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 (?)

W. Scheithauer[1]. [1]*University of Vienna, Department of Internal Medicine I, Vienna, Austria*

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

pCR had lower T-stage tumours at baseline, which implicates a lower risk of incomplete resection and distant metastases, simply the latter fact might have been the reason for an improved long-term outcome.
In conclusion, rectal cancer patients with a pCR after having undergone combined RCT and surgery have a better long-term prognosis than those with residual disease. Conclusions about the benefit of adjuvant chemotherapy in these patients are difficult to make. Until further evidence is available, the treatment decision should be based on risk factors for local or distant recurrence including pretreatment staging and the response to chemoradiation.

254 INVITED

Tailored Follow-up According to Staging

Abstract not received

Scientific Symposium (Mon, 26 Sep, 09:00−11:00) **Non-Small Cell Lung Cancer − Advanced Disease**

255 INVITED

Targeting Galectin-1, a Hypoxia Induced Protein, in Non-Small Cell Lung Cancers

A. Banh[1], J. Zhang[1], H. Cao[1], D. Bouley[2], S. Kwok[3], C. Kong[3], A. Giaccia[1], A. Koong[1], Q. Le[1]. *[1]Stanford University, Radiation Oncology, Stanford CA, [2]Stanford University, Comparative Medicine, Stanford CA, [3]Stanford University, Pathology, Stanford CA, USA*

Non-small cell lung cancer (NSCLC) is a highly lethal disease. Despite dose escalation with conformal radiotherapy (RT) in combination with modern chemotherapy, there is still a significantly high rate of intrathoracic failure and poor overall survival in patients with locally advanced disease. A novel approach is needed to improve RT and chemotherapy effectiveness in these tumours. We have previously demonstrated that hypoxia does exist in NSCLC though to a lesser extent than head and neck cancer. Using proteomic analysis, we identified Galectin-1 (Gal-1) as a hypoxia-regulated protein at the level of secretion in several cancer cell types, including NSCLC. Galectin-1 (Gal-1) is a secreted carbohydrate binding lectin that is well known for its role in modulating T-cell homeostasis. More recently, it has been shown to play a major role in cancer progression. It is expressed in many cancers, including NSCLC, where increased Gal-1 expression is closely associated with larger tumours, more nodal metastasis and lower overall survival. In human head and neck cancer, expression of Galectin-1 was inversely related to intratumoral T-cell level and correlated with prognosis. Mechanistically, Gal-1 has been implicated in several pathologic processes including tumour proliferation, adhesion, migration, angiogenesis and enhancing T-cell apoptosis, which can, in turn, can confer tumour immunity. In addition to hypoxia, Gal-1 secretion was also enhanced by RT, raising the hypothesis that it may counteract RT effectiveness in cancers.
Applying a combination of down-regulating Gal-1 in a non-NSCLC cell line and knocking-out the gene in host mice, we show that tumour-derived Gal-1 is more important than host-derived Gal-1 in promoting tumour growth and spontaneous metastasis. Further mechanistic studies suggested that Gal-1 mediated its tumour promoting function by enhancing intratumoral T-cell death while protecting hypoxic tumour cells from apoptosis. Clonogenic studies also showed that Gal-1 down regulation increased radiation sensitivity in these cells, especially under hypoxia. Based on these data, it is logical to evaluate Gal-1 as a new target in NSCLC in combination with radiation and chemotherapy.

256 INVITED

Intensity Modulated Radiotherapy: Fixed-Beam and Arc Delivery Techniques for Locally Advanced Disease

