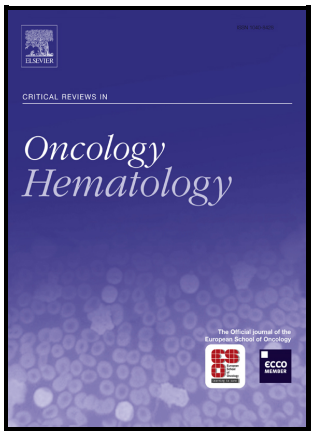

The role of radiation therapy in the multidisciplinary management of male breast cancer: a systematic review and meta-analysis

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The role of radiation therapy in the multidisciplinary management of male breast cancer: a systematic review and meta-analysis

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Keywords: male breast cancer; radiotherapy; radiation therapy; breast-conserving therapy; post-mastectomy radiotherapy; metanalysis.

Data statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Abstract

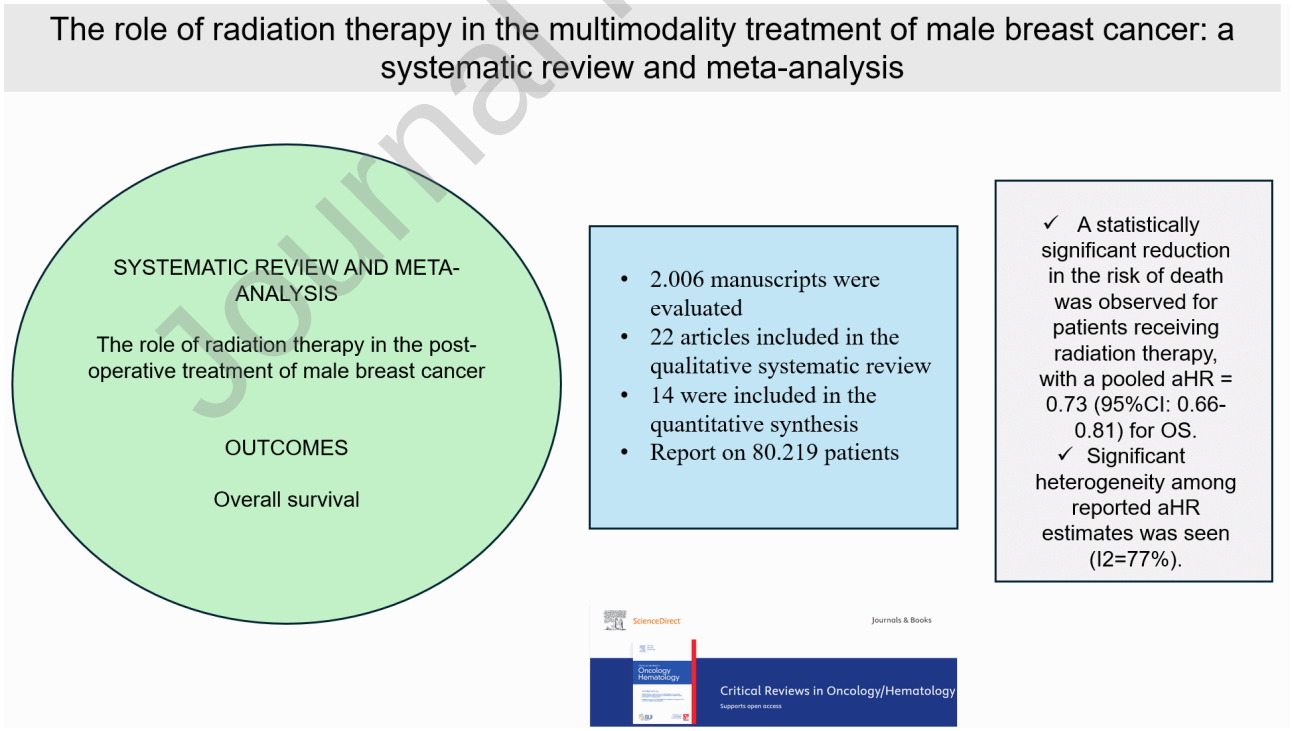
Male breast cancer (MaBC) is an uncommon disease. It is generally assimilated to post-menopausal female breast cancer and treated accordingly. However, the real impact of radiation therapy, after both mastectomy and breast conservation, has yet to be established. We performed a systematic review and meta-analysis to assess the clinical impact of radiation therapy in MBC patients to support the clinical decision-making process and to inform future research.

We performed a systematic search of ‘male’, ‘breast’, ‘cancer’, ‘radiotherapy’ and corresponding synonyms on PubMed/MEDLINE and EMBASE databases. We included interventional studies reporting on radiation therapy effect on overall survival (OS) in MBC patients. Reviews, editorials, letters to the editor, conference abstracts and case reports, and studies with less than 20 MaBC patients or without data on OS were excluded. We extracted relevant characteristics and outcomes for each study, including the hazard ratio (HR) for OS, after adjustment for potential confounders. We calculated an overall adjusted hazard ratio (aHR) for OS for patients receiving radiation therapy compared to those who did not. A random effect model was used.

The search strategy yielded 10,260 articles. After removal of duplicates (n = 8,254), 2,006 articles remained and underwent abstract screening. A total of 168 manuscripts was selected for full text screening. After full text screening, 22 articles were included in the qualitative systematic review. Among them, 14 were included in the quantitative synthesis, reporting on 80.219 MaBC patients. A statistically significant reduction in the risk of death was observed for patients receiving radiation therapy, with a pooled aHR = 0.73 (95%CI: 0.66-0.81) for OS. Significant heterogeneity among reported aHR estimates was seen (I2=77%).

A significant clinical benefit on OS has been observed when including radiation therapy in the therapeutic algorithm of patients with MaBC. These findings, which are based on retrospective studies and tumour registry reports, deserve further investigation to identify MaBC patient subgroups who most benefit from radiation therapy.

Graphical abstract



Introduction

Male breast cancer (MaBC) is a uncommon disease, comprising, less than 1% of all breast tumours and all cancers in the male population, in Western countries (1-3). The overall estimated incidence is 1 case/100.000 person-years, with geographical variations reflecting the different genetic susceptibility of the population and the exposure to risk factors (4). It has been suggested that the rate of MaBC is increasing by 1.1% per year (1,2). Although breast carcinoma presents some common risk factors in both genders (age, family history, ethnicity, and genetic mutations such as BRCA1 and BRCA2), MaBC has some peculiar predisposing conditions such as rare genetic diseases (e.g., Klinefelter syndrome) and/or endocrine factors (liver damage, testicular function impairment) (5). However, several characteristics may differ. The mean age at presentation is roughly ten years older than for female cases (6). Most MaBC patients present with clinically palpable lumps, in view of the small size of the male breast (7). Other clinical, biological, and pathological features tend to differ as well, together with survival rates, which are lower in the male population (8). All this could be partially due to the higher presence of hereditary forms caused by germline mutations in inherited susceptibility genes, and to the fact that MaBC is usually diagnosed later in a population with a shorter average life expectancy, such as males (5,9).

