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One life saved by four prevented recurrences?

Update of the Early Breast Cancer Trialists confirms: postoperative radiotherapy improves survival after breast conserving surgery

Background. The debate about the impact of local control on survival in early breast cancer patients is still going on, in spite of the continuously growing evidence that avoidance of locoregional disease reduces the risk of tumor-specific death [4][5][13][14]. Recently, B. Fisher, one of the pioneers of breast conserving therapy claimed that during the last two decades, as a result of the use of systemic therapy in conjunction with breast conserving surgery and radiation, the incidence of locoregional recurrence has been reduced to a level where further reduction is likely to have little impact on survival [8]. The penultimate meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported the effect of radiotherapy in early breast cancer on recurrence and survival in 2005 and provided the essential message that four prevented local recurrences at 5 years would avoid one breast cancer death in 15 years [5]. The scientific community has eager-

ly awaited the quinquennial update of the EBCTCG which has now been published [6].

Patients and methods. A total of 17 randomized studies comparing postoperative radiotherapy vs. none were analyzed and comprised 7 new studies in addition to follow-up data of from 9 previously reported trials. A total of 10,801 patients with pT1–2 tumors were included, the majority of whom (n=7,287) were node negative, while 1,050 were node positive (2,464 unknown). In contrast to the previous meta-analysis [5], all patients received breast conserving surgery, consisting of lumpectomy (n=8,422) or more extensive techniques like quadrantectomy or sectoral resection (n= 2,399).

The effect of radiotherapy on 10-year recurrences of any type and their relation to the 15-year breast cancer death rate were studied in correlation to various prognostic parameters and treat-

ment characteristics (e.g., surgery, tamoxifen use). Moreover, a subgroup analysis was performed according to low, intermediate, and high initial risk of recurrence, from which the expected absolute benefit was derived by respective modeling of the prognostic factors.

Results. Overall, radiotherapy reduced the 10-year recurrence rate (local or distant) from 35% to 19.3%, corresponding to an absolute benefit of 15.7% (2p < 0.0001) for irradiated women (node negative (pN0) 15.4%, node positive (pN+) 21.2%). The 10-year rate of locoregional recurrence as first event was substantially higher for non-irradiated women: 25.1 vs. 7.7%, i.e., an absolute difference of 17.4% (pN0 15.5%, pN+ 30.6%) ([6] web Fig. 2 a,b,c).

Moreover, radiotherapy reduced the 15-year breast cancer death rate from 25.2% to 21.4% corresponding to an absolute gain of 3.8% (pN0 3.3%, pN+ 8.5%).

Tab. 1 The 10-year recurrence^a rate and mortality [6]

| | All patients (n=1 0,801) | | pN0 (n=7,287) | | pN+ (n=1,050) | |
|--------------------------------|--------------------------|--------|---------------|--------|---------------|--------|
| | BCS | BCS+RT | BCS | BCS+RT | BCS | BCS+RT |
| 10-year any recurrence (%) | 35.0 | 19.3 | 31.0 | 15.6 | 63.7 | 42.5 |
| 10-year locoregional first (%) | 25.1 | 7.7 | 22.8 | 7.3 | 43.0 | 12.4 |
| 10-year distant first (%) | 9.9 | 11.6 | 8.2 | 8.3 | 20.7 | 30.1 |
| 15-year BC mortality (%) | 25.2 | 21.4 | 20.5 | 17.2 | 51.3 | 42.8 |

BC breast cancer, BCS breast conserving surgery, RT radiotherapy, pN0 node negative, pN+ node positive^a
 Women with distant plus locoregional disease as first recurrence were counted as distant.

Tab. 2 Comparison of the 15-year breast cancer mortality in the EBCTCG meta-analyses 2005 [5] and 2011 [6]

| | 2011 | | 2005 | |
|-----|------|------|------|------|
| | + RT | - RT | + RT | - RT |
| pN0 | 17.2 | 20.5 | 26.1 | 31.2 |
| pN+ | 42.8 | 51.3 | 47.9 | 55.0 |

RT radiotherapy, pN0 node negative, pN+ node positive.

Finally, radiotherapy reduced the 15 year risk of any death from 37.6% to 34.6%, providing an absolute gain of 3.0% (pN0 2.8%, pN+10.7%). Mortality without recurrence was slightly but not significantly higher in irradiated women (relative risk 1.09, 0.97–1.22, 2p = 0.14).

Conclusion of the authors. Radiotherapy halved the average annual rate of disease recurrence (RR 0.52, 0.48–0.56) and reduced the annual breast cancer death rate by about one sixth (RR 0.82, 0.75–0.90). On average, in all patients, about one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10. Little variation of the proportional benefit was seen in the different prognostic subgroups or with different types of surgery. In contrast, the absolute benefit from radiotherapy substantially depended on the patient’s characteristics in terms of prognostic factors [6].