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Increasing tumour sizes have long posed a challenge to the delivery of curative irradiation, as large fields increasing the radiation doses to critical normal organs such as the healthy lung. Historically, some European centers consider primary tumours exceeding 6−8 cm in diameter as being 'incurable' by radiation. A previous review considered the following groups of patients as being at high risk for toxicity of concurrent chemo-radiotherapy as their radiotherapy plans would involve excessive lung irradiation [Senan 2005], including patients with metastases in the contralateral hilus, those with peripheral lower lobe lesions with contralateral upper mediastinal nodes and large retro cardiac tumours with nodal metastases. At present, the availability of intensity-modulated radiotherapy (IMRT) routinely allows many such patients to undergo full-dose concurrent chemo-radiotherapy to 66 Gy or higher, while ensuring compliance with normal organ constraints specified in the EORTC recommendations for delivery of high precision thoracic radiotherapy [DeRuysscher 2011].
Intensity-modulated radiotherapy (IMRT) was introduced in the 1990's, and essentially involves dividing each large radiation beam into numerous small beamlets, with adjustments to the intensity of each beamlet individually. IMRT provides greater flexibility in controlling each beam, ultimately improving dose distributions and reducing toxicity. Traditionally, IMRT that is delivered using fixed beams and also requires more beams (5−9) for delivery of each fraction than for conventional radiotherapy. Some IMRT techniques can prolong the time that a patient spends on the radiotherapy machine and decreasing patient throughput. Furthermore, an IMRT can result in a larger volume of normal tissue receiving low doses of radiation. Recently, arc therapy, including Tomotherapy and fast volumetric modulated arc therapy, has emerged as a technique to address some of the limitations of fixed-field treatments. In contrast to fixed-field IMRT, arc therapy incorporates rotation of the beam relative to the patient while the beam is on. In most cases, the patient is treated from all angles, in one or more 360-degree rotations. The major conceptual advantage of arc therapy over standard fixed-field IMRT techniques is that since the radiation source is rotating around the patient, all angles are available to deliver radiation to the target while avoiding critical structures, and time is used efficiently because the radiation delivery does not stop in between different beam angles.
While IMRT clearly represents an improvement radiotherapy delivery, the learning curve has been exposed by reports of fatal lung toxicity in patients whose plans failed to limit volumes of healthy lung receiving doses in the range of 5−15 Gy. Furthermore, IMRT has allowed for increasingly larger tumour volumes to be treated to high doses, leading to concerns about sub-acute and late in-field toxicity, particularly esophageal toxicity. An update of the clinical toxicity data will be provided. As larger tumours are associated with an increased risk of distant metastases, the patterns of disease relapse following such IMRT approaches are of key interest. Finally, it is essential to ensure that all other aspects of target definition using multi-modality imaging, and of the so-called image guided radiotherapy delivery, are optimized when using IMRT. Typical clinical examples of how large stage III NSCLC tumours undergo this treatment scheme used will be provided.

257 INVITED

Integrating Systemic and Radiation Therapy in Locally Advanced Tumours

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Concomitant chemoradiotherapy (CCRT) has been established as the treatment of choice in patients fit to receive it, with a 4.5% survival benefit over sequential chemoradiotherapy (SCRT) at 5 years, and a 5 year survival of 15% in a meta-analysis of 7 trials and over 1200 participants. Current trials addressing ways to improve this outcome include studies of dose escalation, prophylactic cranial irradiation, cetuximab, different chemotherapies, vaccines and technical radiotherapy changes with IMRT, 4D planning and incorporation of CT-PET into radiotherapy planning.
However, these attempts to further intensify an already aggressive treatment will affect only a small proportion of those with stage III NSCLC. In line with a similar review of practice in Maastricht between 2002−5 [1], a review of patients seen in our centre with stage III NSCLC from 2004−8 identified 992 patients with stage III disease, of whom 59 had surgery, 105 radical radiotherapy (RRT), 133 CCRT and 138 SCRT. Two and 5 year survivals were 50% and 22% with CCRT, 30% and 8% with SCRT, and 17% and 3% with RRT. Less aggressive treatment was associated with increasing age (CCRT median 61 years, SCRT median 68 years and RRT median 75 years) and decreasing performance status (CCRT 0% PS 2, SCRT 12% PS2, RRT 29% PS2).
While considerable research continues on patients receiving CCRT, a greater focus is required on those not deemed fit for CCRT. This might include radiotherapy dose escalation where 66 Gy in 24 fractions is known to be safe, a renewed interest in altered fractionation which meta-analysis suggests may confer a small survival benefit, randomised trials of low dose concomitant chemotherapy and trials of targeted agents.
Substantial improvements have been made in those patients with stage III NSCLC fit to receive CCRT, although the large majority will still die from their lung cancer. Those not fit for CCRT have been largely ignored in research and studies are needed. The results for patients with stage III disease unfit for chemotherapy, a group growing because of the aging demography of this disease, have improved little in the last 25 years.

References

[1] de Ruysscher D et al., Ann Oncol. 2009;20:98–102