

# Postoperative radiotherapy for invasive micropapillary carcinoma of the breast: an analysis of Surveillance, Epidemiology, and End Results database

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**Introduction:** Invasive micropapillary carcinoma (IMPC) of the breast poses a high risk of locoregional recurrence, and postoperative radiotherapy (PORT) may be beneficial in IMPC. Hence, we determined the clinical value of PORT in IMPC patients.

**Patients and methods:** We assessed clinicopathological factors extracted from the Surveillance, Epidemiology, and End Results database (2004–2013). Univariate and multivariate Cox proportional hazards regressions were performed to assess the independent prognostic factors on breast cancer-specific survival (BCSS) and overall survival (OS).

**Results:** Of the 881 study patients, 444 (50.4%) and 437 (49.6%) underwent breast-conserving surgery (BCS) and mastectomy (MAST), respectively, of whom 357 (80.4%) and 153 (35.0%) underwent PORT, respectively. Patients with young age, large tumor size, or advanced nodal stage were more likely to undergo MAST and PORT compared with MAST alone. Patients with progesterone receptor-positive disease were more likely to receive BCS and PORT compared with BCS alone. The 5-year BCSS and OS were 95.7% and 90.9%, respectively. On multivariate analyses, tumor size, histological grade, and estrogen receptor status were independent predictors of BCSS and OS. The types of surgical procedures (MAST vs. BCS) were not an independent predictor of survival outcomes. Patients who underwent MAST with or without PORT had similar BCSS and OS in the multivariate analyses. Those who underwent BCS plus PORT did not have better BCSS and OS than those who underwent BCS alone. In the low-, intermediate-, and high-risk groups, PORT was not associated with better BCSS and OS than non-PORT groups in patients who received BCS or MAST.

**Conclusion:** IMPC has favorable BCSS and OS. Regardless of the types of surgical procedures (MAST or BCS), PORT groups were not inferior to non-PORT groups on BCSS and OS.

**Keywords:** invasive micropapillary carcinoma, SEER, radiotherapy, survival

## Introduction

Invasive micropapillary carcinoma (IMPC) is a rare histological subtype of breast carcinoma, accounting for 3%–6% of all invasive breast cancers.<sup>1</sup> IMPC was first described in 1993, and the World Health Organization classified IMPC as an independent breast tumor in 2003.<sup>1,2</sup> It is generally accepted that IMPC is associated with a higher probability of lymphovascular invasion (LVI) and regional lymph node metastasis (66%–90%) than invasive ductal carcinoma (IDC).<sup>3–10</sup> Abnormal expression of several markers, including MUC1, N-cadherin, E-cadherin, and CD44, may be related to the highly aggressive tumor biology, resulting in lymph node metastases, high recurrence

rates, and short disease-free survival.<sup>11–21</sup> However, whether IMPC histology is an independent prognostic factor in breast cancer remains controversial. Several studies have reported that there is no significant difference in outcomes between IMPC and IDC patients matched for lymph node status.<sup>22–24</sup> Two population-based studies that contributed to the Surveillance, Epidemiology, and End Results (SEER) database have also confirmed that survival outcomes are similar for the IMPC and IDC subtypes.<sup>25,26</sup>

Postoperative radiotherapy (PORT) is an important adjuvant therapy in breast cancer patients after breast-conserving surgery (BCS) or in high-risk patients after mastectomy (MAST).<sup>27,28</sup> Several studies have found that the locoregional recurrence (LRR) rate of IMPC is higher than that of IDC,<sup>10,29</sup> possibly because unlike IDC, IMPC is associated with several high risk factors for LRR, including LVI and lymph node metastasis. Therefore, PORT may play an important role in IMPC. However, the clinical value of PORT in patients with IMPC remains unclear. In this study, we used the SEER database to determine the clinical value of PORT in patients with IMPC.

## Patients and methods

### Patients

The study population consisted of patients with pathologically proven IMPC of the breast treated between 2004 and 2013, according to the current SEER program.<sup>30</sup> The inclusion criteria for this study were as follows: 1) women with localized or regional IMPC of the breast; 2) IMPC as the primary cancer diagnosis; 3) treated with local surgery including MAST and BCS; 4) availability of data on whether postoperative beam radiation was performed; and 5) availability of data on ethnicity, tumor size, histological grade, nodal stage, and estrogen receptor (ER) and progesterone receptor (PR) statuses. This study was approved by the ethics committee of The First Affiliated Hospital of Xiamen University and Sun Yat-sen University Cancer Center.

