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Cure versus normal tissue toxicity in early breast cancer

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The last century brought us a major step forward in the treatment of patients with breast cancer. From only palliative measures in the past, cure became possible for a large number of patients with early breast cancer. Major contributions with developments in the multidisciplinary approach have led to the gradually increasing survival rate. However, the gain in reduction of breast cancer mortality, for example postmastectomy radiotherapy (PMRT), has disappeared because of an increase of cardio-vascular mortality during follow-up. Fortunately, recent developments in radiotherapy made it possible that one can avoid late side effects such as cardio-vascular mortality after PMRT with modern irradiation techniques.

To avoid the mutilating nature of mastectomy several attempts were undertaken to perform breast-preserving treatment first with low dose radiotherapy. Soon it was discovered that for acceptable cure rates higher radiation doses were needed. With the progress made in radiotherapy equipment it became possible to deliver higher radiation doses resulting in a much higher local control rates, leading to equal survival rates after mastectomy and breast conserving therapy. Long-term follow-up revealed however that higher radiation doses are associated with an increase of fibrosis in the treated breast and therefore a slightly worse cosmetic outcome. In the consecutive dose escalation studies the gain in local control was weighted against induced side effects. The optimal radiation doses could therefore be established, depending for example on the age of the patients and the freedom of the margins. Adding adjuvant systemic treatment saw further improvement in both local control as well as survival, although also here long-term side effects have to be evaluated. These side effects of radiotherapy has led to an intensive search for avoiding radiation by careful selection of patients who could benefit from wide excision or quadrantectomy only, or partial breast irradiation. Until so far, however, detailed criteria are lacking for selecting the optimal treatment. Hopefully new molecular biology techniques, as the micro-arrays will allow us in the near future to select the proper treatment regimen.

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The selection of patients for partial breast treatment – the pathologist's update

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The occurrence of local tumor recurrence after breast-saving therapy is related to the extent and multifocality of the index tumor. Various reports focused on the microscopic distribution and extent of cancer in mastectomy specimens. These pathologic whole-organ studies showed that breast carcinomas typically have a segmental or unicentric distribution involving a single tumor area of various sizes. Multicentric distribution, defined as tumor involvement in two or more remote areas separated by uninvolved glandular tissue of 3–4 cm is a rare event [1,2].

DCIS: Size/extent is an important factor in the management of DCIS. The assessment of extent of DCIS is complex and needs in optimal conditions the correlation of the mammogram, the specimen X-ray and the histologic slides. Since the majority of DCIS is non-palpable, the mammographic estimate is the sole guide for resection. Therefore, data on the mammographic- pathologic correlation of the tumor size are essential for guiding the extent of surgery. The mammographic extent of a DCIS is defined as the greatest distance between the most peripherally located clusters of suspicious microcalcifications, and the histologic extent as the greatest distance between the most peripherally located, histologically verified, DCIS foci. Histologic evaluation supported by correlation with the X-ray of the sliced specimen allows a precise and reproducible assessment of the extent of any DCIS present. Whole organ studies showed that mammography, on the basis of significant microcalcifications, generally underestimates the histologic or "real" size of DCIS by an average of 1–2 cm. In a series of DCIS cases with mammographic sizes up to 3 cm, the size difference was less than 2 cm in more than 80% of the cases [2,3]. On the basis of these data, the relationship between incrementally increased margin sizes and the chance of resecting the entire tumor can be calculated. If the 35 DCIS cases of our study had been resected with a 1-cm margin around the mammographic lesion (field of microcalcifications), 34% would have had incomplete excision. With a 2-cm or 3-cm margin this percentage decreases to 17% and 11% respectively (Tables 1, 2). These data indicate that in any DCIS tumor a 1- to 2-cm margin should be resected around the field of the mammographic calcification to limit the amount of residual tumor to a minimun.

DCIS is regarded as a genuine multifocal process due to its histologic appearance in the two-dimensional plane sections showing multiple tumor foci on the cross-section of the tumorously involved ductal network. However, these tumor spots may not necessarily represent separate foci. Intraductal tumor growth on three-dimensional studies appears to be continuous rather than discontinuous [4]. More specifically, whereas poorly differentiated DCIS shows a predominantly continuous growth, the well-differentiated DCIS, in contrast, presents a discontinuous (multifocal) distribution in the majority of the cases. These results have a direct implication on the reliability of the margin assessment of surgical specimens. In cases of poorly differentiated DCIS, margin assessment should, theoretically, be more reliable than in well-differentiated DCIS. In a multifocal process with discontinuous growth, the surgical margin may lie between the tumor foci, giving the false impression of a free margin.