Regarding clinical management, MaBC is generally assimilated to post-menopausal female breast cancer. Treatment indications are most often extrapolated from study results on that female population (1). Thereby, in the absence of well-designed clinical trial results, specifically addressing treatment strategies in MaBC, most of the therapeutic indications followed by clinicians are in fact derived from female breast cancer guidelines (1).

Newly diagnosed early-stage MaBC with hormonal receptor positive disease should be offered adjuvant endocrine treatment with tamoxifen, after surgery (10,11). For men with true contraindications to tamoxifen, the use of an aromatase inhibitor combined to a GnRH analogue (to suppress testicular estrogen production) could be considered (10,11). The St. Gallen International

Consensus Guidelines for treatment of early-stage breast cancer 2021 mentioned about male breast cancer. Apart from that it is an indicator for performing genetic counselling, genomic signature testing should equally be considered in MaBC, both for N0 or N1 stages, when chemotherapy is being contemplated for hormonal receptor positive, HER2-negative disease (12).

Modified radical mastectomy is the most frequently offered surgical procedure (13). However, breast-conserving surgery (BCS) is increasingly performed, with an estimated rate of almost 20% (14). While radiation therapy (RT) is usually offered to MaBC patients after BCS, conflicting results exist for the indication to post-mastectomy radiotherapy (PMRT) (1). Although there is no solid reason to use more aggressive treatment strategies as compared to the female counterpart, with risk classification being equal, it is a common practice to offer PMRT to MaBC patients, mostly due to a perception of a high tumour to breast size ratio (15,16). Other clinical reports highlighted the fact that PMRT should be used with the same principle guiding the indication in female cases, since no evidence was found that gender may have a prognostic significance with respect to locoregional relapse free (LRFS), breast-cancer specific (BCSS) or overall (OS) survival after mastectomy and that early-stage disease may have a limited risk of loco-regional recurrence (LR) (16,17). The real impact of PMRT on survival in MBC has yet to be fully established, particularly considering the relevant rate of competing causes of death in this patient population (1).

The aim of the present systematic review and meta-analysis is to assess the clinical impact of RT in MaBC patients after either mastectomy or BCS, to support the clinical decision-making process and to inform future research in this clinical setting.

Material and methods

This systematic review has been registered in the PROSPERO international database, available at https://www.crd.york.ac.uk/prospero/ under the registration number CRD42022324694. The present study is compliant to the PRISMA 2020 guidelines for reporting systematic reviews (18).

Development of the clinical review question

The research question was developed according to the PICO criteria, identifying the patient population (P), the intervention being evaluated (I), the comparator (C) and the clinical outcomes assessed (O) (15). For the present review, the clinical research question was declined as follows: is post-operative RT (I) effective in improving OS (O) in non-metastatic MaBC patients (P) after either mastectomy or BCS compared to surgery alone (C)?

Search strategy

A systematic search of the literature was carried out and finally updated on August 31st, 2023. The search terms 'male', 'breast', 'cancer', 'radiotherapy' and corresponding synonyms were employed to search PubMed/MEDLINE, Embase and Cochrane Library databases, following the search strategy which is displayed in Table 1. All articles were then combined into a single list, and duplicates were excluded.

Data extraction

Two independent reviewers extracted data from each publication, focusing on study design, patient and tumor characteristics, type of surgery, RT details, and outcomes. The initial screening was based on titles and abstracts, excluding reviews, editorials, letters to the editor, conference abstracts, and case reports. The same authors then reviewed the full text of the remaining articles. We included studies with more than 20 male invasive breast cancer patients that reported Hazard Ratios (HR) comparing the impact of RT versus no RT on overall survival (OS), and were published in English between January 1, 2000, and December 31, 2022. Studies published before 2000 were excluded due to outdated diagnostic, staging, treatment, and RT techniques, limiting their generalizability. Articles non reporting on radiation therapy or OS analysis were also excluded. If multiple articles overlapped significantly, only the one with the largest study population was included. Reference lists of the included articles were also screened for other potentially relevant

studies. The extracted data were compared, and any disagreements were resolved through discussion, with a third reviewer providing oversight.

Outcomes and quality assessment

We selected, as primary outcome measure, the hazard ratio (HR) for OS in patients treated with RT versus no intervention. The outcomes measures were taken as aggregate data extracted from the publications and were not based on individual-level data. Since no prospective randomized trial is available in this setting, we considered effect estimates derived from non-randomized studies if adjusted for potential confounders in either propensity score matching, inverse probability treatment weighting (IPTW) or multivariable analysis. This adjusted HR (aHR) was chosen, according to the Cochrane Handbook for Systematic Reviews recommendations, being the least biased within-study estimate compared to unadjusted HR or crude survival point estimates (19). Overall survival was chosen as the primary outcome because it accounts for 'death of all causes', which was deemed as the most reliable and least biased event. Data on loco-regional control, disease free survival (DFS), BCSS, and treatment related toxicity were also collected for the qualitative synthesis. One investigator (P.F.) assessed the study quality and the possible biases of the articles included in the meta-analysis, using the Cochrane Risk Of Bias In Nonrandomized Studies of Interventions tool (ROBINS-I) and visualized using the associated risk-of-bias visualization tool (robvis) (20,21)

Statistical analysis

Reported independent associations between RT and HR, expressed as aHRs were pooled for the quantitative synthesis. The precision of the effect sizes was reported in terms of 95% confidence intervals (95% CIs). The DerSimonian and Laird random-effects model was used to compute the pooled estimates (22). Heterogeneity across aHRs of individual studies was assessed using the I2 statistic and graded according to the Cochrane Handbook for Systematic Reviews (19). We summarized 5 and 10-year OS rate estimates as median values and mean values weighted for study sample size. These summary estimates are crude (univariable) survival estimates, since they were

not adjusted for confounders, and therefore are less reliable than the pooled aHR estimates. All analyses were performed using Stata 17.0 SE software (StataCorp LLC, College Station, Texas; 'metan' package).

Results

Study selection

The selection of studies is reported in Figure 1. The search strategy yielded 10,260 articles. After removal of duplicates (n = 8,254), 2,006 articles remained and underwent abstract screening. Among them, 1,838 were excluded since inclusion criteria were not fulfilled. A total of 168 manuscripts was selected for full text screening. After full text screening, 139 articles were excluded for various reasons, including different patient population, different intervention, and lack of OS data. A total of 29 articles remained eligible for inclusion in this systematic review, of which 14 were appropriate for quantitative meta-analysis with pooling of aHRs (23-50). Twelve studies reported aHR for the use of RT with no RT as a reference. Two studies reported aHRs for the omission of RT with RT as a reference (26,35). For these studies the inverse of the aHR point estimate and the corresponding confidence intervals were computed. One study reported two different aHR estimates, for patients treated with BCS and mastectomy respectively (25). The weighted average of the aHR and confidence intervals were computed and used for quantitative assessment, employing the relative patient proportion as weight. The fifteen studies excluded from quantitative analysis reported no HR for OS (1,24,28-23,37-38,42,46-50).