### Clinicopathological factors

The following clinicopathological factors were extracted from the SEER database: age at diagnosis, ethnicity, tumor size (T stage), histological grade, lymph node staging (N stage), surgical procedures, and hormone receptor status. Lymph node stage was based on the number of metastatic lymph nodes, according to the current Union for International Cancer Control/American Joint Committee on Cancer staging system.

## Statistical analysis

Statistical analyses were performed using the SPSS statistical software package (version 21.0; IBM Corporation, Armonk, NY, USA). The  $\chi^2$  test and Fisher's exact probability test were used to evaluate differences between qualitative variables. Breast cancer-specific survival (BCSS) and overall survival (OS) rates were estimated by the Kaplan–Meier method and compared with the log-rank test. Univariate and multivariate analyses were performed to investigate the risk factors for BCSS and OS by using the Cox proportional hazards model. For all statistical analyses, a *p* value of <0.05 was considered as significant.

## Results

### Patient characteristics and treatment

In total, 881 patients with IMPC of the breast were included in this study. The characteristics of the patients are listed in Table 1. The median age was 59 years (range, 25–95 years). Of the 881 patients, 511 (58.0%) had T1 stage disease. The median tumor size was 18 mm. A total of 344 (39.0%) patients had poorly differentiated or undifferentiated tumors, and 462 (52.4%) patients had node-positive disease. ER and PR positivity was observed in 90.0% and 77.0% of patients, respectively.

A total of 444 (50.4%) and 437 (49.6%) patients underwent BCS and MAST, respectively. In each group, 357 (80.4%) and 153 (35.0%) patients received PORT, respectively. Patients with younger age ( $\leq 49$  years), larger tumors (T2–3 stages), and advanced nodal stage (N2–3 stages) were more likely to have received MAST and PORT compared to patients who received MAST alone. In BCS groups, patients with PR-positive disease were more likely to receive BCS with PORT. There were no significant differences in age, ethnicity, tumor size, tumor grade, nodal stage, and ER status between patients who received BCS alone and those who received BCS with PORT.

### Factors influencing patient survival

The median follow-up was 39 months (range, 0–119 months). A total of 64 patients died, including 31 patients who died of breast cancer-related disease. The 5-year BCSS and OS rates were 95.7% and 90.9%, respectively. Univariate analyses revealed that age, tumor size, histological grade, nodal stage, ER status, and PR status were prognostic factors for BCSS and OS (Table 2). Patients who had received MAST had significantly worse BCSS and OS than those who had received BCS.

**Table 1** Clinicopathological characteristics of the study patients

Characteristics	n	BCS	BCS + RT	MAST	MAST + RT	<i>p</i> <sup>a</sup>	<i>p</i> <sup>b</sup>	<i>p</i> <sup>c</sup>
Age (years)								
≤49	204	14 (15.1)	55 (15.4)	74 (26.1)	61 (39.9)	<0.001	0.237	0.011
50–69	477	44 (50.6)	213 (59.7)	152 (53.5)	68 (44.4)			
≥70	200	29 (33.3)	89 (24.9)	58 (20.4)	24 (15.7)			
Ethnicity								
White	682	64 (73.6)	278 (77.9)	226 (79.6)	114 (74.5)	0.858	0.637	0.457
Black	107	13 (14.9)	41 (11.5)	31 (10.9)	22 (14.4)			
Others	92	10 (11.5)	38 (10.6)	27 (9.5)	17 (11.1)			
Tumor size								
T1	511	65 (74.7)	259 (72.5)	153 (53.9)	34 (22.2)	<0.001	0.916	<0.001
T2	284	21 (24.1)	94 (26.3)	104 (36.6)	65 (42.5)			
T3	86	1 (1.1)	4 (1.1)	27 (9.5)	54 (35.3)			
Grade								
G1	66	8 (9.2)	31 (8.7)	21 (7.4)	6 (3.9)	0.026	0.217	0.115
G2	471	42 (48.3)	208 (58.3)	149 (52.5)	72 (47.1)			
G3–4	344	37 (42.5)	118 (33.0)	114 (40.1)	75 (49.0)			
Nodal stage								
N0	418	60 (69.0)	206 (57.7)	142 (50.0)	10 (6.5)	<0.001	0.118	<0.001
N1	280	18 (20.7)	118 (33.0)	93 (32.7)	51 (33.3)			
N2	107	4 (4.6)	20 (5.6)	32 (11.3)	52 (34.0)			
N3	75	5 (5.7)	13 (3.6)	17 (6.0)	40 (26.1)			
ER status								
Negative	88	11 (12.6)	23 (6.4)	36 (12.7)	18 (11.8)	0.037	0.051	0.782
Positive	793	76 (87.4)	334 (93.6)	248 (87.3)	135 (88.2)			
PR status								
Negative	203	25 (28.7)	68 (19.0)	67 (23.6)	43 (28.1)	0.070	0.046	0.300
Positive	678	62 (71.3)	289 (81.0)	217 (76.4)	110 (71.9)			

**Notes:** <sup>a</sup>BCS vs. BCS + RT vs. MAST vs. MAST + RT. <sup>b</sup>BCS vs. BCS + RT. <sup>c</sup>MAST vs. MAST + RT.

