Original Study

The Impact of Radiotherapy and Histological Risk Factors on Outcomes in Malignant Phyllodes Tumors

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Abstract

Relapse rates are high in malignant phyllodes tumors (PT) and there are knowledge gaps in the literature regarding the role of adjuvant radiotherapy (RT). Three-year LRFS was higher in the RT group, but there were no differences in 3-year distant disease-free and overall survival. We recommend that adjuvant RT be discussed for malignant PT for local control, even after mastectomy.

Purpose: Breast phyllodes tumors (PT) are classified into benign, borderline, and malignant grades based on histopathologic characteristics. Specific to malignant PT (MPT), surgery is the mainstay yet relapse rates are high and knowledge gaps in the literature exist regarding adjuvant radiotherapy (RT). We aimed to investigate the outcomes of patients with MPT treated in a tertiary Asian institution. **Methods and materials:** Patients with nonmetastatic MPT treated from February 1992 to June 2019 were analyzed retrospectively. RT details and relapse fields were studied. Outcomes of patients with and without RT were compared and hazard ratios were calculated using Cox proportional hazard test. Multivariable analysis was performed. **Results:** Twenty-two of 89 patients received adjuvant RT and the median dose was 60 Gy. In the no-RT group, 4 patients received RT on relapse and had no further recurrences; a further 2 received RT for fungating relapses with good symptomatic relief. RT was only increasingly prescribed after 2004. Median follow-up in the RT group was 3.31 years, compared with 6.17 years in the no-RT group. In the RT group, 15 patients (68.2%) underwent mastectomy, versus 39 (58.2%) in the no-RT group. One patient in the RT group developed an infield local relapse, compared with 21 of 67 patients in the no-RT group. Multivariate model showed that RT decreased risk of locoregional failure (hazard ratio 0.12, 95% confidence interval [CI] 0.02-0.92, $P = .04$). Three-year locoregional recurrence-free survival was higher in the RT group, 92.3% (95% CI, 78.9-100) versus 73.3% (95% CI, 63.1-85.1) in the no-RT group ($P = .03$). There were no differences in 3-year survival. **Conclusions:** We recommend that adjuvant radiotherapy be discussed for malignant PT for local control, even after mastectomy.

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Introduction

The World Health Organization (WHO)[1] classifies phyllodes tumors (PT) as benign, borderline, and malignant (MPT) grades based on the following histological parameters: stromal features of cellularity, mitoses, atypia, overgrowth, and tumor borders. Specific to MPT, although the mainstay of treatment is surgery, the local recurrence rate after wide surgical resection remains high (8%-36%).[2]

A recent meta-analysis[2] combined 17 studies and concluded that radiotherapy (RT) was associated with a lower local recurrence rate

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in all types of PT, particularly for younger patients, patients post breast conservation surgery (BCS), close margins, larger tumors, and malignant subtype. An interrogation of the Surveillance, Epidemiology, and End Results (SEER) database showed that higher-risk patients underwent RT but there were no differences in cancer-specific survival between RT and no-RT.[3] Some smaller studies also concluded that RT was useful only in certain scenarios, for example, margins less than 1 cm.[4] Due to the rarity of MPT, prospective evidence is lacking and much work remains to be done.

This current work aimed to investigate the association of RT and histological risk factors on outcomes in patients with MPT treated in a tertiary Asian institution.

Materials and Methods

Patients with MPT post curative surgery were queried from an institutional registry. Surgical specimens were reviewed by pathologists in a tertiary setting, in accordance with WHO recommendations.[1] Most decisions were made in a multidisciplinary setting. There were no standard criteria for RT recommendation. Adjuvant chemotherapy was not offered because of lack of evidence.[2] This study was approved by our institutional review board (reference 2012/93/A).

The primary end point was locoregional recurrence-free survival (LRFS); secondary end points were distant disease-free (DDFS) and overall survival (OS). Other objectives were to describe the utility of RT in recurrent and palliative settings, and trends in RT usage.

RT was prescribed in accordance with standard sarcoma dose fractionation regimen. Most plans were delivered with tangents to the breast or chest wall via 3-dimensional conformal technique. A further boost to the tumor bed in breast-conserved cases was optional. Nodal irradiation was not the usual practice for cases without proven nodal involvement.

