Chapter 8

Breast conserving surgery with or without radiotherapy in older patients with early stage breast cancer – a systematic review and meta-analysis

Willemien van de Water
Esther Bastiaannet
Astrid N. Scholten
Mandy Kiderlen
Anton J.M. de Craen
Rudi G.J. Westendorp
Cornelis J.H. van de Velde
Gerrit-Jan Liefers

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Abstract

Background

In early stage breast cancer, radiotherapy is an integral part of locoregional treatment with breast conserving surgery. However, few older patients are included in the clinical trials upon which these recommendations are based. Therefore, we performed a systematic review and meta-analysis to evaluate outcomes of radiotherapy after breast conserving surgery in older patients.

Methods

A systematic search of Pubmed and Embase was undertaken. Inclusion was restricted to randomized controlled trials in postmenopausal breast cancer patients. Pooled odds ratios were calculated for locoregional recurrence, distant recurrence and overall survival.

Results

We included 5 randomized clinical trials comprising 3,190 patients. Overall, 39% of the patients was ≥70 years, and most had hormone receptor positive T1 tumors without nodal involvement. All patients received adjuvant systemic therapy. Patients who received radiotherapy had a lower relative risk of locoregional recurrence (pooled OR 0.36 (95%CI 0.25-0.50)). The 5-years absolute risk was 2.2% (95% CI 1.6-3.1) among patients who received radiotherapy, versus 6.5% (95% CI 5.3-7.9) among patients who did not. The absolute risk difference was 4.3% (95% CI 2.9-5.7), corresponding with a number needed to treat of 24. No differences were observed for distant recurrence or overall survival.

Conclusion

Although patients who received radiotherapy had a lower relative risk of locoregional recurrence, the absolute risk was low and overall survival was not affected. We propose that the debate should not only focus on the *relative* risk but also on the *absolute* benefit of radiotherapy and the number needed to treat. Both treatment options may be reasonable in clinical practice.

Introduction

In early stage breast cancer, adjuvant breast irradiation is an integral part of locoregional treatment with breast conserving surgery in order to obtain locoregional control[1]. However, with increasing age, patients are less often included in the clinical trials upon which these recommendations are based. Despite comprising more than 40% of new breast cancer patients, older patients are underrepresented in clinical trials[2]. Only 1-2% is estimated to participate in clinical trials, and only those who are considered fit enough are included[3].

Next to an underrepresentation in clinical trials, different factors may play a role in the evaluation of radiotherapy after breast conserving surgery in older as compared to younger patients. First, older patients suffer from a higher risk of competing mortality[4] and have a lower remaining life expectancy. Consequently, the absolute benefit of anticancer therapy may be smaller, while long term adverse events may be less relevant. Second, concurrent disease and medication use may directly affect tolerability of treatment and increase toxicity of systemic treatment[5;6]. Last, relevant treatment outcomes may vary with age[7]. Therefore, results obtained in a younger trial population may not necessarily be applicable to or appropriate for older breast cancer patients.

The outcome of radiotherapy after breast conserving surgery specifically in older patients has been studied by others. However, conclusions were inconsistent[8-15]. Meanwhile, observational studies show that administration of radiotherapy after breast conserving surgery decreases with increasing age[16;17]. Also among patients included in a randomized clinical trial on endocrine therapy, administration of radiotherapy after breast conserving therapy decreased with age[4]. It remains unclear whether this omission of radiotherapy is appropriate or whether radiotherapy should be an integral part of breast conserving surgery in older patients with early stage breast cancer.

Therefore, we performed a systematic review and meta-analysis to assess the efficacy of radiotherapy after breast conserving surgery in older patients with early stage breast cancer.

Methods

The focus of this systematic review and meta-analysis was to specifically address the outcomes of breast conserving surgery with or without radiotherapy in older patients with early stage breast cancer. A systematic search of Pubmed and Embase was undertaken, using several different search strategies and keywords comprising early stage breast cancer, breast conserving surgery, and radiotherapy (Figure 1), without restriction of publication dates, until June 1st 2013. A priori inclusion criteria were the following; studies had to be a primary research article specifically addressing outcomes of breast conserving surgery with and without radiotherapy in early stage breast cancer. At least a subgroup analysis comprising older patients was to be