**Abbreviations:** BCS, breast-conserving surgery; ER, estrogen receptor; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated; MAST, mastectomy; N, node; PR, progesterone receptor; RT, radiotherapy; T, tumor.

On multivariate analyses, tumor size, histological grade, and ER status were found to be independent prognostic factors for BCSS and OS (Table 3). The types of surgical procedures were not an independent prognostic factor for survival outcomes. Patients who had undergone MAST had similar BCSS and OS rates in the multivariate analyses, regardless of whether PORT was performed. In addition, patients who received BCS plus PORT did not show improved BCSS and OS compared to patients who received BCS alone.

## Clinical value of PORT

We further classified patients into the following subgroups to determine the clinical value of PORT in IMPC: low-risk group (T1–2N0; *n* = 410), intermediate-risk group (T1–2N1; *n* = 266), and high-risk group (T3N0 and T1–3N2–3; *n* = 205). Our results indicated that in patients who had undergone BCS, PORT did not improve BCSS (log-rank test: low-risk group, *p* = 0.072; intermediate-risk group, *p* = 0.764; high-risk group, *p* = 0.564) or OS (log-rank test: low-risk group, *p* = 0.402; intermediate-risk group, *p* = 0.734; high-risk group, *p* = 0.413). Similarly, in patients who had undergone

MAST, PORT was not associated with better survival in the low-risk group (log-rank test: BCSS, *p* = 0.537; OS, *p* = 0.394), intermediate-risk group (log-rank test: BCSS, *p* = 0.981; OS, *p* = 0.896), or high-risk group (log-rank test: BCSS, *p* = 0.127; OS, *p* = 0.069).

## Discussion

Owing to the low incidence of IMPC and the small sample sizes of previous studies, the clinical value of PORT for IMPC of the breast remains unclear. In this study, we used population-based analyses to examine the role of PORT in patients with IMPC and found that PORT did not improve the survival of patients in the overall cohort or in different subgroups based on recurrence risk, regardless of the types of surgical procedures.

LRR is a major factor in determining the use of PORT in breast cancer. Yu et al<sup>29</sup> found that regardless of adjuvant PORT, IMPC patients had a significantly higher 5-year LRR rate than IDC patients (20.9% vs. 6.7%, *p* = 0.0024). A study by Chen and Ding<sup>9</sup> included 95 patients with IMPC, of whom 74 patients underwent MAST and 21 underwent BCS; PORT

**Table 2** Univariate prognostic analyses

Characteristics	BCSS		OS	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Age (years)				
≤49	1		1	
50–69	1.347 (0.533–3.399)	0.529	1.386 (0.654–2.940)	0.395
≥70	1.258 (0.422–3.751)	0.681	3.254 (1.528–6.930)	0.002
Ethnicity				
White	1		1	
Black	1.967 (0.795–4.864)	0.143	1.640 (0.852–3.158)	0.139
Other	0.933 (0.279–3.123)	0.911	0.551 (0.199–1.528)	0.252
Tumor size				
T1	1		1	
T2	2.474 (1.023–5.981)	0.044	1.973 (1.138–3.420)	0.016
T3	9.074 (3.748–21.966)	<0.001	3.823 (1.961–7.454)	<0.001
Grade				
G1–2	1		1	
G3–4	4.282 (1.915–9.572)	<0.001	1.909 (1.165–3.129)	0.010
Nodal stage				
N0	1		1	
N1	0.971 (0.370–2.552)	0.953	1.011 (0.559–1.827)	0.971
N2	2.473 (0.898–6.809)	0.08	1.615 (0.779–3.350)	0.198
N3	4.839 (1.908–12.270)	0.001	2.144 (1.004–4.577)	0.049
ER status				
Negative	1		1	
Positive	0.234 (0.112–0.488)	<0.001	0.392 (0.223–0.691)	0.001
PR status				
Negative	1		1	
Positive	0.434 (0.213–0.887)	0.022	0.567 (0.340–0.945)	0.030
Treatment				
BCS + RT	1		1	
BCS	3.115 (0.697–13.921)	0.137	1.946 (0.840–4.509)	0.121
MAST	4.962 (1.659–14.847)	0.004	2.106 (1.157–3.833)	0.015
MAST + RT	4.762 (1.434–15.818)	0.011	1.443 (0.661–3.153)	0.357

