Symposia

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Pathology of local recurrence and occult axillary lymph node metastases

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The initial part of this talk will concentrate on local recurrence after breast conserving treatment for invasive carcinoma. There are three main mechanisms of local recurrence: arising from residual disease at the site of local excision, intramammary metastasis and new primary. New primaries tend to occur later and have a better prognosis. Tumour at the margins of the excision specimen is associated with increased risk of local recurrence, but the significance of tumour close to the margin is uncertain. Extensive ductal carcinoma in situ appears not to be important if the margins are negative. Vascular invasion and clinical factors, including age and treatment, are also associated with local recurrence. Histological grade and tumour size may have a role, but lymph node status does not appear to be important. There are no ideal studies with large patient numbers, long follow-up and high quality prospective pathology, so the relative importance of the above factors in determining local recurrence is uncertain. Local recurrence after breast conserving treatment appears to be independently associated with distant metastases and poor survival. The nature of the relationship between local and distant recurrence is difficult to assess because of competing risks. Local recurrence may be a marker of aggressive disease or distant metastases may arise from local recurrence. Margins are the major pathological risk factor for recurrence in ductal carcinoma in situ, with grade and extent of less importance. Axillary lymph node status has traditionally been regarded as the most important prognostic factor in invasive carcinoma, but about 25% of node-negative patients will develop distant metastases. One approach has been to look for nodal metastases missed by conventional assessment. The definition of such 'occult' metastases is controversial. There are a number of pitfalls in the assessment of occult metastases. Although some studies have found an effect on univariate analysis, there is little evidence that occult metastases are an independent prognostic indicator. Thus the current evidence does not support the routine use of special techniques such as immunohistochemistry or RT-PCR. Trials in progress may provide useful information. Other factors including histological grade and primary tumour size are however of proven value in node-negative patients. Occult metastases in sentinel nodes may have a role in predicting involvement of non-sentinel nodes.

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Surgical input to local control and axillary staging

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Surgical treatment remains the most influential factor in achieving local control. Appropriate surgery alone (be it mastectomy, or wide-local excision) results in local control in over 80% of cases. The local recurrence rate can be further reduced by use of radiotherapy. Local therapy matters as recurrences may be inoperable and are psychologically damaging. Newer techniques of radiotherapy administration may reduce the side effects of radiotherapy and reduce the time burden for the patient.

Knowledge of the axillary status of the patient remains important in decision making but the widespread rush to sentinel node biopsy may not be in the patient's best interest. A negative sentinel node result in the hands of a properly trained surgeon indicates a greater than 96% chance of no further axillary disease. The management of the patient who is found to have an involved node at the time of sentinel node biopsy remains controversial and trials have yet to establish whether good control can be achieved with axillary radiotherapy alone or whether further surgery gives better control.

Breast reconstruction following mastectomy does not lead to an increased incidence of local failure, providing radiotherapy is given if indicated. Breast reconstruction must be performed in such a way as not to delay radiotherapy.

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The role of radiotherapy

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Radiotherapy in the treatment of breast cancer has evolved considerably during the last two decades. It has now become the standard part of the breast conserving procedure, as well as in patients who underwent mastectomy with an increased risk on local recurrences. In the meantime, the technical possibilities resulted in a new more effective and less damaging treatment method.

In several clinical trials, it was shown that the relapse rate in the ipsilateral breast is reduced with a hazard ratio of four if whole breast irradiation is given after tumorectomy. The update of the Oxford meta-analysis demonstrated that this improvement in local control has also led to an improved survival in these patients. More information is recently gained on the required radiation dose in breast conserving therapy. Especially patients less then 50 years of age have to be treated with a high radiation dose, 50Gy + 16 Gy boost, while a dose of 50 Gy in 5 weeks seems sufficient for patients older than 50 years, who have a microscopically complete excision. Further optimization of the radiotherapy technique is found in imaged guided approaches and intensity-modulated radiotherapy. Combining these efforts allows for a more precise delivery of the radiation dose to a limited volume, so that the side effects like fibrosis will be reduced.

Partial breast irradiation, instead of whole breast irradiation, is now being tested in a few randomized trials. Although this approach may be useful in certain patients groups, it still cannot be accepted as standard treatment, as no proper selection criteria exist and no long term follow up data have been presented.

Further improvements are explored by better imaging of the tumor area and development of predictive arrays, i.e. micro-array to predict the need and dose of radiotherapy.