Statistics

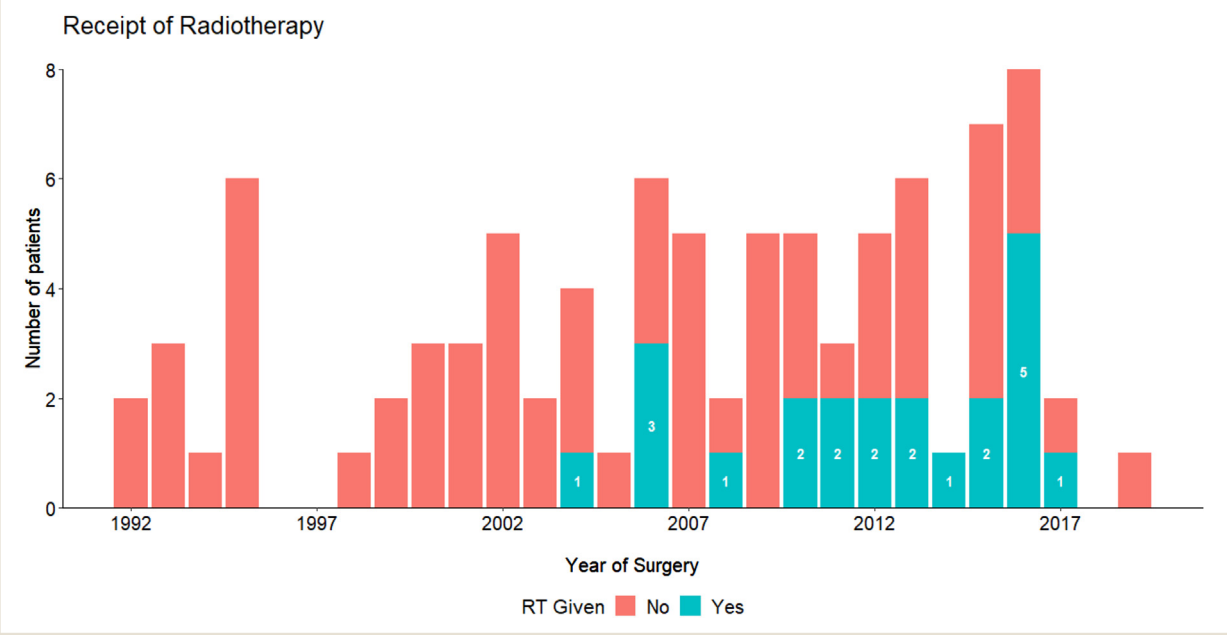
LRFS was defined as time from surgery to a locoregional event, and DDFS was defined as time from surgery to distant relapse, censored at death or last follow-up. OS was defined as time from surgery to death from any cause, censored at last follow-up. Death data were derived from the Singapore Birth and Death Registry. Mann-Whitney U test, χ^2, or Fisher test was used to examine baseline differences between RT and no-RT groups. Log-rank test was used to assess for statistical significance. Cox proportional hazard regression was used to estimate the hazard ratio. Factors with P value < 0.1 in univariate analysis (UVA) were included in multivariate analyses (MVA), and statistical significance was defined as $P < .05$. Subgroup analysis was done with age 45 years and tumor size 5 cm as cutoff for ease of comparison with previous studies. All analyses were run on R Studio (Vienna, Austria, 2019).

Table 1 Baseline Characteristics and Histological Risk Factors Among RT and No-RT Groups

