Baseline expression of RAD23B protein in circulating tumor cells correlates with complete pathological response of neoadjuvant chemoradiotherapy for locally advanced rectal cancer

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Background: The pivotal IDEA trial showed marginal differences in survival outcomes for 3 vs 6 months of adjuvant chemotherapy (ACT) in stage II and III colon cancer (CC). Severe treatment toxicity was substantially lower in the short treatment regimen. Therefore, in 2017 the Dutch colorectal cancer (CRC) guideline was revised and currently recommends 3 months of oxaliplatin (OK)-based ACT. In addition, the definition of high-risk stage II CC was restricted to include only pathological T4 (pT4) tumors (instead of presence of poor differentiation, lymph node harvest or involving organ invasion) to increase these rates. The objective of this prospective study was to analyze whether the protein expression of RAD23 homolog B (RAD23B) in the circulating tumor cells (CTCs) at baseline could correlate with the response to NCRT.

Methods: Between 2016 and 2020, 63 patients (pts) with LARC who underwent NCRT followed by radical surgery, were included in the study. Blood samples were collected before the beginning of NCRT (CT1) and the evaluation of RAD23B protein expression in CTCs was correlated with the anatomicopathological examination of response of patients undergoing surgery (n=56). CTCs were isolated and quantified by ISET®. RAD23B protein was analyzed by immunocytochemistry and visualized by bright field microscopy.

Results: The mean age was 56 years old (34-92). Among the pts analyzed, 34 (54%) carried tumors at the distal rectum, 57 (90%) had clinical tumor stage (cT) T3/T4, 58 (92%) clinical nodal (cN) positive and 32 (52%) had preoperative carcinoembryonic antigen (CEA) >3 ng/mL. Thirteen (23.2%) patients had pCR with NCRT. RAD23B expression in CTCs was present in 54% of non-responders, while in pCR group, it was absent in the majority of pts (91.7%; p = 0.019). In multivariable logistic regression models for pCR, including CEA, gender, cT and RAD23B expression in CTCs, the latter was an important independent prognostic factor [Odds Ratio (OR) 0.064; 95% confidence interval (CI): 0.006 – 0.751; p = 0.029].

Conclusions: This prospective study demonstrated the correlation between the absence of expression of RAD23B in CTCs (C1) and pCR, being an important result for future clinical studies. This analysis may identify NCRT responders candidates, helping to choose the best therapeutic approach for each individual.

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Translation of the IDEA trial into clinical practice: Evaluation of implementation of a new guideline

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Background: The presence of preoperative systemic inflammatory response (SIR) is an established negative prognostic factor for patients diagnosed with colorectal cancer (CRC). C-reactive protein (CRP) is known to be implicated in detrimental immune responses. The biological differences between right-sided and left-sided CRC are

Results: Of all patients receiving ACT (n=8,170), the proportion treated with CAPOX increased from 75% in 2015/2016 (before guideline revision) to 83% in 2018/2019 (after guideline revision). Intravenous S-fluorouracil containing ACT was administered in 5% of patients in 2015/2016 and decreased to 2% in 2018/2019. Mean duration of ox-based ACT decreased from 18.6 ± 8.0 weeks in 2015 to 9.5 ± 3.8 weeks in 2019. The proportion of patients receiving ACT was stable over time, 61-69% in stage III and 26-29% in pT4 stage II. ACT in patients with previous high-risk pT4N0 disease decreased from 15% to 3% before and after guideline revision. At the same time the use of ox-based ACT increased from 27% to 49% in patients ≥ 75 years old.

Conclusions: The revised Dutch CRC guideline, recommending 3 months of ACT and restriction of ACT in stage II to pT4N0 C, was rapidly implemented in clinical practice. The shortened duration of ACT led to an increase in elderly patients that received ox-based ACT.

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Chemoradiation versus less intensive treatments in stage I squamous cell carcinoma of the anal canal (SCCA)

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Background: Patients (pts) with stage I SCCA are underrepresented in randomized trials of chemoradiation (CRT). While most pts are cured with CRT, this may lead to significant acute and long-term adverse events. Thus less intensive treatments (LT) for these pts could be as effective and less toxic than CRT. We compared the outcomes of real-world stage I SCCA pts treated with CRT versus LT.

Methods: Retrospective study using the population database of FOSP (Fundação Onco-Centro de São Paulo), which collects epidemiological and outcomes data on cancers from 77 hospitals across the state of São Paulo, Brazil. Pts with stage I SCCA were eligible. The primary endpoint was to compare disease-free survival (DFS) times between pts treated with CRT (radiation plus chemotherapy with or without adjunctive surgery) and LT (only surgery, radiation or chemotherapy, or surgery and radiation). DFS were compared with the log-rank test and adjusted by a Cox regression model. Logistic regression was used to evaluate factors associated with LT.

Results: From 2000 to 2020, 171 out of 2,401 SCCA pts had stage I tumors and were included. The median time from diagnosis to treatment was 67 days, 131 (76%) was female, median age was 59 years (35 – 90); 100 pts (58%) received CRT and 71 (42%) LT, with 98 (57%) being treated in the public system. In a median follow up of 43 months, 21 (12.2%) pts recurred (12 in CRT and 9 in LT). Median DFS was 39.2 and 24 months for CRT and LT (p=0.57), respectively. Either treatment type (CRT vs LT), sex, age or time from diagnosis to treatment initiation 60 days were associated with DFS. After controlling for sex, health care setting (insurance/private vs public) and treatment location (within or outside (residential city), age 70 years was associated with receipt of LT (OR: 2.34; 95% CI: 1.15 – 4.87; p = 0.019). There was also no difference in DFS (p=0.52) in the subgroup treated with CRT (79) or radiation only (17).

