The Role of Postoperative Radiotherapy After Primary Tumor Resection in Patients With De Novo Stage Iv Breast Cancer

Yeon Joo Kim
Asan Medical Center https://orcid.org/0000-0003-2858-0644
Su Ssan Kim (watermountain@hanmail.net)
Seung Do Ahn
Asan Medical Center
Jinhong Jung
Asan Medical Center
Sei-Hyun Ahn
Asan Medical Center
Byung Ho Son
Asan Medical Center
Jong Won Lee
Asan Medical Center
Hee Jeong Kim
Asan Medical Center
Beom Seok Ko
Asan Medical Center
Sung-Bae Kim
Asan Medical Center
Kyung Hae Jung
Asan Medical Center
Jin-hee Ahn
Asan Medical Center
Jeong-eun Kim
Asan Medical Center
Eun Kyung Choi
Asan Medical Center

Research

Keywords: Breast, Carcinoma, Radiotherapy, Surgery, Survival

Posted Date: June 11th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-34340/v1

Version of Record: A version of this preprint was published at Asia-Pacific Journal of Clinical Oncology on November 11th, 2020. See the published version at https://doi.org/10.1111/ajco.13506.

Abstract

Background: To investigate the role of postoperative radiotherapy (PORT) in stage IV breast cancer patients who underwent planned primary tumor resection (PTR).

Methods: This study enrolled 112 patients diagnosed with de novo stage IV breast cancer who were treated with potentially curative PTR with or without PORT. The primary outcome was overall survival (OS), and the secondary outcomes were locoregional recurrence-free survival (LRRFS) and distant progression-free survival (DPFS).

Results: At a median follow-up of 48.9 months (range, 3.5–183.4 months), the median OS was 54.9 months (range, 5.3–185.9 months) with a 5 year OS rate of 59.6%. Luminal A or B type tumors and PORT were significantly predictive of longer OS. The 5 year LRRFS and DMFS rates were 79.0% and 34.3%, respectively. PORT was the only significant predictor of LRRFS (hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.15–0.86; $p = 0.021$). A comparison of patients who did and did not receive PORT showed that patients with disseminated metastasis more likely did not receive PORT and were excluded from the analysis. Multivariate analysis showed that PORT was significantly predictive of LRRFS (HR, 0.31; 95% CI, 0.11–0.91; $p = 0.033$) but not of OS.

Conclusions: De novo stage IV breast cancer patients who received planned PTR showed favorable survival outcomes compared with historical cohorts. PTR may be predictive of a good prognosis, especially in patients with luminal A or B type tumors. PORT was significantly predictive of LRRFS, suggesting that patients may benefit from this treatment.

Trial registration: The present study was not registered due to its retrospective nature.

Background

Breast cancer is the most common malignancy in women in the United States (1) and the second most common malignancy in the Republic of Korea (2). Approximately 5–8% of patients with breast cancer are initially diagnosed with distant metastases (3). Due to the heterogeneous demographic and tumor characteristics of stage IV breast cancer patients, their survival varies from months to years (4, 5). The standard of care for stage IV breast cancer is a systemic treatment, as the disease itself is regarded as incurable, with primary tumor resection (PTR) usually performed for palliative purposes only (6).

Advances in systemic agents since the mid-1990s have prolonged survival in patients with metastatic breast cancer (7), suggesting that early PTR may be beneficial. Several retrospective studies have reported that PTR has a positive impact on local control and overall survival (OS) (8–10). Although three prospective randomized controlled trials (RCTs) in India, Turkey, and Austria, compared PTR with systemic therapy alone (11–13), conflicting results were observed, suggesting that the benefits of PTR remain unclear.

In real-world practice, however, PTR has been performed on 35–80% of patients with stage IV breast cancer (8, 9). Thus, the incidence of postoperative radiotherapy (PORT), including post-mastectomy radiotherapy (PMRT), has also increased (14). Despite these increases, relatively little is known about the efficacy of PORT in patients with stage IV breast cancer. A study in Turkey reported that 38% of patients who underwent PTR received PMRT, with no difference in OS between patients who did and did not receive PMRT (12). A retrospective study of patients with advanced T-/N-stage tumors found that PMRT improved local control and OS, but the differences were not significant (9). By contrast, another retrospective study reported that PORT was a significant predictor of OS and progression-free survival (PFS) (10).

The present study evaluated the impact of PORT on clinical outcomes in patients with stage IV breast cancer who underwent PTR. Also, subgroup analyses of several prognostic factors were performed to identify populations that would benefit most from locoregional treatment.

Methods

Patients

Patients who presented with de novo stage IV breast cancer and who underwent PTR between December 2000 and December 2014 were retrospectively analyzed. Patients who progressed after neoadjuvant chemotherapy or within 2 months after PTR were excluded, as were patients with bilateral breast cancer. Of the 131 patients who underwent PTR during the study period, 19 were excluded, including eight with rapid progression after PTR, five with progressive disease after neoadjuvant chemotherapy, three with bilateral breast cancer, one lacking follow-up information, one lacking information on RT, and one with double primary cancer.

The medical records of the remaining 112 patients were extracted. Because this study included patients treated over a 14-year period, the first author reviewed the data of all the patients and determined their TNM stage according to the American Joint Committee on Cancer (AJCC), 7th edition. Staging work-up included physical examination, mammography, ultrasound, pathologic confirmation, chest computed tomography (CT), and abdomino-pelvic CT (APCT). Patients with symptoms suggesting cranial nerve system involvement were also evaluated by brain imaging. In addition, 5.4% of patients were evaluated by 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) alone, and 76.8% by FDG-PET/CT. Further, biopsies of possible metastatic sites were obtained from 17.0% of the patients. Metastatic burden was assorted into three categories: single, oligo, and disseminated metastases, as described (15). Patients who satisfied all of the following criteria were considered as having oligometastases: 1) ≤ 2 organs involved other than the breast and its regional lymph nodes (LNs), 2) ≤ 5 metastases per organ (≤ 10 in patients with tiny, unclear lesions in the lungs and/or bones), and 3) lesion size ≤ 5 cm. The study protocol was approved by the local institutional review board, which waived requirements for informed consent.

Treatments and follow-up

Overall treatments were decided by multidisciplinary teams, which included a surgeon, a medical oncologist, a radiation oncologist, and a radiologist. Types of PTR (breast conserving operation [BCO] or mastectomy) and nodal evaluation (axillary LN dissection [ALND], sentinel LN biopsy [SLNB], or none) were determined by the surgeon based on factors associated with individual tumors and patients. Neoadjuvant and/or postoperative chemotherapy was administered to selected patients. Hormonal therapy and trastuzumab were administered based on immunohistochemical detection of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2). Tumors weakly positive for HER2 were further assessed by silver-enhanced *in situ* hybridization. Response after neoadjuvant chemotherapy was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (16). The decision to administer postoperative chemotherapy and/or PORT after PTR was made by the treating physicians. After the completion of planned treatment, patients were routinely followed up every 3 months, including by relevant imaging methods.

Statistical analysis

The primary outcome of the present study was 5 year OS, and secondary endpoints were 5 year locoregional recurrence-free survival (LRRFS) and distant PFS (DPFS). Locoregional recurrence (LRR) was defined as a failure in the breast/chest wall or regional nodal areas. Distant progression included the appearance of any new lesions and/or a ≥ 20% increase in the sum of the diameters of the target metastatic lesions, relative to the last preoperative measurements. Follow-up durations were calculated from the date of PTR. Survival was calculated as the duration of time from the date of PTR until death and was plotted by the Kaplan–Meier method.

