

# Effects of adjuvant radiotherapy on borderline and malignant phyllodes tumors: A systematic review and meta-analysis

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**Abstract.** The standard treatment for borderline and malignant phyllodes tumors is wide local excision (margins  $\geq 1$  cm), in the context of either breast-conserving surgery (BCS) or total mastectomy (TM). Due to the high risk of local recurrence (LR) following surgical intervention alone, the addition of adjuvant radiotherapy (RT) has been previously investigated; however, the conclusions have been inconsistent. This systematic review and meta-analysis was designed to assess the efficacy of adjuvant RT for borderline and malignant phyllodes tumors. PubMed and Web of Science were systematically searched to identify relevant studies assessing the effect of adjuvant RT on borderline and malignant phyllodes tumors from the inception of this technique through May, 2014. A total of 8 studies were identified among 332 citations. In this meta-analysis, patients who received adjuvant RT had a lower relative risk of LR [hazard ratio (HR) = 0.43, 95% confidence interval (CI): 0.23-0.64]. The absolute risk difference was 10.1% (95% CI: 4.9-17.6), corresponding to a number needed to treat of 10. Our pooled meta-analysis clearly demonstrated a decreased risk of LR in patients with borderline and malignant phyllodes tumors who received RT following BCS (HR=0.31, 95% CI: -0.10-0.72). However, the combined HR for LR in the TM group did not demonstrate that adjuvant RT was superior to no RT (HR=0.68, 95% CI: -0.28-1.64). No significant differences were observed in overall survival (OS) or disease-free survival (DFS) between the two groups. Our analysis suggested that adjuvant RT for borderline and malignant phyllodes tumors decreased the LR rate in patients undergoing BCS. However, adjuvant RT was not found to exert an effect on OS or DFS.

## Introduction

Phyllodes tumors have a low incidence (1 in 100,000 women) and account for only 0.5% of all breast neoplasms (1). The majority of these tumors arise in women aged 35-55 years (approximately 20 years later compared to fibroadenomas) (2). In men, phyllodes tumors are very rare, with only few cases described to date (3,4). The World Health Organisation classifies phyllodes tumors into benign, borderline and malignant, according to the histopathological characteristics. Borderline and malignant phyllodes tumors are distinguished from benign phyllodes tumors by the presence of 'moderate or marked stromal cellularity and atypia, stromal overgrowth, brisk mitotic activity ( $\geq 5/10$  high-power fields) and permeative margins' (5). Clinically, borderline and malignant phyllodes tumors are characterized by their propensity for local and distant recurrence. The primary treatment for borderline and malignant phyllodes tumors is wide local excision (margins  $\geq 1$  cm), in the context of either breast-conserving surgery (BCS) or total mastectomy (TM) (1,6-18). Local recurrence (LR) occurs in 10-65% of the patients and distant recurrence rates range between 5 and 40% postoperatively (7,8,11,12,19-24). Due to the high risk of LR following surgical intervention alone, the addition of adjuvant radiotherapy (RT) to the treatment of borderline and malignant phyllodes tumors has been previously investigated; however, the conclusions have been inconsistent. Furthermore, an observational study reported a trend toward increased utilization of RT, despite its uncertain effect on outcome (25). The current guidelines only recommend consideration of RT for malignant phyllodes in the setting of LR (level 2B evidence) (26).

We thus performed a systematic review and meta-analysis to assess the efficacy of adjuvant RT for borderline and malignant phyllodes tumors.

## Materials and methods

**Study selection.** The focus of this systematic review and meta-analysis was to specifically assess the postoperative outcomes of borderline and malignant phyllodes tumors with and without RT. A systematic search of PubMed and Web of Science was undertaken, using the following terms: (phyllodes tumor OR phyllodes tumour OR phyllodes tumors OR phyllodes tumours OR cystosarcoma phyllodes OR cystosarcoma phyllode OR phyllode tumor OR phyllode tumour OR phyllode tumors

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**Key words:** phyllodes tumors, radiotherapy, local recurrence, overall survival, disease-free survival

OR phyllode tumours OR biphasic tumors OR biphasic tumor OR biphasic tumour OR biphasic tumours OR cystosarcoma phylloides OR cystosarcoma phylloides tumor OR cystosarcoma phylloides tumors OR cystosarcoma phylloides tumour OR cystosarcoma phylloides tumours OR phylloides tumor OR phylloides tumors OR phylloides tumour OR phylloides tumours) and (breast OR mammary OR mammary OR mammary glands OR mammary gland OR mammary gland OR mammary glands) and (radiation therapy OR radiotherapy OR radiation oncology OR radiation OR radiation treatment OR radiotreatment OR ray therapeutics OR ray treatment), up to May 1, 2014.

**Inclusion and exclusion criteria.** The inclusion criteria were as follows: The studies had to be primary research articles specifically investigating the outcomes of postoperative borderline and malignant phyllodes tumors with and without RT; at least one subgroup analysis comprising borderline or malignant phyllodes tumors was to be reported. Patients with positive margins were excluded. To increase the number of potentially interesting articles, no limits or language restriction were applied during the search.