Table 1. Difference between histologic and mammographic size of DCIS; mammographic size $\leqslant$ 30 mm

Predominant type of DCIS	Number of cases	Difference in size (%) Histologic size > mammographic size	
		⩽20 mm	>20 mm
Poorly differentiated	14	11 (79)	3 (21)
Well-differentiated	14	12 (86)	2 (14)
Intermed. differentiated	7	6 (86)	1 (14)

Table 2. Total tumour clearance by margin width; mammographic size $\leqslant$ 30 mm (35 cases)

Gross surgical margin beyond mammographic tumour	Total tumour clearance (%)
1 cm	23/35 (66)
2 cm	29/35 (83)
3 cm	31/35 (89)

Various studies showed the relationship between surgical margin involvement and rate of local recurrence. These data consistently show an approximately 5-times higher rate of recurrence for patients with involved margins in comparison to uninvolved margins (Table 3). The Van Nuys data showed, in addition, that the free margin width measured in mm has a major influence on recurrence rate [5]. A 10-mm free margin in those studies resulted in a very low (2% to 3%) recurrence rate, irrespective whether post operative radiotherapy was given, in contrast to 29% to 33% when the microscopically free margin was less than 1 mm. (Table 4).

Table 3. Microscopic margins and local recurrence of invasive breast cancer (LE + RT)

Study	No. of patients	Follow-up (mos)	Local recurrence margin	
			pos.	neg.
Smitt	289	75	9%	2%
Anscher	259	44	10%	2%
Gage	343	109	16%	2%
Borger	1026	66	16%	2%
Spivack	272	48	18%	4%

Table 4. Recurrence and margin width in patients with DCIS. FU: 8 years

Margin width (mm)	LE	LE + RE	p
⩾10	2/92 (2%)	1/40 (3%)	0.92
1–9	23/124 (19%)	15/100 (15%)	0.24
<1	13/39 (33%)	21/73 (29%)	0.01

Silverstein et al., N. Engl. J. M. 2000; 340.

Concerning local distribution of **invasive cancers**, in a series of studies on mastectomy specimens we concluded that, though some 60% of the tumors are multifocal, about 15% only have a high multifocal tumor burden, and, that this is mostly due to a very extensive intraductal component (EIC++), often extending several cm beyond the outlines of the invasive mass [6]. The risk of local recurrence after breast-saving therapy is significantly influenced by the amount and type of this intraductal component. Residual tumor may be absent to massive in a genuine unifocal and a highly multifocal tumor, respectively. In some patients, with tumors

without any additional foci outside the primary (non-multifocal tumors), radiation therapy theoretically may be avoided after the complete resection of the tumor. In some other patients with multifocal tumors, both type and quantity of the expected residual tumor should direct the total dose of radiation, or a decision for re-excision. For some remaining patients with widely spread and high tumor burden, mastectomy might be the optimum approach instead of breast conserving therapy [7–8].

Our studies on tumor distribution show that approximately 50% of invasive ductal carcinomas have a limited extent, that is, they are localized processes: "breast carcinomas of limited extent" (BCLE) [9]. These tumors could be regarded as the proper candidates for breast-conserving therapy and a subset of those may be the candidate for breast-conserving surgery without radiotherapy. A BCLE is defined as having no tumor foci (in situ, invasive or lymphatic) beyond 1-cm from the edge of the dominant mass.

- Such tumor should first be selected by state-of-the-art mammography. Magnification views should be performed as a routine to rule out suspicious microcalcifications and densities as signs of possibe multifocality beyond the edge of the index tumor.
- The tumor should then be excised with a macroscopically free margin of approximately 2-cm of which the outer 1-cm microscopically tumor free.

The histologic evaluation of the surgical margins is a critical part of the assessment of any patient being considered for breast-saving therapy. This should include the inking of the specimen, the use of specimen mammography before and after the sectioning of the specimen and the generous sampling of the area of microcalcifications and margins. Pathologists should be trained to assess the expected type and amount of residual tumor in the remainder of the breast as either none to minimal, moderate, or massive, using the quantitative involvement of the biopsy margins as a guideline. This information is essential in guiding the further choice of management of, respectively, either local radiotherapy only, re-excision with or without radiotherapy, or mastectomy.