A Cox proportional hazard model was used for univariate analysis, and stepwise backward elimination Cox regression was used for multivariate analysis. Factors with a p-value ≤ 0.2 on univariate analysis were included in the multivariate analysis. Characteristics of patients in PORT arm and No PORT arm were compared by Student's t-tests. The Kaplan-Meier method was used to estimate survival. All statistical analyses were performed using R version 3.4.1 (web-r.org).

Results

Patient characteristics

The characteristics of the 112 patients who were included are listed in Table 1. Their median age was 45 years (range, 26–72 years), with the numbers of patients who underwent PTR increasing over time (from 2000 to 2014). About half of the patients were clinical T2 stage (51.8%), and clinical N-stage was evenly distributed among N0 (27.7%), N1 (34.8%), and N3 (31.2%). The most common site of distant metastases was the bones (58.0%), followed by distant LNs (25.2%). About 40% of the patients had a single metastatic lesion, whereas 43.8% had oligometastatic disease. Besides, 59.8% of patients presented with luminal A (ER and/or PR positive, but HER2 negative), 12.5% with luminal B (ER and/or PR positive, and HER2 positive), and 14.3% with HER2-enriched (ER and PR negative, but HER2 positive) tumors. Furthermore, 24.1% of patients had a high (≥ 30%) Ki-67 labeling index (LI). Neoadjuvant

chemotherapy was administered to 59.8% of the patients, resulting in overall down-staging of pathological T- and N-stages. Of the 67 patients who received neoadjuvant chemotherapy, 5 (7.5%) showed a complete response, 57 (85.1%) showed a partial response, and 5 (7.5%) showed stable disease. Mastectomy (67.0%) was the main type of PTR, with 76.8% of these patients also undergoing ALND. PORT was administered to 21.4% of the patients after BCO and to 33.9% after mastectomy. Hormonal therapy was administered to 73.2% of these patients, correlating with the percentages of patients diagnosed with luminal A or B type tumors (75.0%). Trastuzumab was utilized in 25.9% of the patients, which also correlated with the percentage of patients having HER2 positive tumors (luminal B and Her2-enriched types, 27.8%). Forty-five patients underwent surgery or radiotherapy of all metastatic lesions within 3 months after PTR or postoperative chemotherapy.

Table 1
Patient characteristics

Characteristics	Total (n = 112) n (%)	No PORT (n = 50) n (%)	PORT (n = 62) n (%)	p-value
Median age (range), years	45 (26–72)	45 (26–72)	46 (26–70)	0.541
<45	54 (48.2)	22 (44.0)	32 (51.6)	
≥45	58 (51.8)	28 (56.0)	30 (48.4)	
Period of primary tumor resection	20 (17.9)	14 (28.0)	6 (9.7)	< 0.001
2000–2005	28 (25.0)	18 (36.0)	10 (16.1)	
2006–2010	64 (57.1)	18 (36.0)	46 (74.2)	
2011–2014				
Laterality	62 (55.4)	29 (58.0)	33 (53.2)	0.753
Left	50 (44.6)	21 (42.0)	29 (46.8)	
Right				
Histologic grade	63 (56.3)	26 (52.0)	37 (59.7)	0.408
Low (1–2)	47 (42.0)	24 (48.0)	23 (37.1)	
High (3)	2 (1.7)	0 (0.0)	2 (3.2)	
Unknown				
Clinical T-stage	77 (68.8)	37 (74.0)	40 (64.5)	0.357
T1/2	33 (29.5)	12 (24.0)	21 (33.9)	
T3/4	2 (1.7)	1 (2.0)	1 (1.6)	
Tx				

Abbreviations: ALND = axillary lymph node dissection; HER2 = human epidermal growth factor 2; LI = labeling index; NA = not applicable; PORT = postoperative radiotherapy; SLNB = sentinel lymph node biopsy.

*Oligometastases defined according to Kobayashi et al.(15)

†All interventions were performed within 3 months after surgery or postoperative chemotherapy.

Characteristics	Total (n = 112) n (%)	No PORT (n = 50) n (%)	PORT (n = 62) n (%)	p-value
Clinical N-stage	70 (62.5)	37 (74.0)	33 (53.2)	0.050
N0/1	41 (36.6)	13 (26.0)	28 (45.2)	
N2/3	1 (0.9)	0 (0.0)	1 (1.6)	
Nx				
Metastatic site	55 (49.1)	24 (48.0)	31 (50.0)	0.227
Bone only	10 (8.9)	7 (14.0)	3 (4.8)	
Bone and other	47 (42.0)	19 (38.0)	28 (45.2)	
Other (No bone)				
Metastatic burden*	45 (40.2)	13 (26.0)	32 (51.6)	< 0.001
Single	49 (43.8)	20 (40.0)	29 (46.8)	
Oligo	18 (16.1)	17 (34.0)	1 (1.6)	
Disseminated				
Molecular subtypes	67 (59.8)	26 (52.0)	41 (66.1)	0.548
Luminal A	14 (12.5)	8 (16.0)	6 (9.7)	
Luminal B	16 (14.3)	8 (16.0)	8 (12.9)	
HER2-enriched	12 (10.7)	7 (14.0)	5 (8.1)	
Triple negative	3 (2.7)	1 (2.0)	2 (3.2)	
Unknown (Luminal A or B)				
Ki-67 LI status	46 (41.1)	17 (41.7)	29 (46.8)	0.943
Low (< 30%)	27 (24.1)	11 (24.3)	16 (25.8)	
High (≥ 30%)	39 (34.8)	22 (34.0)	17 (27.4)	
Unknown				

Abbreviations: ALND = axillary lymph node dissection; HER2 = human epidermal growth factor 2; LI = labeling index; NA = not applicable; PORT = postoperative radiotherapy; SLNB = sentinel lymph node biopsy.

*Oligometastases defined according to Kobayashi et al.(15)

†All interventions were performed within 3 months after surgery or postoperative chemotherapy.

Characteristics	Total (n = 112) n (%)	No PORT (n = 50) n (%)	PORT (n = 62) n (%)	p-value
Pathological T-stage	87 (77.7)	40 (80.0)	47 (75.8)	0.763
T0/is/1/2	25 (22.3)	10 (20.0)	15 (24.2)	
T3/4				
Pathological N-stage	61 (54.5)	28 (56.0)	33 (53.2)	0.524
N0/1	45 (40.2)	17 (34.0)	28 (45.2)	
N2/3	6 (5.3)	5 (10.0)	1 (1.6)	
Nx				
Chemotherapy	53 (47.3)	13 (26.0)	40 (64.5)	< 0.001
Neoadjuvant	34 (30.4)	20 (40.0)	14 (22.6)	
Postoperative	14 (12.5)	7 (14.0)	7 (11.3)	
Both	11 (9.8)	10 (20.0)	1 (1.6)	
None				
Type of primary tumor resection	37 (33.0)	13 (26.0)	24 (38.7)	0.223
Breast conserving	75 (67.0)	37 (74.0)	38 (61.3)	
Mastectomy				
Method of axillary node evaluation	86 (76.8)	36 (72.0)	50 (80.6)	0.142
ALND	20 (17.9)	5 (10.0)	1 (1.6)	
SLNB	6 (5.4)	9 (18.0)	11 (17.7)	
None				

Abbreviations: ALND = axillary lymph node dissection; HER2 = human epidermal growth factor 2; LI = labeling index; NA = not applicable; PORT = postoperative radiotherapy; SLNB = sentinel lymph node biopsy.

*Oligometastases defined according to Kobayashi et al.(15)

†All interventions were performed within 3 months after surgery or postoperative chemotherapy.