Study characteristics

The main characteristics of the 29 studies included in the literature analysis are summarized in Table 2. All the studies were retrospective observational studies enrolling male patients treated between 1970 and 2019 (23-50). Studies included in the quantitative synthesis enrolled patients treated between 1970 and 2016 (23,25-27,34-36,39-41,43-45,50). Two studies reported on patients

treated exclusively with mastectomy with/without PMRT (23,34). Four studies reported on treatment outcomes for patients treated with BCS or mastectomy with/without post-operative RT (26,27,38,343). All the others included a mixed population with respect to surgery and the use of post-operative RT (1,25,28-33,34-37,39-42,44,46-50). Only one trial reported on loco-regional control (38). Eight studies reported on DFS (24,29,32,33,35,46-48). Nine studies reported on BCSS (1,29-31,233,34,37,47,50). Twenty-three studies reported on OS at 5 years (1,23-30,32-35,39-43,46-50), while 13 studies reported on 10-year outcomes (1,26-28,30,34,35,39-41,43,45,46). Treatment-related toxicity is provided in one study only (42). RT characteristics, including radiation dose/fractionation, treatment volumes and techniques are scarcely available in the reviewed manuscripts. Fourteen studies, including 80,219 MaBC patients, provided an adjusted HR for OS and were eligible for quality assessment and quantitative meta-analysis. Among these fourteen selected papers, six provided data on crude 5- and 10-year OS rates (23,25,26,34,43,45).

Qualitative assessment

The quality assessment results are presented in Figure 2. The overall quality of the studies included was considered as moderate. Patients' data was mostly retrieved from tumour registries on a retrospective frame, but inclusion and exclusion criteria were appropriately applied. The patients included in the studies had a median age ranging from 61 to 79 years, with a median follow-up duration from 30 to 314 months. A significant proportion of cases involved loco-regional advanced disease, with 0-80.2% presenting with node-positive status and 0-62.5% diagnosed with T4 invasive breast cancer. Bias due to confounding by surgical treatment was considered moderate for those studies reporting on aggregated aHR, regardless of the type of surgery performed (mastectomy versus BCS), not allowing to obtain an HR estimate adjusted for the type of surgical approach (43,26,36,39-41,43-45). No concern regarding missing data, classification of interventions or measurement of outcomes was highlighted. No reported deviation from the intended intervention (RT) was described. However, in most of the studies the variable RT was treated as a categorical

dichotomous variable, with details on dose/fractionation, technique, or compliance to treatment. A moderate concern was hence expressed for this domain. Bias in selection of the reported result was considered of low concern because of the stable nature of the outcome used in the present analysis (i.e., OS).

Quantitative assessment

Fourteen studies provided adjusted HRs for OS (23,25-27,34-36,39-41,43-45,50). All studies had a retrospective observational design. A total of 80,219 MaBC patients was included, among whom 23.697 (29.5%) received RT. Twelve studies used a Cox proportional hazards model to adjust for the effect of clinical covariates (23,27,34-36,39-41,43-45,50). The most frequently employed clinical covariates were age, ethnicity, tumour grade and size, nodal involvement, histological type, hormonal receptor status, year of diagnosis, endocrine treatment, and chemotherapy. Two separate studies performed an IPTW Cox regression model with propensity score matching to account for selection bias/confounding and determine clinical factors associated with OS (25,26). Pooled analysis across the 14 studies that provided an aHR demonstrated a statistically significant beneficial OS with an overall pooled aHR of 0.73 (95% CI: 0.66–0.81) (Figure 3). The I2 statistic revealed a significant heterogeneity in aHR estimates among the studies (I^2 =77.0%). Crude (univariable) OR outcome data as reported in all studies included in this quantitative synthesis are summarized in Table 3 (aggregate OS). At 5 years, median reported OS among 4 studies was 78.4% versus 64.3% for patients who received RT versus no RT, respectively. Weighted for study sample size, the average 5-year OS across studies was 75.8% versus 62.2%, respectively. At 10 years, median reported OS among 4 studies was 54.3% versus 54.1%, respectively. Weighted for study sample size, the average 10-year OS across studies was 52.3% versus 50.1%, respectively. No further quantitative synthesis or significance testing of these studies was performed due to the lack of adjustment for confounders in these estimates.

Discussion

Male breast carcinoma is understudied compared to the female counterpart. Information about treatment strategies and outcomes of MaBC are mostly derived from mono-institutional retrospective series or tumour registry databases. Most of the guidelines relies on data extrapolated from trials conducted in postmenopausal female breast cancer patients. This applies to RT as well. In female early-stage breast cancer patients, post-operative RT is a standard after BCS, halving the 10-year rate of any breast cancer recurrence and reducing by one sixth the 15-year breast cancer-related mortality (51). Post-mastectomy irradiation can reduce by more than 10% the rate of any recurrence at 10 years in node positive women, with an 8% reduction of 20-year breast-cancer mortality (52). This is confirmed in both patients with $\geq$ 4 positive nodes after axillary surgery and in those in the group 1-3 positive axillary nodes (52). Hence, it is increasingly common practice to offer PMRT to node positive female breast cancer patients. Additional risk factors that may drive the indication to RT in this setting are young age, primary tumour size and grade, presence of lymph vascular invasion, surgical margin status, hormonal receptor status and response to primary systemic therapy (23). In MaBC, since robust prospective data are lacking, PMRT is usually offered to high-risk patients, while RT is given as a standard in early-breast cancer after BCS, which is a surgical strategy that is currently used also in MaBC patients (23,30). It is hence important to estimate the clinical benefit of RT in MaBC. In this meta-analysis, we provided an aggregate estimate of the effect size for the addition of RT to the therapeutic strategy of MaBC. We chose, as primary outcome measure, the adjusted HR to account for potential confounding factors, which are very likely to be present given the retrospective observational nature of the included studies. In addition, we chose OS as the primary endpoint of interest, since it is less prone to biases related to the outcome measurement or potential misclassification, as compared to other endpoints, such as breast-cancer related mortality or disease-free survival. The pooled analysis across the 14 studies reporting on aHR, showed a significant effect of RT on OS, with a 27% overall reduction in the risk of death (aHR=0.73; 95%CI:0.66–0.81), favouring RT as intervention in this setting. This OS benefit might be driven by a reduction in breast-cancer mortality which is led by the established

beneficial effect of RT in preventing loco-regional recurrences. This finding is particularly relevant, since MaBC patients comprise a population in which competing causes of death are significant and may have a strong impact on OS. High rates of severe intercurrent diseases (cardiovascular, respiratory and neurological conditions) have been described in MaBC patients, together with a rate of second malignancies, as high as 12% (1,38).