Reviews and case reports on the subject were excluded. Published abstracts without complete articles were excluded due to our inability to obtain detailed information. All the citations were independently reviewed by two authors (SYZ and XDZ) and categorized as relevant, not relevant, or potentially relevant. Citations that were classified as relevant and potentially relevant by one of the authors were selected for abstract review. Following review of the abstract, potentially relevant and relevant abstracts were selected for full-text evaluation. Upon evaluation of the full text, patients were included if they were surgically treated for borderline or malignant phyllodes tumor and information on the use of RT was available; women with history of breast cancer or distant metastatic disease at presentation were excluded.

**Extracted data.** The following information was extracted from each eligible study: Authors' names, source of patients, number of patients, patient age, type of surgery, margin status, radiation dose, follow-up period and conclusion (Table I). The numbers of events were extracted to conduct a meta-analysis of the different outcomes under investigation. If the numbers of events were not available, the LR rates or survival rates were used to estimate them.

**Statistical analysis.** Stata software, version 12.0 (StataCorp, College Station, Texas, USA) was used to pool the different outcome estimates. The outcomes were analyzed as hazard ratios (HRs). Statistical heterogeneity was assessed using the  $I^2$  statistic (27). We considered  $I^2 < 25\%$  to represent low heterogeneity,  $I^2 > 75\%$  high heterogeneity and  $25\% < I^2 < 75\%$  moderate heterogeneity. The evidence classification was performed using GRADEprofiler software, version 3.6 (the Cochrane Collaboration Network). We classed outcomes as high-, moderate-, low- or very low-quality (28,29).

Next to relative outcome measures, we calculated pooled absolute risks (ARs). The AR difference was calculated as the pooled estimate of the AR difference for each study, including a 95% confidence interval (CI). Subsequently, the number needed to treat was calculated as 1 divided by the AR difference.

## Results

**Study selection process.** A total of 332 unique citations were identified following a search through PubMed and Web of Science after removing duplicates by EndNote; of the 332 articles, 87 were selected for abstract review and, of those, full-text evaluation was undertaken for 23 publications (Fig. 1). Overall, 6 publications were excluded due to lack of sufficient data; 4 were excluded as they were reviews; 3 were excluded as they did not focus on the outcome under investigation and 2 were excluded due to overlapping. Finally, a total of 8 studies were included in the present systematic review and meta-analysis (13,14,25,30-34).

**Description of studies.** The characteristics of the included studies are listed in Table I. The total number of participants included in this systematic review and meta-analysis was 2,708. The studies were published between 2001 and 2014. Inclusion in all the studies was restricted to patients with primary borderline and malignant phyllodes tumors, without identified metastasis at presentation. All the patients underwent surgery and the majority (~90%) had negative resection margins. A proportion of the patients consented to undergo RT. None of the patients had a history of breast cancer or other malignant tumors and none had priorly received adjuvant RT. In the studies, only a small proportion of the patients (<1%) also received chemotherapy or endocrine therapy during the treatment. Therefore, we decided to include all these patients in the meta-analysis.

Moreover, the primary outcome of the majority of the studies was LR, which was defined as recurrence or a secondary phyllodes tumor in the ipsilateral breast. Frequent secondary outcomes were overall survival (OS) and disease-free survival (DFS). Since our meta-analysis only included 8 studies, we did not perform formal tests for funnel plot asymmetry.

**Meta-analysis.** Of the 8 studies included in the meta-analysis, 6 studies described LR. Since Gnerlich *et al* (25) reported the HR of LR and did not report the exact number of LR in patients with and without RT, we calculated the 5-year risk ratio (RR) of the remaining 5 involved studies. The pooled analysis confirmed a lower relative risk of LR in patients who received RT (RR=0.45, 95% CI: 0.26-0.77). Subsequently, a pooled analysis of these 6 studies also demonstrated a lower relative risk of LR in patients with RT (HR=0.43, 95% CI: 0.23-0.64) with an  $I^2$  of 0%, indicating low heterogeneity (Fig. 2). A meta-analysis on the different types of surgery is likely to be very helpful in this regard, identifying subgroups of patients undergoing BCS and TM. The meta-analysis was repeated without the study results of Soumarova *et al* (31) and Pandey *et al* (32), as there was no available information for comparable subgroups (BCS vs. TM). The pooled HR of LR in the BCS group demonstrated a lower relative risk of LR in patients with RT compared to those not receiving RT (HR=0.31, 95% CI: -0.10-0.72); however, the combined HR for LR in the TM group did not indicate that adjuvant RT was superior to no RT (HR=0.68, 95% CI: -0.28-1.64; Fig. 3).

Of the included studies, 4 reported data on OS. The results of our pooled meta-analysis demonstrated that surgery plus RT vs. surgery alone was associated with a decreased

Table I. Characteristics of the included studies.