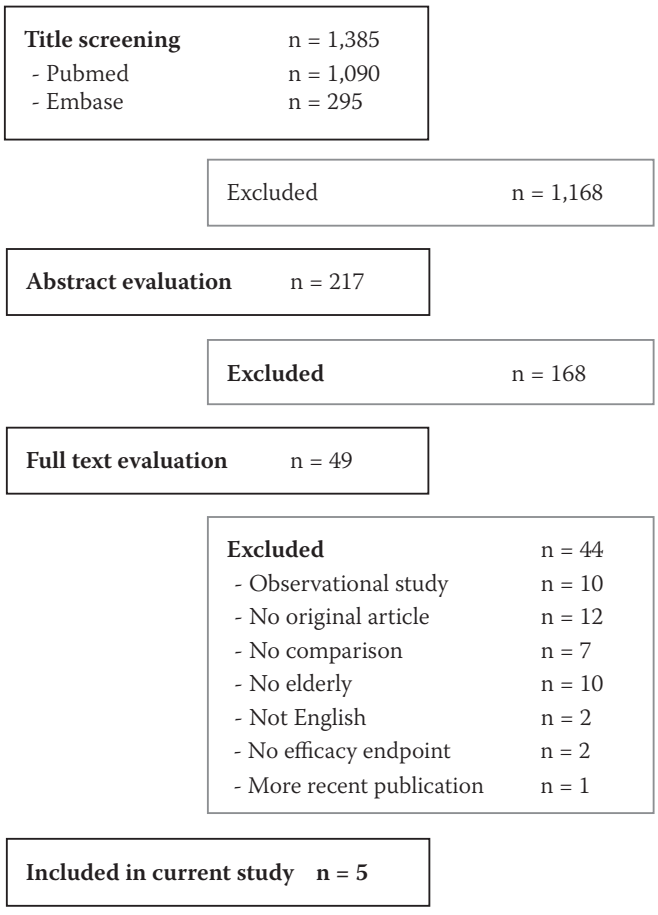


Figure 1. Search strategy and study selection.

reported. To increase the number of potentially interesting papers, older patients were defined as postmenopausal patients.

Studies were excluded if they were a review or meta-analysis on the subject. Published abstracts without complete articles were excluded because of the inability to obtain detailed information. All citations were independently reviewed by two of the authors (WW and EB) and categorized as relevant, potentially relevant, or not relevant. Citations categorized as relevant or potentially relevant by one of the authors, were selected for abstract review. After review of the abstract, potentially relevant and relevant abstracts were selected for full text evaluation. Upon full text evaluation, it was decided not to include any of the observational studies, as outcomes in observational data are prone to confounding by indication[18]. Therefore, inclusion in the current study was further restricted to randomized controlled trials.

For each included study, we recorded study characteristics (aim; randomization; eligibility criteria; number of patients), and main outcomes and conclusions as reported by the authors (primary and secondary outcomes; conclusions; comments). Numbers of events were extracted to conduct a meta-analysis of the different outcomes under study. If the numbers of events were not available, then survival graphs or survival rates were used to estimate the numbers of events. All data were obtained from the intention-to-treat analyses.

STATA SE 12 was used to pool the different outcome estimates. Outcomes were analysed as odds ratios. The I^2 statistic was used to test for heterogeneity across studies[19]. An I^2 value greater than 50% was considered to represent substantial heterogeneity. Publication bias was tested by using funnel plots; an inverted symmetrical funnel plot assumes the absence of publication bias[20].

Next to relative outcome measures, pooled absolute risks were calculated. The pooled absolute risk per study arm was calculated as Σ(number of events in study arm) / Σ(N study arm), including a 95% confidence interval (CI). The absolute risk difference was calculated as the pooled estimate of the absolute risk difference per study, including a 95% CI. Next, number needed to treat was calculated as 1 divided by the absolute risk difference.

Results

Results of search strategy

Overall, 1,385 unique citations were identified, of which 217 citations were selected for abstract review, and of those, full text evaluation was undertaken for 49 publications. Overall, 10 publications were excluded because they were observational studies; 12 publications were excluded because they were no original research article; 7 were excluded because they did not report on a direct comparison between breast conserving surgery versus breast conserving surgery plus radiotherapy; 10 were excluded because no (subgroup) analysis of older patients was included; 2 were excluded because they were not in English; 2 were excluded because no primary efficacy endpoint was included; and 1 was excluded because a more recent publication of the same study was available[21]. This resulted in 5 studies which were included the current systematic review and meta-analysis[11-13;22;23].

Description of studies

Characteristics of the included studies are shown in Table 1. The total number of patients included in this systematic review and meta-analysis is 3,190. The studies included patients between 1981 and 2005 and were published between 2004 and 2013. Inclusion in all studies was restricted to patients with relatively favourable tumor characteristics; the majority of patients had T1 tumors, without nodal involvement, and with positive hormone receptor status. All patients received adjuvant systemic therapy; in the majority of the studies, patients

Table 1. Study characteristics of the included randomized clinical trials.