Indeed, OS at 10 years in our meta-analysis is only just above 50%, with breast cancer being the cause of death in 20-30%. To put this into perspective, we recall the fact that the recent EBCTCG meta-analysis on regional lymph node RT in female breast cancer patients found a much higher overall survival of more that 75% and more than 65% at 10- and 15-years, respectively, of which about ¾ was tumor-related at 10 years and 2/3 at 15 years (53). Of note, this applies to a patient population who participated in clinical trials starting after 1989.

Hence, we postulate that, with RT showing a significant OS advantage in a clinical setting in which patients are prone to die due to causes other than cancer, RT has demonstrated clinical benefit in the specific clinical setting of MaBC patients.

The benefit of RT, according to surgical treatment, is difficult to elucidate. Most of the studies report on aHR, combining results for patients treated with mastectomy or BCS. The only study reporting on separated aHR for patients treated with BCS and mastectomy was by Bakalov et al, whose results were aggregated for meta-analytic purposes (25). Hence, it is likely that the benefit of RT in MaBC showed in the present study comes from a mixture of an OS benefit for both high-risk MaBC patients receiving PMRT (most of the patients included) and early-stage MaBC patients receiving post-operative RT after BCS (smaller proportion of patients).

The attempt to elucidate the clinical benefit of PMRT in MBC patients has been carried out through small retrospective studies or dedicated analyses performed on tumour registry data. Yu et al found a significant reduction in the rate of local recurrence after PMRT compared to no RT, in a series of 81 MaBC patients, with the greatest benefit for patients deemed at high risk of relapse (node

positive, advanced stage, unknown or ≤2mm resection margin). No benefit in terms of OS was observed in this small study (54). Conversely, Chakravarthy et al showed low rates of loco-regional failure in patients treated with exclusive mastectomy and adjuvant systemic therapy, with PMRT omission, in early-stage MBC, highlighting the importance of risk stratification and suggesting employing similar indication criteria as per female breast cancer patients (17).

The study by Abrams et al analysed 1933 MaBC patients within the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database (23). The authors performed a case-matched analysis on 630 patients to account for potential confounding factors and showed improved OS for patients receiving PMRT. A subset analysis on the unmatched cohort showed a persisting OS benefit for all node positive patients, regardless of the number of involved lymph nodes, but with the largest benefit in those with ≥4 positive nodes. Intuitively, a significant interaction was found between PMRT and well-established risk factors such as large tumour size, high tumour grade and increasing number of positive lymph nodes, providing support for using them as strong drivers for RT prescription in this clinical setting (23).

Our meta-analysis confirms the OS benefit of RT in MaBC patients, including those undergoing PMRT. Given the heterogeneity of the patient population included, we were not able to perform any subset analysis or to test for the impact of prognostic variables via meta regression. Hence, the key questions to be addressed is still which patients would mostly benefit of PMRT. The classical clinical, pathological, and biological features we normally employ in female breast cancer stratification may be of help, but the magnitude of their predictive discrimination with respect to the benefit of RT in MaBC may be different and hence, deserves further investigation. Additional risk factors that deserve consideration in MaBC are young patient age, presence of lymph vascular invasion, hormonal receptor status, surgical margins, intrinsic subtyping, and response to primary systemic therapy. The overall management of these variable during the clinical decision-making process for PMRT in MaBC is still challenging and probably needs to rely on similar consideration

we normally apply to female patients, bearing in mind that a clinical benefit for PMRT is present, as shown in our study. This observed benefit for RT aligns reasonably with the observation that MaBC cases are primarily of Luminal subtype, with a predominance of Luminal B tumors, and that compliance to endocrine adjuvant therapy has been observed to be suboptimal in these patients (55-57).

The OS demonstrated in our metanalysis by the addition of RT in MaBC is also driven by the clinical benefit of RT after BCS. This finding confirms the observation by Bateni et al, who performed a retrospective analysis of the MaBC patients retrieved from the National Cancer Database (NCD) from 2004 to 2014 (26). Despite total mastectomy being more likely to be performed, breast conserving therapy was shown to provide a higher rate of OS compared to total mastectomy (with or without RT) and to partial mastectomy alone (26). Interestingly, the same study reported on equivalent survival benefit for stage I MaBC treated with BCS and RT vs total mastectomy followed by PMRT, supporting the hypothesis that RT is the factor explaining the favourable outcome after breast conserving therapy, also in small-sized tumours (26).

A substantial heterogeneity among studies in the effect estimates was found in our metanalysis, since the I2 statistics was found to be 77%. This heterogeneity can be due to the broadly framed research question that can lead to differences in data and study design, including heterogeneity in target population, survey recruitment and administration methods, dose and schedules of interventions including RT, timing of outcome measurements, and analytical methods, such as covariates adjustments. Despite the heterogeneity, the effect estimates seem to be consistently favouring RT, with an acceptable degree of overlapping for the respective confidence intervals, supporting the reliability of the measured effect.

The limitations of the present work derive from the nature of the studies included, which may have been biased by residual confounding factors in the aHR estimate. Most studies included did adjust for confounders such as patient age, year of diagnosis, tumor stage and grade, nodal stage, ethnicity,

and hormonal receptor status. In most studies adjustment for treating centre, chemotherapy, endocrine therapy, margin status and presence of lymph vascular invasion was not possible. Additional issues comprise the potential deviations from the intended interventions, since no accurate technical data with respect to RT delivery were provided, nor with respect to its quality assurance or compliance to treatment. Given that most of the studies were based on NCD or SEER analyses, another issue involves the incompleteness of coding of RT, especially for PMRT, as noted by Jagsi et al, which lead to under identification of RT that was related to geographic location (58). Another potential bias involves selection of patients with respect to PMRT, which is usually used in case of doubt about the effectiveness of exclusive surgery in preventing loco-regional recurrence. This may have led to a misestimation of the true effect of PMRT, due to group imbalances. However, this should favour the outcomes in the no-PMRT group. The status of surgical margins may be a peculiar issue for MaBC, given the smaller volume of breast tissue and the higher potential rate of close to positive resection margin and involvement of nipple-areola complex and chest wall (59). These biases may have led to an inaccuracy of the effect size aggregate estimation. Lastly, dose fractionation was reported in only 4 of the included manuscripts (28, 33, 46, 49). All used conventional fractionation, with a median delivered dose of 50 Gy. However, the lack of data on dose schedules, particularly regarding hypofractionation, makes it challenging to draw conclusions on modern radiation therapy strategies, but we can infer from female patients.