Variable	RT (n = 22)	No-RT (n = 67)	*P* Value
Age	49 (IQR: 42-53)	51 (IQR: 43-58)	.37
Follow-up, median (y)	3.3 (IQR: 2.3- 3.7)	6.2 (IQR: 2.23- 14.1)	.02
Surgery, n (%)			.41
Mastectomy	15 (68.2)	39 (58.2)	
BCS	7 (31.8)	28 (41.7)	
Median size (mm)	81 (IQR: 43-146)	60 (IQR: 40-120)	.25
Stromal atypia, n (%)			.20
Mild	3 (13.6)	3 (4.5)	
Moderate	6 (27.3)	28 (41.8)	
Marked	13 (59.1)	36 (53.7)	
Stromal hypercellularity, n (%)			.13
Marked	16 (72.7)	38 (56.7)	
Moderate	4 (18.2)	26 (38.8)	
Mild	2 (9.1)	3 (4.5)	
Tumour borders			.56
Circumscribed	4 (18.2)	16 (23.9)	
Infiltrative	18 (81.8)	51 (76.1)	
Malignant heterologous element present, n (%)			.28
No	21 (95.5)	56 (83.6)	
Yes	1 (4.6)	11 (16.4)	
Surgical margin, n (%)			.49
Negative	15 (68.2)	48 (71.6)	
Involved	7 (31.8)	19 (28.4)	
Local Recurrence, n (%)	1 (4.6)	21 (31.3)	.03
Distant recurrence, n (%)	5 (22.7)	16 (23.9)	1

Abbreviations: BCS = breast conservation surgery; IQR = interquartile range.

Figure 1 Proportion of Patients Who Received Radiotherapy (RT) Over the Years



Results

Population and Treatment Characteristics

Eighty-nine patients treated from February 1992 to June 2019 were eligible. All patients had nonmetastatic disease at diagnosis. Twenty-two patients underwent adjuvant RT at diagnosis. Four patients in the no-RT group received RT on local recurrence. Median follow-up in the RT group was 3.31 years, compared with 6.17 years in the no-RT group. Median age at diagnosis was 49 and 51 years in the RT and no-RT groups. The proportion of patients with stromal overgrowth was higher in the RT group ($P = .05$). Twelve patients had malignant heterologous elements seen in the histological specimens (Table 1). Fifty-four patients underwent a mastectomy. There

Figure 2 Locoregional Recurrence-free Survival according to Radiotherapy (RT) Receipt

