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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