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Breast cancer in elderly women: Can radiotherapy be omitted?

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ABSTRACT

It is tempting to spare elderly women the burden of adjuvant radiotherapy after breast cancer surgery, even if such a treatment would be justified in light of the available clinical evidence. The reason is that evidence-based radiotherapy derives from clinical trials that excluded elderly women, and that breast cancer is often believed to be more indolent at advanced ages.

Unfortunately, the epidemiological evidence, and the few clinical trials recruiting patients over 65 or 70 year of age, all point to the need for postoperative irradiation in a similar set-up as in younger patients. So far, there is no evidence that a subgroup exists in which radiotherapy can be safely omitted. Therefore, the decision to treat or not to treat should be openly discussed with the patient, addressing risks and benefits of both attitudes. Only in frail patients, with an obviously limited life expectancy (months or at most a few years), can omission of radiotherapy be considered, as the burden of local recurrence is likely not to appear before the patient dies from an other cause.

1. Introduction

Breast cancer treatment consists of the association of surgery, radiotherapy (RT) and systemic therapy, all contributing to long-term disease control. It can be a long, sometimes strenuous treatment, though all of its elements are evidence-based, as no cancer has been more subjected to medical research than breast cancer.

The goals of cancer care for elderly patients with breast cancer should include a plan for long-term control of the cancer (cure), maintenance of a maximum level of patient independence, freedom of symptoms and maintenance of personal dignity and lifestyle.[29]

As life expectancy shortens with age, quite obviously, the question arises as to whether the treatment of breast cancer cannot be 'de-escalated' to fit the remaining years to live rather than to stick to the 'maximal' treatment model established for younger patients. *This is no minor topic as up to 30% of all breast cancer are reported to occur in the over 70 year age group.*[21]

More particularly, is it safe to omit the tedious RT treatment, as it only seems to add a few percent to the excellent level of local control already achieved with appropriate surgery. Quoting B. Fisher: 'Breast cancer is a systemic disease involving a complex spectrum of host–tumour interactions; (...) variations in effective local regional treatment are unlikely to affect survival substantially. Only systemic treatment is'.[7]

2. Role of radiotherapy in breast cancer

A large number of trials, on both sides of the Atlantic, have been conducted, establishing breast-conserving surgery (BCS) followed by RT as the standard of care. But RT has long been considered as an adjuvant 'cosmetic' treatment, to ensure maximal local control after BCS, rather than an essential

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element contributing to long-term survival.[5,6,8,9]. It took decades to accumulate sufficient clinical data to assess various, beneficial and deleterious, effects of breast or chest radiotherapy.

The current view has been remodelled by a series of recent trials using state-of-the-art radiotherapy,[16,17,19] allowing to explore its curative impact without 'contamination' by long-term lethal toxicity. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) therefore undertook the complex task of reviewing breast cancer clinical trials that began by 1995, uncovering the favourable effect of adjuvant radiotherapy after surgery to its full extent.[2] It is a rich report, exploring numerous aspects of local treatment (radiotherapy versus no radiotherapy, more versus less surgery, more surgery versus radiotherapy). A short conclusion is that 'differences in local treatment that affect local recurrence rates would, in the hypothetical absence of any other cause of death, avoid about one breast cancer death over 15 years for every four local recurrences avoided'. In other words, the general finding is that a 20% absolute reduction in 5-year local recurrence risk leads to about a 5% reduction in 15-year breast cancer mortality.

Five-year isolated local recurrences were 6.7% versus 22.9% in RT versus no RT trials after BCS and node-negative disease, and 11% versus 41.1% in node positive women. Fifteen-year breast cancer mortality rates were 26.1% versus 31.2% with and without RT in node negative (Logrank $2p = 0.006$), and 47.9% versus 55.0% in node positive cases (Logrank $2p = 0.01$), respectively. The picture was similar after mastectomy in women with positive axillary clearance, both for 5- and 10-year isolated local recurrence and 15-year survival. Even in women with negative nodes, the risk of local recurrence, though small, was favourably influenced by adjuvant RT (6.3% versus 2.3% at 5 years).