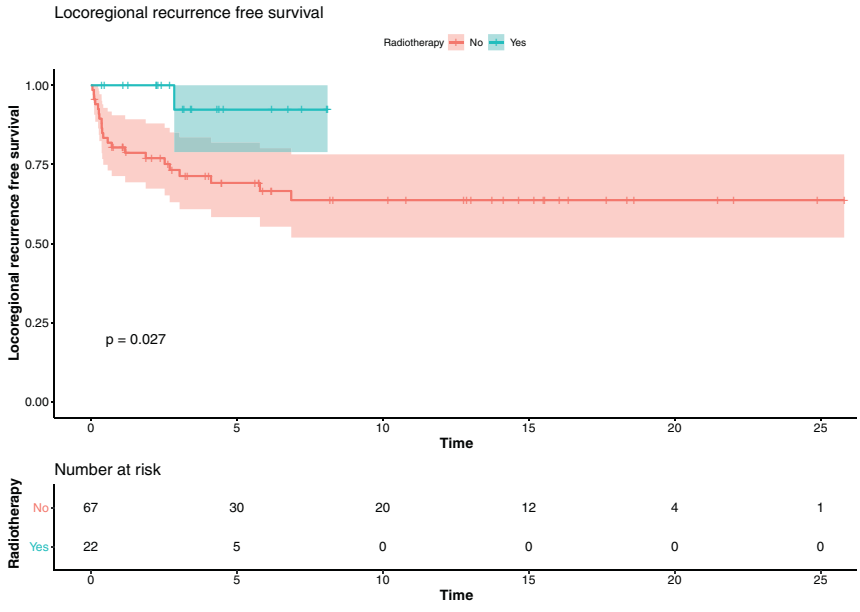
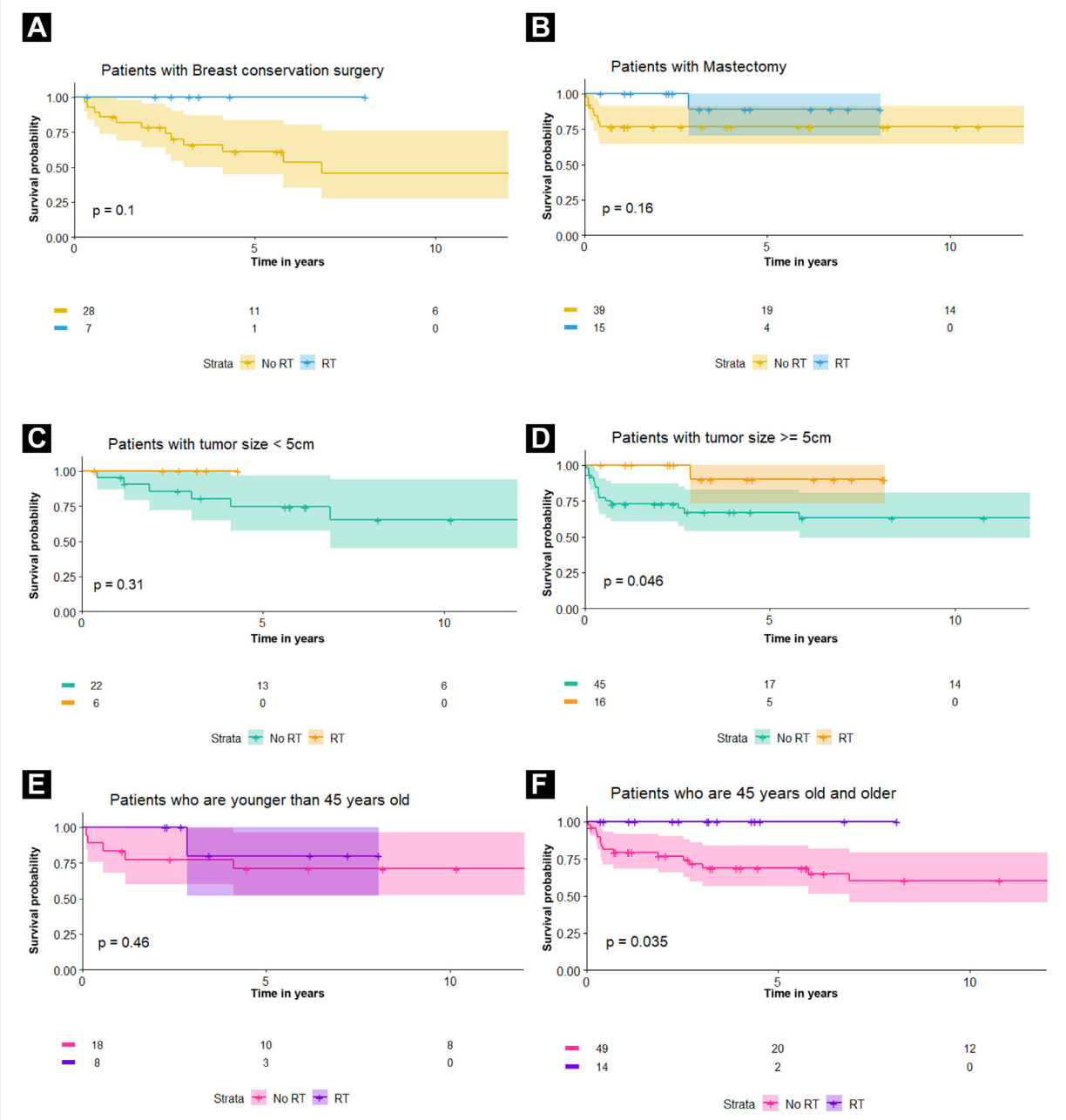


Figure 3 Locoregional Recurrence-free Survival With and Without Radiotherapy (RT) in Different subgroups. (A) Breast Conservation Group (B) Mastectomy (C) Tumor Size < 5 cm (D) Tumor Size ≥ 5 cm (E) Younger than 45 Years Old (F) 45 Years Old and Older



was no difference in median age between surgery types ($P = .25$). The proportion of patients with tumor size 5 cm or larger was higher in the mastectomy group (83.3% vs 45.7%, $P < .01$). Uptake of RT was seen only in a more recent cohort of patients, after 2004 (Figure 1). Median dose was 60 Gy in 30 fractions over 6 weeks (lowest dose was 40 Gy in 15 fractions, highest 66 Gy after boost).