Comment

The baseline message of the previous meta-analysis [5] is once more confirmed: Local control translates into improved breast cancer specific and overall survival

and even the “one-in-four relationship” is roughly corroborated. The presentation of the current study differs from the previous one as the 5-year local recurrence rate as the primary focus of analysis has been replaced by presenting 10-year “first” recurrence of any type, which have been halved by radiotherapy. In his comment on these data, T.A. Buchholz [2] stated: “to put this benefit into context, a 50% proportional reduction in 10-year recurrence exceeds that from chemotherapy alone or hormonal therapy alone” [2].

As radiotherapy reduces the risk of breast cancer death, eradication of residual disease obviously does not only prevent local recurrence but impedes the emergence of distant disease to a similar extent. The observation that in patients with positive axillary nodes the rate of distant disease diagnosed as first recurrence is higher after irradiation than after breast conserving surgery (BCS) alone (■ Tab. 1) must not be misinterpreted: the fact that radiotherapy (RT) substantially prevents or delays local recurrence may lead to an increased proportion (but not absolute number) of patients presenting with metastases as first recurrence that would otherwise have been preceded by locoregion-

al relapse. On the other hand, it is obvious that increased local control can only translate into improved survival in the absence of pre-existing distant micrometastatic disease which is not eradicated by systemic treatment [2]. Noteworthy, RT provided the largest absolute survival advantage for those women with node-positive disease (pN+ 8.5%). This observation suggests that even though positive axillary lymph nodes strongly indicate the potential of later distant recurrence, a fraction of metastases is not present prior to treatment but develops later on the basis of residual local disease.

This affirms the hypothesis of a “late wave of metastases” that has been propagated for prostate cancer [3] but not yet corroborated with the same extent of evidence as for breast irradiation.

In the current meta-analysis, six studies (n= 2,911) were confined to low risk patients with lumpectomy and adjuvant tamoxifen. Treatment results for this patient group support the assumption that the expectable absolute benefit of radiotherapy is related to the primary risk of recurrence and to the extent to which recurrence is preventable. As the authors conclude: halving a big risk provides more absolute gain than halving a small risk. While the proportional reduction of the 10-year recurrence rate was 65% (RR 0.35, 0.27–0.45) in these low-risk patients, the absolute reduction was only 13.6%. This is plausible as the 10-year recurrence rate was only 19.9% in patients without RT and 6.3% in irradiated women. For comparison: in the older lumpectomy trials with mixed risk groups, the absolute gain was 20.1% according to the fact that the 10-year recurrence rate in this group was much higher (47.9% without RT). Nonetheless, the proportional reduction was smaller (RR 0.53, 0.46–0.61)([6], web Fig. 5e). Interestingly, the 50% proportional reduction also applied for those patients who had more extensive surgery ([6], web Fig. 5d).

The EBCTCG update makes another important contribution to the ever-lasting discussion about radiation toxicity that may counteract the benefit of RT. Mortality without recurrence was slightly higher in the irradiated group (1.09, 2p 0.14) but the excess was not significant and identi-

cal to the excess- mortality observed by the EBCTCG for 1 year of tamoxifen vs. none [7]. The authors did not provide a further cause-specific analysis of non-breast cancer-related deaths. Assuming that some of these might be attributable to radiation, there is definitely a high potential to further eliminate or at least reduce these effects with modern treatment techniques [1][11][12][15].

In contrast to the 2005 meta-analyses, survival has improved: the 15-year breast cancer death rate was lower in the present study (■ **Tab. 2**; [5][6]. Patient groups may not be totally comparable because of the new studies with different inclusion criteria and adjuvant systemic treatment. Nonetheless, this trend indicates that the tools to combat breast cancer have gained potency. The present analysis provides convincing evidence that preventing local recurrence in the first decade yields the promise of improved survival in the second. Hence, local and systemic treatment should be regarded as a corporate interdisciplinary challenge as the strength of each enforces the potential of the other.

Several new treatment modalities are currently being discussed like partial breast irradiation [10], or omitting axillary dissection (without irradiating the axilla instead!) in patients with a positive sentinel node and a clinically negative axilla [9]. This should be scrutinized with regard to the large absolute gain of 20% (proportional reduction of 50%) in of the 10-year recurrence risk in patients with 1–3 positive axillary nodes (n=718; [6], web Fig. 11a). These patients had not received nodal irradiation but as level I–II is supposedly covered by whole breast RT, occult disease in the axilla may “inadvertently” have received a tumoricidal dose. These findings strongly support the suggestion of Haffty et al. [9] concerning the implications of a positive SNB for the radiation oncologist: his approach is using dedicated high tangents with deliberate inclusion of level I–II in these patients.

Conclusion

Thus, it should be borne mind that in light of the large number of affected women, even small incremental changes will impact thousands of lives.

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