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The influence and impact of chemotherapy on local control (incl. the problem of sequencing)

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Adjuvant systemic therapies decrease the risk for loco-regional- and distant relapses. These therapies also reduce breast cancer mortality and improve overall survival, being valid both for pre- and postmenopausal patients, both for axillary lymph node positive and negative disease. This strategy will result in overall major beneficial effects, but many patients will be overtreated and some will relapse despite given therapies, being undertreated. Loco-regional radiotherapy reduces loco-regional relapses and improves breast cancer survival, but the overall survival implications have by some been considered to be more controversial, while the therapy increased the risk for late cardio-vascular mortality. This increased risk is by many considered to be due to less optimal radiotherapy techniques. Based on retrospective analyses of 5352 patients included in several randomised studies by the International Breast Cancer Study Group tumour size, grade, vascular invasion and number of nodes were risk factors for local recurrence in patients receiving different chemotherapy regimens and/or tamoxifen, but no primary loco-regional radiotherapy after mastectomy. Similarly, Eastern Cooperative Oncology Group analysed the loco-regional failure rate in 2016 patients participating in studies with adjuvant chemotherapy with and without tamoxifen, but with no addition of primary radiation. This group found an increased risk for local recurrence for tumour size, few examined nodes and number of positive nodes together with oestrogen receptor negativity. Randomised studies by the Danish Breast Cancer Group have revealed an important overall survival benefit from adding up-front loco-regional radiotherapy to a less optimal CMF regimen and tamoxifen for a too short period, respectively. Taken together, systemic therapies decrease the risk for loco-regional failures, but for certain risk groups loco-regional radiotherapy must be added, while

systemic therapy alone will result in inferior results. Many investigators support the use of radiotherapy after the completion of chemotherapy. The recent and rapid development and application of the microarray technology for identification of patients at risk for relapse should also be focused on identifying those patients who have tumours tending to relapse only locally versus systemically aiming at tailoring the up-front therapy more optimally.

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Epidermal Growth Factor Receptor (EGFR) therapies in colorectal carcinoma - the European data

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EGFR is expressed or upregulated in 60-85% of CRC and its expression is associated with poor survival. The two most extensively evaluated therapeutic approaches targeting the EGFR signalling pathway are the use of monoclonal antibodies (mAb) and tyrosine kinase inhibitors (TKI). Cetuximab is a chimeric mAb that specifically binds to the EGFR. Two US phase II non-randomised studies, conducted in patients with advanced CRC refractory to irinotecan and fluorouracil based chemotherapy, have shown an objective response rate (ORR) of 22.5% when combined with the same dose and schedule of irinotecan and ORR of 10.5% when cetuximab was used as monotherapy. A large European multicentre randomised study was performed comparing combination of cetuximab and irinotecan with cetuximab monotherapy in the same patient population. 218 patients were randomised to the combination arm and 111 to the monotherapy arm. Baseline characteristics were balanced with 63% of patients had prior oxaliplatin exposure. The ORR was 22.9% (95% confidence interval [CI]: 17.5-29.1%) in the combination arm and 10.8% (95% CI 5.7-18.1%) in the monotherapy arm and this difference in ORR was significant (p=0.0074). ORR in both arms were similar in those with prior oxaliplatin treatment and appeared to correlate with the occurrence of skin reaction, although no correlation was seen with the intensity of immunohistochemical EGFR staining on tumour samples. In addition, time to tumour progression was significantly longer in the combination arm compared to the monotherapy arm (median 4.1 months vs. 1.5 months respectively; log rank p

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EGFR inhibitors in the treatment of lung cancer

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Epidermal Growth Factor Receptor (EGFR) is commonly overexpressed in a number of epithelial malignancies and is often associated with an aggressive phenotype (e.g. non-small cell lung cancer (NSCLC), bladder cancer). EGFR is present in over 50% of cases of NSCLC, head & neck squamous cell carcinomas (HNSCC) and colon cancer. Several EGFR-targeting agents have been recently developed (C225, ABX-EGF, E7.6.3, EMD 55900, ICR62, ZD1839, CP358774, PD168393, CGP75166/PKI166, CGP59326A, BIBX1382). The 2 most advanced EGFR inhibitors in development are C225 (CetuximabTM) and ZD1839 (IressaTM). C225 is an antibody directed against the ligand binding domain of human EGFR, which competes for receptor binding with EGF and other ligands. In vitro, CetuximabTM inhibits EGFR tyrosine kinase (TK) activity and proliferation of EGFR-overexpressing squamous cell carcinoma cell lines. Synergy was observed with doxorubicin, cisplatin and radiation in preclinical models. In phase I trials, major toxicity has been dermatological (rash and acneic skin reactions); allergic reactions have also been observed in about 3% of cases. This agent, administered iv. weekly, is presently in phase III trials in HNSCC and colon cancer. IressaTM, a synthetic molecule which targets the EGFR ATP binding site, is a very specific inhibitor of EGFR TK activity. Synergy has been observed with paclitaxel and cisplatin. In phase I trials, responses were seen in advanced NSCLC, and cutaneous toxicity and diarrhea were the most important side effects. Oral chronic administration daily is feasible. Two large randomized trials have been completed in advanced NSCLC in combination with chemotherapy. A large phase II study in second and third line has demonstrated a single agent activity of 18.5%. Another large phase II study in patients who received prior platinum and docetaxel obtained a response rate of 11%. There was no difference in response rate between the 250 and the 500 mg/day doses, but side effects were higher in patients who received the 500 mg dose. A very similar small molecule, OSI-774 (Tarceva), has also shown activity in this setting. Two large randomized phase III studies of Iressa have recently been completed and analyzed in which 2 doses of Iressa (250 or 500 mg/day) or placebo were given in combination with 2 different chemotherapy regimens (carboplatin-paclitaxel or carboplatin-gemcitabine). These studies failed to demonstrate an increase in survival by adding Iressa together with chemotherapy in patients with advanced NSCLC.