Local Recurrence

One (4.55%) of 22 patients who had upfront adjuvant RT suffered a local recurrence compared with 31.3% ($P = .03$) in those without RT. This patient had 60 Gy adjuvant RT but experienced a local relapse (including multiple distant metastases) 3 years after; the relapse was infield at the chest wall. This patient was a 44-year-old woman with a large and histologically high-risk MPT. Four patients in the no-RT group received RT after surgery for local recurrence and experienced no further local relapses. On UVA, RT was associated with a lower risk of local recurrence (hazard ratio [HR] 0.14; 95% confidence interval [CI], 0.02-1.07; $P = .03$) (Figure 2). Three-year LRFS was better in the RT group 92.3% (95% CI, 78.9%-100%) vs 73.3% (95% CI, 63.1%-85.1%).

In subgroup analysis, there was a trend for better LRFS with RT than without RT in both BCS (3-year LRFS 100.0% vs 70.0%, $P = .10$, Figure 3A) and mastectomy (88.9% vs 76.5%, $P = .16$, Figure 3B) subcohorts. There was no difference in LRFS between RT and no-RT groups in patients younger than 45 years (80.0% vs 77.4%, $P = .46$, Figure 3E), and in patients with tumors smaller than 5 cm (100.0% vs 85.6%, $P = .31$, Figure 3C). RT was associated with better LRFS in those with tumor size 5 cm or larger (90.0% vs 67.0%, $P = .05$, Figure 3D), and in patients 45 years and older (100.0% vs 71.6%, $P = .04$, Figure 3E). UVA was performed for age, receipt of RT, surgery type, and histological factors of tumor size, stromal hypercellularity, margin status, stromal atypia, stromal mitoses, tumor borders, and presence of heterologous elements. Accounting for factors significant in UVA in MVA, only RT (HR 0.12; 95% CI, 0.02-0.92; $P = .04$) and stromal atypia (mild/moderate atypia with a HR 0.10; 95% CI, 0.02-0.46; $P < .01$) were significant (Table 2).

Distant Recurrence

Of the 21 patients with a distant recurrence, time to death from first distant relapse was 5.08 months (interquartile range: 2.36-12.15). There was no difference in DDFS (HR 0.89, $P = .8$). Three-year DDFS between RT and no-RT groups was 74.0% (56.0%-96.0%) versus 74.8% (64.8%-86.3%). Factors significant for DDFS in UVA were stromal mitoses, surgery type, and age; heterologous elements and tumor borders exhibited a trend to significance ($P = .10$ and .07, respectively). Accounting for these factors in MVA, significant factors were mitoses, surgery, and age.

Overall Survival

Seventeen patients died of metastatic MPT, 6 of other causes. There was no difference in OS (no-RT 78.5% vs RT 84.0%, HR 0.72, $P = .6$). Three-year OS in RT and no-RT groups was 84% (95% CI, 68.8%-100%) versus 78.5% (95% CI, 68.8%-89.6%). Factors significant in UVA for OS were age and surgery type; after MVA, only age was significant.

Table 2 Multivariable Analysis of Factors Predicting LRFS

Variable	Hazard Ratio (95% CI)	*P* Value
RT		
No	Ref	
Yes	0.12 (0.02-0.93)	**.04**
Stromal hypercellularity		
Marked	Ref	
Mild/moderate	0.93 (0.3-2.90)	.89
Stromal mitoses	1.02 (1.00-1.04)	.11
Surgical margin		
Negative	Ref	
Focal/diffuse Involvement	2.09 (0.83-5.25)	.12
Stromal atypia		
Marked	Ref	
Mild/moderate	0.10 (0.02-0.48)	**<.01**

Bold values are $P < .05$.
Abbreviations: CI = confidence interval; LRFS = locoregional recurrence-free survival; RT = radiotherapy.

Palliative RT

Three patients in the no-RT had palliative RT on metastatic relapse for bulky local disease; 2 patients experienced symptomatic relief with reduction in size of the treated tumors, and the last patient died of disease before an evaluation could be made.

