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Title: The value of adjuvant radiotherapy on survival and recurrence in triple-negative breast cancer: a systematic review and meta-analysis of 5,507 patients.

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ABSTRACT:

BACKGROUND: The value of adjuvant radiotherapy in triple negative breast cancer (TNBC) remains unclear. A systematic review and meta-analysis was conducted in TNBC patients to assess survival and recurrence outcomes associated with radiotherapy following either breast conserving therapy (BCT) or post-mastectomy radiotherapy (PMRT).

METHODS: Four electronic databases were searched from January 2000 to November 2015 (PubMed, MEDLINE, EMBASE and Web of Science). Studies investigating overall survival and/or recurrence in TNBC patients according to radiotherapy administration were included. A random effects meta-analysis was conducted using mastectomy only patients as the reference.

RESULTS: Twelve studies were included. The pooled hazard ratio (HR) for locoregional recurrence comparing BCT and PMRT to mastectomy only was 0.61 (95% confidence interval [CI] 0.41-0.90) and 0.62 (95% CI 0.44-0.86), respectively. Adjuvant radiotherapy was not significantly associated with distant recurrence. The pooled HR for overall survival comparing BCT and PMRT to mastectomy only was 0.57 (95% CI 0.36-0.88) and HR 1.12 (95% CI 0.75, 1.69). Comparing PMRT to mastectomy only, tests for interaction were not significant for stage (p=0.98) or age at diagnosis (p=0.85). However, overall survival was improved in patients with late-stage disease (T3-4, N2-3) pooled HR 0.53 (95% CI 0.32-0.86), and women <40 years, pooled HR 0.30 (95% CI 0.11-0.82).

CONCLUSIONS: Adjuvant radiotherapy was associated with a significantly lower risk of locoregional recurrence in TNBC patients, irrespective of the type of surgery. While radiotherapy was not consistently associated with an overall survival gain, benefits may be obtained in women with late-stage disease and younger patients.

Keywords: Triple negative breast cancer, radiotherapy, surgery, meta-analysis, survival, recurrence.

INTRODUCTION:

Triple negative breast cancer (TNBC) accounts for 10-15% of all breast cancer [1] and is defined by an immunohistochemical absence of expression for oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) [2]. Patients with TNBC typically present with high-grade disease and often an early pattern of recurrence [1,3–5]. With no drug-targetable receptors [6], chemotherapy continues to be the mainstay of treatment in TNBC patients.

At present, there are no specific clinical guidelines for treating TNBC [7,8]. Like other breast cancers, locoregional management of TNBC comprises breast conserving therapy (BCT) i.e.: breast conserving surgery followed by radiotherapy, or mastectomy (with or without adjuvant radiotherapy). While there is international consensus on indications for postmastectomy radiotherapy (PMRT) [8–10], these guidelines do not account for breast cancer subtype.

A recent systematic review of over 12,000 patients by Lowery *et al* [11] examined locoregional recurrence risk after breast cancer surgery according to receptor phenotype. The authors compared TNBC patients to other non-TNBC patients and found that TNBC was associated with an increased risk of locoregional recurrence following BCT, as well as mastectomy. The findings of this study are important, as it serves to highlight that TNBC is an aggressive disease with a higher risk of local recurrence compared to other breast cancer subtypes, irrespective of the locoregional therapy. Nevertheless, this systematic review does not provide evidence on whether the surgical procedures *per se*, or adjuvant radiotherapy therein, have any prognostic role in TNBC. In order to address the ongoing debate of

whether adjuvant radiotherapy confers any recurrence-free or survival benefit in patients with TNBC [12–16], there needs to be a direct comparison between various locoregional treatment strategies within patients with triple negative disease.

Previous studies examining recurrence and survival outcomes in patients with TNBC according to locoregional treatment status have produced conflicting results [17–29]. It is likely that several of these studies were underpowered due to their small sample size [19–21,30]. Moreover, potentially important survival differences may exist depending on disease stage [18,22] and age at diagnosis [18]. We therefore conducted a meta-analysis to determine the risk of locoregional/distant recurrence, and overall survival associated with BCT or PMRT, versus mastectomy alone in patients with TNBC. Such analysis is needed for informed decision-making regarding the optimum locoregional treatment strategies in TNBCs.

METHODOLOGY:

Search strategy

This meta-analysis was conducted in accordance to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [31]. Four electronic databases (MEDLINE, EMBASE, PubMED and Web of Science) were searched from January 2000 to November 2015. The year 2000 was chosen as a cut-off, as this is the date from which molecular subtypes of breast cancer were first defined [32]. No other date or language restrictions were imposed. The search strategy (Table 2, online only), developed in MEDLINE, was comprised of several key search terms combined with the boolean operators AND/OR aligned to relevant medical subject headings, and included various terms for ‘breast cancer’, ‘breast conserving therapy/mastectomy’, ‘triple negative’ and ‘survival/recurrence’ outcomes.

Study eligibility

Observational studies and randomised controlled trials reporting hazard ratios (HRs), odds ratios (ORs) or relative risks (RRs) and associated 95% confidence intervals (CIs) for overall and/or locoregional/distant recurrence were included if they examined 1) breast cancer patients with triple negative (non-metastatic) disease at diagnosis who 2) clearly stratified survival/recurrence endpoints by the type of surgery (mastectomy or breast conserving therapy) received and 3) in which radiotherapy status was reported. All studies in which standardised therapy was administered were considered eligible regardless of the exact chemotherapeutic regimens (i.e.: neo-adjuvant/adjuvant) or radiotherapy protocols. A concerted effort was made to contact the authors of all potentially relevant studies to obtain effect

estimates or counts of events by surgical/radiotherapy exposure status that were not reported in the original paper.

Data collection and extraction

Each electronic database was searched by the principal reviewer (MO'R). Three reviewers then indendently scanned the titles and abstracts of all identified papers after duplicate removal (MO'R, NB, LM). The full papers from all potentially relevant studies were then sourced and read. Data extraction was undertaken by two reviewers (MO'R, NB) using a pre-defined excel spreadsheet, recording detailed information on the origin of the study (country and year), characteristics of the population under study (study size, age and follow-up time, stage of disease), survival estimates and associated 95% CIs and covariates for adjustment in the analysis. The methodological quality of included cohort studies was assessed using the Newcastle-Ottawa scale [33] and the Cochrane risk of bias tool was used for assessing randomised trials [34].

Statistical analysis

Effect estimates and associated 95% CIs comparing survival and recurrence outcomes stratified by surgical type (BCT or PMRT) were extracted from all relevant papers. Wherever possible we reported on multivariable adjusted effect estimates. Within studies from which an unadjusted effect estimate could be derived from the raw counts of exposed and unexposed patients, corresponding effect estimates were estimated by calculating a rate ratio in Stata using the 'CSI' command. Individual study authors were also contacted to obtain frequencies not reported in the original article. One study [24], through personal communication with the authors, provided

anonymous individual patient data which enabled its inclusion in specific subgroup analysis. The principal quantitative synthesis involved a comparison of BCT and PMRT. Mastectomy only patients were used as the reference group in all analyses. Study-specific effect estimates were pooled using a random effects model, as described by DerSimonian and Laird [35], to account for both within-study sampling error (variance) and between-study variation. The degree of statistical heterogeniety was assessed using the Cochrane's Q test and the percentage variation in the effect estimate attributable to this heterogeniety was assessed using the I-squared statistic [36]. In post-hoc sensitivity analysis, the influence of each individual study was assessed by excluding each in turn and re-running the analyses monitoring for changes in heterogeniety and the overall summary estimate. Given the reported survival differences with adjuvant radiotherapy in more advanced disease [18,22] and younger patients [18], planned subgroup analyses by age group (<40, 40-64, ≥65 years) and early (T1-2, N0-1) and late stage (T3-4, N2-3) disease were also undertaken. Begg's rank correlation test [37] and Egger's linear regression test [38] were conducted to investigate potential small study effects or other publication biases. Stata IC v. 11.0 (StataCorp, College Station, TX, USA) was used for all analyses.

RESULTS:

A total of 1,539 papers were identified. Of these, 1,473 were clearly irrelevant from the initial screening of their title and abstract. Upon closer inspection of the remaining 66 papers (for which the full text articles were sought), only 12 met the criteria for inclusion. Justification for subsequent study exclusions are documented in Figure 1.