Study	N	Aim	Randomization	Patient criteria	Tumor criteria	Exclusion criteria
Hughes (2013)	Total: 636 RT: 317 No RT: 319	To evaluate whether elderly women with ER-positive EBC who had BCS, can be safely treated with tamoxifen instead of RT plus tamoxifen,	Tamoxifen 20mg + breast irradiation (45Gy) + boost (14Gy) versus Tamoxifen 20mg for 5 years.	≥70 years	T1N0M0, positive/ unknown ER status**	Previous malignancy <5 years (except in situ cervical cancer or nonmelanoma skin cancer); no radical breast conserving surgery.
Tinterri (2009)	Total: 749 RT: 373 No RT: 376	To assess the role of radical breast RT in postmenopausal women with EBC undergoing BCS.	Breast conserving surgery + breast irradiation (50Gy) + boost (10Gy) versus breast conserving surgery. Adjuvant treatment was based on nodal status and biological tumor parameters.	50-75 years Postmenopausal	T12N01M0, <2.5cm	Multifocal breast cancer; multicentric breast cancer; extensive intraductal or vascular invasion like component; >3 axillary lymph nodes involved; previous malignancy.
Potter (2007)	Total 831 RT: 414 No RT: 417	To assess the role of whole breast RT in women with a favorable subgroup of EBC.	Breast irradiation (mean 51Gy) + boost (mean 10Gy) + Tamoxifen 20mg for 2 years followed by Anastrozol 1mg for 3 years versus Tamoxifen 20mg for 2 years followed by Anastrozol 1mg for 3 years	Postmenopausal	T12N0M0, <3 cm, BRI/II IDAC, BRx ILAC, HR-status positive	Previous chemotherapy, radiotherapy or endocrine therapy; no radical breast conserving surgery.
Ford (2006)	Total: 400 (205*) RT: 208 (104*) No RT: 192 (101*)	To evaluate the need for RT following BCS in women with EBC.	Breast irradiation (max. 54Gy) ± regional irradiation (50Gy) + boost (10Gy) versus no irradiation. All patients received adjuvant therapy based on hormone receptor-status.	<70 years	T12N01M0	Multifocal breast cancer; significant cardiac or renal impairment; previous malignancy.
Fyles (2004)	Total: 769 RT: 386 No RT: 383	To define the role of adjuvant RT in women ≥50 years with EBC who had BCS.	Breast irradiation (40Gy) + boost (12.5Gy) + Tamoxifen 20mg for 5 years versus Tamoxifen 20mg for 5 years.	≥50 years 734/769 (95%) postmenopausal	pT12N0M0 for patients <65 years; pT12c/ pN0M0 for patients ≥65 years ***	Bilateral breast cancer; multifocal breast cancer; previous malignancy <5 years (except in situ cervical cancer or nonmelanoma skin cancer); previous breast cancer <10 years; previous tamoxifen or chemotherapy; concurrent illness that would preclude use of tamoxifen.

EBC: early breast cancer; BCS: breast conserving surgery; RT: radiotherapy; BR: Histological grade according to Bloom Richardson; IDAC: intraductal adenocarcinoma; ILAC: intralobular adenocarcinoma; HR: hormone receptor; ER: estrogen receptor. * Number of postmenopausal patients. ** Eligibility criteria were amended in 1996 to enhance inclusion: original criteria were T12N0M0, irrespective of estrogen receptor status. *** No criteria regarding hormone receptor-status.

received adjuvant tamoxifen; in one study patients received either tamoxifen or chemotherapy depending on hormone receptor status.

As shown in Table 2, most studies restricted inclusion to postmenopausal patients. Although Ford et al included patients under 70 years of age (range 25-69 years), subgroup analyses by menopausal status were performed and hence only the results of postmenopausal patients were included in the meta-analysis[11]. Fyles et al included patients aged 50 years or older with a median age of 68 years, and reported that more than 95% of the participants were postmenopausal, 3% were premenopausal and 2% had an unknown menopausal status[12]. Therefore, we decided to include all these patients in the meta-analysis. Although the overall median age of all studies could not be calculated directly, one can derive from the data that the median age was over 65 years of age. Moreover, at least 1,254/3,190 (39%) patients were 70 years or older.

The primary outcome of most studies was locoregional recurrence, which was defined as a recurrence or a secondary breast tumor in the ipsilateral breast, or a recurrence in ipsilateral axillary lymph nodes or infra- or supraclavicular lymph nodes[11;13;22;23] (Table 3). Frequent secondary outcomes were distant recurrence or distant disease free survival, and overall survival.

Meta-analysis

The odds ratios for locoregional recurrence, distant recurrence and overall survival are shown in Figure 2. All studies observed a lower risk of locoregional recurrence for patients who were randomized to radiotherapy in addition to breast conserving surgery. The pooled analyses confirmed a lower relative risk of locoregional recurrence in patients who received radiotherapy; OR 0.36 (95% CI 0.25-0.50). There was no substantial heterogeneity across the studies (I^2 was 43%, p=0.130).