Discussion

We found that only 1 of 22 patients in the RT group experienced a local recurrence versus 21 of 67 in the no-RT group. Four patients in the no-RT group received RT on recurrence without further recurrences. Overall, RT improved 3-year LFRS (HR 0.14; 95% CI, 0.02-1.07; $P = .03$). In subgroup analysis, RT was either associated with better local control, or exhibited a trend for improved local control. In MVA, RT was independently associated with better LRFS. RT was used more frequently after 2004, mirroring a trend reported by another group.[5] There was in vivo demonstration that RT was efficacious in the patients with good partial responses post palliative RT.

A large meta-analysis included 1700 patients with MPT and reported a crude local recurrence rate of 18%,[6] suggesting that BCS was associated with a higher local recurrence, but RT was not assessed. The largest single study on PT included 3000 patients from the National Cancer Database and found that RT was associated with better local control (HR 0.5) without OS impact.[5] An analysis of the SEER database found that RT was given in higher-risk patients and yet locoregional recurrence was not higher.[3] Another series of 70 Korean patients, 15 of whom had adjuvant RT, revealed that the only significant predictor for disease recurrence was presence of tumor necrosis, although there was a trend to significance for RT.[7] A larger Korean study recommended that RT be given after margin-negative BCS if the tumor was larger than 5 cm.[8] A recent French study found RT to be effective in terms of LRFS but not OS.[9] On the contrary, an Indian study could not demonstrate benefit with RT.[10]

The importance of margin status is controversial. A study from the Mayo Clinic that explored margin status for borderline and malignant PTs reported that extent of surgical resection had no impact on local recurrence, and only histological features predicted for that.[11] Likewise, a study from Vancouver published similar findings.[12] Yet, a separate British Columbian study found that margin status was predictive.[13] All 3 studies did not address the role of RT. A more recent French paper with 212 patients recommended that margins of at least 3 mm be achieved.[9] This current study included histological risk factors and in MVA, found only RT and stromal atypia to be predictive for local recurrence.

Like other studies, we found that RT did not affect DDFS and OS.[5,7,8] We found that mitoses, surgery type, and age were associated with distant events. In UVA, mastectomy was associated with a higher hazard of distant events. This is likely due to a much higher proportion of larger tumors in mastectomy patients.

We report a median time to death after a distant relapse of 5.08 months. Other studies have a longer OS finding of 7.5 to 11.5 months.[4,9,14,15]

Of the 2 evaluable patients who received palliative RT, both had symptomatic relief of their local fungating tumors. Conclusions regarding the efficacy of palliative RT cannot be drawn due to the small sample size. Two separate European studies, 1 French and 1 Polish, on metastatic MPT reported that approximately 30% of patients received palliative RT but did not report on RT response.[14,15] Reports on efficacy of palliative RT are scant.

The strengths of this study are that we specifically included only MPT and every specimen was reviewed by experienced breast pathologists in a tertiary institution. We also detailed RT doses and local relapse field.

Our limitations include short follow-up and small sample size for the group that received RT, as RT was used in a more recent cohort. The retrospective nature of this study has its inherent bias too.

Future RT-related research for MPT should address dose. Randomized trials have established hypofractionation for breast cancers, yet for MPT, the current practice is still conventional high-dose fractionation as extrapolated from adult-type sarcoma trials.

Local recurrences are very debilitating, with patients often presenting with large symptomatic fungating chest wall masses. Although RT is not associated with OS, it should still be considered to prevent local recurrences.

In summary, we recommend that RT be discussed in every patient with MPT.

Clinical Practice Points

- Malignant phyllodes tumor (MPT) is a rare yet devastating condition. There are no randomized trials yet to guide practice.
- Although some previous studies report that radiotherapy (RT) was associated with better local recurrence-free outcomes, some smaller studies only recommend RT in certain scenarios (eg, after breast conservation surgery, with close margins).
- Some studies also mentioned no role for adjuvant treatment due to lack of impact on overall survival.
- A large study from the National Cancer Database showed that RT was used more frequently in recent years.
- We strive to determine the efficacy of RT in MPT.
- In a large tertiary single institution, we report the outcomes of 89 patients with MPT and the role of RT.
- RT was associated with better locoregional control after multivariable analysis taking into consideration histological risk factors.
- RT was not associated with better distant disease-free and overall survival.
- We recommend that adjuvant RT be considered in MPT.

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

Disclosure

The authors have stated that they have no conflicts of interest.

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