Table 1 summarises the characteristics of the 12 included studies. Of these, the majority (9 out of 10) were retrospective cohort studies and two were randomised controlled trials. The methodological quality of the included cohort studies was moderate to high with a mean score of six out of a possible nine (range 4 to 8; Table 3, online only). There appeared to be a low risk of bias in the included randomised controlled trials across all domains (Table 4, online only); however, blinding of surgical procedure and radiotherapy receipt was not practicable in this context. The median follow-up period ranged between 1.9 to 7.2 years across the studies and locoregional recurrence was the most commonly assessed endpoint in 9 studies [17,19–23,25,29,30]. The median age at diagnosis ranged from 50 to 59 years with the largest study including 1,138 TNBC patients [18], and the two smallest [19,30] consisted of 62 TNBC patients each. In 5 studies, patients who had undergone neo-adjuvant chemotherapy prior to surgery were excluded [17,19,25,29,30]. The majority of studies were conducted in the USA or Asia.

Locoregional recurrence

Six studies [17,19–21,29,30] examined locoregional recurrence in a total of 1,795 patients. Comparing BCT to mastectomy only, the pooled HR was 0.61 (95% CI

0.41, 0.90), Figure 2. Seven studies (2,487 patients) [17,19–23,25] compared PMRT to mastectomy only, the pooled HR was 0.62 (95% CI 0.44, 0.86), Figure 2. There was no evidence of heterogeniety in either analyses. In subgroup analysis only two studies [17,29] (1,114 patients) examined locoregional recurrence in early-stage (T1-2, N0) disease. Comparing BCT to mastectomy only, the pooled HR was 0.55 (95% CI 0.32-0.95), with no evidence of heterogenity. Two additional studies [22,23] compared PMRT to mastectomy alone and locoregional recurrence risk among women with late-stage disease (T3-4, N2-3), with a pooled HR of 0.32 (95% CI 0.16-0.65). No significant heterogeniety was present. No studies reported on the influence of age at diagnosis on locoregional recurrence by radiotherapy administration.

Distant recurrence

Five studies (1,615 patients) reported on distant recurrence [17,19,21,29,30]. The pooled HR comparing BCT to mastectomy only patients was HR 0.88 (95% CI 0.63, 1.25), Figure 3. There was no evidence of heterogeniety. Four studies (1,059 patients) [17,19,21,23] compared PMRT to mastectomy only, the pooled HR was 1.40 (95% CI 0.63, 3.10), and significant heterogeniety was detected $P_{heterogeniety}$ =0.000, I^2 = 87.6%, Figure 3. Only one study [29] examined distant recurrence in patient's with early-stage disease. It was not possible to examine the impact of late-stage disease (T3-4, N2-3) or age at diagnosis and the risk of distant recurrence by radiotherapy receipt.

Overall survival

Six studies (3,184 patients) compared BCT to mastectomy only for overall survival [17–19,21,24,29]. The pooled HR was 0.57 (95% CI 0.36-0.88), Figure 4; moderate heterogeniety was present ($P_{heterogeniety}$ =0.07, I^2 = 50.5%). There was little difference when the analysis was restricted to four studies [17,18,24,29] with multivariable adjusted estimates HR 0.57 (95% CI 0.31-1.02). Comparing PMRT to mastectomy only, the pooled HR from seven studies (3,219 patients) [17–19,21,24,27,29] was 1.12 (95% CI 0.75, 1.69) Figure 4. Again, significant heterogeniety was present ($P_{heterogeniety}$ =0.001, I^2 = 77.0%). Four studies (1,973 patients) examined overall survival in early-stage (T1-2, N0) disease [17,18,24,29], comparing BCT to mastectomy only, with a pooled HR of 0.74 (95% CI 0.43-1.29), $P_{heterogeniety}$ =0.031, I^2 = 66.1%, Figure 5 (online only). Two further studies [18,24] additionally provided an estimate of overall survival comparing PMRT to mastectomy only within T1-2, N0 tumours; pooled HR 1.10 (95% CI 0.33-3.64). Both of the above studies [18,24] also examined overall survival in relation to late stage disease (T3-4, N2-3). The pooled HR comparing BCT and PMRT to mastectomy only was 0.25 (95% CI 0.10-0.62) and 0.53 (95% CI 0.32-0.86) respectively; no statistical heterogeniety was detected. There was no statistically significant interaction between disease stage and BCT/PMRT on overall survival, $P_{interaction}$= 0.983. Combining data from two studies [18,24], the effect of age at diagnosis on overall survival comparing PMRT and BCT to mastectomy only was examined, the corresponding pooled effect estimates were HR 0.30 (95% CI 0.11-0.82) and HR 0.22 (95% CI 0.04, 1.13) age <40 years, HR 0.76 (95% CI 0.37-1.58) and HR 0.38 (95% CI 0.11, 1.31) aged 40-64 years, and HR 0.67 (95% CI 0.14-3.18) and HR 0.79 (95% CI 0.22-2.76) aged ≥65 years respectively, Figure 6 (online only). No statistically significant interaction was detected, $P_{interaction}$ =0.847.

Sensitivity analyses

For each comparison undertaken (i.e.: BCT/PMRT versus mastectomy only), in post-hoc sensitivity analysis we excluded each study in turn to monitor for individual study effects on heterogeniety and the overall effect estimate. One relatively large (n=768) study of stage T1-3, N0-3 patients [17], had a strong influence on the observed effect estimates for several of the outcomes studied. For locoregional recurrence (6 studies) comparing BCT to mastectomy only, removal of this one study [17], resulted in a slight attenuation of the overall effect estimate HR 0.72 (95% CI 0.46, 1.15), $P_{heterogeniety}$ =0.823, I^2 = 0.0%. For distant recurrence comparing PMRT to mastectomy only (4 studies), the exclusion of this same study [17], attenuated the pooled estimate HR 0.94 (95% CI 0.58-1.52) $P_{heterogeniety}$ =0.196 and explained much of the observed heterogeniety (I^2 =38.7%). For overall survival, comparing PMRT to mastectomy only (7 studies), exclusion of the study by Abdulkarim *et al* [17], again attenuated the pooled effect estimate HR 0.86 (95% CI 0.72-1.02) and significantly lowered heterogeniety (I^2 = 7.6%, P=0.363). The systematic removal of other studies, including those of different study designs (i.e.: randomised trial versus cohort study) or from conference proceedings only, failed to materially alter the overall pooled effect estimates or heterogeniety (data not shown).

Publication bias

Begg and Egger tests were undertaken to assess for publication and other small study biases. There was no evidence of publication/small-study bias in comparisons where locoregional recurrence or overall survival were study outcomes (data not shown). However, in comparisons of BCT to mastectomy alone for distant recurrence (5 studies), there was some evidence of publication or other small-study

bias (Begg p=0.221, Egger p=0.009). The resulting Egger regression plot showed deviation of the intercept from zero, indicating marked asymmetry with relatively few studies of higher precision.

DISCUSSION:

There is a paucity of studies that have examined the prognostic impact of adjuvant radiotherapy in breast cancer patients with triple negative disease. The findings from this study show that administration of adjuvant radiotherapy confers a locoregional recurrence-free survival benefit in TNBC, irrespective of the type of surgery initially received. The administration of adjuvant radiotherapy was not significantly associated with distant recurrence, and there was no consistent overall survival benefit observed between locoregional treatment groups.

Previous studies evaluating the value of radiotherapy in TNBC patients have shown conflicting results. A study of 768 patients from a comprehensive cancer centre in a single Canadian province, reported an increased risk of locoregional recurrence in T1-2, N0 TNBC patients treated with mastectomy only in comparison to those receiving BCT, suggesting that adjuvant radiotherapy may be an important factor in optimising local control; however there was no observed difference in overall survival [17]. Conversely, a retrospective study of 646 T1-2, N0 TNBC patients in the USA, reported no significant difference in locoregional recurrence between patients receiving BCT or mastectomy [29]. Several other studies which also included patients with more advanced cancer stages showed that BCT administration was associated with lower risk of locoregional recurrence than mastectomy alone, albeit not achieving statistical significance [20,21,30]. It is however likely that these studies were underpowered due to their small sample size.