Study (Refs.)	Patient source	Patient no., total/ RT/no RT	Patient age, mean or median (years)	Tumor size, mean or median (cm)	Grade, M/B	Type of surgery, BCS/TM/UN	Margins, NE/PO/UN	Radiation dose, Gy (range)	Follow-up (months)	Conclusion
Haberer <i>et al</i> (30)	Paris, France	22/5/17	52	6.5	22/0	5/17/0	20/0/2	52 (45-55)	Median, 65	Uncertain
Soumarova <i>et al</i> (31)	Brno, Czech Republic	25/17/8	52	10	25/0	4/21/0	Not provided	46-70	Median, 139.5	Adjuvant RT decreased the LR incidence
Pandey <i>et al</i> (32)	Trivandrum, India	36/25/11	39	10.8	36/0	6/26/4	17/6/13	45-50	Median, 43	Adjuvant RT decreased the risk of LR and also improved survival
Kim <i>et al</i> (33)	Seoul, South Korea	42/5/37	40.5	4.0	13/29	38/4/0	42/0/0	Not provided	Median, 43	Recurrence rates were very low for benign PT, regardless of surgical margin status or RT
Belkacemi <i>et al</i> (14)	17 Rare Cancer Network Institutions (Europe)	159/36/123	40	4.6	79/80	109/50/0	Not provided	50 (37-60)	Median, 106	Adjuvant RT after BCS had no effect on survival
Gnerlich <i>et al</i> (25)	National Cancer Data Base (USA)	3,210 (1,774 available)/459/2,751	51.1	4.2	3,210/0	1,838/1,363/9	2,787/275/148	Not provided	Median, 53	Adjuvant RT reduced LR but had no effect on DFS or OS
Badar <i>et al</i> (34)	Lahore, Pakistan	32/21/11	40.3	9.2	32/0	Not provided	Not provided	Not provided	Longest, 152.8	Uncertain
Macdonald <i>et al</i> (13)	National Cancer Institute's SEER program (USA)	618/68/550	50	Not provided	618/0	297/321/0	Not provided	Not provided	Median, 68.4	Uncertain

RT, radiotherapy; M, malignant; B, borderline; BCS, breast-conserving surgery; TM, total mastectomy; UN, unknown; NE, negative; PO, positive; LR, local recurrence; DFS, disease-free survival; OS, overall survival; SEER, Surveillance, Epidemiology and End Results.

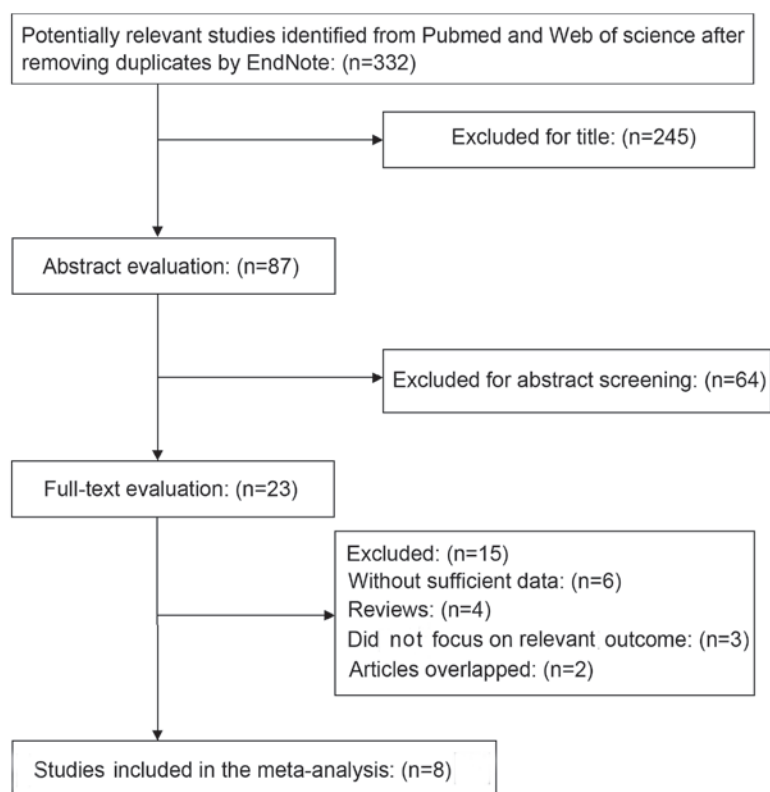


Figure 1. Results of the literature search and disposition of articles screened for inclusion.