Nevertheless, our meta-analysis showed the beneficial effect of adding RT to the treatment algorithm of MaBC patients, with a significant reduction in the risk of death. Although a homogenous estimation of the benefit across the studies was not feasible, this favourable effect seems to be consistent for both patients receiving RT after mastectomy and BCS. Waiting for high quality data derived from specific MaBC trials, including prospective real-life data registries, to identify clear drivers of RT indications, it seems sensible that the main risk factors and existing recommendations/guidelines for female patients apply also to MaBC. Nevertheless, the

improvements in systemic therapies in recent years could potentially be able to modify the magnitude of this observed benefit.

In conclusion, in a scenario involving a rare disease, such as MaBC, artificial intelligence could play a key role to support decision-making. Advanced computational tools can identify patterns and predict outcomes, even for extremely rare conditions, providing crucial insights on how to treat these patients both effectively and safely (60).

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Captions

Table.1 Search strategy and results.

N°	Search query	Pubmed	Embase	Cochrane
#1	Cancer* OR tumor* OR tumour* OR carcinoma* OR neoplasm* OR malignancy*	5.366.728	7.561.422	1.231.567
#2	Breast OR mammary	644.223	845.231	458.654
#3	Male OR man OR men	9.659.247	11.567.983	3.679.874
#4	Radiation OR radiotherapy OR X-ray OR irradiation OR RT	3.463.124	4.567.843	1.234.618
#5	#1 AND #2 AND #3 AND #4	3.154	5.569	1.537

Legend: RT: radiation therapy.

Table.2 Patient demographics, treatment characteristics, survival, and toxicity profile.

Author	Period	Sample size	N+ patients	T4 patients	Median age, years	DFS	BCSS	OS	Median FU (months)	Main results
Abrams [23]	1998-2013	PMRT: 315 No PMRT: 315	54.3%	6.5%	61-80			**PMRT**: 83% **No PMRT**:54 %		Improved OS were use of PMRT (HR= 0.551, 0.412-0.737)

Arslan [24]	1986-2009	118	50.0%	20.7%	60.5 (29–83)	3y: 72% 5y: 60%		3y: 91% 5y: 82%	40.9 (3.8–186)	Higher stages had poor OS
Bakalov [25]	2004–2015	RT: 2318 No-RT: 3899						**BCS+RT**: 75% **BCS**: 52% **MS+RT**: 50% **MS:** 56%	53.78 (29.9–82.5)	After BCS: RT improve 5y-OS and remained beneficial in all stages; After MS: RT improve OS only in stage III cancers.
Bateni [26]	2004-2014	BCS: 67 BCS+RT: 178 MS: 507			BCS: 78.9 (± 5.7) BCS+RT: 76.0 (± 4.4) MS: 76.9 (± 5.2)					No differences between BCS+ RT and MS
Bourhafour [28]	1985-2007	127	80.2%	62.5%	62 (32-91)			5y: 63% 10y: 55%	30 (3-168)	
Bradley [29]	2000-2010	146			69.5 (33-93)	5y: 62%	5y: 86%	5y: 72%		
Cloyd [30]	1983-2009	718	39.4%	3.8%			5y: 88% 10y: 83.5%	5y: 66% 10y: 46.9%	54.0 (0–294)	
Fields [31]	1973-2008	4256			65-69		**BCS+RT** 5y: 98.8% **MS** 5y: 95.5%		66 (0-431)	BCSS is positively associated with ethnicity, age and hormonal status. Increased stage and grade were bad prognostic factors.
Foerster [32]	1995-2007	108	43.6%	25.0%	67 (43-89)	5y: 53.4%		5y: 71.41%	56 (1-143)	Tumor size and a lack of progesterone receptor expression were correlated with poor patients outcome.
Johnson [33]	2000-2017	100			64 (16–87)	5y: 86%	5y: 96.2%	5y: 91.5%	112 (1–220)	
Sroufe [34]	1988-2007	**MS alone** 1888 **PMRT** 494	43.7%	20.9%	67		**MS alone** 5y: 95.6% **PMRT** 5y: 95.6%	**MS alone** 5y: 74.7% 10y: 50.8% **PMRT** 5y: 72.4% 10y: 46.3%	53 (6–235)	There was a significant improvement in OS, but not BCSS for those patients who received PMRT compared to surgery alone.
Xu [35]	1987-2012	116			62.8	**TAM adherence** 5y: 95.4% 10y: 72.8%		**TAM adherence** 5y: 97.9% 10y: 79.6% **No TAM adherence** 5y: 84.7% 10y: 50.4%	7.08 years	Higher TNM stage, negative ER, and Her-2 + and AR status increased mortality risk. Patients in the low-

						No TAM adherence 5y: 72.6% 10y: 42.3%				adherence group (adherence\ 80 %) were at significantly higher risk of death (HR = 2.93, 95 % CI = 1.19–7.24) .
Yadav [36]	2004-2014	10873	35.8%	4.8%	64			5y: 79.1%		RT was associated with improved OS in all stages
Zaenger [37]	1998-2011	1777	0%	0%			**MRM alone** *Stage I* 5y: 97% *Stage II* 5y: 91% **MRM+RT** *Stage I* 5y: 100% *Stage II* 5y: 93.6 % **BCS alone** *Stage I* 5y: 100% *Stage II* 5y: 100%: **BCS+RT** *Stage I* 5y: 96% *Stage II* 5y: 92%			
Bateni [27]	2004 - 2014	BCS + RT: 1539 BCS: 695 MS: 5165 MS+RT: 1046	28.5%	0%	BCS + RT: 61.4 BCS: 66.7 MS: 66.3 MS+RT: 63.4			**5y:** BCS + RT: 86.8% BCS: 84.9% MS: 80.6% MS+RT: 81.9% **10y:** BCS + RT: 73.8% BCS: 56.3% MS: 58% MS+RT: 56.3%	52 (IQR 30-79)	Partial mastectomy alone, total mastectomy alone, and total mastectomy with RT were associated with worse OS compared to BCT (p<0.001 all).
Cardoso [38]	1990-2010	MS+RT: 367 BCS + RT: 30 S only: 422	38.8%		68.4			OS median: 10.4 y[CI, 8.8– 11.8]	98 (0 – 286)	
Cutuli [1]	1990-2005	S+ RT: 417 S only: 72	52.8%	20.5%	66 (24-94)		5y: 89% 10y: 72%	5y: 81% 10y: 59%	58	In a multivariate analysis, axillary nodal involvement and high SBR remain prognostic factors.