A prospective, randomised controlled multi-centre study, which was conducted in the era before TNBC was recognised as a specific entity, had documented that in

women with stage I or stage II TNBC undergoing mastectomy, administration of radiotherapy combined with chemotherapy, was associated with superior local recurrence-free survival compared to chemotherapy alone [27]. In a study from the Danish Breast Cancer Co-operative Group 82 b and c trials, Kyndi et al [23] examined the impact of breast cancer subtypes on PMRT response. The trial included data from 152 TNBC patients with high-risk disease (i.e.: either positive lymph nodes or T3/4 disease), 74 of which were randomised to receive PMRT. In multivariable analysis, the authors reported significantly smaller locoregional recurrence reductions in the TNBC subtype. While the authors suggested that this was perhaps a result of increased radioresistance in these tumours, these results may be explained by the higher mitotic index and aggressive clinical course of TNBCs, which may not necessarily be radioresistant [17]. Moreover, the predisposition to BRCA mutations in TNBC patients, which renders the tumour defective in DNA repair, has been argued as a mechanism for increased radiosensitivity [12]. A prospective single institutional study of 77 TNBC patients with T1-4, N0-2 tumours in the USA [21] had found that women who did not undergo PMRT had a significantly higher risk of locoregional recurrence. Corroborating these findings, a retrospective analysis of 553 TNBC patients from a single institution in Shanghai, Chen *et al* [22] also reported that the addition of PMRT to the treatment of patients with high-risk disease (stage T3-4, N2-3) led to superior locoregional recurrence outcomes; a finding which compliments the results of the present meta-analysis.

Recently, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a meta-analysis of individual patient data from 22 randomised trials

including over 8,000 women [39]. Whilst not specifically reporting on patients with TNBC, this study found that PMRT among women with one to three positive axillary nodes, significantly reduced not only locoregional, but also distant recurrence, even when systemic therapy was given [39]. In line with this evidence, Kyndi et al [23] using data from the Danish Breast Cancer Co-operative Group trials, reported a significant increased risk of distant recurrence among TNBC patients not receiving PMRT. However, other studies have shown non-significant increased risks of distant recurrence in patients undergoing PMRT compared to mastectomy only [17,19,21]. In pooled analysis in the present study, distant recurrence was not significantly associated with either PMRT or BCT in comparison to patients recieving mastectomy only. The absence of any clear effect may be attributable to the small number of studies (low power) examining this endpoint.

In this meta-analysis, radiation therapy does not appear to be consistently associated with an overall survival benefit in TNBCs. This is in view of the fact that we only observed a higher overall survival in patients subjected to BCT compared to mastectomy only, but not in patients undergoing PMRT. Steward et al [24] conducted a retrospective investigation of 468 patients with stage I-III (T1-4, N0-3) TNBC from a single USA centre. Similar to the current findings, the authors only found a survival benefit associated with radiotherapy in women undergoing breast conservation and not in those receiving mastectomy. This observation may be partly explained by the underlying differences in patient selection for type of surgery, whereby breast conserving surgery is typically indicated for patients with smaller tumours (T1-2) [40], and conceivably a better baseline prognosis [41]. This notion is supported by the findings of the present meta-analysis, wherein the initial survival benefit associated

with BCT compared to mastectomy in all-stage patients was attenuated and non-significant within patients with very early stage disease (T1-2, N0 tumours).

Based on the pooled HRs from the current meta-analysis there was a suggestion of a stronger overall survival benefit associated with BCT compared to mastectomy alone in women with late-stage disease (T3-4, N2-3) and younger age at diagnosis (<40 years). However, these findings should be interpreted with caution as we found no evidence of effect modification by stage or age, perhaps owing to the small number of studies available for stratified analyses. Further prospective studies in these subgroups are warranted. Whilst the mechanism for a preferential overall survival benefit of adjuvant radiotherapy in younger patients is unknown, one potential explanation may be that the presence of underlying BRCA gene mutation in these patients may have influenced RT response [42], as it is suggested that tumours that arise in BRCA carriers are likely to be more sensitive to the effects of ionizing radiation [43].

A strength of the present analysis was the stratification of TNBC patients according to locoregional management (i.e.: BCT versus PMRT), as patients with a less favourable prognosis may be more likely to receive PMRT than BCT [41], making it inappropriate to classify the BCT and PMRT as a composite adjuvant radiotherapy group. In planned subgroup analysis, we attempted to ascertain differences in response to adjuvant radiotherapy by both stage of disease and age at diagnosis. The average follow-up time among the 12 included studies in this systematic review was 4.6 years (range 1.9-7.2), although in two studies follow-up was under 3 years [20,21]. Accounting for other known prognostic factors, it has been previously

reported that TNBCs exhibit a distinctive early pattern of recurrence, peaking at 2-3 years, with the majority occurring within the first 5 years [44]. Therefore, the follow-up periods in the majority of the included studies in the present review are likely adequate to determine their intended survival endpoints.

The limitations of this systematic review principally relate to the fact that it is not a meta-analysis of individual patient data and that there were only a small number of contributing studies, which were often limited by the lack of details reported in the original publication. Wherever possible, efforts were made to contact the authors of the original paper to obtain stratified frequencies of events by type of surgery and radiotherapy receipt. In all, 16 authors were contacted by e-mail for data requests. Of the 7 replies received, only 2 authors provided additional information [19,24]. Of note, two of the studies included in the present analysis were from conference proceedings only [20,30] and two were randomised controlled trials [23,27]. However, their exclusion in post-hoc sensitivity analysis did not materially alter the pooled findings. The majority of included studies were single institution, retrospective, non-randomised study designs with likely differences in the clinical and pathologic characteristics of their patient populations (Table 1). This may have inevitably contributed to the observed high heterogeneity in certain estimates.

It is also important to note that the TNBC subtype *per se*, is not in itself an indication for post-mastectomy radiotherapy [45], and that the decision to irradiate is influenced by many factors including tumour-related prognostic features (i.e.: involved margins, larger tumour size, positive lymph node status, lymphovascular invasion), patient-related factors (i.e.: socioeconomic status, patient preference/values) and health

system-related factors (physician-preference/values, availability of radiotherapy machines). Whilst some of these aspects were accounted for in the analyses of several studies included in the current meta-analysis, other factors are inherently difficult to capture and may have impacted our findings to some extent.

While it is conceivable that systemic treatment may have varied between the different settings where the studies in this review were conducted, it is felt that this may not have influenced the results to a great extent. This review addresses patients with non-metastatic triple negative breast cancer, in whom the (global) standard of care for neoadjuvant/adjuvant treatment during the study period was anthracycline +/- taxane based chemotherapy, to which TNBCs have been shown to be particularly sensitive [46]. Dose intensity may well have differed between the different study populations, particularly in Asia [47]. However, other than specifying chemotherapy regimen, this information was not available in the studies included in the current review. Only five studies reported the exclusion of patients who had undergone neo-adjuvant chemotherapy prior to surgery [17,19,25,29,30]. This may be particularly important to bear in mind, as the response to neo-adjuvant treatment may differentially affect the patterns of recurrence and overall survival in TNBC patients [48]. Many included studies whilst reporting on the raw frequencies of outcomes by type of surgery and radiotherapy use, did not conduct multivariable survival analysis. In such studies, we calculated an unadjusted risk ratio, which unfortunately leaves open the potential for confounding.

In summary, this systematic review and meta-analysis shows that adjuvant radiotheray, irrespective of the extent of initial breast surgery, is associated with

locoregional recurrence benefits in patients with TNBC. However radiotherapy, was not consistently associated with an improvement in overall survival. While subgroup analyses seem to suggest that adjuvant radiotherapy may be more strongly associated with an overall survival gain in patients with T3-4,N2-3 tumors, as well as in women aged less than 40 years, these observations need to be interpreted with caution in light of the small number of contributing studies, and absence of effect modification by stage, and age at diagnosis. There is hence a need, for future prospective clinical trials to assess the role of adjuvant radiotherapy in TNBC subgroups who currently fall outside the remit of conventional radiotherapy guidelines. In future work, the authors plan to conduct an individual participant data meta-analysis to improve understanding on the continued debate of adjuvant radiotherapy in TNBC.

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LEGENDS:

Table 1: Characteristics of included studies

Figure 1: Flow diagram illustrating study identification, selection and inclusion.

Figure 2: Forest plots of locoregional recurrence comparing breast conserving therapy or post mastectomy radiotherapy to patients receiving mastectomy only.

Figure 3: Forest plots of distant recurrence comparing breast conserving therapy or post mastectomy radiotherapy to patients receiving mastectomy only.

Figure 4: Forest plots of overall survival comparing breast conserving therapy or post mastectomy radiotherapy to patients receiving mastectomy only.

Figure 5 (online only): Forest plot of overall survival comparing breast conserving therapy to mastectomy only in a subgroup of patients with early and late-stage disease.