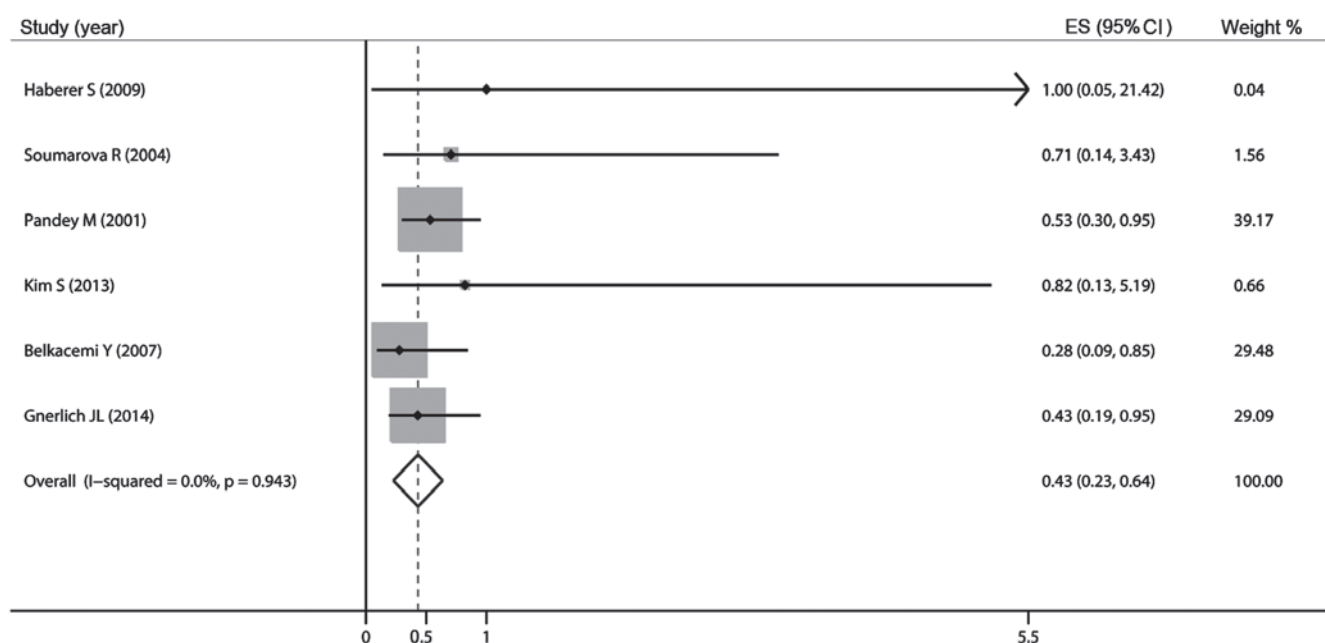


Figure 2. Pooled results of local recurrence in patients treated with adjuvant radiotherapy. ES, effect size; CI, confidence interval.

5-year OS (HR=0.89, 95% CI: 0.79-0.99; Fig. 4) with an  $I^2$  of 58.0%, indicating moderate heterogeneity. The meta-analysis was repeated without the study results of Badar *et al* (34), as there was no available information for comparable subgroups (BCS vs. TM). However, in the subgroups by different types of surgery, the pooled HR of OS in the BCS group (HR=0.95, 95% CI: 0.79-1.12) and the TM group (HR=0.89,

95% CI: 0.73-1.04; Fig. 5) revealed that adjuvant RT exerted no effect on 5-year OS.

A total of 4 studies reported on the effect of RT on DFS. The results of this pooled analysis demonstrated that adjuvant RT following surgery exerted no effect on 5-year DFS (HR=0.93, 95% CI: 0.74-1.12; Fig. 6) and the  $I^2$  of DFS was 37.8%, indicating moderate heterogeneity. A meta-analysis