Konduri [39]	2004-2014	RT: 6,647 No RT: 12,826					Median: 11.4y 5y: 75% 10y: 56%		Predictors of mortality include surgery, chemotherapy, radiation, and hormonal therapy.
Leone [40]	2003-2012	No RT: 2283 RT: 709	42.5%	6.2%	65 (23-97)		5y: 70.6 % 10y: 53.7 %	36 (0-119)	General decrease in OS in those patients did not receive surgery or radiotherapy
Leone [41]	1988-2012	No RT: 1102 RT: 161	0%	0%	66 (27-103)		5y: 85.1% 10y: 66.5%	62 (1-294)	Independent prognostic significance of age at diagnosis, tumour grade, surgery, number of lymph nodes examined and marital status.
Park [42]	2006-2016	No RT: 608 RT: 230					5y: 73.7%		Independent predictors of survival were no history of surgery, and no tamoxifen use.
Weir [43]	1998-2012	BCS only: 2455 BCS + RT: 3744 MS only: 5745 MS+RT: 4708	29.1%	4.8%	65 (58-77)		**10y BCS+RT:** 74% **10y BCS only:** 60% (p<0.001) **10y MS+RT**: 44% **MS only: 41**% (p<0.001)	55	The use of adjuvant radiation therapy was associated with a statistically significant improvement in survival
Moten [44]	1988-2008	S only: 89 RT only: 5 No treatment: 16 S + RT: 45		9.0%	68 (48-88)	**5y** 82.9% **10y** 82.9%			The patients who had received S + RT had better survival compared with the patients who had received S only (HR 0.91, 95% CI 0.87e0.95), or neither (HR 0.55, 95% CI 0.48e0.55).
Eggemann [45]	1970 - 1989	MS + RT: 348			65.5		**10y RT**: 26.4%	314 (228 – 456)	Post-mastectomy radiotherapy

		MS alone: 316						**10y S:** 11.9% **20y RT**: 18.4% **20y S**: 6.8%		is associated with longer OS in male patients with stage III breast cancer.
Fogh [46]	1990-2003	42			62 (24-90)	**RT** 5y: 90% 10y: 75% **no RT** 5y: 83.4% 10y: 69.7% **RT+TAM** 5y: 100% 10y: 83.3% **TAM alone** 5y: 90% 10y: 70% **RT alone** 5y: 50% 10y: 50% **No adj tp** 5y: 80.8% 10y: 67.9%		**RT** 5y: 90% 10y: 90% **no RT** 5y: 87% 10y: 68% **RT+TAM** 5y: 100% 10y: 100% **TAM alone** 5y: 81% 10y: 65% **RT alone** 5y: 92% 10y: 83% **No adj tp** 5y: 85% 10y: 65%	8 y (3-18 y)	5 and 10-year OS in patients who received tamoxifen and radiation was 100%, compared with 81% and 65%, respectively, with tamoxifen alone (P = .06), 92% and 83% radiation alone (P = .05), and 85% and 65% without adjuvant therapy (P = .03). Five- and 10-year DFS was 100% and 83.3% with tamoxifen and radiation, 90% and 70% with tamoxifen alone (P = .45), 50% and 50% with radiation alone (P = .05), and 80.8% and 67.9% without adjuvant therapy (P = .27).
Mc Donald [47]	1989-1998	60	47.0%	11.0%	64.5	5y: 82% 10y: 77%	5y: 89% 10y: 81%	5y: 75% 10y: 53%	7.9 years (4.5–14.3)	Males who received no adjuvant RT had a poorer survival outcome
Rogowski [48]	1998-2014	BCS + RT: 7 MS + RT: 14 S only: 36	41.3%	10.3%	66.38	**5y RT**: 76.8% **5y S**: 57.4%		**5y RT**: 88.9% **5y S**: 88.4%		
Rolf [49]	2003-2019	71			62	**RT** 5y: 67% **No RT** 5y: 47%		**RT** 5y: 95% **No RT** 5y: 100%		Higher LC in patients receiving adjuvant HT (96% vs 67%, p= .003), CT (100% vs 84%, P=.034), and RT (100% vs 75%, P=.004

Wu [50]	2010-2015	MS only: 864 MS + RT: 311 BCS only: 55 BCS + RT: 81	42.6%	8.9%	65 (22-97)		92.6%	**5y** 81.0% **8y** 69.4%	Better 5-year DFS adjuvant HT (62% vs 25%, p= .014) and RT (67% vs 47%, p= .04 Postoperative radiation therapy could improve the survival of Male BC patients undergoing BCS, with four or more node-positive or larger primary tumours.

Abbreviations*:* Adj: adjuvant*;* BCS: breast conserving surgery; BCSS: breast cancer specific survival; CT: chemotherapy; DFS: disease free survival; FU: follow-up; HT: hormone therapy; LC: local control; MS: mastectomy; MBC: male breast cancer; MRM: modified radical mastectomy; n: number; OS: overall survival; PMS: partial mastectomy; PMRT: post-mastectomy radiotherapy; PPNI: extensive nodal involvement; SBR: Scarff, Bloom and Richardson grade; SMR: standardized mortality rate; y: year

Table.3 Crude survival outcome for patients receiving or not post-operative radiation therapy.

Study, year	**Surgery**	**5-year OS**		**10-year OS**	
		RT	*No RT*	*RT*	*No RT*
Sroufe 2012	Mastectomy	72.4%	74.7%	46.3%	50.8%
Eggeman 2016	Mastectomy	NA	NA	35.1%	34.2%
Abrams 2017	Mastectomy	83%	54%	NA	NA
Weir 2018	BCS	NA	NA	74%	60%
	Mastectomy	NA	NA	44%	41%
Bateni 2019	BCS	86.8%	84.9%	73.8%	56.3%
	Mastectomy	81.9%	80.6%	56.3%	58%
Bakalov 2021	BCS	75%	52%	NA	NA
	Mastectomy	56%	50%	NA	NA
Median		78.4%	64.3%	54.3%	54.1%
Weighted mean		75.8%	62.2%	52.3%	50.1%

Legend: RT: radiation therapy; OS: overall survival; BCS: breast-conserving surgery; NA: not available.