The issue of life-threatening side effects (mainly heart disease and secondary lung cancer) cannot be fully explored in recent trials, but there is a strong attempt to minimise both heart and lung dose with modern breast irradiation techniques.

These findings are very much in line with Hellman's view: 'Breast cancer is a heterogeneous disease – a spectrum ranging from a disease that remains local throughout its course to a disease which is systemic when first detectable. Thus there could be situations where metastases would develop as a consequence of residual inadequately treated loco-regional disease'.[11]

Hence, the signification of a local recurrence can be somewhat benign, a simple 'accident' in the patient's history (if handled properly), or it can become the source of metastasis. The former case has no impact on the life expectancy of the patient, whereas the latter is eventually lethal.

3. Omitting radiotherapy after BCS

After breast conserving surgery or mastectomy, the risk of local recurrence is a function of several tumour characteristics, including tumour size, grade, receptor status, surgical margins and nodal invasion or not. In the last EBCTCG meta-analysis, the following factors were found to be significant predictors of local control: grade, size, oestrogen receptor (ER) status and number of nodes (see Table 1).

The difference in local recurrence rates remained strikingly significant, even in women with a good prognostic disease, in the treatment arms without adjuvant radiotherapy. The lowest rate of recurrence was observed in women over 70, but a further analysis of the age effect was not possible as a result of the (inappropriate) policy of excluding older patients from randomised trials. Still, in this age group, the recurrence rate was a two-digit figure whenever radiotherapy was omitted.

Moreover, the occurrence of local recurrences after BCS was an early event, with a significant difference between irradiated and un-irradiated patients after 1 year already.

Attempts to replace radiotherapy by an adjuvant hormonal treatment did not offer a similar level of local control. In a randomised trial comparing tamoxifen (TAM) to radiotherapy after BCS in T1–T2 node negative patients, the rate of local relapse was 7.7% at 5 years in the TAM group versus 0.6% only in the RT group. At 8 years, the rate of relapse increased to 17.6% versus 3.5%.[10]

A similar trial was conducted in women 70 years of age and older, but restricted to T1 tumours. In the TAM arm, the local recurrence rate at 5 years was 4% versus 1% in the TAM + RT arm.[12]

Kunkler et al. recently reviewed the case for RT omission in operable breast cancer pT1–2 pN0 in women over 65 (the PRIME trial). They conclude that, at present, data are insufficient to identify a subset of women from whom postoperative radiotherapy after BCS can be omitted.[13]

Another piece of the puzzle has been added in December 2006 at the 29th Annual San Antonio Meeting by Bartelink et al., presenting an update of the European Organisation for Research and Treatment of Cancer (EORTC) 22881-10882 data (so-called boost versus no boost trial).[1] 5318 patients

Table 1 – Effect of age and tumour characteristics on 5-year risk of local recurrence in trials of radiotherapy after breast conserving surgery in women with node-negative disease[2]

	Five-year local recurrence risk (%) in BCS trials (node negative)	
	RT	Control
Age (years)		
<50	11	33
50–59	7	23
60–69	4	16
⩾70	3	13
Tumour grade		
Well differentiated	4	14
Moderately differentiated	9	26
Poorly differentiated	12	34
Tumour size (T category)		
1–20 mm (T1)	5	20
21–50 mm (T2)	14	35
ER status		
ER poor	12	30
ER positive	6	25

were randomised after BCS to RT alone (50 Gy) or followed by a boost dose (16 Gy) on the tumour site. With a median follow-up of 10.75 years the cumulative incidence of local recurrence was 10.2% versus 6.2% for the no boost and the boost group, respectively ($P < 0.0001$). A significant absolute risk reduction was recorded in all age groups (<40, 41–50, 51–60 and >60). The figure for the group aged 60+ was 7.3% versus 3.8%.[1] Although this does not directly demonstrate the usefulness of post-BCS radiotherapy, it indicates that the radiation dose matters, and that recurrence rates, within the framework of a clinical trial with extensive quality control of surgery (margins) are far from insignificant, even after appropriate radiotherapy. This does surely not lend support to omit radiotherapy beyond the age of 60.