**Abbreviations:** BCS, breast-conserving surgery; BCSS, breast cancer-specific survival; CI, confidence interval; ER, estrogen receptor; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated; HR, hazard ratio; MAST, mastectomy; N, node; OS, overall survival; PR, progesterone receptor; RT, radiotherapy; T, tumor.

was performed depending on the indications in individual patients. The 5-year LRR rates in the entire cohort and in node-positive patients were 28.6% and 35.8%, respectively, which were significantly higher than the rates in patients with triple-negative breast cancer (10.2% and 18.3%, respectively). The 5-year LRR rates in patients with N0-, N1-, N2-, and N3-stage diseases were ~10%, 20%, 40%, and 50%, respectively,<sup>9</sup> which were significantly higher than the rates reported for IDC in prospective studies.<sup>27,28</sup> As the N2 and N3 stages are absolute indications for PORT, the LRR rate was high in the study by Chen and Ding.<sup>9</sup> However, a retrospective multicenter case-control study from Korea found that regardless of PORT, the LRR rate was significantly higher in IMPC than in IDC (8.2% vs. 3.7%,  $p = 0.03$ ).<sup>10</sup> Other studies have not found differences in LRR between the IMPC and IDC subtypes.<sup>24,31</sup> Thus, the reported LRR rates of IMPC vary widely, and this may have an impact on the use of PORT. Owing to the limitations of

the SEER database, we were unable to obtain the LRR data of the patients. Although more than half of the patients had lymph node metastases, the 5-year BCSS was 95.7% in our study, which is similar to that reported in the two previous SEER studies.<sup>25,26</sup> These results suggest that IMPC patients have favorable survival outcomes, which are not inferior to those of IDC patients.<sup>25,26</sup>

To date, no study has specifically aimed to determine the value of PORT in patients with IMPC. In a retrospective multicenter case-control study from Korea, of the 2, 17, and 75 patients with N0-, N1-, and N2–3-stage diseases who underwent breast/chest wall radiotherapy with or without regional lymph node radiotherapy, a total of 0, 1, and 12 patients developed LRR, which was significantly higher than the LRR rates in patients with IDC ( $p = 0.03$ ). However, PORT was not associated with reduced LRR in IMPC ( $p = 0.94$ ).<sup>10</sup> Yu et al<sup>29</sup> included 72 IMPC patients, of whom

**Table 3** Multivariate prognostic analyses

Characteristics	BCSS		OS	
	HR (95% CI)	p	HR (95% CI)	p
Age (years)				
≤49	–		1	
50–69	–	–	1.416 (0.664–3.020)	0.368
≥70	–	–	4.837 (2.215–10.564)	<0.001
Tumor size				
T1	1		1	
T2	2.126 (0.875–5.163)	0.096	2.090 (1.174–3.721)	0.012
T3	7.756 (3.195–18.827)	<0.001	5.229 (2.414–11.325)	<0.001
Grade				
G1–2	1		1	
G3–4	3.270 (1.437–7.440)	0.005	1.720 (1.026–2.886)	0.040
Nodal stage				
N0	1		1	
N1	0.799 (0.295–2.166)	0.659	1.231 (0.660–2.297)	0.514
N2	0.986 (0.297–3.280)	0.982	1.190 (0.498–2.844)	0.695
N3	1.623 (0.493–5.344)	0.426	1.816 (0.735–4.484)	0.196
ER status				
Negative	1		1	
Positive	0.339 (0.160–0.720)	0.005	0.391 (0.215–0.709)	0.002
PR status				
Negative	1		1	
Positive	1.483 (0.442–4.976)	0.523	0.945 (0.437–2.046)	0.886
Treatment				
BCS + RT	1		1	
BCS	2.421 (0.527–11.124)	0.256	2.122 (0.903–4.986)	0.084
MAST	2.528 (0.801–7.980)	0.114	1.631 (0.864–3.078)	0.132
MAST + RT	1.334 (0.342–5.210)	0.678	0.762 (0.316–1.836)	0.546

**Note:** '–' indicates no data.

**Abbreviations:** BCS, breast-conserving surgery; BCSS, breast cancer-specific survival; CI, confidence interval; ER, estrogen receptor; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated; HR, hazard ratio; MAST, mastectomy; N, node; OS, overall survival; PR, progesterone receptor; RT, radiotherapy; T, tumor.