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229 INVITED

Optimization of follow-up

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What are the worries and problems of a patient after optimal locoregional and adjuvant systemic treatment of her breast cancer? Where should we take care of?

1. The fear of disease relapse.
2. Recovery.
3. Long-term sequela of treatment.

Ad 1: The fear of recurrence can be divided into the fear of loco-regional recurrence, distant dissemination and second new primaries.

The prognosis after the detection of locoregional recurrence (LRR) is mainly related to the initial tumour parameters (grade, size, nodal status), the interval between primary treatment and detection, and the extent of the relapse: the smaller the relapse, the better the prognosis. The prognosis is independent of primary local treatment (ie. mastectomy or breast conserving therapy). About 3/4 of the recurrences are detected either by routine physical examination or by mammography (after BCT). These findings may be a rationale for regular follow-up for the early detection of LRR: this follow-up may be more intensive for patients at high risk for LRR (younger, bad risk tumours) and less intensive or even none for patients at very low risks.

According to the well known randomised trials performed in Italy 10–15 years ago, and evidence from many retrospective studies, there is currently no role for so called "early" detection of distant disease by routine tests (imaging, biochemistry): early treatment (= treatment for asymptomatic but apparent distant disease) appears to have no impact on survival. However, times are changing:

- Better imaging tools are emerging: PET-scanning, CT-PET scanning, MRI.
- More sensitive serum markers, also with the help of proteomics.
- Better systemic treatments, particularly Taxanes and new hormonal agents (Aromatase inhibitors, pure oestrogen blockers) and other receptor blockers (Trastuzumab), leading to improvement in survival for patients with disseminated disease.

These new developments warrant new studies in which, for some groups of patients, intensified follow-up with the new tests and subsequent optimal treatment may lead to better survival. Breast cancer survivors do have an on average twofold increased risk (0.7% per annum, lifetime) for a second primary breast cancer, justifying screening by annual mammography. Indirect evidence suggests that there is no benefit of annual mammography over mammography every two years in women over the age of 60 years. For younger women with a family history, suspected or even to be related to a BRCA1/2 mutation, MRI screening is an option.

Ad 2: Recovery has different domains for which we should have attention: the physical, psychological, social (family life, work), financial and esthetical domain. Evidently there will be interaction between these domains. The level of impairment of the different domains should be assessed at different time points, particularly after ending initial therapy (surgery, radiotherapy, chemotherapy), and addressed when these events are debilitating. Unfortunately, till date reliable and reproducible measuring instruments in this respect are lacking, in the sense that certain interventions are meaningful, except aesthetic recovery by immediate or delayed breast reconstruction and early physiotherapies. So, no universally applicable reach to recovery interventions are at hand. Nevertheless, according to most patient wishes, major attention should be given to psychological and social rehabilitation.

Ad 3: The most frequent sequela of treatments are: pain (dysaesthesias), ipsilateral shoulder function impairment, lymph oedema, fatigue, impairment of cognitive functions, oestrogen withdrawal effects (hot flushes, libido, vaginal complaints, osteoporoses) and some rare late effects of radiotherapy. The possibility that these effects could emerge should be communicated to the patient. Further, the level of these impairments should be assessed regularly and treated in a timely and adequate fashion (ie.lymph oedema, osteoporoses). The Breast Clinic should have protocols for each of these sequela and the possible interventions, and the patient should be aware of these protocols.

Much debate exists on who should do the follow-up: a surgical oncologist, a radiation oncologist, a medical oncologist, a nurse-practitioner/oncologist, a general or family practitioner or all together? From the patients point of view there are 4 important issues: commitment, knowledge (experience), continuity, accessibility.

It is not that much important who is doing the follow-up, unless these aspects are met. This may well depend on the preference of the patients, her age, the stage of the primary disease, the initial treatments. It is of great importance that the patient is informed and educated in an honest way on the sense and nonsense of follow-up. Further she should know who is the primary person she can refer to in case of emerging uncertainties. An individualized follow up programme should be discussed and agreed with the patient: nurse practitioners as well as oncological specialists from the same breast team should be part of this programme. There is nothing like a universally applicable policy; nor outpatient clinic visits every 3 months with every specialist with all kind of tests for years and years, neither sending the patients away 2 or 3 years after primary treatment.

A last, but important point of the value of follow-up is the prospective registration of the whereabouts of the patients, enabling analyses of treatment results and audit.