Characteristics	Total (n = 112) n (%)	No PORT (n = 50) n (%)	PORT (n = 62) n (%)	p-value
Postoperative radiotherapy	24 (21.4)	0 (0.0)	24 (38.7)	NA
Post-breast conserving	38 (33.9)	0 (0.0)	38 (61.3)	
Post-mastectomy	50 (44.7)	50 (100.0)	0 (0.0)	
None				
Hormone therapy	75 (67.0)	29 (58.0)	46 (74.2)	0.194
Postoperative	7 (6.2)	4 (8.0)	3 (4.8)	
Neoadjuvant/postoperative	30 (26.8)	17 (34.0)	13 (21.0)	
None				
Trastuzumab	1 (0.9)	0 (0.0)	1 (1.6)	0.813
Neoadjuvant	12 (10.7)	6 (12.0)	6 (9.7)	
Postoperative	16 (14.3)	7 (14.0)	9 (14.5)	
Both	83 (74.1)	37 (74.0)	46 (74.2)	
None				
Intervention to all metastatic lesions[†]	45 (40.2)	7 (14.0)	38 (61.3)	< 0.001
Yes	67 (59.8)	43 (86.0)	24 (38.7)	
No				

Abbreviations: ALND = axillary lymph node dissection; HER2 = human epidermal growth factor 2; LI = labeling index; NA = not applicable; PORT = postoperative radiotherapty; SLNB = sentinel lymph node biopsy.

[*]Oligometastases defined according to Kobayashi et al.(15)

[†]All interventions were performed within 3 months after surgery or postoperative chemotherapy.

Specific information on chemotherapy and radiotherapy is provided in Supplementary Table 1. Patients received various chemotherapy regimens in both neoadjuvant and postoperative settings. Commonly used agents included doxorubicin, cyclophosphamide, docetaxel, and paclitaxel. Similar to PTR, the number of patients who received PORT increased over time (from 2000 to 2015). The supraclavicular LN (SCLN) area was irradiated in 87.1% of patients, with 27.4% also undergoing irradiation of the internal mammary LN (IMLN). Median dose irradiated to breast/chest wall and SCLN was 50 Gy. After breast/chest wall irradiation, a 10-Gy boost was applied to the tumor bed and/or scar in 31 patients, with

24 previously undergoing BCO. The median intervals between surgery and PORT were 1 month (range, 1–2 months) in patients who did not receive postoperative chemotherapy, and 7 months (range, 3–9 months) in patients who did receive postoperative chemotherapy.

Survival analyses of all patients

At a median follow-up time of 48.9 months (range, 3.5–183.4 months), the median duration of OS was 54.9 months (range, 5.3–185.9 months), and the 5-year OS rate was 59.6%. (Fig. 1A) Univariate and multivariate analyses were performed to identify factors predictive of OS (Table 2). Because of the strong multi-collinearities between molecular subtypes and hormonal and trastuzumab therapy, hormonal therapy and trastuzumab were not utilized in these analyses. Univariate analysis showed that age, the period of operation, clinical T-stage, metastatic burden, molecular subtypes, pathologic T-stage, postoperative chemotherapy, PORT, and intervention at all metastatic lesions within 3 months after surgery or postoperative chemotherapy were significant predictors of OS. On multivariate analysis, HER2-enriched, triple negative molecular subtypes, and omission of PORT were significant predictors of poorer OS. Median survival was 61.3 months (range, 5.9–185.9 months) in patients with luminal A or B type tumors, compared with 27.6 months (range, 5.3–103.1 months) in patients with HER2-enriched or triple negative molecular type tumors. Median survival in patients who did and did not receive PORT was 56.3 months (range, 5.9–179.4 months) and 46.6 months (range, 5.3–185.9 months), respectively.

Table 2
Univariate and multivariate analyses of factors predictive of overall survival in the entire patient population

Characteristics		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age	< 45 years (vs. ≥45 years)	0.57 (0.32–0.99)	0.048		
Period of primary tumor resection	2006–2010 (vs. 2000–2005)	0.57 (0.28–1.13)	0.106		
	2011–2014 (vs. 2000–2005)	0.38 (0.20–0.74)	0.004		
Histologic grade	Grade 1/2 (vs. Grade 3)	0.58 (0.34–1.00)	0.050		
Clinical T-stage	T1/2 (vs. T3/4)	0.56 (0.32–0.98)	0.041		
Clinical N-stage	N0/1 (vs. N2/3)	0.97 (0.55–1.72)	0.919		
Metastatic site	Bone and others (vs. Bone only)	1.79 (0.72–4.43)	0.207		
	Others (vs. Bone only)	1.44 (0.81–2.55)	0.209		
Metastatic burden	Single (vs. Disseminated)	0.40 (0.19–0.82)	0.012		
	Oligo (vs. Disseminated)	0.53 (0.27–1.03)	0.062		

Abbreviations: ALND = axillary lymph node dissection; CI = confidence interval; HER2 = human epidermal growth factor 2; LI = labeling index; SLNB = sentinel lymph node biopsy.

*All interventions were performed within 3 months after surgery or postoperative chemotherapy.

Characteristics		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Molecular subtypes	Luminal B (vs. Luminal A)	1.44 (0.62–3.35)	0.392	7.96 (2.25–28.22)	0.001
	HER2-enriched (vs. Luminal A)	3.95 (1.93–8.09)	< 0.001	6.19 (2.04–18.81)	0.001
	Triple negative (vs. Luminal A)	3.62 (1.60–8.16)	0.002		
	Luminal A or B (vs. Luminal A)	0.59 (0.08–4.65)	0.618		
Ki-67 LI status	< 30% (vs. ≥30%)	0.50 (0.22–1.09)	0.082		
Pathological T-stage	T0/is/1/2 (vs. T3/4)	0.49 (0.28–0.87)	0.014		
Pathological N-stage	N0/1 (vs. N2/3)	0.62 (0.35–1.09)	0.096		
Neoadjuvant chemotherapy	Yes (vs. No)	0.62 (0.36–1.07)	0.086		
Type of primary tumor resection	Mastectomy (vs. Breast conserving)	1.79 (0.96–3.36)	0.068		
Method of axillary node evaluation	None (vs. ALND)	0.77 (0.26–2.31)	0.644		
	SLNB (vs. ALND)	0.80 (0.36–1.79)	0.595		
Postoperative chemotherapy	Yes (vs. No)	2.03 (1.17–3.51)	0.011		

Abbreviations: ALND = axillary lymph node dissection; CI = confidence interval; HER2 = human epidermal growth factor 2; LI = labeling index; SLNB = sentinel lymph node biopsy.

*All interventions were performed within 3 months after surgery or postoperative chemotherapy.

Characteristics		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Postoperative radiotherapy	Yes (vs. No)	0.43 (0.25–0.74)	0.003	0.41 (0.17–0.99)	0.048
Interventions to all metastatic lesions*	Yes (vs. No)	0.53 (0.29–0.97)	0.038		

Abbreviations: ALND = axillary lymph node dissection; CI = confidence interval; HER2 = human epidermal growth factor 2; LI = labeling index; SLNB = sentinel lymph node biopsy.

*All interventions were performed within 3 months after surgery or postoperative chemotherapy.