Smith et al. searched the SEER database, looking at the prevention of local relapse in patients (66 and older) with ductal carcinoma *in situ* (DCIS) treated with or without irradiation after conservative surgery. In this group of elderly women, radiotherapy significantly reduced the 5-year local relapse rate, both in high-risk and low-risk DCIS patients.[24]

The same group investigated the effect of radiotherapy after conservative surgery for invasive breast cancer.[25] 8724 women aged 70 and older were identified in the SEER database, treated in the 1992–1999 period with a small invasive, lymph-node negative, oestrogen-receptor positive (or unknown) tumour. All women benefited from BCS, whether they were followed or not by radiotherapy. Two endpoints were used: incidence of second ipsilateral cancer and/or a subsequent mastectomy. Radiotherapy significantly reduced the composite outcome in all age groups, but more so in the 70–79 age group.

Truong et al. conducted another epidemiological survey in the cancer database of British Columbia Cancer Agency.[26] 4836 women aged 50–89 were treated with BCS for T1–T2, Nx–N1, M0 invasive breast cancer (period 1989–1998). Median follow-up was 7.5 years. Relapse rates, overall survival and cancer survival were significantly correlated with the use or not of adjuvant radiotherapy, even in the women aged 75 years and older. For instance, 5-year breast cancer-specific survival was 91% versus 94%, without and with RT ($P = 0.002$) in the entire cohort, and 88% versus 94% in the 75 year and older cohort ($P = 0.004$).

These last two communications point to a very relevant element, namely, that elderly women are not aged 65, but rather 75 or more. The relevance of data comparing women aged <65 with >65 is limited to the problem of making treatment decisions in elderly women.

4. Substituting BCS and radiotherapy by radical surgery

The conclusions of the many trials that established BCS + RT as an equivalent treatment to mastectomy can be reversed: in patients who want to avoid the long radiotherapy treatment that follows BCS, mastectomy offers an alternative with equal chance for cure.

In old or frail patients, or in women that for whatever reason, do not want to spend 5 or 6 weeks in radiotherapy, mastectomy is a valid approach. Yet, one has to remember that women aged 70 and over are usually not included in prevention campaigns. As a consequence, they are often diagnosed at a more advanced stage (tumour can be palpated), with a higher rate of nodal involvement. In Flanders, for the period 2000–2001, the cancer registry has recorded an incidence of stage 0 (*in situ*) and stage 1 larger than 50% in women aged 50–69 versus a little more than 30% in women over 70.[27] And then, mastectomy or not, if the lymph nodes contain tumour cells, adjuvant radiotherapy is indicated to prevent the high risk of chest recurrence.

The complete picture is thus that (1) substituting BCS by mastectomy will not *automatically* prevent the need for adjuvant radiotherapy and (2) mastectomy in node positive patients could have been avoided as RT is still indicated.

For instance, Lee et al., from the British Columbia Cancer Agency retrospectively reviewed clinical charts from 233 women aged 70+, and treated between 1989 and 1997.[14] All had locally advanced cancer (tumour >5 cm or $\geqslant$4 invaded nodes), and received hormonal therapy. 147 received post-mastectomy radiotherapy (PMRT) and 86 did not. Despite a less favourable tumour profile, women after PMRT had a 16% recurrence rate versus 26% without PMRT ($P = 0.03$, median follow-up time 5.5 years).

Smith et al. recently reviewed SEER data in 11,594 women aged 70 years and older, treated with mastectomy for invasive breast cancer.[23] A total of 502 (7%) of 7416 low-risk, 242 (11%) of 2145 intermediate-risk, and 785 (38%) of 2053 high-risk patients received PMRT. Median follow-up was 6.2 years. PMRT was associated with a significant improved survival in the high-risk group. Five-year adjusted survival was 50% after mastectomy without adjuvant therapy, 56% with PMRT and 59% with both PMRT and chemotherapy, respectively. Randomised clinical trials are urgently needed to confirm this finding and define optimal treatment strategies for this patient group.