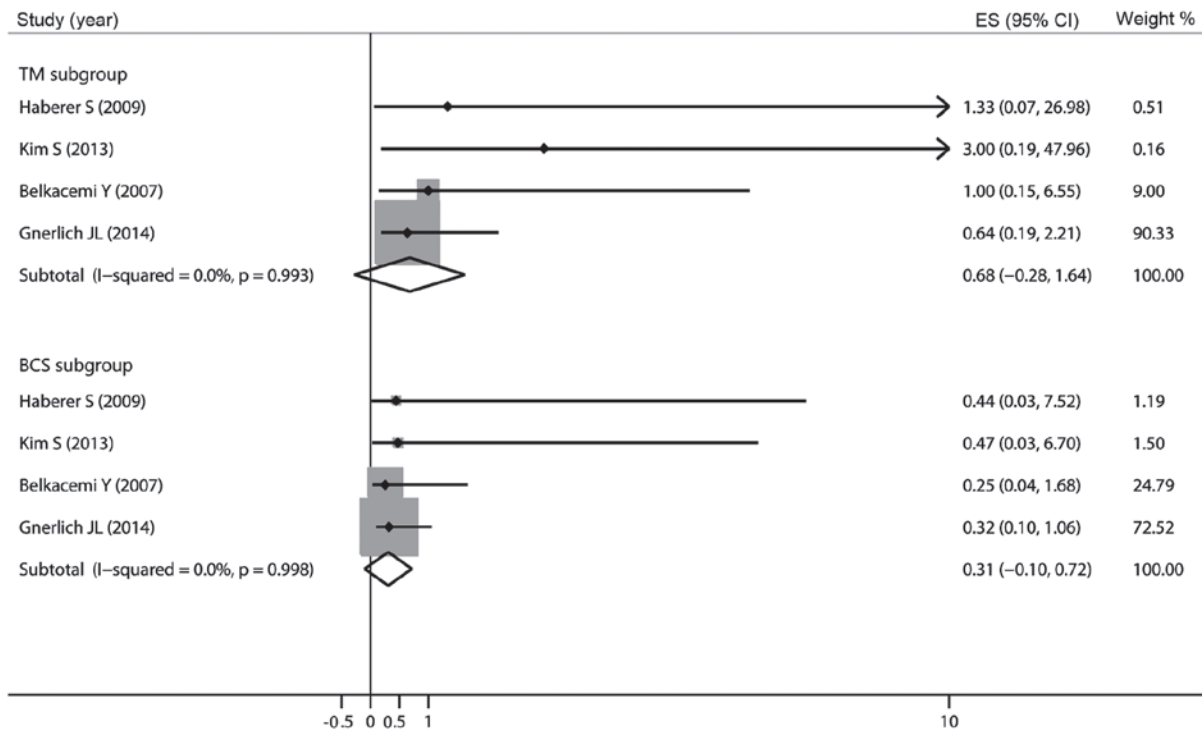


Figure 3. Pooled results of local recurrence in subgroups of patients treated with adjuvant radiotherapy. ES, effect size; CI, confidence interval.

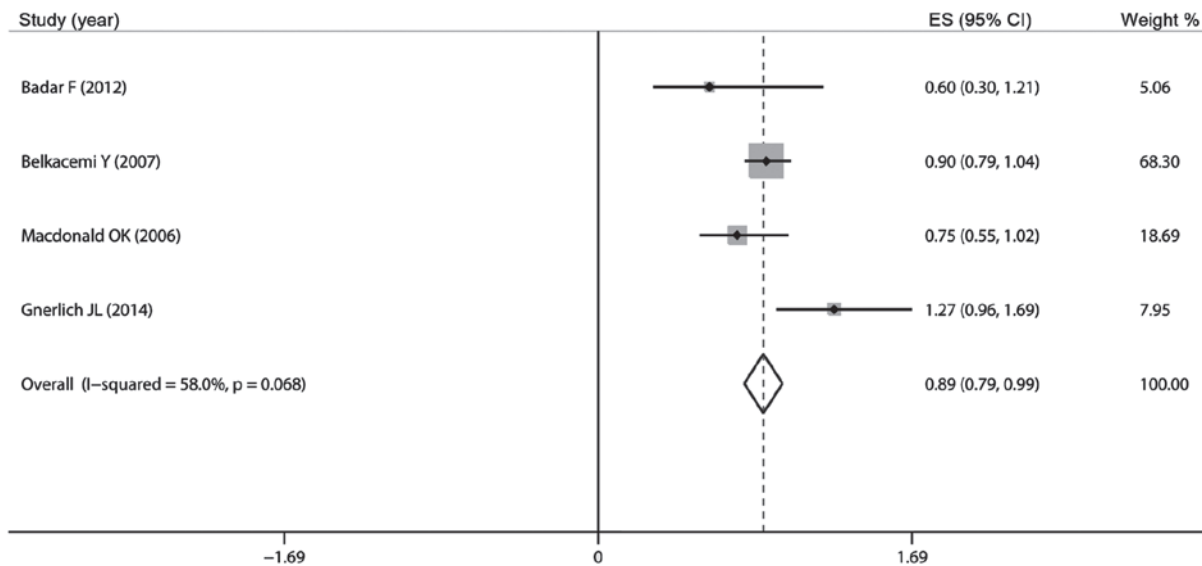


Figure 4. Pooled results of overall survival in patients treated with adjuvant radiotherapy. ES, effect size; CI, confidence interval.

of specific subgroups was not possible, as information from half of the studies were available for incomparable subgroups alone. Based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, the level of evidence of the involved studies was very low (Table II).

**AR.** The pooled AR of LR, OS and DFS were calculated for patients in both study arms. Since ARs are dependent on the duration of follow-up, we calculated the 5-year AR of these outcomes. The 5-year AR of a LR among patients who received RT was 19.3% (17 of 88, 95% CI: 11.6-29.1) compared to 29.4%

(58 of 197, 95% CI: 23.1-36.3) among patients who did not receive RT. The AR difference was 10.1% (95% CI: 4.9-17.6). The results were in favor of those who received RT in addition to surgery, corresponding to a number needed to treat of 10 to prevent one LR in 5 years.

The 5-year AR of OS was 52% (65 of 125, 95% CI: 42.9-61.0) in patients who received RT compared to 59.2% (405 of 684, 95% CI: 55.4-62.9) in those who did not. For DFS, the 5-year ARs were 59.8% (49 of 82, 95% CI: 48.3-70.4) among patients who received RT compared to 63.9% (92 of 144, 95% CI: 55.5-71.7) among those who did not.