The 5 year LRRFS rate was 79.0% (Fig. 1B), and the median LRRFS was 45.1 months (range, 3.5–178.2 months). Six patients experienced breast/chest wall recurrence alone, 14 experienced regional nodal failure only, and three experienced both. Of 23 patients with LRR, 14 (60.9%) were simultaneously diagnosed with distant progression, which preceded regional failure in three patients. Administration of PORT was the sole factor predicting good prognosis on univariate analysis (HR, 0.32; 95% CI, 0.14–0.76; $p = 0.010$; Fig. 2A) and multivariate analysis (HR, 0.36; 95% CI, 0.15–0.86; $p = 0.021$). The 5 year LRRFS rates were 85.8% and 74.9% in the group that did and did not receive PORT, respectively. In addition, seven patients (11.3%) who received PORT experienced in-field recurrence.

Survival outcomes were analyzed in subgroups of patients who underwent mastectomy and BCO. Of the 75 patients who underwent a mastectomy, 38 (50.7%) received PMRT. PMRT, however, was not significantly predictive of LRRFS on univariate analysis (HR, 0.52; 95% CI, 0.19–1.42; $p = 0.203$; Fig. 2B) and multivariate analysis. Of the 37 patients who underwent BCO, 24 (64.9%) received PORT. PORT was significantly predictive of LRRFS on univariate analysis (HR, 0.10; 95% CI, 0.01–0.87; $p = 0.037$; Fig. 2C) but not on multivariate analysis.

The 5 year DPFS rate was 34.3% (Fig. 1C), and the DPFS median was 30.7 months (range, 3.5–183.4 months). Distant progression was the major failure pattern observed in 74 patients, with 29 (39.2%) receiving palliative chemotherapy. Multivariate analysis showed that the latest period of PTR, single/oligo metastatic burden, lower pathologic T-stage, and low histologic grade were significantly predictive of improved DPFS, whereas PORT was not.

Effects of PORT in patients without disseminated metastases

In general, the percentage of patients with a favorable prognosis was higher among those who did than those who did not receive PORT (Table 1). Although the percentage of patients with clinical N2/3 tended to be higher in the PORT group, the percentages of patients with disseminated metastases (34.0% vs.

1.6%, $p < 0.001$) and who did not receive chemotherapy (20.0% vs. 1.6%, $p < 0.001$) were significantly higher in patients who did not receive PORT. By contrast, interventions to treat distant metastatic lesions were significantly more frequent in the PORT group (14.0 vs. 61.3%, $p < 0.001$).

To compensate for the differences between patients who did and did not receive PORT, patients with disseminated metastases were excluded, and the effects of PORT were analyzed in the 94 patients without disseminated metastases (Table 3). Median follow-up time was 51.1 months (range, 3.5–183.4), and median OS was 54.9 months (range, 5.3–185.9 months). The 5 year OS, LRRFS, and DPFS rates were 65.6%, 83.8%, and 38.3%, respectively. Period of operation, receipt of chemotherapy, and treatment of all metastatic lesions within 3 months after surgery or postoperative chemotherapy differed significantly between patients who did and did not receive PORT. The between-group difference in chemotherapy rates was mainly due to the increased use of neoadjuvant chemotherapy in the PORT group.

Table 3
Characteristics of the patients without disseminated metastasis who did and did not receive postoperative radiotherapy

	Without disseminated metastasis (n = 94)			Luminal A or B type tumors without disseminated metastasis (n = 70)		
Characteristics	No PORT (n = 33) n (%)	PORT (n = 61) n (%)	p-value	No PORT (n = 22) n (%)	PORT (n = 48) n (%)	p-value
Age, years	16 (48.5)	31 (50.8)	1.000	14 (63.6)	25 (52.1)	0.519
<45	17 (51.5)	30 (48.4)		8 (36.4)	23 (47.9)	
≥45						
Period of primary tumor resection	12 (36.4)	6 (9.8)	< 0.003	8 (36.4)	4 (8.3)	0.010
2000–2005	7 (21.2)	10 (16.4)		4 (18.2)	7 (14.6)	
2006–2010	14 (42.4)	45 (73.8)		10 (45.5)	37 (77.1)	
2011–2014						
Laterality	20 (60.6)	33 (54.1)	0.697	17 (77.3)	26 (54.2)	0.478
Left	13 (39.4)	28 (45.9)		5 (22.7)	22 (45.8)	
Right						
Histologic grade	14 (42.4)	36 (59.0)	0.134	10 (45.5)	17 (35.4)	0.637
Low (1–2)	19 (57.6)	23 (37.7)		12 (54.5)	30 (62.5)	
High (3)	0 (0.0)	2 (3.3)		0 (0.0)	1 (2.1)	
Unknown						
Clinical T-stage	25 (75.8)	39 (63.9)	0.287	18 (81.8)	31 (66.0)	0.285
T1/2	7 (21.2)	21 (34.4)		4 (18.2)	16 (34.0)	
T3/4	1 (3.0)	1 (1.6)		0 (0.0)	0 (0.0)	
Tx						

Abbreviations: ALND = axillary lymph node dissection; HER2 = human epidermal growth factor 2; LI = labeling index; PORT = postoperative radiotherapy; PTR = primary tumor resection; SLNB = sentinel lymph node biopsy.

*All interventions were performed within 3 months after surgery or postoperative chemotherapy.

	Without disseminated metastasis (n = 94)			Luminal A or B type tumors without disseminated metastasis (n = 70)		
Clinical N-stage	25 (75.8)	32 (52.5)	0.057	17 (77.3)	28 (59.6)	0.243
N0/1	8 (24.2)	28 (45.9)		5 (22.7)	19 (40.4)	
N2/3	0 (0.0)	1 (1.6)		0 (0.0)	0 (0.0)	
Nx						
Metastatic site	20 (60.6)	30 (49.2)	0.559	16 (72.7)	25 (52.1)	0.191
Bone only	1 (3.0)	3 (4.9)		0 (0.0)	3 (6.2)	
Bone and other	12 (36.4)	28 (45.9)		6 (27.3)	20 (41.7)	
Others (no bone)						
Metastatic burden*	13 (39.4)	32 (52.5.)	0.320	10 (45.5)	26 (54.2)	0.675
Single	20 (60.6)	29 (47.5)		12 (54.5)	22 (45.8)	
Oligo	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Disseminated						
Molecular subtypes	16 (48.5)	40 (65.6)	0.572	16 (72.7)	40 (83.3)	0.543
Luminal A	5 (15.2)	6 (9.8)		5 (22.7)	6 (12.5)	
Luminal B	6 (18.2)	8 (13.1)		0 (0.0)	0 (0.0)	
HER2-enriched	5 (15.2)	5 (8.2)		0 (0.0)	0 (0.0)	
Triple negative	1 (3.0)	2 (3.3)		1 (4.5)	2 (4.2)	
Unknown (Luminal A or B)						

Abbreviations: ALND = axillary lymph node dissection; HER2 = human epidermal growth factor 2; LI = labeling index; PORT = postoperative radiotherapy; PTR = primary tumor resection; SLNB = sentinel lymph node biopsy.

*All interventions were performed within 3 months after surgery or postoperative chemotherapy.

