

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 than 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