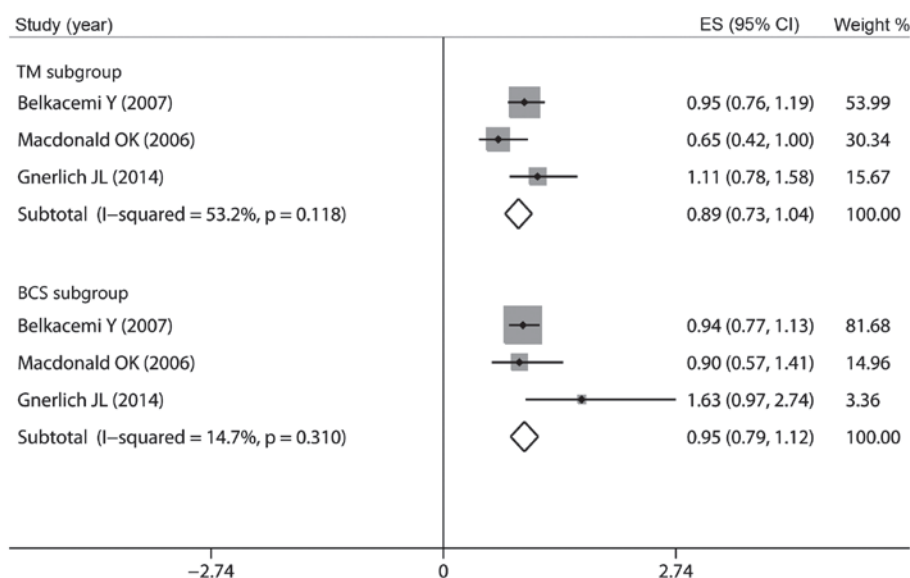


Figure 5. Pooled results of overall survival in subgroups of patients treated with adjuvant radiotherapy. ES, effect size; CI, confidence interval.

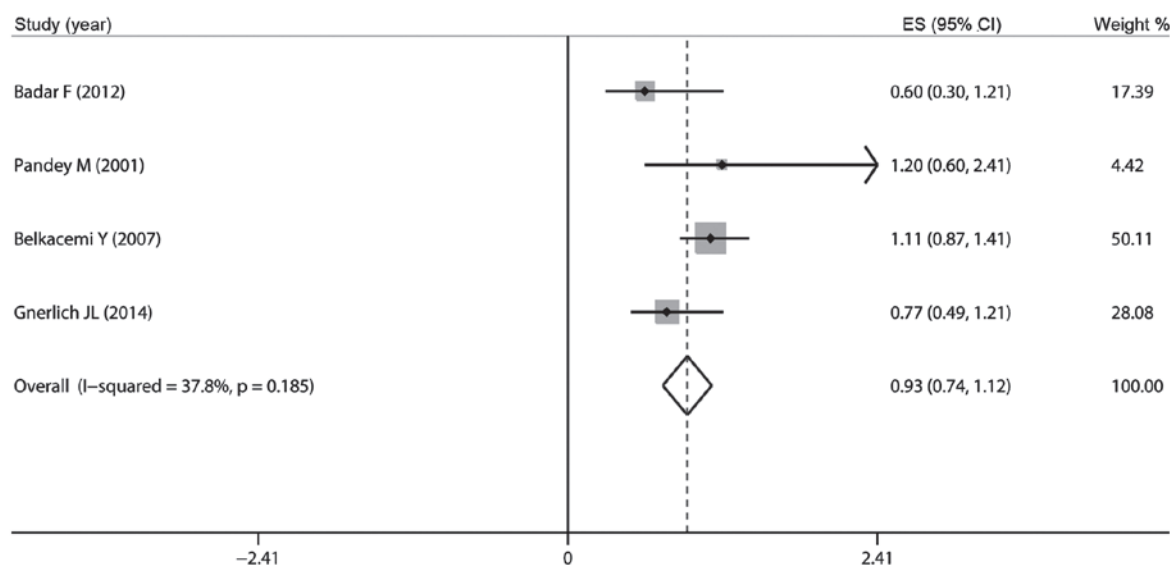


Figure 6. Pooled results of disease-free survival in patients treated with adjuvant radiotherapy. ES, effect size; CI, confidence interval.

## Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to investigate the effects of adjuvant RT on borderline and malignant phyllodes tumors. Our pooled meta-analysis clearly demonstrated a decreased risk of LR in patients with borderline and malignant phyllodes tumors who received RT following BCS. The results of this pooled analysis revealed that adjuvant RT exerts no effect on OS or DFS.

The standard treatment for borderline and malignant phyllodes tumors is wide local excision (margins  $\geq 1$  cm), in the context of either BCS or TM. However, the risk of LR following margin-negative resection of borderline or malignant phyllodes tumors is significant. Although the addition of adjuvant RT to the treatment of borderline and malignant phyllodes tumors has been investigated, no consensus has been reached. Gnerlich *et al* (25) reported a significant increase in

RT use for BCS as well as TM patients, despite its uncertain efficacy. Therefore, we performed this systematic review and meta-analysis to integrate the results from recent studies that investigated the effect of adjuvant RT on borderline and malignant phyllodes tumors.

Our pooled analysis confirmed a lower relative risk of LR in patients receiving adjuvant RT following surgical resection compared to surgery alone. The AR difference was 10.1% (95% CI: 4.9-17.6). The results were in favor of patients who received RT in addition to surgery, corresponding to a number needed to treat of 10 to prevent one LR in 5 years. This number is expected to be relatively higher in a non-trial population. To decrease the number needed to treat and to personalize treatment, we attempted to identify subgroups of patients (BCS vs. TM) in which RT may be safely omitted on the basis of the risk of LR. The pooled HR of LR in the BCS group revealed a lower relative risk of LR (HR=0.31, 95% CI: -0.10-0.72);

Table II. Quality assessment of the included studies based on the GRADE system.

