Overall, based on preclinical observation that mTOR is involved in the resistance of trastuzumab, clinical programs have been developed that will determine whether everolimus could improve outcome in patients with Her2-overexpressing breast cancers.

249 INVITED

mTOR an Attractive Drug Target in Breast Cancer: How to Reverse Resistance to mTOR Inhibitors

Abstract not received

Scientific Symposium (Mon, 26 Sep, 09:00−11:00) **Tailored Neoadjuvant Therapy in Rectal Cancer**

250 INVITED

Tailored Preoperative Treatment According to Initial Staging and Biology Predictors

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Recent developments in imaging techniques allow us to more adequately stage our patients prior to the start of treatment. With endoscopic ultrasound it is possible to distinguish early stage tumours from more advanced tumours. Patients with T1sm1/sm2 without adverse prognostic factors (differentiation grade, lymphovascular invasion) can be treated with TEM (Transanal Endoscopic Microsurgery). MRI is a prerequisite for accurate staging of more advanced rectal cancers. Phased array MRI is very reliable in predicting CRM (Circumferential Resection Margin) involvement. Also extramural depth of spread and the presence of vascular invasion can be assessed on phased array MRI and are important factors in determining treatment strategy. Diffusion Weighted-MRI is very promising in rectal cancer, not only as a staging tool (prediction of lymph node involvement) but also as a way to predict the prognosis of patients. The ADC (Apparent Diffusion Coefficient) values before the start of treatment seem to be a prognostic marker with tumours having a low ADC value at the start of treatment doing better. A low ADC value before the start of treatment might be indicative of a better oxygenation status of the primary tumour. Oxygenation status has been shown to be an important prognostic and predictive factor in many tumour sites. However, these findings need validation in larger, preferentially multicenter studies. Also FDG-PET might have a prognostic value with higher SUV's (Standardized Uptake Value) being correlated with worse prognosis. Other tracers still need further study. Depending on the staging patients can be classified as having good, bad and ugly tumours. Also the location of the primary tumours (low, middle, high) plays a role in the decision on the most appropriate treatment approach. The preoperative treatment should be adapted accordingly varying from a short course radiation to a long course of radiation combined with chemotherapy. Several attempts have been made to integrate targeted agents into the preoperative treatment. So far, none of these have proven to be successful. This can partly be explained by the absence of molecular selection criteria for patients that are most likely to benefit. In the face of current and future schedules and the increasing number of therapeutic options, translational research is urgently needed for the identification of patients, by both clinicopathological features and molecular markers who will gain maximum benefit from more intensified treatment.

251 INVITED

Tailored Therapy During Neoadjuvant Treatment

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CRT has been reported to induce significant tumour downsizing and downstaging, with a pathologic complete response (pCR) after CRT observed in 10 to 30% of patients. Although some studies showed no correlation, a recent pooled analysis of radio(chemo)therapy randomized confirmed that patients showing a pCR following preoperative CRT have improved long-term outcomes including excellent local control rates and disease-free survival, regardless of their initial clinical T- and N-stages.
Molecular imaging along the treatment seems to be predictive of outcomes in some studies. The evaluation of the SUV(max)-based RI calculated after the first 2 weeks of RCT provided in 30 rectal cancer patients the best predictor of pathological treatment response, reaching AUCs of 0.87 and 0.84 for the TRG and the ypT stage, respectively.
Studies on radiobiological parameters like number of tumour stem cells, intrinsic radiosensitivity, and number of radiobiologically hypoxic tumour cells appear when analyzed in animals after two week of therapy seem promising to predict outcome after fractionated irradiation.
Possible implication of the evaluation of the response along the treatment in the reduction or intensification of the ongoing therapies are reported.

252 INVITED

Tailored Surgery According to Clinical Response

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The surgical treatment of rectal cancer is based on the removal of the rectum enveloped in it's mesorectal fascia. In case of successful surgery the specimen will be covered with this shining fascia and it is easy for the pathologist to determine if the resection was radical and if the tumour was removed with sufficient margins. If quality of surgery is poor as a result of breaching the mesorectal fascia and/or tearing the mesorectal fat, chance of exposing the tumour to the resection margin is high, and subsequent risk for local recurrence is also high. Another reason for a high chance of local recurrence or even irresectability is when the tumour invades or perforates the mesorectal fascia (T4).
It is obvious, that the surgeon should plan or, if you like, tailor his resection according to the extension of the tumour. Therefore preoperative imaging should delineate the tumour borders from the other soft tissues of the pelvis with a high resolution. Only two techniques can do so: for very early rectal cancer endoluminal ultrasound can be used, but for most tumours a high resolution MRI is mandatory. In all cases where a local excision is an option endoluminal ultrasound should be complemented by an MRI, as suspicion for lymphnode metastases can not be evaluated with ultrasound. (Further workup should include assessment of distant metastatic disease, preferably with CT scan of thorax and abdomen: the presence of mets can influence the surgical treatment plan).
Surgery is always part of a multidisciplinary treatment plan. Even if no neoadjuvant treatment is necessary, all patients should be discussed before commencement of any treatment in a multidisciplinary panel. Modern neoadjuvant treatment is effective in reducing the chance of local recurrence, even after radical resections. In resectable tumours, even when the margin is not involved a short course of radiotherapy will reduce the chance of local recurrence. However, some patients will not benefit from short course of radiotherapy (early T stage and stage 2 patients) and even experience a worse outcome. On the other hand neoadjuvant long course of treatment may be necessary to downsize and downstage an advanced tumour. After this, restaging may demonstrate, that threathened margins no longer are threathened and a standard TME approach has become possible, or that in T4 cases the extent of involvement of surrounding tissues has become less and a more limited extended procedure is possible. Again, MRI plays an important role. In selected cases, downstaging and downsizing will permit an organ preservation local excision.
Concluding: Definitive surgical treatment is the result of a multidisciplinary team discussion. This discussion will take into account operative risks of the patients due to age and comorbidity, extent and possible response to neoadjuvant treatment, need for more extended than TME resection, or quite the opposite chance of organpreservation.

253 INVITED

Tailored Adjuvant Chemotherapy According to Pathological Response (?)

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As opposed to colon cancer the available data from randomised trials for rectal cancer investigating the value of adjuvant chemotherapy in addition to preoperative radio(chemotherapy; RCT) and surgery are limited. Its therapeutic value in patients with a pathological complete response (pCR) after RCT is an even more controversial issue: A recently published pooled analysis of 3105 individual patient data having undergone RCT and total mesorectal excision in 14 different studies revealed a 5-year disease-free survival (DFS) of 83.3% for patients with pCR ($n = 410$) and 65.6% for those without pCR ($n = 2265$; $HR = 0.44$; $p = 0.0001$). The corresponding 5-year overall survival (OS) rates were 87.6% vs. 76.4% (unadjusted $HR = 0.44$; $p < 0.0001$). A multivariate analysis confirmed other independent risk factors associated with recurrence or death, including pT4, positive lymph nodes and type of surgery; the administration of adjuvant chemotherapy did not have a favourable effect on DFS: In the subgroup of patients with pCR the HR for adjuvant chemotherapy was 0.88 (95% CI 0.39–2.02). Apart from the wide confidence interval for this finding, which precludes definitive conclusions about the benefits of adjuvant treatment, it should be kept in mind that 1) most of the trials included in this analysis were non-randomised and/or retrospective studies, 2) there were differences in tumour stage, 3) different RCT regimens were used, 4) pCR assessment might not have been uniform in all studies, and 5) not all patients, predominantly those with pCR (only 39%) received adjuvant chemotherapy. Furthermore, since significantly more patients with