	Without disseminated metastasis (n = 94)			Luminal A or B type tumors without disseminated metastasis (n = 70)		
Ki-67 LI status	13 (39.4)	28 (45.9)	1.000	11 (50.0)	25 (52.1)	0.768
Low (< 30%)	7 (21.2)	16 (26.2)		3 (13.6)	11 (22.9)	
High (≥ 30%)	13 (39.4)	17 (27.9)		8 (36.4)	12 (25.0)	
Unknown						
Pathological T-stage	28 (84.8)	46 (75.4)	0.422	20 (90.9)	36 (75.0)	0.221
T0/is/1/2	5 (15.2)	15 (24.6)		2 (9.1)	12 (25.0)	
T3/4						
Pathological N-stage	21 (67.7)	32 (52.5)	0.137	15 (68.2)	26 (54.2)	0.215
N0/1	8 (24.2)	28 (45.9)		5 (22.7)	21 (43.7)	
N2/3	4 (12.1)	1 (1.6)		2 (9.1)	1 (2.1)	
Nx						
Chemotherapy	11 (33.3)	39 (63.9)	0.009	10 (45.4)	33 (68.7)	0.069
Neoadjuvant	11 (33.3)	14 (23.0)		6 (27.3)	11 (22.9)	
Postoperative	6 (18.2)	7 (11.5)		2 (9.1)	3 (6.3)	
Both	5 (15.2)	1 (1.6)		4 (18.2)	1 (2.1)	
None						
Type of PTR	8 (24.2)	23 (37.7)	0.273	6 (27.3)	19 (39.6)	0.466
Breast conserving	25 (75.8)	38 (62.3)		16 (72.7)	29 (60.4)	
Mastectomy						

Abbreviations: ALND = axillary lymph node dissection; HER2 = human epidermal growth factor 2; LI = labeling index; PORT = postoperative radiotherapy; PTR = primary tumor resection; SLNB = sentinel lymph node biopsy.

*All interventions were performed within 3 months after surgery or postoperative chemotherapy.

	Without disseminated metastasis (n = 94)			Luminal A or B type tumors without disseminated metastasis (n = 70)		
Method of axillary node evaluation	22 (66.7)	49 (80.3)	0.079	17 (77.3)	39 (81.2)	0.397
ALND	4 (12.1)	1 (1.6)		2 (9.1)	1 (2.1)	
SLNB	7 (21.2)	11 (18.0)		3 (13.6)	8 (16.7)	
None						
Hormone therapy	18 (54.5)	45 (73.8)	0.166	18 (81.8)	44 (91.7)	0.356
Postoperative	3 (9.1)	3 (4.9)		2 (9.1)	3 (6.2)	
Neoadjuvant/postoperative	12 (36.4)	13 (21.3)		2 (9.1)	1 (2.1)	
No						
Trastuzumab	0 (0.0)	1 (1.6)	0.775	0 (0.0)	0 (0.0)	0.472
Neoadjuvant	5 (15.2)	6 (9.8)		2 (9.1)	4 (8.3)	
Postoperative	5 (15.2)	9 (14.8)		4 (18.2)	4 (8.3)	
Both	23 (69.7)	45 (73.8)		16 (72.7)	40 (83.3)	
None						
Intervention to all metastatic lesions[a]	7 (21.2)	38 (62.3)	< 0.001	5 (22.7)	32 (66.7)	0.002
Yes	26 (78.8)	23 (37.7)		17 (77.3)	16 (33.3)	
No						

Abbreviations: ALND = axillary lymph node dissection; HER2 = human epidermal growth factor 2; LI = labeling index; PORT = postoperative radiotherapy; PTR = primary tumor resection; SLNB = sentinel lymph node biopsy.

*All interventions were performed within 3 months after surgery or postoperative chemotherapy.

Univariate analysis showed that the period of operation, molecular subtypes, and PORT were significant predictors of OS in patients without disseminated metastases (Table 4; Fig. 3A). By contrast, multivariate analysis showed that higher clinical T-stage and Ki-67 index were independent predictors of poor prognosis. Multivariate analysis showed that PORT was significantly predictive of longer LRRFS (HR, 0.31; 95% CI, 0.11–0.91; $p = 0.033$; Fig. 3B), whereas higher pathological N-stage was significantly predictive of poorer LRRFS (HR, 3.31; 95% CI, 1.12–9.79; $p = 0.031$). Higher pathological T-stage was the sole predictor of DPFS on multivariate analysis, whereas PORT did not affect DPFS (Fig. 3C).

Table 4
Univariate and multivariate analyses of factors predictive of overall survival in patients without disseminated metastasis

Characteristics	Without disseminated metastasis				Luminal A or B type tumors without disseminated metastasis			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age <45 years (vs. ≥45 years)	0.69 (0.36–1.32)	0.257			1.00 (0.42–2.38)	0.996		
Period of primary tumor resection	0.36 (0.14–0.88)	0.026			0.17 (0.04–0.78)	0.023	0.10 (0.02–0.48)	0.004
2006–2010 (vs. 2000–2005)	0.34 (0.16–0.70)	0.003			0.62 (0.24–1.60)	0.325		
2011–2014 (vs. 2000–2005)								
Histologic grade Grade 1/2 (vs. Grade 3)	0.60 (0.32–1.13)	0.114			0.76 (0.34–1.70)	0.501		
Clinical T-stage T1/2 (vs. T3/4)	0.60 (0.31–1.14)	0.113	0.35 (0.13–0.93)	0.036	0.56 (0.25–1.23)	0.150		
Clinical N-stage N0/1 (vs. N2/3)	0.95 (0.49–1.85)	0.890			0.63 (0.27–1.47)	0.289		
Metastatic site	0.70 (0.09–5.25)	0.728			Not available due to infinite value			
Bone and others (vs. Bone only)	1.53 (0.81–2.88)	0.190						
Others (vs. Bone only)								
Metastatic burden Single (vs. Oligo)	0.56 (0.71–2.56)	0.353			0.56 (0.25–1.28)	0.170		

Abbreviations: ALND = axillary lymph node dissection; CI = confidence interval; HER2 = human epidermal growth factor 2; LI = labeling index; SLNB = sentinel lymph node biopsy.

*All interventions were performed within 3 months after surgery or postoperative chemotherapy.

Characteristics	Without disseminated metastasis				Luminal A or B type tumors without disseminated metastasis			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Molecular subtypes								
Luminal B (vs. Luminal A)	1.24 (0.42–3.68)	0.700			1.31 (0.44–3.94)	0.625		
HER2-enriched (vs. Luminal A)	4.16 (1.86–9.30)	0.001						
Triple negative (vs. Luminal A)	3.17 (1.24–8.10)	0.016						
Luminal A or B (vs. Luminal A)	0.67 (0.08–5.33)	0.701						
Ki-67 LI status								
<30% (vs. ≥30%)	0.53 (0.21–1.35)	0.182	0.12 (0.12–0.92)	0.033	0.56 (0.17–1.89)	0.349		
Pathological T-stage								
T0/is/1/2 (vs. T3/4)	0.56 (0.28–1.09)	0.085			0.49 (0.19–1.27)	0.141		
Pathological N-stage								
N0/1 (vs. N2/3)	0.57 (0.30–1.10)	0.093			0.98 (0.38–5.50)	0.966		
Neoadjuvant chemotherapy								
Yes (vs. No)	0.69 (0.37–1.31)	0.262			0.79 (0.35–1.79)	0.578		
Type of primary tumor resection								
Breast conserving (vs. Mastectomy)	0.60 (0.29–1.22)	0.158			0.47 (0.19–1.18)	0.115		

Abbreviations: ALND = axillary lymph node dissection; CI = confidence interval; HER2 = human epidermal growth factor 2; LI = labeling index; SLNB = sentinel lymph node biopsy.

*All interventions were performed within 3 months after surgery or postoperative chemotherapy.