Since distant disease free survival was not uniformly described in all studies, we specifically extracted the number of distant recurrences in order to assess the pooled risk of a distant breast cancer recurrence. The relative risk of a distant recurrence was not affected by radiotherapy; the pooled OR was 0.96 (95% CI 0.68-1.36). Overall survival was also similar for both treatment modalities; the pooled OR for overall survival was 0.92 (95% CI 0.74-1.15). Again, there was no substantial heterogeneity among the studies for both outcomes.

Two sensitivity analyses were performed. First, the meta-analyses were repeated without the study results of Fyles et al[12], since a minority of the patients in this study may not have been postmenopausal. The results were unchanged (data not shown). Second, the analyses were repeated without the study results of Ford et al[11] and Hughes et al[13], since the median follow-up of these studies was twice as long, as compared to 4.5-5.6 years in the other studies. Instead we included the prior publication by Hughes et al, comprising the 5-years results[21]. Again,

the results were unchanged (data not shown). The associated funnel plots did not suggest significant publication bias (Supplementary figure 1).

Table 2. Age and tumor characteristics of patients in the included randomized clinical trials.

Study	Age	Tumor characteristics
Hughes (2013)	All ≥70 years; 351/636 (55%) ≥75 years	622/636 (98%) T1, 636/636 (100%) N0, 618/636 (97%) ER+
Tinterri (2009)	All postmenopausal; range 50-75 years; 361/749 (48%) ≥65 years	649/749 (87%) T1, 619/749 (83%) N0, 658/749 (88%) ER+
Potter (2007)	All postmenopausal; range 46-80 years; median age 66 years; 587/831 (71%) ≥60 years; 293/831 (35%) >70 years	753/831 (91%) T1, 831/831 (100%) N0, 831/831 (100%) HR+
Ford (2006)	All postmenopausal; range 44-69 years; median age 59 years	57/205 (28%) T1, 155/205 (76%) N0, 278/400 (70%) ER+*
Fyles (2004)	734/769 (95%) postmenopausal; median age 68 years; 586/769 (76%) ≥60 years; 325/769 (42%) ≥70 years	639/769 (83%) T1, 639/639 (100% N0, 621/769 (81%) HR+**

ER+: estrogen receptor positive; HR+: hormone receptor positive. * Calculated for the whole population of pre- and postmenopausal patients; ** 127/769 (17%) unknown hormone receptor status, 46/769 (6%) negative hormone receptor status.

Absolute risk

Additionally, we calculated the pooled absolute risk of locoregional recurrence, distant recurrence and all cause death for patients in both study arms. Since absolute risks are dependent on the duration of follow-up, the study by Ford et al[11] and Hughes et al[13] were not included in the calculation; the median follow-up of these studies was more than twice as much as compared to the other studies. For the study by Hughes et al, we used the prior publication in which the 5 years results were presented[21]. After a median follow-up of approximately 5 years, the absolute risk of a locoregional recurrence among those who received radiotherapy was 2.2% (33/1,490, 95% CI 1.6-3.1), versus 6.5% (97/1,495, 95% CI 5.3-7.9) among patients who did not receive radiotherapy. The absolute risk difference was 4.3% (95% CI 2.9-5.7), in favour of those who received radiotherapy in addition to breast conserving surgery, corresponding with a number needed to treat of 24 to prevent one locoregional recurrence in five years.

The 5-years absolute risk of a distant recurrence was 2.7% (40/1,490, 95% CI 1.9-3.5) in patients who received radiotherapy, versus 2.3% (35/1,495, 95% CI 1.6-3.1) in patients who did not receive radiotherapy. For all cause death, the 5-years absolute risks were 7.7% in both study arms (115/1,490, 95% CI 6.4-9.1; 115/1,495, 95% CI 6.3-9.0).

Table 3. Main outcomes and conclusions as reported by the authors of the included randomized clinical trials.

