Local and Systemic Outcomes in DCIS Based on Tumor and Patient Characteristics: The Radiation Oncologist’s Perspective

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Four randomized clinical trials have shown unanimously the benefit of 50 Gy whole-breast radiotherapy in breast-conserving therapy (BCT) for ductal carcinoma in situ (DCIS). The risk of both DCIS and invasive local recurrence is reduced with about 50%, and this effect is similar for all clinical and histological subgroups analyzed. Younger age and involved margin status are the most important factors for an increased risk of local recurrence. In these subgroups, even with radiotherapy, the observed local recurrence rates are more than 20% at 10 years, which is considerably higher than reported local recurrence rates after BCT for invasive breast cancer. The optimal radiotherapy dose in BCT for DCIS has yet to be established. Also, at present, a subgroup of lesions in which the recurrence rate is so low that radiotherapy can be safely omitted has not yet been identified.

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Four randomized controlled trials have shown the benefit of radiotherapy after breast-conserving surgery for ductal carcinoma in situ (DCIS) (1–4). Radiotherapy reduces the risk of both DCIS and invasive local recurrence with about 50%, with a similar relative reduction of the recurrence risk in all clinical and pathological subgroups analyzed (5). Age and margin status are the most important factors related to the risk of local recurrence. The impact of young age on the outcome of treatment of DCIS has been studied by several groups (2,6–9). In the EORTC 10853 trial, women aged 40 years or younger had a 34% risk of local recurrence at 10 years compared with 19% of the women older than 40 years (Figure 1). Potential factors responsible for the increased risk of local recurrence after breast-conserving therapy (BCT) for DCIS in young women are adverse prognostic pathological features that appear to occur more frequently in young women and treatment-related factors such as a smaller excision volume (10). However, to date, data are limited and sometimes inconsistent (10). In the EORTC trial, young women had a higher rate of clinically detected lesions than older women (63% vs 24%) (11). Younger women had a similar rate of excisions without free margins (11). At present, young age per se should not be a contraindication for BCT, especially because it is unknown whether these patients have a superior long-term prognosis if treated by mastectomy. Local recurrences following—both skin sparing and simple—mastectomy after DCIS are reported and also seem to occur particularly in younger women (12,13).

Numerous studies have shown an increased risk of local recurrence when DCIS was excised with doubtful or involved margins (2,6,7,14,15). Various thresholds have been reported as a safe margin status, from “the inked margin not being involved with DCIS,” to ≥1, 2, 3, or 5 mm, or even ≥1 cm. Single institutional studies have suggested that radiotherapy can safely be omitted when margins are ≥1 cm (16); however, prospective studies have not confirmed this (17). In the EORTC trial, when margins were not reported free, the local recurrence rate at 10 years was overall 32% (Figure 2), with 39% in the local excision group and 24% in the excision plus radiotherapy group. To conclude, when margins are involved, the risk of recurrence is high, even after radiotherapy. Yet, it remains unknown which is an optimal minimal margin for BCT.

Involved margins after lumpectomy for DCIS are an indication for further surgery. If, after excision and/or re-excision, no clear margins can be obtained, a mastectomy will be indicated. Particularly in larger lesions, the chance of performing a microscopically complete local excision is considered low. In practice, 25%–30% of women with DCIS are treated with mastectomy (18). The extent of the DCIS and inability to obtain clear margins with breast-conserving surgery are likely to be responsible for this percentage.

In all randomized trials, the dose delivered was 50 Gy without an additional dose to the tumor bed: a boost. In invasive breast cancer, it has been shown that a boost can further reduce the risk of local recurrence by a factor of 2 (19). To date, no randomized trial has been published investigating the value of adding a boost dose in DCIS, but a study from the Rare Cancer Network suggests the value of a boost in DCIS, especially in younger women (20). In this study, 373 women aged 45 years or younger with DCIS were retrospectively analyzed concerning the influence of radiotherapy. Fifteen percent had no radiotherapy, 45% had whole-breast irradiation without a boost, and 40% had whole-breast irradiation with a boost. With a median follow-up of 72 months, the 10-year local relapse-free survival rates were 47%, 72%, and 86%, respectively. The hazard ratio for local recurrence was 0.33 with 50 Gy, and 0.15 with 50 Gy plus boost, indicating a dose-effect relationship (20). An international phase III study is forthcoming investigating the role of the boost in women with DCIS (TROG 07.01, BIG 3-07, EORTC 22085-10083).
Recently, the effect of a boost dose of 16 Gy appeared to be similar to that of a re-excision in a cohort of 208 women with close or minimally involved margins after local excision for DCIS (15). The authors concluded that a re-excision may be avoided with satisfactory local control by increasing the radiation dose to the tumor bed with a boost. However, prospective studies would have to confirm this finding.

Despite a reduced risk of local recurrence, to date, none of the randomized trials have observed an impact of radiotherapy on the risk of distant metastases or death. Both after excision alone and excision plus radiotherapy for DCIS, the risk of dying from metastasized breast cancer is only about 3%–4% at 10 years; this figure includes events from a subsequent contralateral breast carcinoma. For invasive breast cancer, the Early Breast Cancer Trialists' Collaborative Group meta-analysis has shown that a follow-up of at least 15 years is required before the impact of local recurrence on survival becomes apparent (21). For DCIS, with longer follow-up, an increased risk of invasive recurrence may ultimately have a small survival impact.

About half of the local recurrences after BCT for DCIS are invasive cancers. It was observed that the differentiation type of the DCIS is related to the grade of the invasive (recurrent) tumor (22). In the EORTC trial, 36% of women with an invasive local recurrence after BCT for poorly differentiated DCIS developed distant metastases compared with 15% of the women with an invasive local recurrence after BCT for a well-differentiated DCIS. Therefore, women with poorly differentiated DCIS at high risk of local recurrence, like young women or those with lesions that cannot be excised with tumor-free margins, may ultimately have a risk of dying from metastasized disease. With these women, the alternative of mastectomy, optionally followed by immediate reconstruction, should always be discussed.

Although radiotherapy reduces the risk of local recurrence in all clinical and histological subgroups, there is a continuous search for subsets in which the absolute risk of local recurrence is so low that radiotherapy could be safely omitted. In a subgroup analysis of the EORTC trial, the only patients with an exceptionally low risk of recurrence were those with a well-differentiated DCIS and a clumping or micropapillary growth pattern (2). However, subgroup analyses should be interpreted with caution, and prospective studies would be needed to confirm this.

Several studies investigating (accelerated) partial breast irradiation (APBI) in breast cancer have considered patients with DCIS eligible for trial entry. Reported recurrence rates after BCT for DCIS tend to be higher than for invasive breast cancer. The often discontinuous growth of DCIS, with frequently observed “gaps” of uninvolved breast tissue, may be in part responsible for this observation (23). Therefore, it is advised to use APBI for DCIS only within clinical trials and await their results before considering this procedure safe in general clinical practice.

In conclusion, at present, whole-breast irradiation after microscopically complete excision remains the standard of care in BCT for DCIS. Whether the addition of a boost dose will further improve results will be investigated in a worldwide randomized controlled trial. At present, a subgroup of lesions in which the risk of recurrence is so low that radiotherapy can safely be omitted has not yet been identified.

References
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