Characteristics	Without disseminated metastasis				Luminal A or B type tumors without disseminated metastasis			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Method of axillary node evaluation								
None (vs. ALND)	0.74 (0.20–2.67)	0.640			0.54 (0.11–2.62)	0.441		
SLNB (vs. ALND)	0.74 (0.29–1.92)	0.540			0.28 (0.04–2.10)	0.216		
Postoperative chemotherapy								
Yes (vs. No)	2.18 (1.15–4.14)	0.017			1.39 (0.62–3.12)	0.419		
Postoperative radiotherapy								
Yes (vs. No)	0.53 (0.28–0.99)	0.046			0.76 (0.34–1.70)	0.501		
Interventions to all metastatic lesions*								
Yes (vs. No)	0.64 (0.33–1.23)	0.178			0.62 (0.27–1.44)	0.267		

Abbreviations: ALND = axillary lymph node dissection; CI = confidence interval; HER2 = human epidermal growth factor 2; LI = labeling index; SLNB = sentinel lymph node biopsy.

*All interventions were performed within 3 months after surgery or postoperative chemotherapy.

The effect of PORT was also evaluated in patients subgrouped by the molecular characteristics of their tumors. Of the 94 patients without disseminated metastases, 70 had luminal A or B type tumors and 24 had HER2-enriched and triple negative molecular types. Of the 70 patients with luminal A or B type tumors, 48 received PORT, and 22 did not (Table 3). The Median follow-up time of these 70 patients was 54.9 months (range, 3.5–183.4 months), and median OS was 61.9 months (range, 5.9–185.9 months). The 5 year OS, LRRFS, and DPFS rates in this group were 75.5%, 87.3%, and 40.1%, respectively. Period of operation and treatment of all metastatic lesions within 3 months after surgery or postoperative chemotherapy differed significantly between patients who did and did not receive PORT. Period of operation (2006–2010) was the only significant predictor of OS on univariate and multivariate analyses. PORT was not a significant prognostic factor for OS (Fig. 4A). PORT was a significant predictor of LRRFS on univariate analysis (Fig. 4B) but not on multivariate analysis, with the latter showing that higher pathological N-stage was the sole independent predictor of LRRFS. Similar to OS, the period of operation (2006–2010) was the only significant predictor of DPFS, whereas PORT did not affect DPFS (Fig. 4C).

Of the 24 patients having HER2-enriched and triple negative molecular types without disseminated metastases, 13 received PORT and 11 did not, with no significant differences between these subgroups (Supplementary Table 2). Median follow-up time was 28.9 months (range, 5.3–98.4 months), and median OS was 29.9 months (range, 5.3–103.1 months). Five-year OS, LRRFS, and DPFS rates were 37.0%, 71.1%, and 34.1%, respectively. Period of operation and PORT were significant predictors of OS on univariate analysis (Supplementary Fig. 1A), but PORT was not on multivariate analysis (Supplementary Table 3). Univariate analysis showed no significant predictors of LRRFS, including PORT (HR, 0.69; 95% CI, 0.11–4.37; $p = 0.689$; Supplementary Fig. 1B). In addition, PORT was not a significant predictor of DPFS (Supplementary Fig. 1C).

Discussion

The present study showed that PORT following PTR yielded favorable outcomes in patients with de novo stage IV breast cancer. Median OS was 55 months, in agreement with the results of previous studies, which reported median OS ranging from 19.2 to 56.1 months (Supplementary Table 4) (8, 11–13, 17). This was likely due to the strict inclusion criteria of the present study, in that patients who progressed after neoadjuvant chemotherapy or within 2 months after PTR were excluded. A previous RCT in India also excluded patients who showed progressive or stable disease after neoadjuvant chemotherapy because these patients were deemed unfit for PTR (11). The present study, therefore, focused on the patients who could benefit most from planned PTR, with or without PORT.

Several RCTs and retrospective trials have assessed the effects of PTR in patients with stage IV breast cancer (Supplementary Table 4). A recent systematic review and meta-analysis, which included a total of 67,986 patients, found that PTR may benefit selected patients with limited disease burden (18). In the present study, luminal type A or B was significantly predictive of a good prognosis in the overall patient population, although it was not significant in patients without disseminated metastases. This difference was likely due to the better median OS of 57.6 months (range, 10.9–118 months), which was observed in patients with luminal A or B type tumors and disseminated metastases. These results were in good agreement with those of previous studies, which reported that the expression of ER or PR was independently associated with OS (HR, 0.37–0.79) (8, 11, 19). Moreover, a subgroup analysis of the MF07-01 study found that PTR had significant survival benefit in patients with luminal types A and B and HER2-negative tumors (12).

Although PORT was also a significant predictor of OS in the entire population, there may have been a possible bias due to differences between patients who did and did not receive PORT. Because the percentage of patients with disseminated metastases was significantly higher in patients who did not receive PORT, we attempted to minimize this bias by excluding patients with disseminated metastases. Although PORT was not significantly predictive of OS in patients with single or oligometastases, PORT remained significantly predictive of LRRFS. In the entire patient population, all of whom underwent PTR, the overall 5 year LRRFS rate was 79.0%, and the crude incidence of local recurrence was 20.5%. The result was comparable to that of a previous study, which evaluated the effects of PTR on chest wall

control in patients with stage IV breast cancer, finding that the local control rate was significantly higher in patients who did undergo PTR than in patients who did not undergo PTR (82% vs. 34%; $p = 0.001$) (20). Similar to our study, a retrospective evaluation of 227 patients found that PORT significantly improved OS, with an HR of 0.40 (95% CI, 0.24–0.68; $p = 0.001$) on multivariate analysis (10). That study, however, did not compare the characteristics of patients who did and did not receive PORT, suggesting a possible selection bias. The present study found that PORT was significantly predictive of OS in the entire patient population, although additional studies are needed to determine whether PORT can increase OS. Also, the combination of PTR and PORT may enhance locoregional control, especially in patients with higher N-stages.

The present study also evaluated the effect of a planned intervention to metastatic lesions performed within 3 months after PTR or postoperative chemotherapy. Although not significantly predictive of survival, these interventions may benefit patients. For example, a phase II trial evaluating the effects of radical radiotherapy to all metastatic sites (≤ 5 lesions) showed promising results, with 1 and 2 year PFS rates of 75% and 53%, respectively; and 2 year local control and OS rates of 97% and 95%, respectively (21). The results of an ongoing phase II/III trial (NRG-BR002) assessing the role of stereotactic body radiotherapy or surgical ablation in patients with oligometastatic breast cancer are pending (22).

The present study had several limitations, including its retrospective design making it susceptible to possible selection bias and its inclusion of patients treated over 14 years. In addition, the number of patients was relatively small, such that not all factors were well balanced between groups of patients who did and did not receive PORT. Furthermore, this study did not assess toxicity on quality of life. Despite these limitations, the present study is the second largest retrospective study, with the longest median follow-up time, to evaluate the effects of PORT in a homogenous population of stage IV breast cancer patients diagnosed and treated in a single tertiary medical center.

Conclusions

Patients with de novo stage IV breast cancer who received planned PTR showed favorable survival outcomes compared with historical cohorts, suggesting that PTR may benefit these patients, especially those with luminal A or B type tumors. Administration of PORT was significantly predictive of longer LRRFS, suggesting that PORT may benefit these patients. Large randomized control trials focusing on patients with good prognoses are needed.