Study	FU*	Primary outcomes	Secondary outcomes	Conclusions authors	Comment authors
Hughes (2013)	10y	Locoregional recurrence (LR): supra- or infraclavicular, ipsilateral breast or lymph nodes); mastectomy for recurrence (MfR); breast cancer specific survival (DSS); distant recurrence (DR); overall survival (OS).	Cosmetic results; adverse events after up to 4 years	LR was higher in control arm. No differences were observed for MfR, DSS, DR or OS. Cosmetic results and adverse events were lower in the control arm[21].	Irradiation adds no significant benefit in terms of survival, time to distant metastasis, or ultimate breast preservation. Omission of radiotherapy is a reasonable choice in this selection of patients.
Tinterri (2009)	5y	In-breast recurrence (IBR: local recurrence, second primary in ipsilateral breast).	Distant disease free survival (DDFS; contralateral breast cancer, distant recurrence, second other primary cancer, death in the absence of cancer); overall survival (OS).	IBR was higher in the control arm, although not statistically significant. No differences were observed for DDFS and OS.	Breast irradiation after BCS can be avoided without exposing these patients to an increased risk of distant disease recurrence.
Potter (2007)	4.5y	Local relapse free survival (LRFS).	Disease free survival** (DFS; local relapse or distant metastasis); overall survival (OS); contralateral breast cancer (CBC); distant recurrence (DR).	LRFS and DFS were lower in control arm. No differences were observed for OS and DR.	For patients with favorable early stage breast cancer as addressed in the study, radiotherapy remains the major integral part of adjuvant treatment after BCS.
Ford (2006)	13.7y	Locoregional recurrence (LR); Distant recurrence (DR; not otherwise specified).	Overall survival (OS); disease free survival (DFS; not otherwise specified).	LR was higher in control arm. No differences were observed for DR, DFS or OS.	The results support a role for breast irradiation in patients who have had BCS for breast cancer, and it should be considered in every case.
Fyles (2004)	5.6y	Disease free survival (DFS; locoregional or distant recurrence, or death).	Locoregional recurrence (LR; breast or axilla); overall survival (OS)	DFS was lower and LR was higher in control arm. No differences were observed for OS.	Radiotherapy significantly reduces the risk of breast and axillary recurrence after BCS in women with small, node negative, HR–positive breast cancer.

FU: follow-up. * Median. ** The authors' definition of DFS corresponds with overall recurrence free period rather than disease free survival, since death is not included as an event.

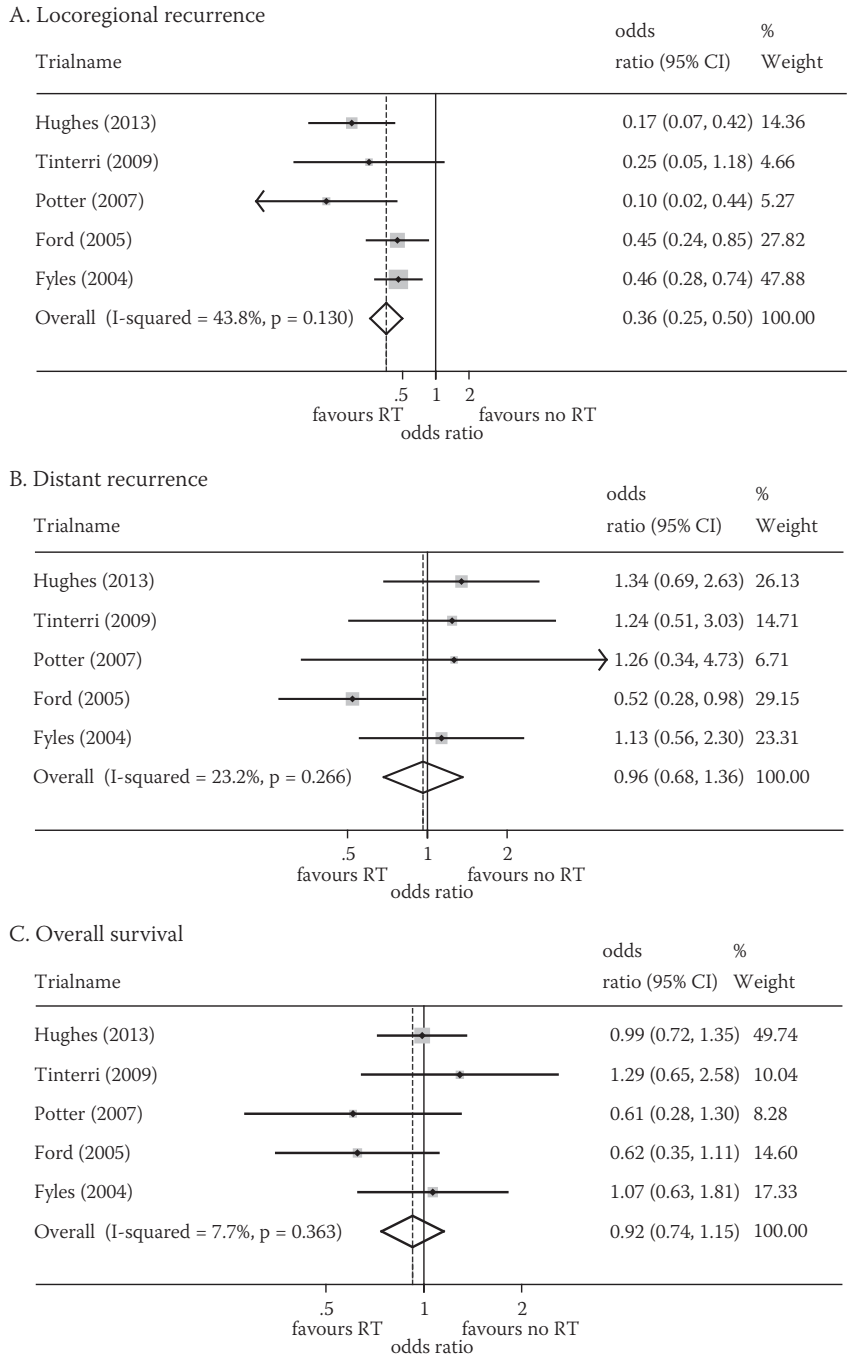


Figure 2. Odds ratios for locoregional recurrence, distant recurrence and overall survival.

