meaningful differences. This is also supported by the relatively high inter-modality DICE coefficients. Thus, radiotherapy target delineation for anal cancer is performed quite consistently among observers and is not strongly dependent on whether PET or MRI is used.

High tumour glycine concentration - an adverse prognostic factor in locally advanced rectal cancer
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Purpose or Objective: In locally advanced rectal cancer (LARC), further advances in individualised treatment approaches require identification of robust biomarkers. Although metabolic reprogramming has been regarded essential for cancer cell proliferation, the systematic characterisation of activated metabolic pathways in aggressive cancer is scarce. Hence, by recognising the link between altered tumour metabolism and disease aggressiveness, we aimed to identify associations between pretreatment tumour metabolic profiles and therapeutic outcome in LARC.

Material and Methods: Tumour metabolic profiles were acquired from 54 LARC patients, receiving induction neoadjuvant chemotherapy followed by long-course chemoradiotherapy and surgery, by using high-resolution magic angle spinning magnetic resonance spectroscopy. Metabolite concentrations were correlated to TNM and presence of disseminated tumour cells (DTC) at time of diagnosis, and to ypTN and tumour regression grade (TRG) following the neodjuvant treatment. All patients had either reached 5 years of follow-up or were scored with a progression-free survival (PFS) event at time of analysis. The performance of metabolite concentrations in prediction of PFS was assessed by receiver operating characteristic curves. Univariate Cox regression assessed associations between selected variables and PFS; those being significant were entered into multivariate analysis. Survival differences were assessed by the Kaplan-Meier method.

Results: Pretreatment tumour metabolite concentrations showed no significant associations to TNM, DTC, ypTN or TRG. In univariate regression analysis, high concentrations of glycine, creatine and myo-inositol were significantly associated to poor PFS, with distant metastasis to the lung and/or liver being the main PFS event (87.5% of events). When separating patients above and below the identified cut-off concentrations the respective estimated 5-year PFS were 85% and 50% for glycine, 74% and 29% for creatine and 81% and 50% for myo-inositol. In multivariate analysis, high glycine concentration remained most significantly associated to poor PFS (hazard ratio = 4.4, 95% confidence interval = 1.4-14.3, p = 0.008).

Conclusion: High tumour glycine concentration was identified as adverse prognostic factor for PFS in LARC. In a patient population treated with curative intent but with metastatic disease as main PFS event these results motivate further investigations of glycine as early predictor of metastatic progression and as potential therapeutic target.

Impact of sentinel lymph-node biopsy on staging and treatment in patients with anal cancer
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Purpose or Objective: Anal cancers are treated by definitive chemoradiotherapy of the primary tumor and pelvic nodes. Although survival is high (5y 75%), locoregional recurrence occurs in 24% of patients. Patients are mostly treated with IMRT and VMAT, and therefore precise dose delivery is important. For target volume delineation typically either PET or MRI is used together with planning CT, but practice varies between institutions. In the current work, we aim to investigate the variability between imaging modalities and oncologists with respect to target volume delineation based on either PET/CT or MRI/CT information.