Abbreviations

Abdomino-pelvic CT (APCT)

American Joint Committee on Cancer (AJCC),

Axillary LN dissection (ALND)

Breast conserving operation (BCO)

Computed tomography (CT)

Confidence interval (CI)

Distant progression-free survival (DPFS)

Estrogen receptor (ER)

18-fluoro-deoxyglucose positron emission tomography (FDG-PET)

Hazard ratio (HR)

Human epidermal growth factor 2 (HER2)

Internal mammary LN (IMLN)

Labeling index (LI)

Locoregional recurrence (LRR)

Locoregional recurrence-free survival (LRRFS)

Lymph nodes (LNs)

Overall survival (OS)

Post-mastectomy radiotherapy (PMRT)

Postoperative radiotherapy (PORT)

Primary tumor resection (PTR)

Progesterone receptor (PR)

Progression-free survival (PFS)

Randomized controlled trials (RCTs)

Response Evaluation Criteria in Solid Tumors (RECIST)

Sentinel LN biopsy (SLNB)

Supraclavicular LN (SCLN)

Declarations

Ethics approval and consent to participate

Approval to conduct this study (version 1.1 on 18 April 2019) was granted by the Institutional Review Board of Seoul Asan Medical Center (S2018-1826-0001), and the present retrospective study was conducted in accordance with the Helsinki Declaration.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

SSK designed the trial. SDA, JJ, and EKC contributed to the data acquisition on radiotherapy. SHA, BHS, JWL, HJK, and BSK analyzed the data related to surgery. SBK, KHJ, JA, and JK reviewed the data on chemotherapy, hormonal therapy, and trastuzumab. YJK drafted the manuscript and was responsible for statistical considerations. All authors reviewed relevant clinical outcomes, and have read and approved the final manuscript.

Acknowledgments

This work was supported by the National Research Foundation (NRF) grant funded by the Korean government (NRF-2018R1D1A1B07049970).

Data sharing statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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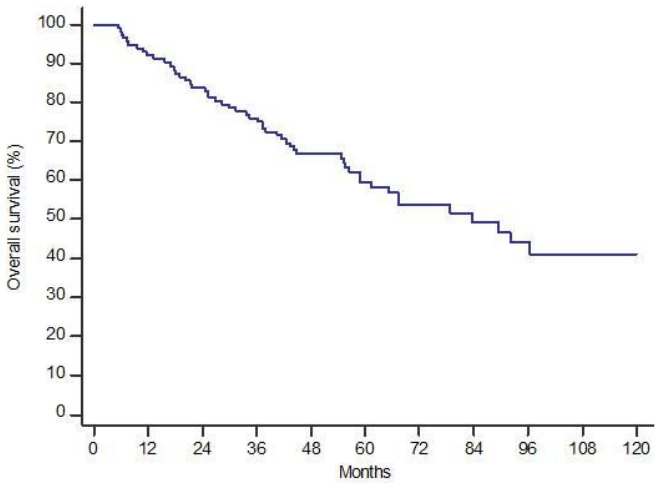
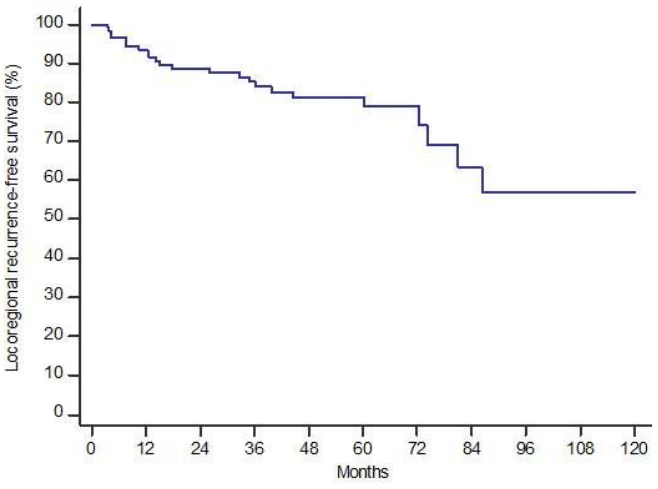
Figures





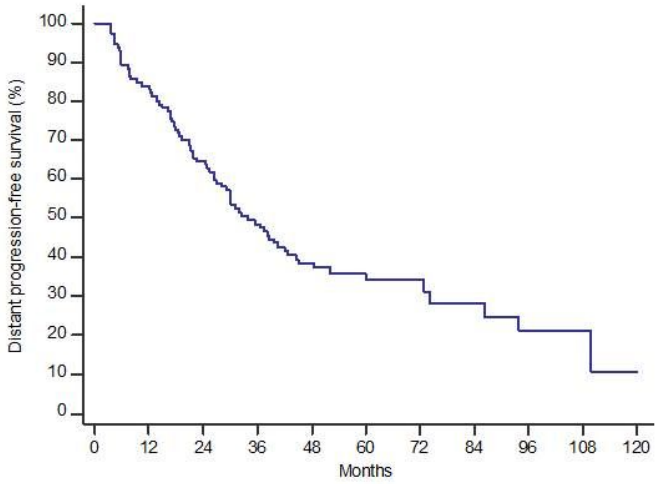
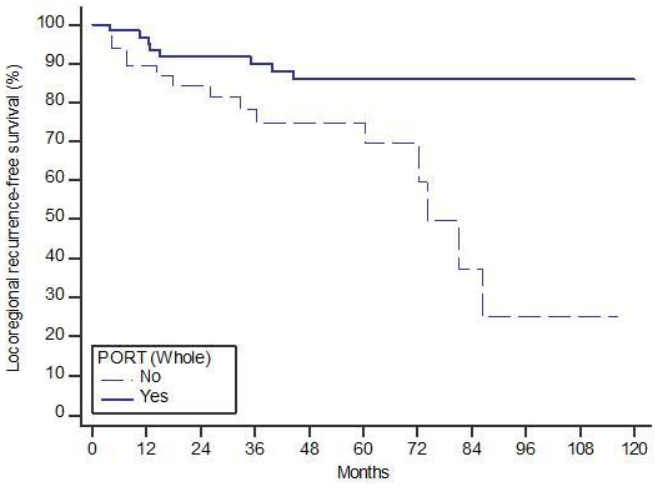
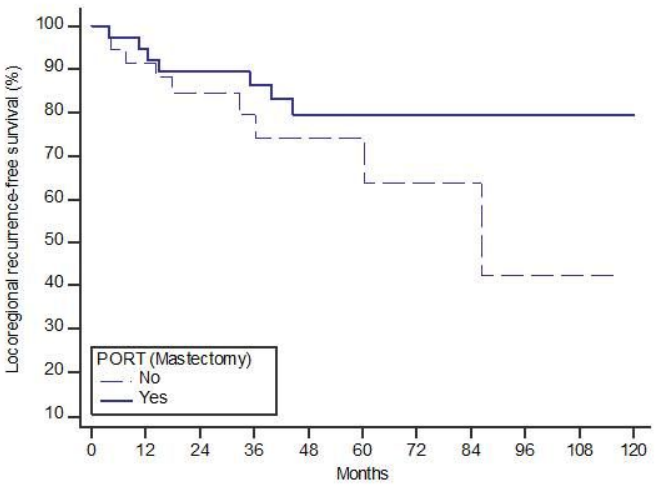


Figure 1

Kaplan–Meier analyses of (A) overall survival, (B) locoregional recurrence-free survival, and (C) distant progression-free survival in all 112 patients.