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EGFR therapies with radiation (the head and neck data)

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Over one half of cancer patients worldwide receive radiation in the treatment of their cancer, and for several tumor types such as squamous cell cancer (SCC) of the head and neck (H&N), radiation represents a central or stand alone form of therapy. The rich overexpression of epidermal growth factor receptor (EGFR) in the vast majority of H&N cancer patients provides a particularly strong clinical/biological rationale for study of EGFR inhibitory strategies in this patient cohort. Substantial preclinical data identifies the capacity of EGFR inhibitory agents to augment the anti-tumor effects of ionizing radiation. Mechanisms for enhanced radiation response following EGFR inhibition include effects on cellular proliferation, apoptosis, damage repair, angiogenesis, invasion and metastases. Clinical trials which specifically evaluate the impact of EGFR inhibition on outcome for advanced H&N cancer patients are maturing. Several phase I/II clinical trials with anti-EGFR monoclonal antibodies and with small molecule inhibitors of the EGFR tyrosine kinase are underway or complete in H&N cancer patients in combination with radiation or with chemoradiation. In the Phase III setting, an international trial has recently completed enrollment of 416 patients treated definitively for advanced SCC of the H&N. Patients received either high-dose radiation alone (majority with hyperfractionation or concomitant boost radiation schedules) or radiation plus weekly infusions of the monoclonal antibody C225 (Erbitux, Cetuximab) during a seven-week treatment course. This represents a very powerful clinical trial for the EGFR field in that it will provide an unencumbered assessment regarding the capacity of EGFR inhibition to modulate radiation response in a large cohort of advanced cancer patients treated with curative intent. Locoregional tumor control and overall survival will be analyzed in this randomized trial. Correlative studies will also be performed from tumor materials gathered from patients for EGFR analysis. In light of consistently high expression levels of EGFR, H&N cancer has also served as a valuable model for examining response rates for EGFR inhibitors in the recurrent and metastatic disease setting. The current status of EGFR inhibitor studies in H&N cancer will be updated during this session.

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EGFR therapies in other tumour types

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The EGFR is expressed in a variety of tumors including non-small cell lung cancer, colorectal cancer, head an neck tumor, renal cell carcinoma, ovarian, prostate and pancreatic tumors, among others. In addition of the antitumor activities reported with anti-EGFR compounds in non-small-cell-cancer and colon carcinomas, antitumor activity has also been reported in other tumor types. Studies with the monoclonal antibody (Mab) IMC-C225 (cetuximab) have been conducted. In patients with refractory head and neck cancer, with documented progression after having received at least two cycles of platinum-based therapy, an 11% response rate was observed when IMC-C225 was added to the platinum regimen. A small phase III study in head and neck tumors comparing cisplatin and placebo to cisplatin and IMC-C225, more than doubling of the response rate was observed in the IMC-C225 arm. IMC-C225 can also be administered safely in patients with head and neck cancer, when given in combination with radiation therapy, with 13 complete responses and 2 partial responses in 16 patients. A phase III study of radiation + IMC- C225 in patients with advanced head and neck tumors has completed accrual. In a phase II study of another anti-EGFR Mab, ABX-EGF, in advanced renal cell carcinoma, clinical activity was also documented in patients that had failed or were unable to receive IL-2. EMD-7200, a humanized Mab, has also shown activity against a variety of tumor types. There is also emerging data of clinical activity with low molecular weight erbB (EGFR and related receptor-family members) tyrosine kinase inhibitors (TKI). In a single agent phase II study with the anti-EGFR TKI ZD1839 in tumors of the head and neck, an 11% response rate was seen. No activity has been seen against prostate carcinoma and minimal activity against breast cancer. Studies with OSI-774, another EGFR inhibitor, have also reported activity in ovarian carcinoma, head neck tumors