		Quality assessment					No. of patients		Effect					
		No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery +RT	Surgery alone	Relative (95% CI)	Absolute	Quality	Importance
LR <sup>a</sup>														
5	Observational	High <sup>d</sup>	Not significant	High <sup>e</sup>	High <sup>f</sup>	Increased effect for RR~1 <sup>g</sup>	17/88 (19.3%)	58/197 (29.4%)	HR=0.45 (0.26-0.77)	149 fewer per 1,000 (59-208 fewer)	144 fewer per 1,000 (57-201 fewer)	Very low	Critical	
OS <sup>b</sup>														
3	Observational	High <sup>d</sup>	Not significant	High <sup>e</sup>	High <sup>f</sup>	Increased effect for RR~1 <sup>h</sup>	65/125 (52%)	405/684 (59.2%)	RR=0.804 (0.679-0.952)	116 fewer per 1,000 (28-190 fewer)		Very low	Critical	
DFS <sup>c</sup>														
3	Observational	High <sup>d</sup>	Significant <sup>i</sup>	High <sup>e</sup>	High <sup>f</sup>	Reduced effect for RR>>1 or RR<<1 <sup>h</sup>	49/82 (59.8%)	92/144 (63.9%)	RR=1.033 (0.828-1.288)	21 more per 1,000 (110 fewer-184 more)	21 more per 1,000 (108 fewer-181 more)	Very low	Critical	
Mean follow-up, 5 years; assessed with biopsy. <sup>b</sup> Mean follow-up, 5 years; assessed according to the date of last contact or death. <sup>c</sup> Mean follow-up, 5 years; computed from the date of surgery until disease recurrence. <sup>d</sup> Limitations of retrospective reviews. <sup>e</sup> Not all the studies focused on this outcome. <sup>f</sup> The sample size was too small. <sup>g</sup> Clinical practitioners tend to administer radiotherapy to patients with later-stage tumors. <sup>h</sup> Patient age, tumor size and other factors may alter the efficacy of radiotherapy. <sup>i</sup> No explanation was provided. GRADE, Grading of Recommendations Assessment, Development and Evaluation; RT, radiotherapy; CI, confidence interval; LR, local recurrence; RR, risk ratio; HR, hazard ratio; OS, overall survival; DFS, disease-free survival.														

<sup>a</sup>Mean follow-up, 5 years; assessed with biopsy. <sup>b</sup>Mean follow-up, 5 years; assessed according to the date of last contact or death. <sup>c</sup>Mean follow-up, 5 years; computed from the date of surgery until disease recurrence. <sup>d</sup>Limitations of retrospective reviews. <sup>e</sup>Not all the studies focused on this outcome. <sup>f</sup>The sample size was too small. <sup>g</sup>Clinical practitioners tend to administer radiotherapy to patients with later-stage tumors. <sup>h</sup>Patient age, tumor size and other factors may alter the efficacy of radiotherapy. <sup>i</sup>No explanation was provided. GRADE, Grading of Recommendations Assessment, Development and Evaluation; RT, radiotherapy; CI, confidence interval; LR, local recurrence; RR, risk ratio; HR, hazard ratio; OS, overall survival; DFS, disease-free survival.

however, the combined HR for LR in the TM group did not demonstrate that adjuvant RT was superior to no RT (HR=0.68, 95% CI: -0.28-1.64). Thus, omission of RT in patients following TM may be reasonable. However, these results must be interpreted with caution, considering that we only calculated the 5-year LR rate in TM patients. Belkacémi *et al* (14) observed similar 5-year local control rates in irradiated patients following TM compared to those who did not receive RT (92 vs. 91%, respectively); however, adjuvant RT improved the 10-year local control for borderline and malignant tumors (92 vs. 78%, respectively). Thus, following TM, adjuvant RT should be discussed taking into account the surgical margins, size and pathological criteria of the tumor. Pezner *et al* (22) recommend adjuvant RT following TM for large tumors (>10 cm).

Our results were consistent with those of the individual studies. We also identified 1 study that reported marginally different results. Reinfuss *et al* (35) reported on patients who were treated with the Halsted operation followed by postoperative RT, which proved to be inefficient. In their study, patients who received postoperative irradiation exhibited infiltration of the pectoralis major muscle and limited mobility of the chest wall; in addition, the surgical margin was not microscopically tumor-free. After 5 years of follow-up, all the patients exhibited LR along with pulmonary metastases. Only few of the patients involved in our study exhibited infiltration of the pectoralis major muscle and the majority of the patients (~90%) had negative resection margins. The difference between their results and ours may be explained by the worse overall condition of the patients in the study of Reinfuss *et al* (35). The study of Barth *et al* (20) yielded similar conclusions to ours. In their prospective study, 46 women (30 with malignant and 16 with borderline phyllodes tumors) were treated with margin-negative breast-conserving resection followed by adjuvant RT. The patients were treated in 30 different institutions; after a minimum follow-up of 5 years, none of the patients exhibited LR. A retrospective study by Chaney *et al* (36) that involved 6 patients treated with adjuvant RT for non-metastatic phyllodes tumor of the breast yielded similar results. There was no reported local or distant failure after a median follow-up of 36.5 months. Therefore, adjuvant RT should be considered to minimize LR following breast-conserving resection of borderline and malignant phyllodes tumors.