Discussion

Summary of results

The current systematic review and meta-analysis clearly shows a decreased risk of locoregional recurrence for postmenopausal patients with early stage breast cancer who received radiotherapy after breast conserving surgery. The absolute risk difference for a locoregional recurrence was 4.3% after five years, corresponding with a number needed to treat of 24. No differences were observed with regards to the risks of a distant recurrence, or overall survival.

The effect of radiotherapy after breast conserving surgery has been evaluated by others[1;24]. However, few specifically studied older patients, or addressed age related considerations as competing mortality and remaining life expectancy. We decided not to include observational studies, as treatment outcomes in observational studies are confounded by indication[18]; frailty, age, tumour characteristics and presence of comorbidity all affect treatment decisions as well as outcome. As expected, most observational studies indeed observed a higher overall, disease specific or other cause mortality in patients who received breast conserving surgery as compared to patients receiving radiotherapy in addition to breast conserving surgery[8;9;25;26], although one study did not observe differences in overall survival between both treatment modalities[10]. With respect to locoregional recurrence, most observational studies[14;15;27;28], but not al[10] observed a higher risk for patients who received breast conserving surgery without radiotherapy. Recently, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed an age specific subgroup analysis of 7,287 node negative patients who received either breast conserving surgery plus or minus radiotherapy[1]. The relative risk reduction in 10-years locoregional recurrence by radiotherapy remained similar over age (overall relative risk 0.46 (95% CI 0.41-0.51)). The current study confirms a clear statistically significant benefit of radiotherapy in addition to breast conserving surgery in terms of prevention of a locoregional recurrence, even though the included patients were considered to have a low absolute risk of recurrence; the median age was over 65 years, and the majority of patients had T1 tumors without nodal involvement, with positive hormone receptor status.

To enhance the number of eligible studies, inclusion in the current study was permitted for all trials including postmenopausal patients. We are well aware of the discongruency between 'postmenopausal' and 'older', and the wide variation in age and phenotype among postmenopausal women. However, the median age of all patients in this study was over 65 years and 39% of the patients was 70 years or older. Moreover, sensitivity analyses were performed to exclude potential confounding of one study in which a minority of the patients may not have been postmenopausal. In addition, tumor and treatment characteristics were comparable among the included studies, and all patients received adjuvant systemic therapy. Nevertheless, the variation in phenotype of the included patients in the current study limits explicit recommendations for advocating omission or administration of radiotherapy. Rather than an attempt to indicate specific subgroups of patients, for clinical guidance we propose not

only to focus on relative risks but also on the absolute benefit of postoperative radiotherapy and the number needed to treat.

A low absolute risk results in a higher number needed to treat to prevent one recurrence. The number needed to treat in the current study was 24. This is expected to be higher in a non-trial population; Smith and colleagues evaluated the number of patients needed to be irradiated in order to prevent one local recurrence[15]. Patients of advanced age or those with moderate to severe comorbidity were less likely to benefit from radiotherapy, with an adjusted number needed to treat up to 125. In addition, the EBCTCG meta-analysis showed that the absolute risk reduction of radiotherapy decreased significantly with increasing age, from 24.6 (95% CI 13.2-36.0) to 8.9 (95% CI 4.0-13.8) in the oldest patients, due to a lower absolute recurrence rate[1]. This age specific decrease was also observed in other studies[12;22]. The more recently conducted randomized trials which were included in the current study seemed to observe an even lower locoregional recurrence rate[12;13;22;23]. This may be explained by the fact that studies included in the EBCTCG meta-analysis were mostly conducted in the 1970s and 1980s. These days, selection of patients may have been less precise, and hormonal status was not included in the selection criteria. Improvements in surgical treatment and the increased use and efficacy of currently available systemic treatment may have further tempered recurrence rates[29] and thereby limit the attributive effect of radiotherapy. As mentioned, all patients included in the current study received adjuvant systemic therapy. To summarize, the absolute risk of a locoregional recurrence decreases with increasing age and decreasing fitness. Moreover, the absolute risk has declined in more recent years.