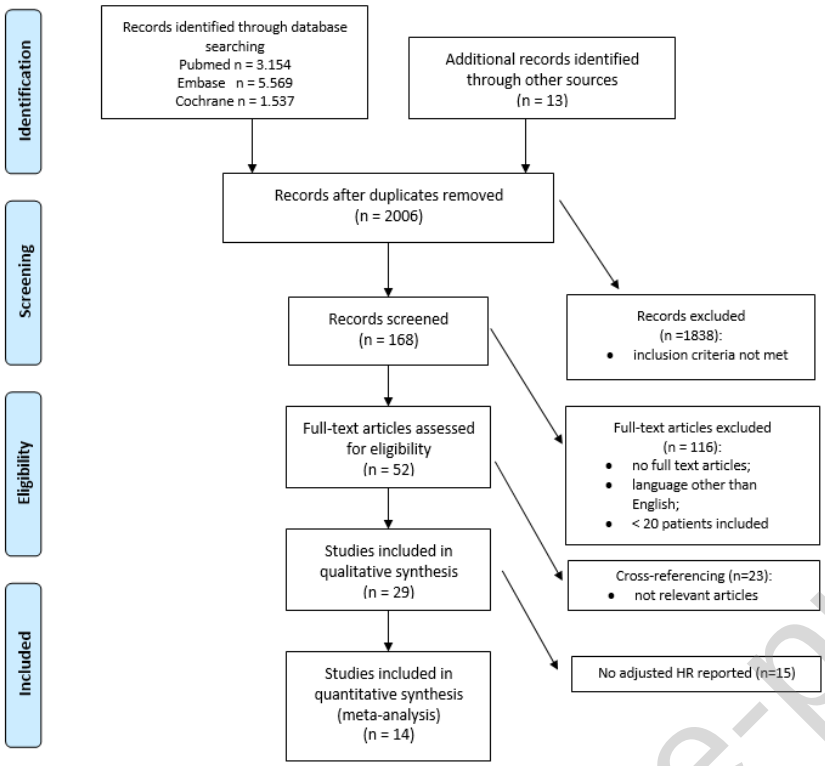

Figure.1 Flowchart summarizing search results and study selection.

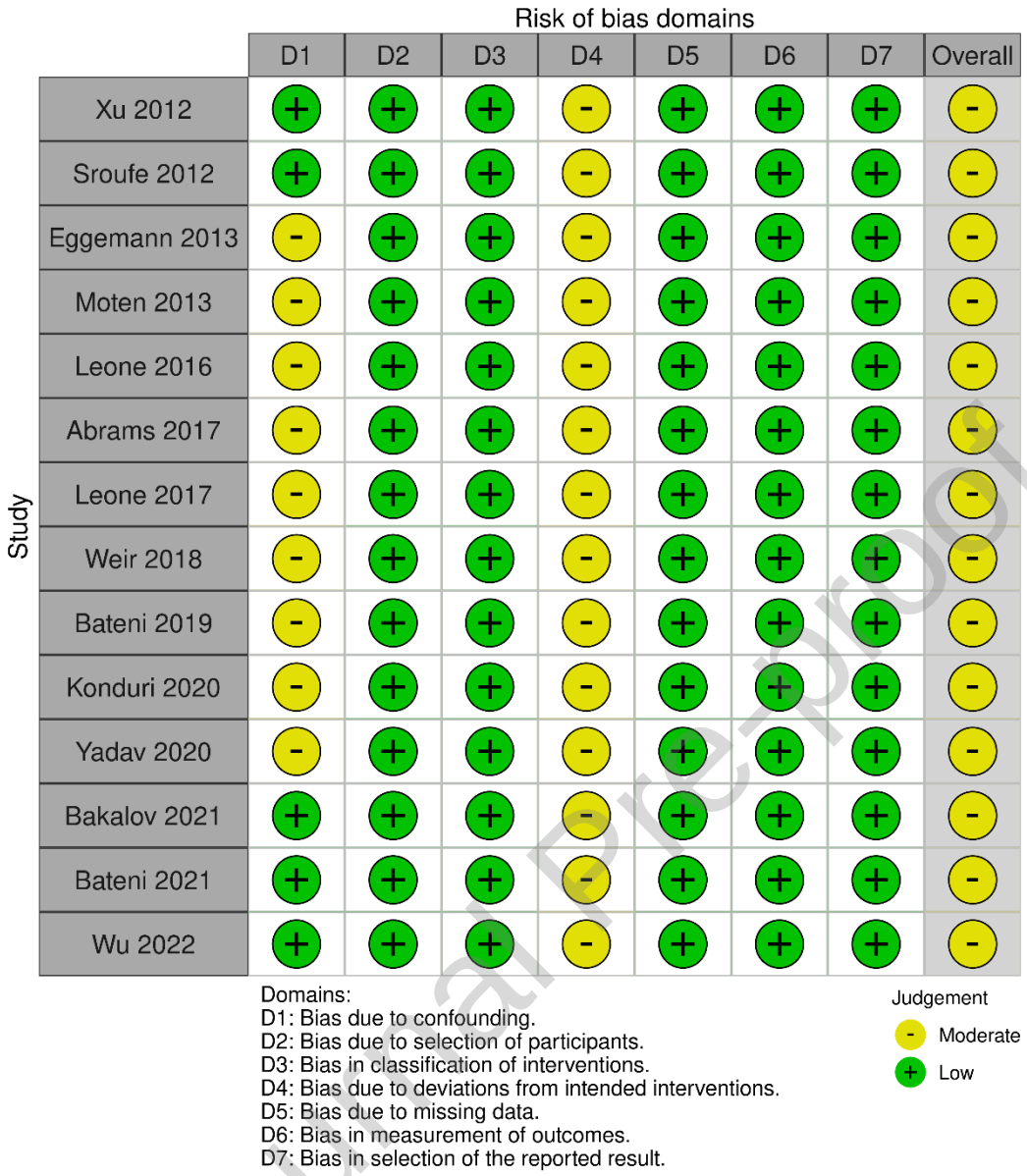

Figure.2 Risk of bias assessment for the 14 studies included in the meta-analysis.