To our surprise, our pooled meta-analysis demonstrated that surgery plus RT was associated with decreased 5-year OS compared to surgery alone (HR=0.89, 95% CI: 0.79-0.99). To the best of our knowledge, there is no study reporting that postoperative RT decreases OS. None of our included individual studies indicated that adjuvant RT exerted a detrimental effect on OS. Moreover, the study by Pandey *et al* (32) demonstrated that adjuvant RT not only decreased the risk of LR, but also improved survival. We performed a subgroup analysis by exclusion of the study by Badar *et al* (34), as it lacks information on comparable subgroups (BCS vs. TM). The pooled HRs of OS in the BCS group (HR=0.95, 95% CI: 0.79-1.12) and the TM group (HR=0.89, 95% CI: 0.73-1.04) revealed that adjuvant RT exerted no effect on OS. This may be due to the small sample size in each group. Furthermore, RT is often administered to patients of poor prognosis. The wide CI may be due to variations in the survival data. Additional randomized controlled studies (RCTs) are required to further elucidate this issue.

Our pooled analysis proved that RT following surgery exerted no effect on 5-year DFS. The 4 included individual studies did not report that adjuvant RT exerted a detrimental effect on DFS. Thus far, we have not identified any studies reporting different results. The 5-year AR of LR among patients who received RT was 19.3% (17 of 88, 95% CI: 11.6-29.1), vs. 29.4% (58 of 197, 95% CI: 23.1-36.3) among patients who did not receive RT. The data of Kim *et al* (33) and Barth *et al* (20) demonstrated that the AR of LR following margin-negative breast-conserving resection of borderline and malignant phyllodes tumors was 16/73 (22%) and 30/134 (22%), respectively. However, our pooled AR data were higher. This may be explained as follows: Although we tried to eliminate patients with positive resection margins, such patients could not be eliminated in 2 of the included studies, whereas the other 2 included studies did not provide data on margin status. An estimated 10% of those patients had positive margins. In this case, our study indicates that adjuvant RT may be effective for patients with positive tumor resection margins.

The goal of adjuvant RT is to reduce disease recurrence and improve the quality of life of the patients. From the time adjuvant RT was first introduced as part of breast cancer treatment, this procedure has gained in popularity and it has been shown to reduce disease recurrence and improve the quality of life. A number of studies have supported the oncological effectiveness and safety of this procedure in phyllodes tumors (20,32,36). Certain clinical practitioners remain cautious regarding adjuvant RT in phyllodes tumors. Our analysis supports the conclusion that postoperative RT for borderline and malignant phyllodes tumors decreases the LR rate for patients undergoing BCS. However, adjuvant RT is not the only factor determining whether patients will develop a relapse; other factors, including age, surgical approach, mitotic activity and surgical margins are significantly correlated with recurrence (P=0.029, 0.020, 0.048 and 0.00018, respectively) (15). Local excision, wide excision, or TM with negative surgical margins yielded high local control rates, but local excision was associated with a relatively high percentage of positive surgical margins (18.3%) (15). Pezner *et al* (22) retrospectively analysed 478 patients with malignant phyllodes tumors of the breast and found that the 5-year local control rates were 100% for 0-2-cm tumors, 95% for 2-5-cm tumors, 88% for 5-10-cm tumors and 85% for 10-20-cm tumors. A multivariate analysis of OS found several factors to be significant, including advancing age with each decade after 50 years, appearance of distant metastases, larger tumor size and local control vs. LR (HR=2.5, P<0.05) (22). Surgical management must be tailored to the clinical situation, with more aggressive management reserved for higher-grade or recurrent tumors (19). In the latter case, if wide local excision is possible while allowing satisfactory cosmesis, BCS could also be considered. Pezner *et al* (22) recommend adjuvant RT following BCS for tumor sizes >2 cm.

There were certain limitations to this analysis. First, we did not consider certain confounding factors, such as chemotherapy and endocrine therapy, as the original data were unavailable, although these patients accounted for an estimated <1%. However, these factors may affect the rate of recurrence. Second, selection bias, particularly the tendency to administer adjuvant RT to patients with later-stage tumors,

was a problem in the majority of the studies. Third, the different follow-up duration may also limit the interpretation of the results. Fourth, all the studies in our analysis were non-RCTs, the results of which are not as convincing as those of RCTs. Finally, according to the GRADE system, the level of the included studies' evidence was very low. Therefore, further investigation may alter our conclusions.

In conclusion, this meta-analysis suggests that adjuvant RT for borderline and malignant phyllodes tumors decreases the LR rate for patients undergoing BCS. However, adjuvant RT exerts no effect on OS or DFS. The majority of the studies were performed via retrospective analysis to investigate small numbers of patients. Therefore, we believe that a multicenter prospective RCT with a longer follow-up period and more clearly defined parameters may be the best way to further elucidate this issue in the future.

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