Figure 6 (online only): Forest plot of overall survival comparing post-mastectomy radiotherapy and breast conserving therapy to mastectomy only by age group

Table 1: Characteristics of included studies

Study ID & country/region	***Study design***	***TNBC study population***	***Study size*** *(TNBC cases)*	***Age*** *(years)*	***Follow-up time*** *(years)*	***Stage of disease***	***Survival estimates***	***Chemotherapy***	***Adjustments***
Abdulkarim 2011 [17] *Canada*	Retrospective cohort study	Newly diagnosed TNBC from Jan 1998 and Dec 2008 in a single cancer centre (Alberta).	768	Median: 56	Median: 7.2	T1-3, N0-2	OS, LRR, DM	Excluded patients with NCT. 85% CT	Tumour size, grade, LN status, LVI, chemotherapy
Bhoo-Pathy 2015 [18] *Asia*	Retrospective cohort study	Non-metastatic TNBC patients from hospital-based cancer registries in five Asian centres (University Malaya Medical Centre, Malaysia, National Cancer Centre, Singapore, National University Hospital, Singapore, Tan Tock Seng Hospital, Singapore, and Queen Mary and Tung Wah Hospital, Hong Kong) diagnosed between 2006 and 2011.	1,138	Median: 53	Median: 3.6	T1-4, N0-3	OS	13% NCT 75.8% CT	Centre (UMMC, NUH, NCCS, TTSH, QMTWH), age at diagnosis, race, tumour size at diagnosis, number of positive axillary lymph nodes, tumour grade (low, moderate, high), surgical margins (free, involved), lymphovascular invasion (present, absent), neo-adjuvant chemotherapy (yes, no) and adjuvant chemotherapy administration and regimen (none, first generation, second generation, third generation).
Chen 2013 [22] *China*	Retrospective cohort study	TNBC from a single institution (Fudan University, Shanghai Cancer Centre, Shanghai China) diagnosed between the 1st January 2000 and the 31st July 2007.	553	52	5.4	T1-4, N0-3	LRR, DFS	88% CT % NCT NR	Age, PMRT treatment, Lymphovascular invasion, grade, tumour size, lymph node status (4 or more positive vs. one to three positive), and chemotherapy regimen.

Study ID & country/region	***Study design***	***TNBC study population***	***Study size*** *(TNBC cases)*	***Age*** *(years)*	***Follow-up time*** *(years)*	***Stage of disease***	***Survival estimates***	***Chemotherapy***	***Adjustments***
Cruz 2014 [19] *Brazil*	Retrospective cohort study	TNBC patients submitted to surgical treatment from Jan 2000 and Dec 2005 at one University hospital (Hospital Santa Casa de Misericordia de Porto Alegre, Brazil).	62	NR	Average: 4.8	T1-4, N0-3	OS, LRR, DM	Excluded patients with NCT. 85.7% CT	Unadjusted
Dragun 2011 [21] *USA*	Prospective cohort study	Prospective study of non-metastatic TNBC patients undergoing treatment between 2004-2009 from the University of Louisville's James Graham Brown Cancer Centre.	77	50	1.9	T1-T4, N0-N2	OS, LRR, DM	32.5% NCT 55.8% CT	Unadjusted
*Eastman 2012** [20] *USA*	Retrospective cohort study	Retrospective review of patients with TNBC undergoing treatment between Jan 2004 and Jan 2011 in a comprehensive, multidisciplinary breast oncology programme at the University of Texas, Dallas, USA.	180	NR	Median: 2.5	T1-4, N0-3	LRR	NR	Unadjusted
Kyndi 2008 [23] *Denmark*	Randomised Controlled Trial	Patients diagnosed from 1982 to 1990 with high-risk breast cancer enrolled onto the Danish Breast Cancer Collaborative Group Trial 82 B & C (pre-menopausal and menopausal women respectively).	152	NR	NR	T3-4, N1-3	LRR, DM	NR	Unadjusted
*Ly 2012** [30]	Retrospective	Retrospective study of TNBC patients with early	62	NR	3.3	T1-2,	LRR, DM	Excluded patients with	Unadjusted

Study ID & country/region	***Study design***	***TNBC study population***	***Study size*** *(TNBC cases)*	***Age*** *(years)*	***Follow-up time*** *(years)*	***Stage of disease***	***Survival estimates***	***Chemotherapy***	***Adjustments***
USA	cohort study	stage disease treated at the Jackson Memorial Hospital, Miami (FL) from 2004 to 2010.				N0-1		NCT. 72.6% CT	
Steward 2014 [24] *USA*	Retrospective cohort study	Retrospective study of TNBC patients from a prospectively maintained database with a diagnosis of stage I-III disease who were treated between Jan 1, 2002 and Dec 31, 2009.	468	Average: 54	Median: 4.3	T1-4, N0-3	OS	32% NCT 50% CT	A backward selection model was chosen (p<0.15). Only stage (1, 2a, 2b, 3 and unknown) was significant in the multivariable model. Other variables considered included age (<50, >=50), ethnicity, clinical T stage, histology, nuclear grade and nodal status.
Tseng 2015 [25] *USA*	Retrospective cohort study	Non-metastatic TNBC diagnosed from 1997 to 2012 at one of 9 participating National Comprehensive Cancer Network institutions including: City of Hope comprehensive cancer centre, Dana-Farber/Brigham and Women's cancer centre, Massachusetts General Hospital, Fox Chase Cancer Centre, The University of Texas MD Anderson cancer centre, Roswell Park cancer institute, University of Michigan, Ohio State University comprehensive	695	Average: 52	Median: 4.2	T1-4, N0-3	LRR	Excluded patients with NCT	Number of positive lymph nodes, tumour size, surgical margin.

Study ID & country/region	***Study design***	***TNBC study population***	***Study size*** *(TNBC cases)*	***Age*** *(years)*	***Follow-up time*** *(years)*	***Stage of disease***	***Survival estimates***	***Chemotherapy***	***Adjustments***
		cancer centre and Duke comprehensive cancer centre.							
Wang 2011 [27] *China*	Randomised Controlled Trial	Multi-centre trial of consecutive patients with TNBC stage I-II breast cancer enrolled between February 2001 and February 2006.	681	NR	Median 7.2	T1-2, N0-3	OS	54% CT	Unadjusted
Zumsteg 2013 [29] *USA*	Retrospective cohort study	TNBC patients identified from clinical pathology reports (an institutional database). These were consecutive patients treated at a single institution (Memorial Sloan-Kettering Cancer Centre) from 1999 to 2008.	646	Median: 59	Median 6.5	T1-2, N0	OS, DM, LRR, DFS	Excluded patients with NCT. 81.3% CT	Age (>50, <=50), Race (black vs non-black), T stage (Tmic/T1a/T1b, T1c, T2) LVI (yes vs. no), Grade (3 vs. 1 or 2), Chemotherapy (yes vs. no).

** Conference abstracts only.*

NR = not reported, TNBC = triple negative breast cancer, LRR= local regional recurrence, DM = distant metastases, DFS= disease-free survival, CT= adjuvant chemotherapy, NCT = neo-adjuvant chemotherapy, PMRT=post mastectomy radiotherapy

Table 2 (online only): Literature search strategy example
MEDLINE: 1946-Week 4 October 2015, Limited to publications from 2000 onwards

1	Breast/ or Breast Neoplasms/ or Triple Negative Breast Neoplasms/
2	breast cancer.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3	1 or 2
4	breast conserving therapy.mp.
5	breast conserving surgery.mp. or Mastectomy, Segmental/
6	breast conservation.mp.
7	breast preservation.mp.
8	breast sparing surgery.mp.
9	wide local excision.mp.
10	lumpectomy.mp. or Mastectomy, Segmental/
11	quadrantectomy.mp.
12	Mastectomy, Subcutaneous/ or Mastectomy, Extended Radical/ or Mastectomy/ or Mastectomy, Radical/ or mastectomy.mp. or Mastectomy, Modified Radical/ or Mastectomy, Simple/
13	Fatal Outcome/ or outcome.mp.
14	Disease-Free Survival/ or Survival/ or survival.mp.
15	Recurrence/ or Neoplasm Recurrence, Local/ or recurrence.mp.
16	overall survival.mp.
17	cancer specific survival.mp.
18	cause specific survival.mp.
19	recurrence free survival.mp.
20	locoregional control.mp.
21	mortality.mp. or Mortality/
22	Disease Progression/ or progression.mp.
23	prognosis.mp. or Prognosis/
24	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
25	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
26	basal like.mp.
27	triple negative.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
28	26 or 27
29	3 and 24 and 25 and 28
30	limit 29 to yr="2000 -Current"

Table 3 (online only): Methodological quality assessment of cohort studies [33] included in the systematic review and meta-analysis