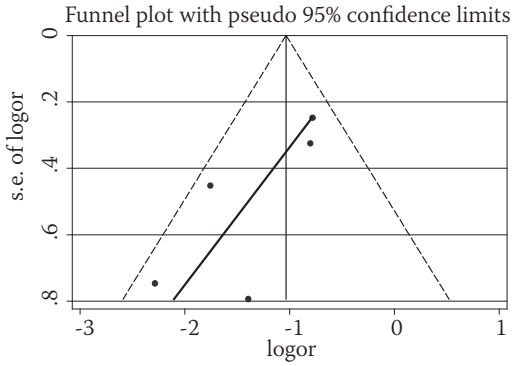
As mentioned, a low absolute risk results in a higher number needed to treat. To decrease the number needed to treat and to personalize treatment, others have tried to identify subgroups of patients in which radiotherapy could be safely omitted, based on the risk of a locoregional recurrence. The American College of Radiotherapy Appropriateness Criteria state that for women older than 70 years, with hormone receptor positive breast cancer less than two centimetre, who receive endocrine therapy, omission of radiotherapy may be reasonable[30]. A comparable statement was included in the most recent National Comprehensive Cancer Network treatment guidelines on senior adult oncology[31]. Although in the recently updated recommendations of the International Society of Geriatric Oncology (SIOG) it is stated that after breast conserving surgery, whole breast irradiation with a boost to the tumor bed should be considered in all older patients, room is left to balance pro and cons in individual cases[32].

In the debate whether or not to treat older breast cancer patients with radiotherapy in addition to breast conserving surgery, and in the identification of subgroups of patients in whom radiotherapy could be safely omitted, which outcome should be leading? The clinical significance of the observed relative risks should be considered critically: as mentioned, the absolute risk of a locoregional recurrence was low, and thereby the absolute risk reduction is rather small. Moreover, the risk of a distant recurrence and overall survival were not

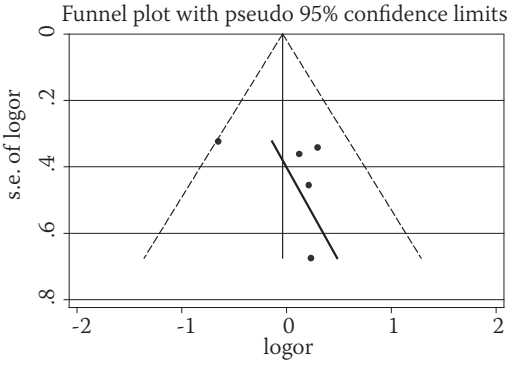
affected by radiotherapy. On the other hand, it was previously shown that older patients were less willing to exchange a prolonged survival for current quality of life[7]. Administration of radiotherapy requires frequent hospital visits, which may be impeded by decreased mobility in old age. Moreover, inferior cosmetic results and adverse events[21] may affect quality of life. Of note, development and treatment of a locoregional recurrence may also impact quality of life.

We propose that the debate should not only focus on the *relative* risk of a locoregional recurrence and on the identification of subgroups based on the relative risk of a locoregional recurrence, but instead should also be focused on the absolute benefit of radiotherapy and the number needed to treat. Both treatment options may be reasonable in clinical practice. The absolute recurrence risk should be discussed with respect to tumor characteristics, other treatment and estimated remaining life expectancy. Recently, a nomogram was developed to predict the absolute risk of mastectomy for a locoregional recurrence in older breast cancer patients in case of omission of adjuvant radiotherapy. These kind of decision tools may further aid in shared decision making when evaluating adjuvant treatment options[33]. Moreover, treatment options and quality of life in case of locoregional recurrence should be considered.

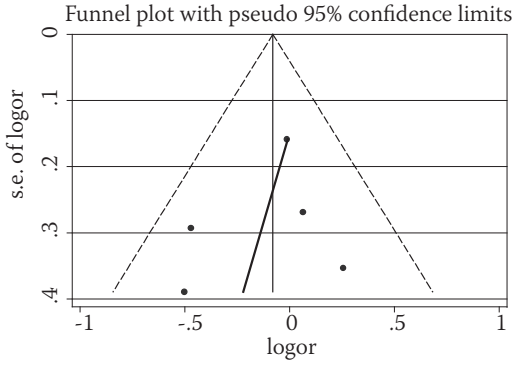
A. Locoregional recurrence



B. Distant recurrence



C. Overall survival



Supplementary figure 1. Funnel plots for evaluation of publication bias.

Reference List

(1) Darby S, McGale P, Correa C et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707-1716.

(2) Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. *J Gen Intern Med* 2011;26:783-790.

(3) Hillner BE, Mandelblatt J. Caring for older women with breast cancer: can observational research fill the clinical trial gap? *J Natl Cancer Inst* 2006;98:660-661.

