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Molecular profiles provide clinical meaningful outcome prediction in stage II colon cancer

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Adjuvant chemotherapy for stage II colon cancer patients with an overall 5-year survival of 80%, has never shown benefit in randomized clinical trials. Three-fourth of patients are cured by surgery alone and therefore, less than 25% of patients would benefit from additional chemotherapy. The identification of the subgroup of patients that are more likely to suffer from a recurrent disease would therefore allow the identification of patients who are more likely to benefit from adjuvant chemotherapy. We have identified by full-genome molecular expression profiling and hierarchical clustering of tumor tissue in a series of 121 stage II and III adjuvantly untreated colon cancer patients, two molecular subgroups that have distinct clinical outcome. For stage II colon cancer patients this results in a cluster of 75% of the patients with ~90% 5-year distant metastasis-free survival, and a second cluster encompassing the remaining 25% of the patients with ~65% 5-year distant metastasis-free survival, logrank p-value <0.001. In a multivariate analysis the molecular profile subgroups are the main significant factor associated with outcome of disease (HR 3.2, 95% CI 1.4−7.0). Moreover, the molecular subgroups outperform the ASCO recommendations for adjuvant chemotherapy selection in outcome prediction. A subset of 100 genes identified by supervised classification shows equally well outcome prediction. Genes involved are known to regulate the Epithelial-Mesenchymal transition (EMT). Importantly, we validated this gene set for outcome prediction in an independent colon cancer publicly available data set (JCO 23, 3526, 2005). In these stage II colon cancer patients the 5-year metastasis-free survival prediction was confirmed; for the good profile subgroup this is 90%, and for the poor profile subgroup 40%, respectively. Identification of the molecular poor survival subgroup allows tailored treatment advice for adjuvant chemotherapy for those patients that would benefit.

Oral presentations (Wed, 26 Sep, 09.00−11.00)
Gastrointestinal malignancies – colorectal cancer (2)

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Acute adverse events in a randomised trial of short course versus long course preoperative radiotherapy for T3 adenocarcinoma of rectum: a Trans-Tasman Radiation Oncology Group trial (TROG 01.04)

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Background: The primary aim of this trial was to compare the efficacy of short course (SC) and long course (LC) preoperative radiotherapy, both of which are considered standard of care for rectal cancer in different countries. This report describes the acute adverse events (AE) and tolerability of these treatment programs.
Materials and Methods: Patients with ultrasound- or MRI-staged T3 adenocarcinoma of rectum within 12 cm of the anal verge and with no evidence of metastasis were randomised to either SC (25 Gy in 5 fractions in 1 week followed by surgery the following week and 6 courses of postoperative 5FU and leucovorin) or LC (50.4 Gy in 28 fractions, with continuous infusion 5-FU followed by surgery in 4 to 6 weeks and 4 courses of postoperative 5FU and leucovorin).
Results: The trial was closed to accrual in May 2006 after 326 patients had been accrued from 27 Australian and New Zealand centres. All SC patients received 25 Gy; 93% of LC patients received 50.4 Gy and 77% received 5FU within 5% of the planned dose. During the preoperative treatment period only one patient experienced a grade 4 AE (CTC, ver 2.0). Grade 3 AEs, for SC and LC, respectively, were: radiation dermatitis 0% and 5.5% (P = 0.016), proctitis 0% and 3.7% (P = 0.016), nausea 0% and 3.1% (P = 0.031), and fatigue 0% and 3.7% (P = 0.016). Grade 3/4 diarrhoea rates were 1.3% and 14% (P < .001), including only one grade 4 AE. The percentages of patients experiencing one or more grade 3/4 AEs were 1.9% (SC) and 28% (LC) (P < .001). Among LC patients 5.6% required chemotherapy dose reduction, 11% experienced central venous catheter problems, and 9.3% did not complete the infusion due to AEs. Fifty-one percent (SC) and 49% (LC) experienced surgical complications, including anastomosis breakdown after low anterior resection (7.1% and 3.5% [P = 0.26] of which approximately 60% healed with conservative treatment), and deep vein thrombosis (3.2% and 1.2% [P = 0.26]). There were three treatment-associated deaths in each arm. Of patients available to receive postoperative chemotherapy, 7.2% (SC) and 11% (LC) did not receive it owing to health or treatment-related AE reasons (P = 0.25).
Conclusions: Both short course preoperative radiotherapy and long course preoperative chemoradiation are well tolerated with expected AE rates. There is no clear evidence that rates of surgical complications or deliverability of postoperative chemotherapy differ between the two arms.

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Abdominoperineal resection and not distance, gender or age associated with circumferential resection margin involvement in a pooled analysis of five large European randomised clinical trials on rectal cancer (n = 5187)

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Introduction: The aim of this study is to identify factors associated with the decision to perform an abdominoperineal resection (APR). Furthermore, it is tested whether the type of surgery itself is associated with circumferential resection margin (CRM) involvement.
Method: Primary data from the Swedish rectal cancer trial (SRCT, n = 1176), TME trial (n = 1861), CAO/ARO/AIO-94 trial (n = 823), EORTC 22921 trial (n = 1011) and Polish Rectal Cancer Trial (n = 316) were pooled. Eligible patients, with a T3−4 tumour, without distant metastases at time of surgery, treated with low anterior resection (LAR) or APR were selected (n = 3609). The following factors were studied in a multivariate logistic regression for their association with the decision for an APR: gender, age and distance of the tumour to the anal verge. Trial and randomisation arm were entered as adjustment. To study whether an APR itself or the factors resulting in the decision to perform an APR were associated with CRM involvement, a multivariate propensity score analysis for prediction of CRM involvement was performed (microscopic or macroscopic tumour in the resection margin; not available for SRCT). From the logistic regression for type of surgery a propensity score was calculated as the predicted likelihood to undergo an APR or LAR given gender, age and distance. In the analysis of CRM, this propensity score and type of surgical resection were entered.
Results: Male gender (OR 1.43), older age (respectively OR 1.36 and 1.53 for age 60−69 and ⩾70 years compared with age <60 years) and tumour location <5.0 cm from the anal verge (OR 20.81 compared with ⩾5.0 cm) were associated with an increased likelihood to undergo an APR. An APR was associated with a positive CRM (OR 2.62, p < 0.001), whereas the factors associated with the choice of an APR were not (p = 0.65 for the propensity score).
Conclusions: An APR was more often performed in distal tumours and in male, older patients. The APR resection itself, and not the factors that usually drive the decision to perform an APR, was associated with a non-radical resection. These findings indicate the necessity to improve the radicality of the APR procedure. Besides, it illustrates the importance of proper preoperative imaging to plan the surgical resection.