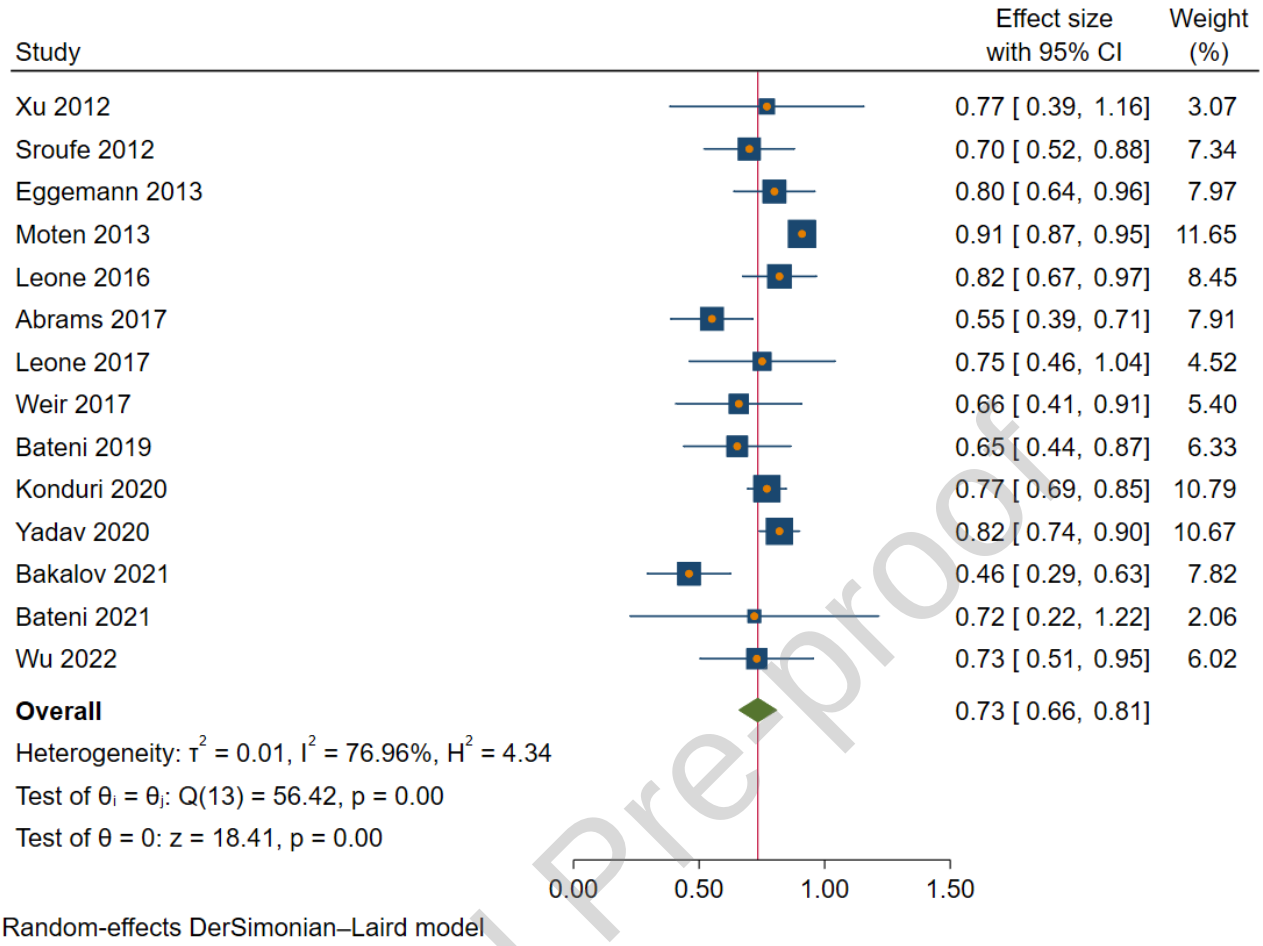

Figure.3 Forest-plot of the pooled analysis of 14 studies reporting on adjusted hazard ratios for patients receiving post-operative radiation therapy.

Biographies

Riccardo Ray Colciago MD is a radiation oncologist and clinical researcher at Università Milano Bicocca and Ospedale San Gerardo Dei Tintori Monza, Italy. He is involved in clinical research in breast cancer.

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Icro Meattini MD is an Associate Professor at the Department of Clinical and Experimental Biomedical Sciences "M. Serio" of the University of Florence (Florence, Italy), Icro Meattini works as Clinical Oncologist since 2011 at the Radiation Oncology Unit of the Oncology Department at the Florence University Hospital, where is responsible for the Outpatient Clinics Unit, Clinical Trials Unit, and leader of the Clinical Oncology Group of the Breast Cancer Multidisciplinary Team. He is an active member of the European Society for Radiation Oncology (ESTRO), the European Organisation for Research and Treatment of Cancer (EORTC), and the Italian Association of Radiotherapy and Clinical Oncology (AIRO). He is actively involved in ESTRO and EORTC network, currently he is member of the Steering Committee of the EORTC Breast Cancer Group (BCG) and of the Radiation Oncology Scientific Council (ROSC), Chair of the Breast Cancer Group of AIRO and Chair of the Clinical Oncology Breast Cancer Group (COBCG)

cooperative network. He has authored of over 200 peer-reviewed international papers and PI/co-PI of several phase 2-3 trials, his main fields of interest are breast cancer, multimodal treatments, oligometastatic disease, health-related quality of life, cardiac prevention toxicity, hypofractionation, partial breast irradiation, clinical trials research.

Pierfrancesco Franco, MD, MSc, PhD is a radiation and clinical oncologist. He is currently appointed as Chair of the Radiation Oncology Department, AOU 'Maggiore della Carità', and Associate Professor of Radiation Oncology, at the Department of Translational Medicine, University of Eastern Piedmont, in Novara, Italy. He is specifically working on breast and head and neck cancers and gastrointestinal malignancies. He is involved in clinical research and cancer education collaborating with the ESTRO, ESO and EORTC. He has a special interest in psycho oncology, health-related quality of life and supportive care.

Disclosure statement

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Declaration of Interest

Riccardo Ray Colciago: no conflict of interest to disclose related to the present manuscript.

Valentina Lancellotta: no conflict of interest to disclose related to the present manuscript.

Maria Carmen De Santis: no conflict of interest to disclose related to the present manuscript.

Elisabetta Bonzano: no conflict of interest to disclose related to the present manuscript.

Fiorenza De Rose: no conflict of interest to disclose related to the present manuscript.

Eliana La Rocca: no conflict of interest to disclose related to the present manuscript.

Bruno Meduri: no conflict of interest to disclose related to the present manuscript.

Nadia Pasinetti: no conflict of interest to disclose related to the present manuscript.

Agnese Prisco: no conflict of interest to disclose related to the present manuscript.

Alessandra Gennari: no conflict of interest to disclose related to the present manuscript.

Trine Tramm: no conflict of interest to disclose related to the present manuscript.

Serena Di Cosimo: no conflict of interest to disclose related to the present manuscript.

Nadia Harbeck: no conflict of interest to disclose related to the present manuscript.

Giuseppe Curigliano: no conflict of interest to disclose related to the present manuscript.

Philip Poortmans: no conflict of interest to disclose related to the present manuscript.

Icro Meattini: no conflict of interest to disclose related to the present manuscript.

Pierfrancesco Franco: no conflict of interest to disclose related to the present manuscript.

Credit author statement

Riccardo Ray Colciago: acquisition and interpretation of data, revising the article critically for important intellectual content.

Valentina Lancellotta: acquisition and interpretation of data.

Maria Carmen De Santis: acquisition and interpretation of data, revising the article critically for important intellectual content.

Elisabetta Bonzano: revising the article critically for important intellectual content.

Fiorenza De Rose: revising the article critically for important intellectual content.

Eliana La Rocca: revising the article critically for important intellectual content.

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Giuseppe Curigliano: revising the article critically for important intellectual content.

Philip Poortmans: revising the article critically for important intellectual content.

Icro Meattini: revising the article critically for important intellectual content.

Pierfrancesco Franco: conception and design of the study, analysis, and interpretation of data, drafting the article.

Highlights

- ✓ Male breast cancer is rare, and therapy mostly relies on female breast cancer indications
- ✓ The role of radiation therapy has yet to be fully clarified
- ✓ A 26% reduction in the risk of death after post-operative radiation therapy was found in the present meta-analysis
- ✓ Heterogeneity among studies in the effect estimates is substantial
- ✓ Further studies to identify patient subgroups who would mostly benefit from radiation therapy are needed