The EORTC is now a participant in the MRC SUPREMO of the Scottish Cancer Trials Breast Group trial, (Selective Use of Postoperative Radiotherapy after MastectOmy) a phase III randomised trial to assess the role of adjuvant chest wall irradiation in 'intermediate risk' operable breast cancer following mastectomy. The goal is to include 3700 patients after mastectomy. Since there is no age constraint in the inclusion criteria it is anticipated that analysis by age group will add some clarification to the question (www.eortc.be).

Last but not least, the common belief that older women do not seek for conservative surgery is wrong. When *offered* the alternative, the vast majority of women aged 70+ prefer conservative surgery.[22]

5. Shortening radiotherapy

An option frequently discussed is hypofractionation. It has the advantage of limiting the number of sessions (better cost-effectiveness, less burden to the patient), but the disadvantage to be more damaging to normal tissues with more long-term morbidity. In the specific case of breast cancer, hypofractionation, if properly adjusted for the tumour BED, would result in more breast oedema and fibrosis, or so it is predicted.

In the absence of a standard fractionation schedule – breast conserving trials actually used diverging fractionation schedules – the NCIC and Ontario Clinical Oncology Group designed a trial to compare two fractionation regimens (50 Gy in 25 fractions versus 42.5 Gy in 16 fractions) in women treated with lumpectomy and with negative nodes (breast irradiation only). 1234 women were randomised and, after a median follow-up of 69 months it was concluded that the two arms were equivalent in terms of local control, disease-free and overall survival. The percentage of patients with good or excellent cosmetic outcome after 3 years was 76.8% and 77%; this result remained unchanged at 5 years. About 17% of enrolled women were over 70; apparently there was no difference between them and the other age groups.[30]

It therefore seems that a 22 day schedule is equivalent to a 35 day one. In countries with long distances and/or in elderly women with difficulties to daily travel to the hospital, this could make a substantial difference. Indeed, it could help to convert mastectomies without radiotherapy into conservative treatments with radiotherapy, or so suggests Whelan.[30]

6. Co-morbidities and treatment of recurrences

Although overall survival remains the Grail in oncology, the morbidity associated with local or loco-regional recurrences should not be overlook.

First of all, a recurrence is a source of considerable psychological distress in cancer patients. Adjusting to the diagnosis of breast cancer is a painful process, and the rate of severe distress and depression is particularly high in this group of patients.[20] In this context, it is not inconceivable that a recurrence will have a deeper negative impact on the patient's psychological status, and turn distress into depression in a substantial proportion of women.

Also, a recurrence is likely to submit the patient to a second surgical intervention (mastectomy after BCS), and probably a change in the systemic treatment (substitution of tamoxifen by an aromatase inhibitor). The cumulative costs of the successive interventions for a recurrence are likely to be more expensive than a simple radiotherapy treatment.

Actual prices vary widely from country to country, but, in Belgium, 1 year of aromatase inhibitor (anastrozole, letrozole and exemestane) costs about the same as a simple breast treatment of radiotherapy with two tangential beams (1.600€ versus 1.800€). The recommended duration of such a treatment in the eventuality of a recurrence is not clear yet. However, assuming a treatment of 5 years, the cost of a single treatment would approximately balance the cost of five radiotherapy treatments. Therefore, omission of radiotherapy in a population of women with a 20% risk of local recurrence would not save any cost to the social security system.

This is far from an economical analysis, barely a rough estimate, but it helps to fix orders of magnitude.

One needs to add a more specific consideration to elderly patients: the increasing frequency of co-morbidities with age renders the prescription of anticancer treatments more difficult, if not simply contra-indicated.[28] Simple guidelines, validated in a younger population through appropriate clinical trials, never take account of potentially competing age-related diseases because, as said before, such patients are excluded from cancer research.