	Methodological quality assessment									
	Selection				Comparability		Outcome			
Study ID	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**Total score†**
Abdulkarim 2011 [17]	-	*	*	*	*	*	*	*	-	7
Bhoo-Pathy 2015 [18]	*	*	*	*	*	*	*	*	-	8
Chen 2013 [22]	-	*	*	*	*	*	*	*	-	7
Cruz 2014 [19]	-	*	*	*	-	-	*	*	-	5
Dragun 2011 [21]	-	*	*	*	-	-	*	-	*	5
Eastman 2012 [20]	-	*	*	*	-	-	*	-	-	4
Ly 2012 [30]	-	*	*	*	-	-	*	*	-	5
Steward 2014 [24]	-	*	*	*	*	*	-	*	-	6
Tseng 2015 [25]	*	*	*	*	*	*	*	*	-	8
Zumsteg 2013 [29]	-	*	*	*	-	*	*	*	-	6

Selection (4*):
A = Representativeness of the exposed cohort
B = Selection of the non-exposed cohort
C = Ascertainment of exposure
D = Outcome of interest not present at the start
Comparability (2*):
E = Comparability – axillary node status
F = Comparability – tumour size or stage
Outcome (3*):
G = Assessment of outcome
H = Was follow-up long enough
I = Adequacy of follow-up

† A total of 9 points can be awarded, 4 for selection, 2 for comparability and 3 for outcome.

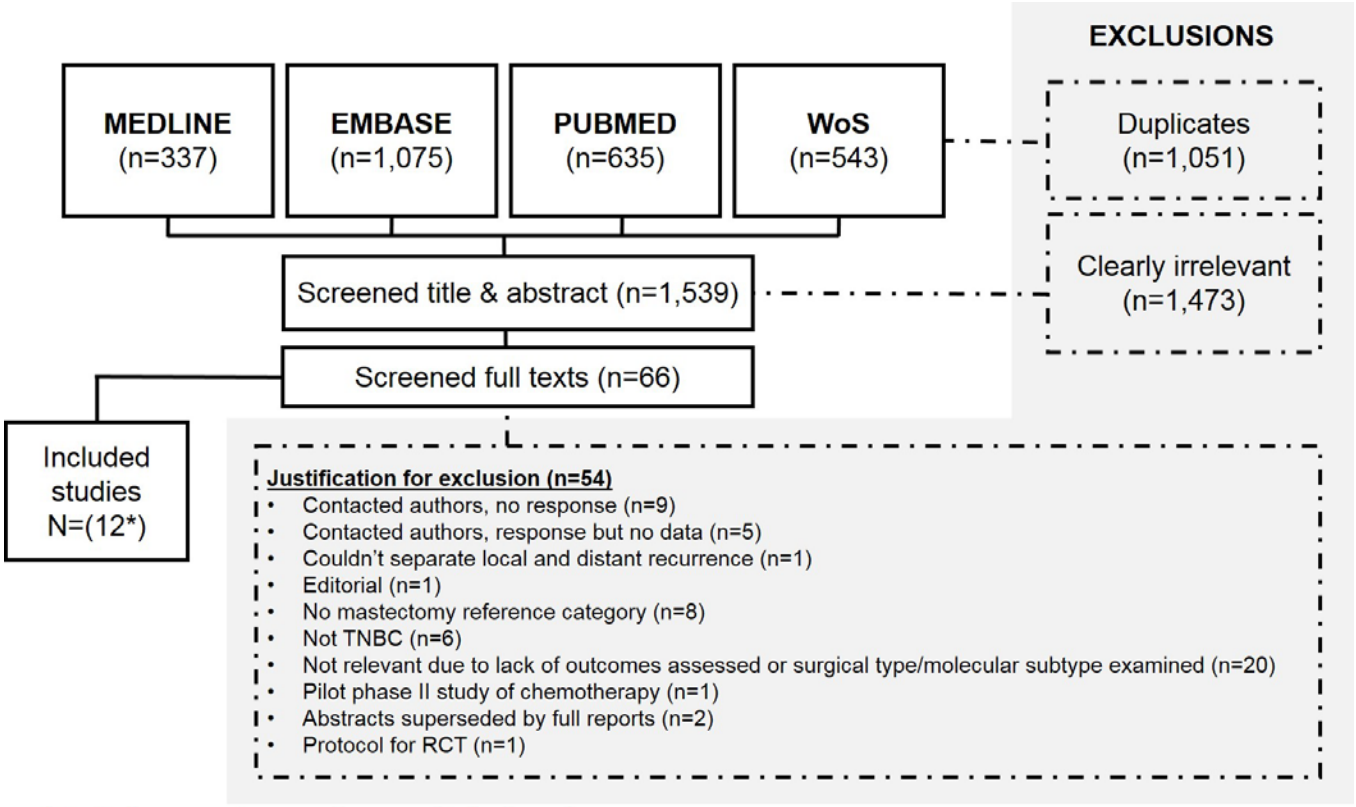
Table 4 (online only): Methodological quality assessment of randomised controlled trials [34] included in the systematic review and meta-analysis

	Risk of bias						
Study ID	A	B	C	D	E	F	G
Kyndi 2008 [23]	+	+	?	?	+	+	+
Wang 2011 [27]	+	+	?	?	+	+	+

A = Random sequence generation
B = Allocation concealment
C = Blinding of participants & personnel
D = blinding of outcome assessment
E = Incomplete outcome data
F = Selective reporting
G = Other bias

Key:
+ Low risk of bias
− High risk of bias
? Unclear risk of bias

Figure 1:



* 2 studies were from conference abstracts only

Figure 2:

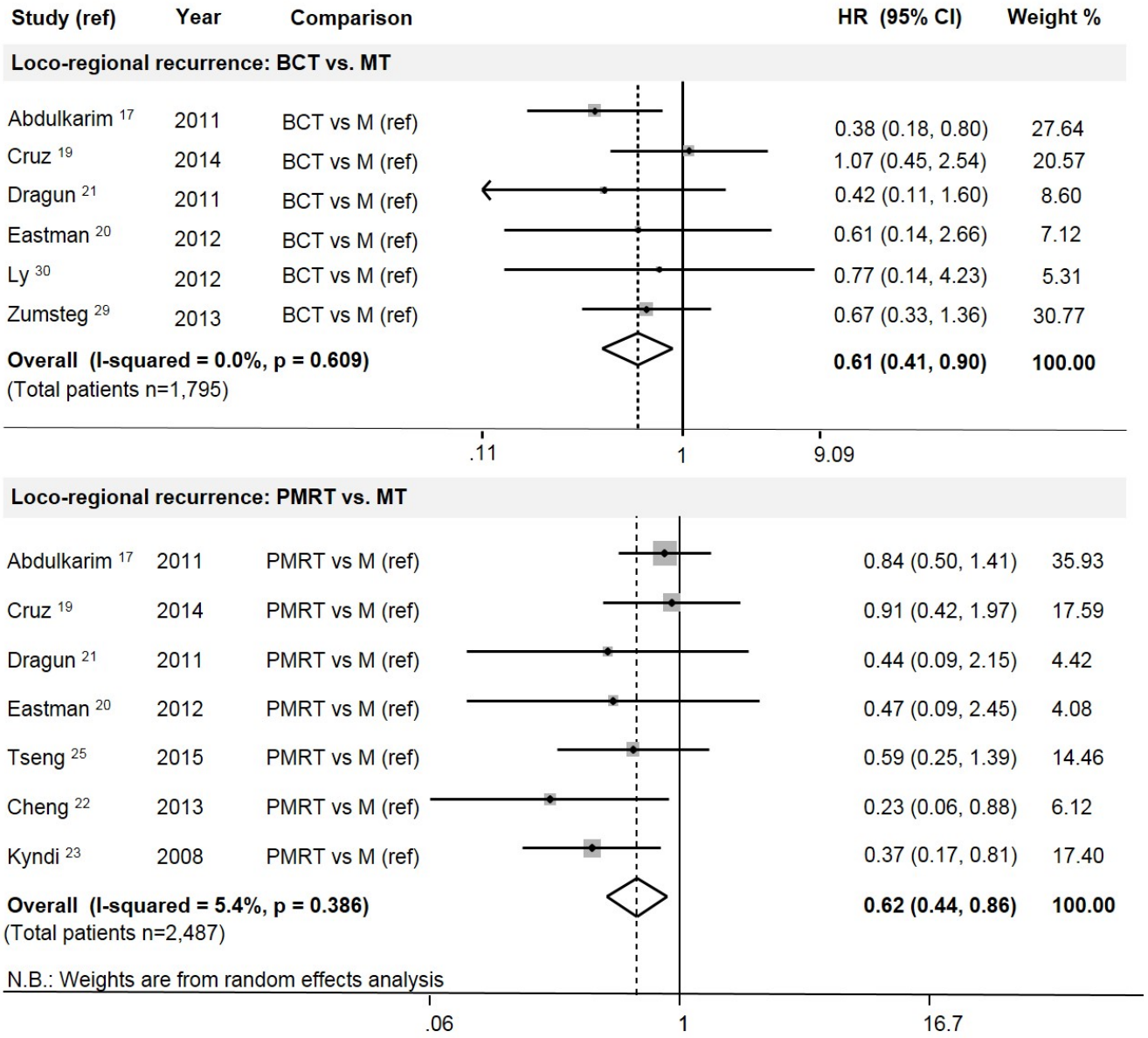

Study (ref) Year Comparison HR (95% CI) Weight %
Loco-regional recurrence: BCT vs. MT
Abdulkarim 17 2011 BCT vs M (ref) 0.38 (0.18, 0.80) 27.64
Cruz 19 2014 BCT vs M (ref) 1.07 (0.45, 2.54) 20.57
Dragun 21 2011 BCT vs M (ref) 0.42 (0.11, 1.60) 8.60
Eastman 20 2012 BCT vs M (ref) 0.61 (0.14, 2.66) 7.12
Ly 30 2012 BCT vs M (ref) 0.77 (0.14, 4.23) 5.31
Zumsteg 29 2013 BCT vs M (ref) 0.67 (0.33, 1.36) 30.77
Overall (I-squared = 0.0%, p = 0.609) 0.61 (0.41, 0.90) 100.00
(Total patients n=1,795)
.11
1
9.09
Loco-regional recurrence: PMRT vs. MT
Abdulkarim 17 2011 PMRT vs M (ref) 0.84 (0.50, 1.41) 35.93
Cruz 19 2014 PMRT vs M (ref) 0.91 (0.42, 1.97) 17.59
Dragun 21 2011 PMRT vs M (ref) 0.44 (0.09, 2.15) 4.42
Eastman 20 2012 PMRT vs M (ref) 0.47 (0.09, 2.45) 4.08
Tseng 25 2015 PMRT vs M (ref) 0.59 (0.25, 1.39) 14.46
Cheng 22 2013 PMRT vs M (ref) 0.23 (0.06, 0.88) 6.12
Kyndi 23 2008 PMRT vs M (ref) 0.37 (0.17, 0.81) 17.40
Overall (I-squared = 5.4%, p = 0.386) 0.62 (0.44, 0.86) 100.00
(Total patients n=2,487)
N.B.: Weights are from random effects analysis
.06
1
16.7

Figure 3:

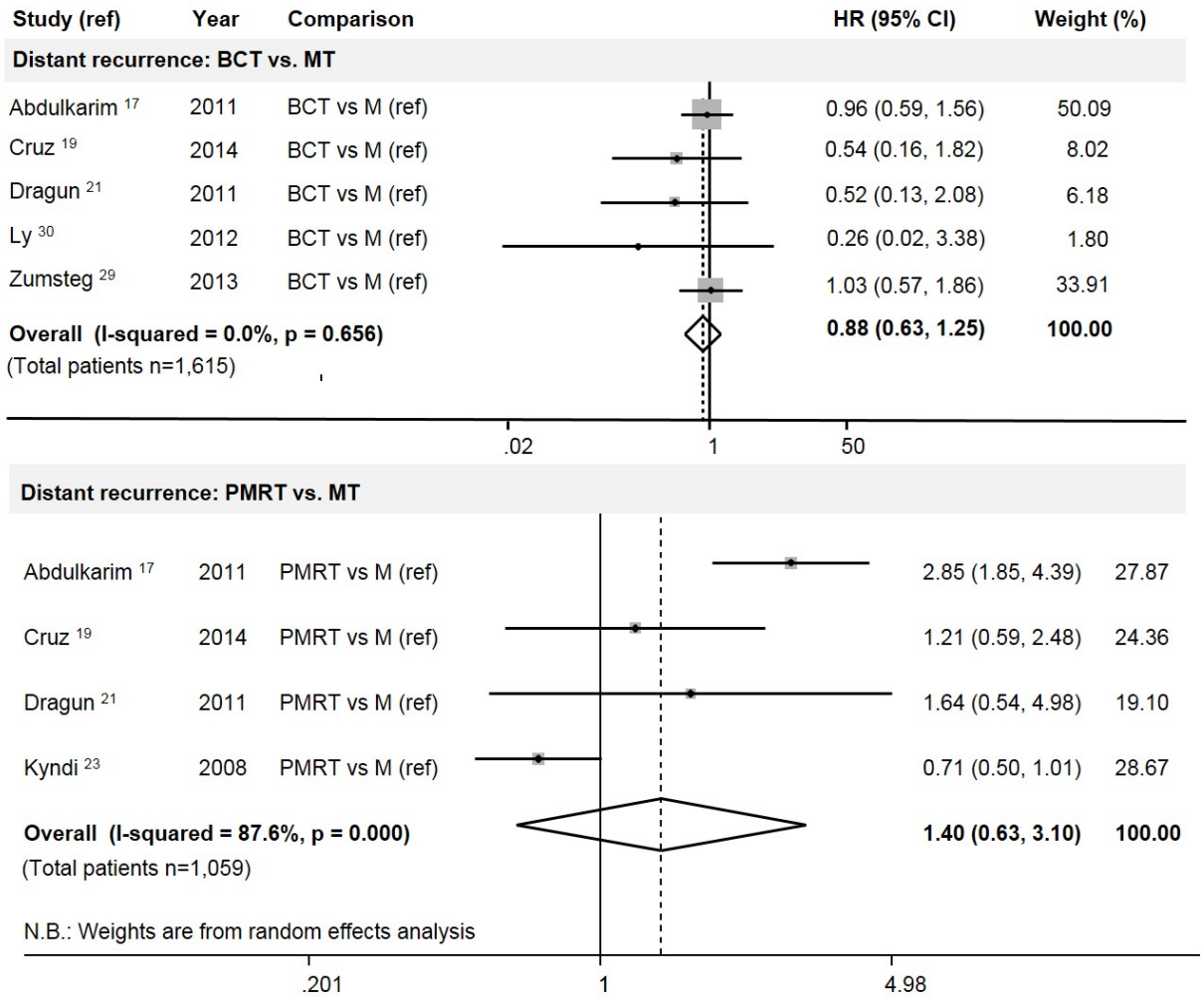

Study (ref) Year Comparison HR (95% CI) Weight (%)
Distant recurrence: BCT vs. MT
Abdulkarim 17 2011 BCT vs M (ref) 0.96 (0.59, 1.56) 50.09
Cruz 19 2014 BCT vs M (ref) 0.54 (0.16, 1.82) 8.02
Dragun 21 2011 BCT vs M (ref) 0.52 (0.13, 2.08) 6.18
Ly 30 2012 BCT vs M (ref) 0.26 (0.02, 3.38) 1.80
Zumsteg 29 2013 BCT vs M (ref) 1.03 (0.57, 1.86) 33.91
Overall (I-squared = 0.0%, p = 0.656) 0.88 (0.63, 1.25) 100.00
(Total patients n=1,615)
.02
1
50
Distant recurrence: PMRT vs. MT
Abdulkarim 17 2011 PMRT vs M (ref) 2.85 (1.85, 4.39) 27.87
Cruz 19 2014 PMRT vs M (ref) 1.21 (0.59, 2.48) 24.36
Dragun 21 2011 PMRT vs M (ref) 1.64 (0.54, 4.98) 19.10
Kyndi 23 2008 PMRT vs M (ref) 0.71 (0.50, 1.01) 28.67
Overall (I-squared = 87.6%, p = 0.000) 1.40 (0.63, 3.10) 100.00
(Total patients n=1,059)
N.B.: Weights are from random effects analysis
.201
1
4.98

Figure 4:

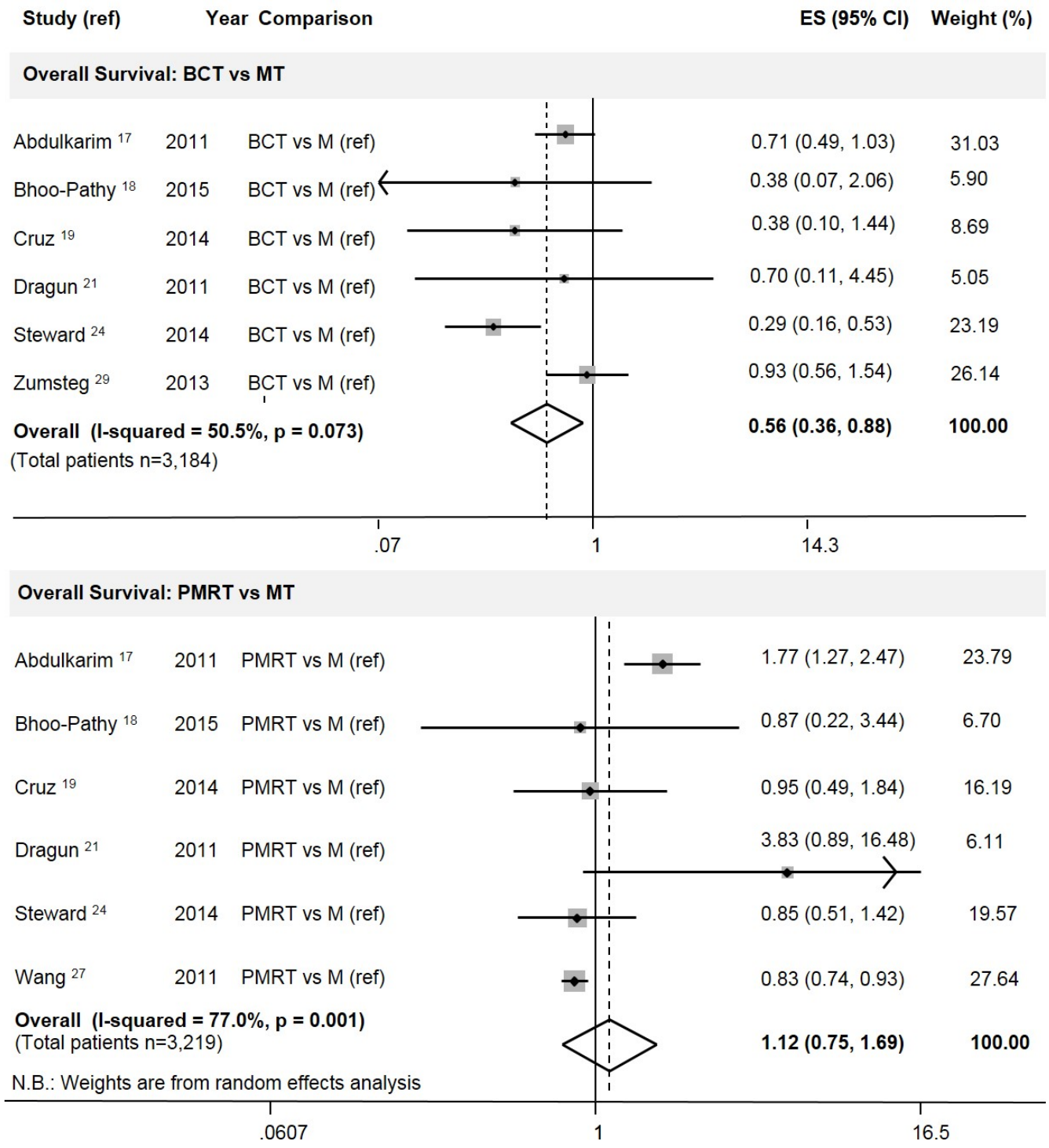

Study (ref)
Year
Comparison
ES (95% CI)
Weight (%)
Overall Survival: BCT vs MT
Abdulkarim [17] 2011 BCT vs M (ref) 0.71 (0.49, 1.03) 31.03
Bhoo-Pathy [18] 2015 BCT vs M (ref) 0.38 (0.07, 2.06) 5.90
Cruz [19] 2014 BCT vs M (ref) 0.38 (0.10, 1.44) 8.69
Dragun [21] 2011 BCT vs M (ref) 0.70 (0.11, 4.45) 5.05
Steward [24] 2014 BCT vs M (ref) 0.29 (0.16, 0.53) 23.19
Zumsteg [29] 2013 BCT vs M (ref) 0.93 (0.56, 1.54) 26.14
Overall (I-squared = 50.5%, p = 0.073) 0.56 (0.36, 0.88) 100.00
(Total patients n=3,184)
.07
1
14.3
Overall Survival: PMRT vs MT
Abdulkarim [17] 2011 PMRT vs M (ref) 1.77 (1.27, 2.47) 23.79
Bhoo-Pathy [18] 2015 PMRT vs M (ref) 0.87 (0.22, 3.44) 6.70
Cruz [19] 2014 PMRT vs M (ref) 0.95 (0.49, 1.84) 16.19
Dragun [21] 2011 PMRT vs M (ref) 3.83 (0.89, 16.48) 6.11
Steward [24] 2014 PMRT vs M (ref) 0.85 (0.51, 1.42) 19.57
Wang [27] 2011 PMRT vs M (ref) 0.83 (0.74, 0.93) 27.64
Overall (I-squared = 77.0%, p = 0.001) 1.12 (0.75, 1.69) 100.00
(Total patients n=3,219)
N.B.: Weights are from random effects analysis
.0607
1
16.5

Figure 5:

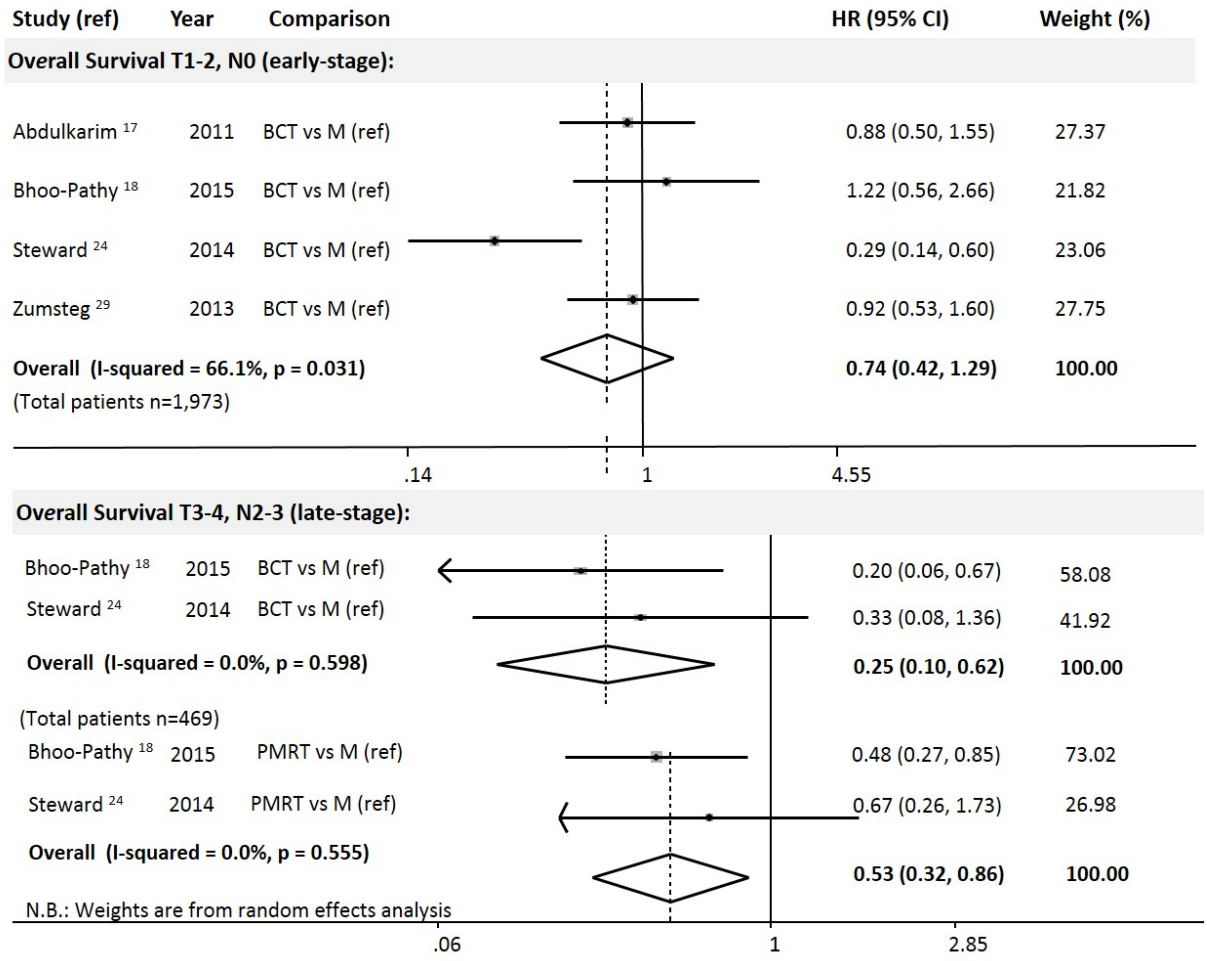
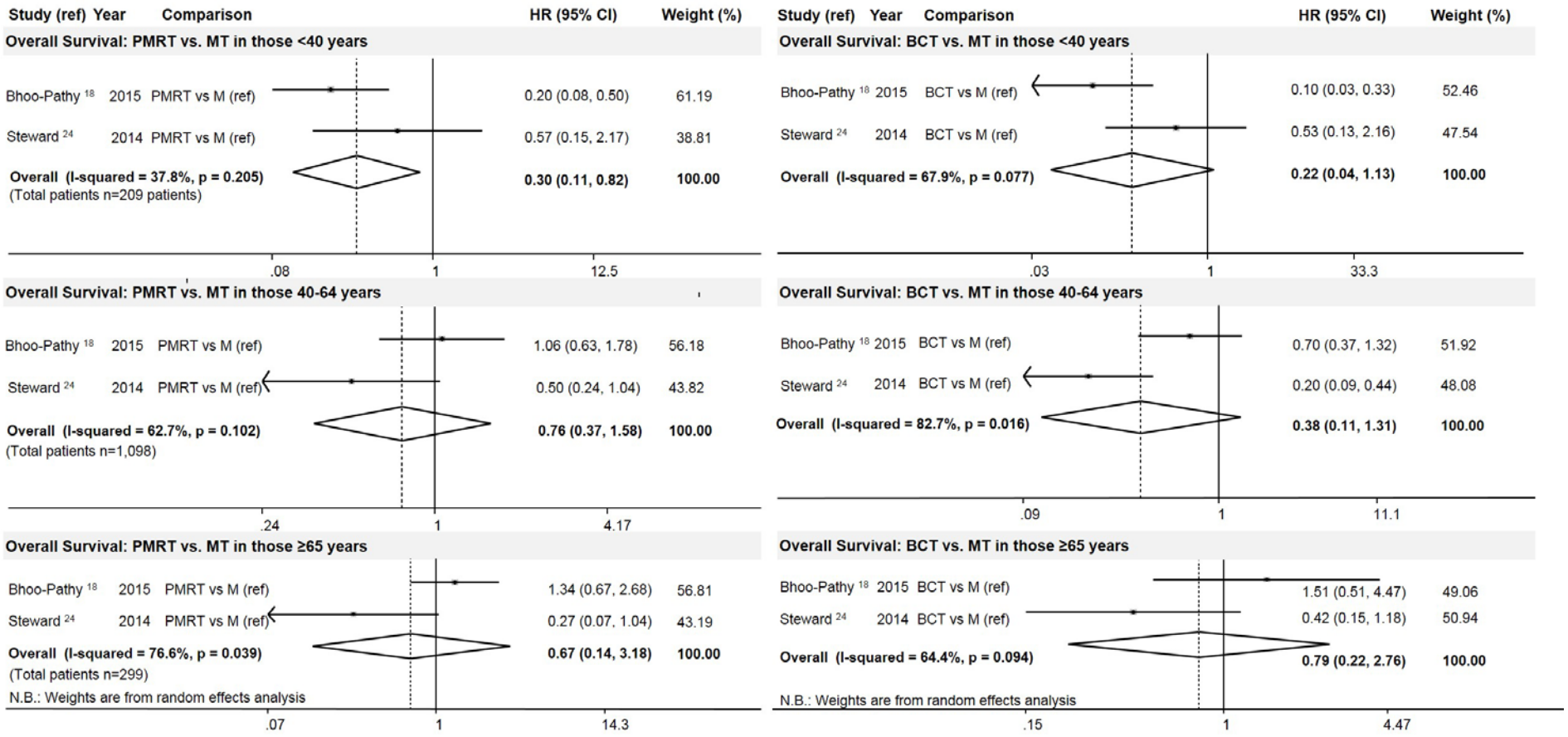

Study (ref)
Year
Comparison
HR (95% CI)
Weight (%)
Overall Survival T1-2, N0 (early-stage):
Abdulkarim [17] 2011 BCT vs M (ref) 0.88 (0.50, 1.55) 27.37
Bhoo-Pathy [18] 2015 BCT vs M (ref) 1.22 (0.56, 2.66) 21.82
Steward [24] 2014 BCT vs M (ref) 0.29 (0.14, 0.60) 23.06
Zumsteg [29] 2013 BCT vs M (ref) 0.92 (0.53, 1.60) 27.75
Overall (I-squared = 66.1%, p = 0.031) 0.74 (0.42, 1.29) 100.00
(Total patients n=1,973)
.14
1
4.55
Overall Survival T3-4, N2-3 (late-stage):
Bhoo-Pathy [18] 2015 BCT vs M (ref) 0.20 (0.06, 0.67) 58.08
Steward [24] 2014 BCT vs M (ref) 0.33 (0.08, 1.36) 41.92
Overall (I-squared = 0.0%, p = 0.598) 0.25 (0.10, 0.62) 100.00
(Total patients n=469)
Bhoo-Pathy [18] 2015 PMRT vs M (ref) 0.48 (0.27, 0.85) 73.02
Steward [24] 2014 PMRT vs M (ref) 0.67 (0.26, 1.73) 26.98
Overall (I-squared = 0.0%, p = 0.555) 0.53 (0.32, 0.86) 100.00
N.B.: Weights are from random effects analysis
.06
1
2.85

Figure 6:


Study (ref) Year Comparison HR (95% CI) Weight (%)
Overall Survival: PMRT vs. MT in those <40 years
Bhoo-Pathy [18] 2015 PMRT vs M (ref) 0.20 (0.08, 0.50) 61.19
Steward [24] 2014 PMRT vs M (ref) 0.57 (0.15, 2.17) 38.81
Overall (I-squared = 37.8%, p = 0.205) 0.30 (0.11, 0.82) 100.00
(Total patients n=209 patients)
.08 1 12.5
Overall Survival: PMRT vs. MT in those 40-64 years
Bhoo-Pathy [18] 2015 PMRT vs M (ref) 1.06 (0.63, 1.78) 56.18
Steward [24] 2014 PMRT vs M (ref) 0.50 (0.24, 1.04) 43.82
Overall (I-squared = 62.7%, p = 0.102) 0.76 (0.37, 1.58) 100.00
(Total patients n=1,098)
.24 1 4.17
Overall Survival: PMRT vs. MT in those ≥65 years
Bhoo-Pathy [18] 2015 PMRT vs M (ref) 1.34 (0.67, 2.68) 56.81
Steward [24] 2014 PMRT vs M (ref) 0.27 (0.07, 1.04) 43.19
Overall (I-squared = 76.6%, p = 0.039) 0.67 (0.14, 3.18) 100.00
(Total patients n=299)
N.B.: Weights are from random effects analysis
.07 1 14.3
Study (ref) Year Comparison HR (95% CI) Weight (%)
Overall Survival: BCT vs. MT in those <40 years
Bhoo-Pathy [18] 2015 BCT vs M (ref) 0.10 (0.03, 0.33) 52.46
Steward [24] 2014 BCT vs M (ref) 0.53 (0.13, 2.16) 47.54
Overall (I-squared = 67.9%, p = 0.077) 0.22 (0.04, 1.13) 100.00
.03 1 33.3
Overall Survival: BCT vs. MT in those 40-64 years
Bhoo-Pathy [18] 2015 BCT vs M (ref) 0.70 (0.37, 1.32) 51.92
Steward [24] 2014 BCT vs M (ref) 0.20 (0.09, 0.44) 48.08
Overall (I-squared = 82.7%, p = 0.016) 0.38 (0.11, 1.31) 100.00
.09 1 11.1
Overall Survival: BCT vs. MT in those ≥65 years
Bhoo-Pathy [18] 2015 BCT vs M (ref) 1.51 (0.51, 4.47) 49.06
Steward [24] 2014 BCT vs M (ref) 0.42 (0.15, 1.18) 50.94
Overall (I-squared = 64.4%, p = 0.094) 0.79 (0.22, 2.76) 100.00
N.B.: Weights are from random effects analysis
.15 1 4.47