(4) van de Water W, Markopoulos C, Van de Velde CJ et al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. *JAMA* 2012;307:590-597.

(5) Aapro M, Bernard-Marty C, Brain EG et al. Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. *Ann Oncol* 2011;22:257-267.

(6) Sokol KC, Knudsen JF, Li MM. Polypharmacy in older oncology patients and the need for an interdisciplinary approach to side-effect management. *J Clin Pharm Ther* 2007;32:169-175.

(7) Yellen SB, Cella DF, Leslie WT. Age and clinical decision making in oncology patients. *J Natl Cancer Inst* 1994;86:1766-1770.

(8) Keating NL, Landrum MB, Brooks JM et al. Outcomes following local therapy for early-stage breast cancer in non-trial populations. *Breast Cancer Res Treat* 2011;125:803-813.

(9) Schonberg MA, Marcantonio ER, Li D, Silliman RA, Ngo L, McCarthy EP. Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. *J Clin Oncol* 2010;28:2038-2045.

(10) Gruenberger T, Gorlitzer M, Soliman T et al. It is possible to omit postoperative irradiation in a highly selected group of elderly breast cancer patients. *Breast Cancer Res Treat* 1998;50:37-46.

(11) Ford HT, Coombes RC, Gazet JC et al. Long-term follow-up of a randomised trial designed to determine the need for irradiation following conservative surgery for the treatment of invasive breast cancer. *Ann Oncol* 2006;17:401-408.

(12) Fyles AW, McCready DR, Manchul LA et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004;351:963-970.

(13) Hughes KS, Schnaper LA, Bellon JR et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol* 2013;31:2382-2387.

(14) Geiger AM, Thwin SS, Lash TL et al. Recurrences and second primary breast cancers in older women with initial early-stage disease. *Cancer* 2007;109:966-974.

(15) Smith BD, Gross CP, Smith GL, Galusha DH, Bekelman JE, Haffty BG. Effectiveness of radiation therapy for older women with early breast cancer. *J Natl Cancer Inst* 2006;98:681-690.

(16) Bastiaannet E, Liefers GJ, de Craen AJ et al. Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. *Breast Cancer Res Treat* 2010;124:801-807.

(17) Kiderlen M, Bastiaannet E, Walsh PM et al. Surgical treatment of early stage breast cancer in elderly: an international comparison. *Breast Cancer Res Treat* 2012;132:675-682.

(18) Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet* 2004;363:1728-1731.

(19) Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-1558.

(20) Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-634.

(21) Hughes KS, Schnaper LA, Berry D et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med* 2004;351:971-977.

(22) Tinterri C, Gatzemeier W, Zanini V et al. Conservative surgery with and without radiotherapy in elderly patients with early-stage breast cancer: a prospective randomised multicentre trial. *Breast* 2009;18:373-377.

(23) Potter R, Gnant M, Kwasny W et al. Lumpectomy plus tamoxifen or anastrozole with or without whole breast irradiation in women with favorable early breast cancer. *Int J Radiat Oncol Biol Phys* 2007;68:334-340.

(24) Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. *J Natl Cancer Inst* 2004;96:115-121.

(25) Dragun AE, Huang B, Tucker TC, Spanos WJ. Disparities in the application of adjuvant radiotherapy after breast-conserving surgery for early stage breast cancer: impact on overall survival. *Cancer* 2011;117:2590-2598.

(26) Yood MU, Owusu C, Buist DS et al. Mortality impact of less-than-standard therapy in older breast cancer patients. *J Am Coll Surg* 2008;206:66-75.

(27) Truong PT, Bernstein V, Lesperance M, Speers CH, Olivotto IA. Radiotherapy omission after breast-conserving surgery is associated with reduced breast cancer-specific survival in elderly women with breast cancer. *Am J Surg* 2006;191:749-755.

(28) Livi L, Paiar F, Meldolesi E et al. The management of elderly patients with T1-T2 breast cancer treated with or without radiotherapy. *Eur J Surg Oncol* 2005;31:473-478.

(29) Fisher B, Dignam J, Bryant J et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst* 1996;88:1529-1542.

(30) Bellon JR, Harris EE, Arthur DW et al. ACR Appropriateness Criteria(R) conservative surgery and radiation--stage I and II breast carcinoma: expert panel on radiation oncology: breast. *Breast J* 2011;17:448-455.

(31) National Comprehensive Cancer Network - guideline senior adult oncology. 4-1-2013.

Ref Type: Internet Communication

(32) Biganzoli L, Wildiers H, Oakman C et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012;13:e148-e160.

(33) Albert JM, Liu DD, Shen Y et al. Nomogram to predict the benefit of radiation for older patients with breast cancer treated with conservative surgery. *J Clin Oncol* 2012;30:2837-2843.