Table 2 – Incidence of serious concomitant conditions by age of consecutive breast cancer patients diagnosed in 1995–2001 in southeastern Netherlands [15]

	Age at diagnosis (years)			
	<50	50–69	70–79	⩾80
Incidence of concomitant conditions (%)				
0	79	67	50	35
1	8	16	27	34
⩾2	1	4	14	22
Unknown	13	12	9	9

Co-morbidities have been prospectively recorded in the population-based Eindhoven Cancer Registry.[4] The proportion of patients with one or more serious coexistent disease at the time of diagnosis of breast cancer was recently derived from this database (and updated); it ranged from 9% for patients younger than 50 years to 55% for patients aged 80 years and older (Table 2).[15] The most frequent conditions were cardiovascular disease (7%), diabete mellitus (7%) and previous cancer (6%).

As expected, 5-year survival was lower in patients with two or more co-morbid conditions than in those without: 72% versus 84% in patients less than 50 years, 65% versus 84% in the patients aged 50–69 years and 35% versus 68% in patients ⩾70 years, respectively. Whether this loss of survival was related to the co-morbid conditions or to understaging/undertreatment of breast cancer, or to both was further explored by using relative survival to estimate disease-specific survival. This showed significantly lower 5-year survival rates for most of the recorded coexistent diseases with rates up to 50% lower. An independent prognostic effect of age was also observed, presumably related to other factors (decreased performance status, lower organ reserves, diminished mental conditions, unfavourable social factors).[15]

Lastly, the common belief that quality of life is negatively affected by a long and strenuous radiotherapy treatment after breast surgery is contradicted by data from the PRIME trial, where the expected improvements in quality of life (QoL) scores when RT was omitted were not recorded.[18]

7. Making individual decisions

Obviously, breast cancer patients are at risk of dying from breast cancer as well as from other cause. Assessing cancer stage, age, and coexistent diseases will help to allocate individual patients to particular subgroups with respective survival probabilities for each of these factors. Using, for example, Charlson's classification of co-morbidities and their severity (as used in[15]), it is possible to estimate the life expectancy of patients, independently of their cancer stage.[3] Other predictors of 1-year mortality have been developed since, that can be used and combined with known recurrence rates for an estimate of the probability of breast cancer to recur within the expected lifespan of an individual patient. Their discussion is beyond the scope of the present paper.

However, predictions are probabilistic in nature, whereas the decision to treat or not is binary. An important element of clinical judgement will always remain necessary, together with a multidisciplinary discussion with other cancer specialists (including the geriatrician), the patient and her family.

8. Conclusions

1. Local recurrence is an early event *after breast cancer surgery. The EBCTCG reports on a recurrence rate of 25.9% after BCS without radiotherapy. In the node-positive subgroup, the recurrence rate at 5 years is 41.1%.*[2]
2. Local recurrence can be the source of *further cancer dissemination* (metastasis).
3. The treatment of *locally recurrent* or metastatic breast cancer incurs a high cost (psychological and financial).
4. This treatment might become difficult to prescribe in elderly patients because of competing co-morbidities, *likely to be less or even absent at the time of primary surgery.*
5. The actual impact of metastatic breast cancer can be compatible with a long survival, particularly in elderly women with hormone sensitive disease.

Survival is unlikely to be affected by adjuvant radiotherapy after adequate breast cancer surgery in patients with a life expectancy shorter than 5 years. At 5 years, the survival curves after BCS with or without adjuvant RT already begin to diverge, particularly in node-positive patients. The number needed to treat for one life saved is 20 in the node-negative disease at 15 years; it is 14 in node-positive patients.[2]

These considerations should help the radiation oncologist to form an opinion to withhold radiotherapy or not after BCS in node negative patients with an otherwise short life expectancy.

In all other patients with an increased risk of local recurrence (positive margins, bulky tumours, unfavourable histology, etc.), *it is unwise to omit radiotherapy*, unless there is a clear consent of the patient to accept mastectomy. Even then, radiotherapy might remain indicated, in case axillary lymph nodes are found to be positive at histology.

Conflict of interest statement

None declared.

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