71.3% received PORT; the 5-year LRR rate was 20.9% in the entire cohort. A study from China included 100 patients with IMPC, of whom 72% received PORT, and 11.2% of the entire cohort developed LRR.<sup>32</sup> Li et al<sup>24</sup> included 33 patients with IMPC, all of whom underwent MAST; 78.2% were lymph node positive, and 42.4% of all patients received PORT, but only one patient developed LRR. Vingiani et al<sup>31</sup> included 49 patients with IMPC, of whom 87.8% received PORT; the LRR rate was 6.1%. We were unable to obtain the LRR data of patients who had undergone PORT in the abovementioned three studies. A SEER study by Chen et al<sup>25</sup> found that PORT was an independent predictor of disease-specific survival and OS in IMPC. However, the impact of PORT after specific types of surgical procedures and in specific risk factor-based groups was not further analyzed.

In the present study, univariate analysis showed similar survival in patients who underwent BCS alone and in those who underwent BCS plus PORT; patients who underwent MAST with or without PORT had poorer survival than those who underwent BCS plus PORT. Selection bias might account

for this finding, as patients with adverse prognostic factors, such as younger age, large tumors, and advanced nodal stage, were more likely to undergo MAST with or without PORT. After adjustments for age, tumor size, tumor grade, nodal stage, ER status, and PR status in the multivariate analyses, patients who underwent BCS alone and those who underwent MAST with or without PORT had similar BCSS and OS to those who underwent BCS plus PORT. Studies on IDC have demonstrated that the improved local control rate in PORT groups is sequentially translated to improvement in the survival rate of patients with distant metastases.<sup>27,28</sup> However, the BCSS and OS rates were similar in the PORT and non-PORT groups in our study, regardless of the type of surgical procedures. In addition, PORT did not improve the survival of patients after BCS or MAST in the low-risk, intermediate-risk, and high-risk groups.

The reasons why PORT did not improve survival in patients after BCS or in high-risk patients after MAST remain unknown. Possible explanations are as follows: 1) we could not obtain the patterns of LRR in the SEER database.

However, IMPC is associated with several risk factors for LRR, including LVI and high probability of lymph node metastasis. In randomized studies of breast cancer, especially for patients who have undergone BCS, individual studies often find significant differences in local recurrence, but not in OS.<sup>33,34</sup> Survival changes due to addition of PORT are often only seen with larger meta-analyses;<sup>35,36</sup> 2) although IMPC includes several high risk factors for LRR, the risk of distant metastasis is not higher in IMPC compared to IDC,<sup>3,10,24,29,32</sup> which suggests that IMPC has a special biological behavior; and 3) the vast majority of IMPC patients in this study had ER-positive disease and may have benefited from endocrine therapy, which may have reduced the potential risk of LRR.

Similar to a previous SEER study,<sup>25</sup> approximately half of the patients in our study underwent BCS, and the BCSS and OS rates in the BCS and MAST groups were similar. Studies have shown that MAST is the most common type of surgical procedure in IMPC and that the types of surgical procedures were not associated with survival outcomes.<sup>9,24,37</sup> However, in a retrospective multicenter case-control study from Korea (n = 267), 57.7% of patients underwent BCS, and BCS patients were found to have better LRR control rates than MAST patients (96.7% vs. 86.5%,  $p = 0.03$ ).<sup>10</sup> Therefore, the survival outcomes of BCS were not inferior to those of MAST in patients with IMPC of the breast.

We need to acknowledge several limitations of our study. First, retrospective studies have inherent bias. Second, detailed histopathological data, including LVI status and resection margin status, were unavailable in the SEER database. Data on the use of systemic therapies (i.e., chemotherapy or endocrine therapy) were also lacking in the SEER database. In addition, the target volume and radiation dose were not recorded, and the patterns of LRR in patients with and without PORT were also unknown. Finally, it has been shown that there are many inaccuracies in the SEER databases, with high rates of underreporting for PORT receipt.<sup>38</sup> However, the primary strength of this study is that we investigated the role of PORT in patients with IMPC of the breast, by using a large population-based database. Therefore, this study population is more diversified and potentially more generalizable than retrospective studies from single institutions.

## Conclusion

IMPC has favorable BCSS and OS rates. Regardless of the types of surgical procedures (MAST or BCS), PORT groups were not inferior to non-PORT groups on BCSS and OS in

IMPC patients. Further prospective large-scale studies are necessary to confirm the clinical value of PORT in IMPC.

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## Disclosure

The authors report no conflicts of interest in this work.

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