Conclusions: In this large study of real-world stage I SCCA pts, LT was more likely to be offered to older pts and was not associated with inferior DFS when compared to CRT. An organ-preserving LT, such as radiotherapy with or without a fluoropyrimidine, can be considered to older pts with stage I SCCA who are ineligible for CRT.

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The clinical value of C-reactive protein and its association with tumour sidedness in patients undergoing curative surgery for colorectal cancer: A Scotland collaborative study


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Background: The presence of preoperative systemic inflammatory response (SIR) is an established negative prognostic factor for patients diagnosed with colorectal cancer (CRC). C-reactive protein (CRP) is known to be implicated in detrimental immune responses. The biological differences between right-sided and left-sided CRC are
gaining increasing attention. Our aim was to analyse the prognostic value of CRP and explore the association between tumour sidedness and SR.

**Results:** Increasing levels of CRP were associated with impaired overall and cancer-specific outcome. Presence of SR was independently associated with right-sided tumour location (OR [95% CI] 1.19, 95% CI 1.07-1.31). The impact of SR on cancer-specific survival was greater for left-sided tumour location (hazard ratio [HR] 1.50, 95% CI 1.18-1.92), compared to the right (HR 1.28, 95% CI 1.00-1.64).

**Conclusions:** This study confirms CRP as an easy, valid and clinically relevant strong prognostic marker of SR in CRC patients. Right-sided tumours were more often associated with SR, but the prognostic impact was stronger in left-sided tumours.

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**406P** Prognostic value of neoadjuvant rectal score in patients with locally advanced rectal cancer after neoadjuvant chemoradiotherapy


**Background:** Neoadjuvant chemoradiotherapy (NACRT) is a standard treatment for patients with clinical stage II/III rectal cancer. Recently, neoadjuvant rectal (NAR) score was suggested as an independent prognostic factor after NACRT for rectal cancer. The aim of this study was to evaluate the prognostic value of NAR score in patients with locally advanced rectal cancer (LARC) who received NACRT followed by surgery.

**Methods:** We performed a univariate, retrospective, consecutive case series analysis of the patients with LARC who received NACRT followed by surgical resection between January of 2016 and December of 2019. NAR scores were calculated using the equation [5yph3(CT-Typ)+7]/9.61 and classified as low (<8), intermediate (8-16) and high (>16). Clinicopathological data and survival outcomes were analyzed and correlated between NAR score and disease-free survival (DFS) were performed with the Kaplan-Meier method and compared by log-rank test.

**Results:** A total of 110 patients were analyzed, 58.2% male and 41.8% female patients, with a median age of 65 years old (36-83) at the time of diagnosis. The median NAR score was 8.4 (0-65.1). Considering the NAR score classification, 35 (38.5%) had low, 52 (57.2%) had intermediate and 23 (25.2%) had high NAR score. The median observation period was 32 months (4.7-62.7). Higher NAR score was associated with higher tumor regression grade (TRG (p<0.001) and higher ypT/NM stage (p<0.001). The 5-year DFS was 81% for low, 71% for intermediate and 41% for high NAR score groups. For high NAR score group the median DFS was 4.17 years (95% CI 0.53 – 7.82). A statistically significant difference in DFS was observed between the three NAR groups (p=0.002), but there was no significant difference in DFS stratifying according to the TRG classification (p=0.229).

**Conclusions:** Our results suggested that NAR score could be useful in predicting DFS following NACRT and surgery for LARC. TRG is a histological measure of score tumor response to NACRT and is associated with survival outcomes in literature. However, in our study there was no association between TRG and DFS. Although our data suggest that NAR score might be a predictor of DFS further studies are needed.

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**407P** Neoadjuvant chemo-radiotherapy response in patients affected by mismatch repair deficient (dMMR) locally advanced rectal cancer


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**Background:** Only few data on microsatellite instability in rectal cancer are available in literature, and dMMR role in pre-operative chemoradiotherapy response is under debate. The aim of our study was to evaluate the frequency and therapeutic implications of dMMR status in patients (pts) with locally advanced rectal cancer belonging to our Center.

**Methods:** Data were retrospectively collected from 201 pts belonging to the Medical Oncology Unit of the University Hospital of Cagliari from 2014 to 2020. All pts were affected by locally advanced rectal adenocarcinoma (cT3-4 +/- N1-2). All pts included in the study underwent neoadjuvant chemoradiotherapy treatment with capecitabine and cetuximab and RT long course (total dose of Gy 50-4) and subsequently underwent total mesorectal excision (TME) followed by adjuvant chemotherapy. Mismatch repair (dMMR) expression was evaluated through immunohistochemistry on surgical samples.

**Results:** Pts median age was 67 years (range 34-89); 130/201 were male and 71 were female. 62 (31%) had stage II disease and 139 (69%) had stage III disease. Considering MMR, 195/201 (97%) pts had proficient mismatch repair (pMMR), while 6/201 (3%) had dMMR. In dMMR pts defective proteins were: MSH2 in 3 patients, MLH1 and PMS2 combined in 2 pts and MS6H in 1 pt. dMMR pts showed, unlike pMMR pts, poor or no response to chemoradiotherapy. Responses were assessed through TRG evaluation (Ryan and Dworak scoring systems) on the primary tumour: 4 pts presented a TRG-3 and 2 pts presented a TRG-4, according to Ryan score. All of them had a grade 1 regression, according to Dworak. (Table)

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