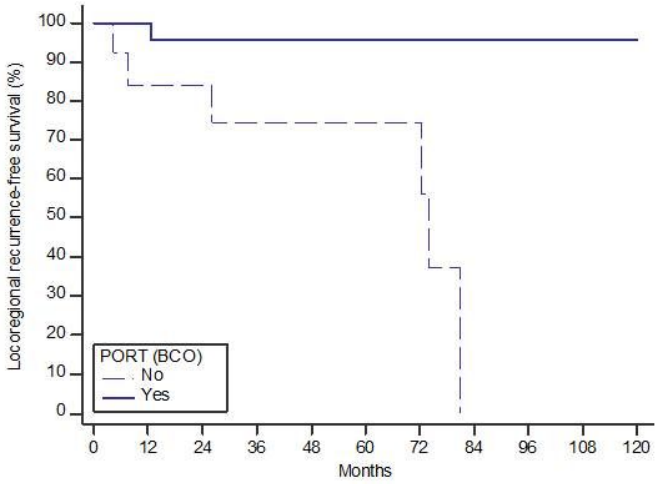
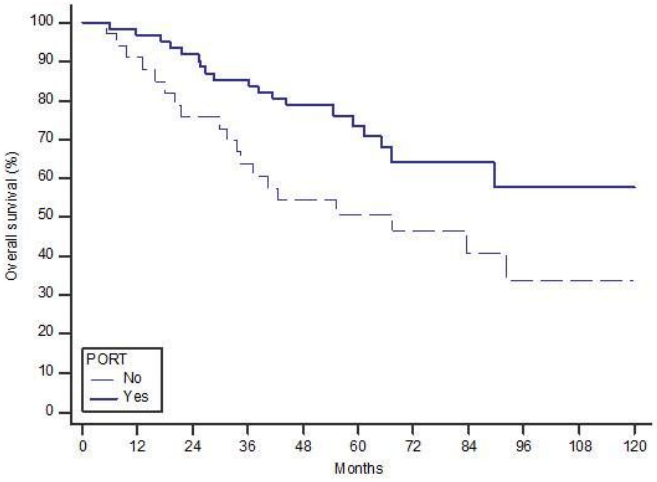
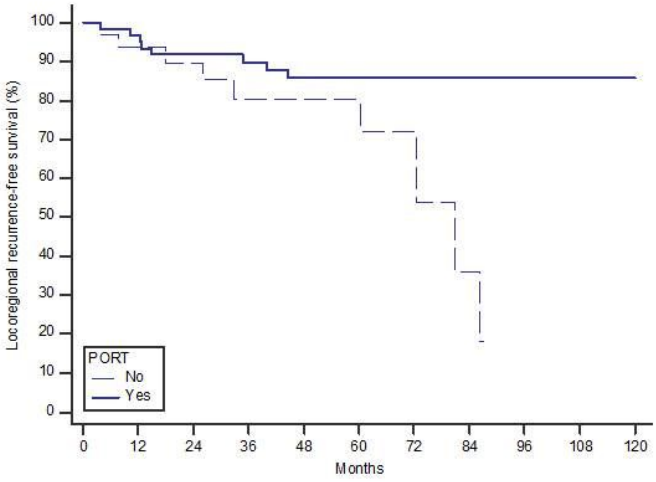


Figure 2

Kaplan–Meier analysis of the effects of postoperative radiotherapy (PORT) on locoregional recurrence-free survival in (A) all patients, (B) patients who underwent mastectomy, and (C) patients who underwent breast conserving operation (BCO).





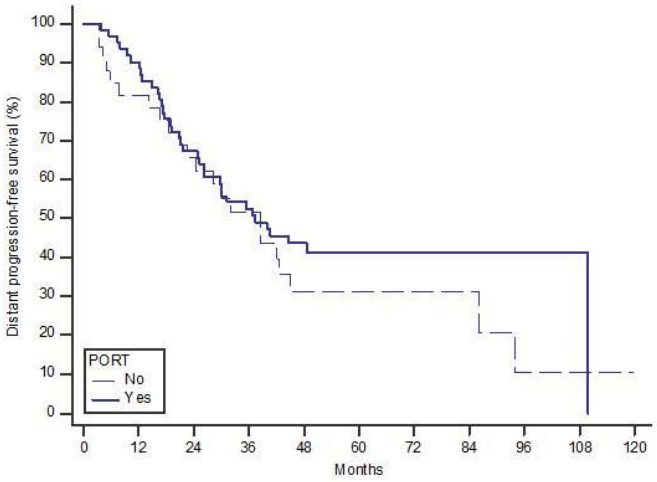
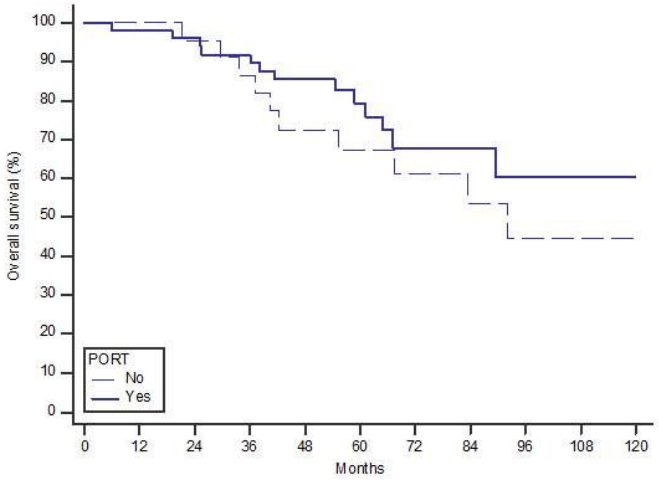
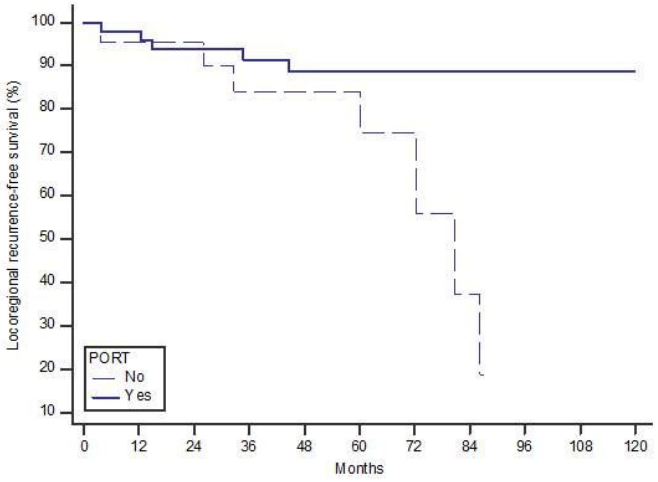


Figure 3

Kaplan–Meier analysis of the effects of postoperative radiotherapy (PORT) on (A) overall survival, (B) locoregional recurrence-free survival, and (C) distant progression-free survival in the 94 patients without disseminated metastases.





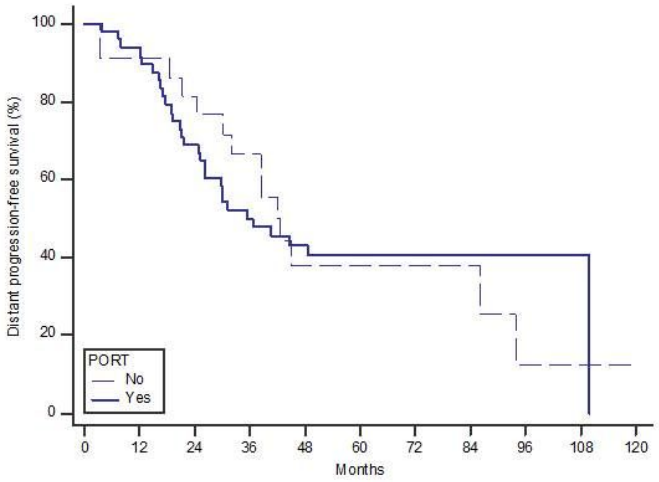


Figure 4

Kaplan–Meier analysis of the effects of postoperative radiotherapy (PORT) on (A) overall survival, (B) locoregional recurrence-free survival, and (C) distant progression-free survival in the 70 patients with Luminal A or B type primary tumors without disseminated metastases.

Supplementary Files

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- supplement9.docx