Received: 6 November 2018 | Revised: 20 November 2018 | Accepted: 21 November 2018
DOI: 10.1111/tbj.13304

SHORT COMMUNICATION

The Breast Journal WILEY

Heart-sparing radiotherapy with three-dimensional printing technology after mastectomy for patients with left breast cancer

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Funding information
National Research Foundation of Korea, Grant/Award Number: NRF-2015R1C1A1A02036613

Abstract

The purpose of this study was to analyze the effectiveness of electron beam therapy (EBT) with patient-tailored bolus (PTB) using three-dimensional printing technology to reduce heart and lung doses during post-mastectomy radiotherapy (PMRT). For 28 patients with left breast cancer, we designed customized virtual bolus for PMRT to compensate for surface irregularities on computed tomography images and developed optimized plans for EBT. As comparison between the PTB and tangential plans, the PTB plan reduced unnecessary exposure to heart and ipsilateral lung with better target coverage compared with the tangential technique.

KEYWORDS
breast cancer, customized bolus, electron beam therapy, heart-sparing radiotherapy, post-mastectomy radiotherapy, three-dimensional printing technology

1 | INTRODUCTION

Post-mastectomy radiotherapy (PMRT) is recommended for patients with a large primary tumor or axillary lymph node metastasis.[1] Breast cancer patients generally showed long survival. As the result, there are increased clinical concerns regarding late effects from breast cancer treatment in long-term survivors. In a meta-analysis of breast cancer patients from 1973 to 2001, radiotherapy (RT) increased the death rate related to heart disease.[2] A large-sized study with long-term follow-up confirmed that major coronary disease after RT increased by 7.4% per Gy, and the effect of RT started within 5 years and persisted over 30 years.[3] Also, another recent study with patients treated since 1989 in the computed tomography (CT)-based RT simulation era suggested that left-sided PMRT and chemotherapy with Adriamycin increased heart disease.[4] Therefore, there are concerns over saving the heart from unnecessary RT exposure during left-sided PMRT. The ipsilateral lung should also be protected from radiation exposure. In studies of lung cancer, RT exposure was associated with decreased lung functions in the long term as well as an increase in radiation pneumonitis.[5]

In this study, we analyzed the results of the optimized electron beam therapy (EBT) with a patient-tailored bolus (PTB) using three-dimensional (3D) printing technology for PMRT to reduce doses to the heart and ipsilateral lung.

2 | METHODS

Between May 2016 and February 2017, twenty-eight patients with left breast cancer were treated with PMRT using PTB. Detail characteristics are shown in Table 1. This study was approved by the Institutional Review Board of Samsung Medical Center.

TABLE 1 Patient characteristics

Patient characteristics (N = 28)	n (%)
Age	
Median, y (range)	46 (33-66)
<50	20 (71.4)
≥50	8 (28.6)
Menopause	
Premenopause	18 (64.3)
Postmenopause	10 (35.7)
Risk factors of heart disease	
History of any heart disease	0
Hypertension	1 (3.7)
Others	0
Histologic type	
IDC	27 (96.4)
ILC	1 (3.6)
Clinical stage	
II	8 (28.6)
III	17 (60.7)
IV	3 (10.7)
Pathologic stage	
0[a]	1 (3.6)
I-II	10 (35.7)
III	16 (57.1)
IV	1 (3.6)
Regional LN[b]	
ALN (+)	26 (92.9)
IMN (+)	2 (7.1)
SCN (+)	2 (7.1)
Hormonal/HER2 status	
ER or PR (+)/HER2 (−)	15 (53.6)
ER or PR (+)/HER2 (+)	4 (14.3)
ER or PR (−)/HER2 (−)	3 (10.7)
ER or PR (−)/HER2 (+)	6 (21.4)
Chemotherapy	
Neo-adjuvant	14 (50.0)
Adjuvant	13 (46.4)
None	1 (3.6)
Radiotherapy (field)	
Chest wall	28 (100)
SCN	25 (89.3)
IMN	2 (7.1)

[a]The pathologic stage 0 was ypTisN0 in the surgical pathologic report.
[b]It included radiologic positive or biopsy-confirmed lymph nodes as well as surgical pathologic results.

Computed tomography simulation for PMRT was set up in a supine and arm-up position with a commonly used breast board. The target volume delineation was based on the ESTRO consensus guidelines and the Danish Breast Cancer Cooperative Group. Heart and ipsilateral left lung were considered organs at risk (OAR). For each patient, a PTB plan was considered for actual PMRT and was generated by one experienced dosimetrist for consistency of plan quality. The PTB plan was compared with a paired conventional plan and finally confirmed for actual treatment (Figure 1). Our decision policy was that the conventional plan was preferred if the PTB plan did not definitely reduce exposed doses to OAR.

For a PTB plan, a one-port electron beam (EB) with appropriate energy was selected to cover the chest wall (CW) on planning CT without PTB, and a virtual PTB was drawn over the CW based on initial dose distribution to provide conformal dose distribution to the distal surface of an irregularly shaped target exposed to a uniform range EB. The virtual PTB was overridden by a predetermined density (water equivalence thickness, 1.12) of material that would be used to make the PTB with a 3D printer. The virtual bolus was printed using a fused deposition modeling 3D printing technique (FDM, Edison multi; Rokit) with Poly Lactic acid 3D printing material (PLA; Rokit, Figure 2). The 3D printing was supported by NRF-2015R1C1A1A02036613 (Korea). In addition, a rival tangential plan was generated using conventional approaches on the same CT. Supraclavicular nodal irradiation using a photon beam was added for 25 patients. The prescription dose to CW was 50 Gy in 25 fractions for 5 days a week. For all plans we verified that the maximum dose was <107% and target coverage was >95% of the prescription dose for treatment. All patients were treated with EBT using PTB following mastectomy and RT was completed as scheduled.

Dosimetric comparisons were performed between PTB plan and conventional plan with the target and OAR as Table 2 in detail. All plans were based on Pinnacle version 9.10 (Philips Medical Systems). For statistical analyses, the Wilcoxon-matched pairs signed rank tests were used with SPSS Statistics version 22 (SPSS, an IBM Company). A value of $P < 0.05$ was considered statistically significant.

3 | RESULTS

Dosimetric comparisons between PTB plan and paired tangential plan for target coverage of CW and OAR doses are shown in Table 2. For heart, mean and maximum irradiated dose were 1.94 and 34.24 Gy with PTB plan and 4.33 and 49.41 Gy with tangential plan, respectively (both $P < 0.001$). Heart volumes irradiated with 30 and 5 Gy were also lower with the PTB plan than the tangential plan: 0.69% and 8.21% with PTB plan vs 4.64% and 11.04% with tangential plan; $P < 0.001$ and 0.019, respectively.

For ipsilateral lung, all parameters were significantly decreased with the PTB plan. Mean irradiated lung doses were 8.00 and 13.46 Gy ($P < 0.001$), and irradiated lung volumes of 20 Gy were 16.82% and 28.45% ($P < 0.001$) with PTB plan and tangential plan, respectively. With the PTB plan, the low-dose area such as $V_{5\ Gy}$ with

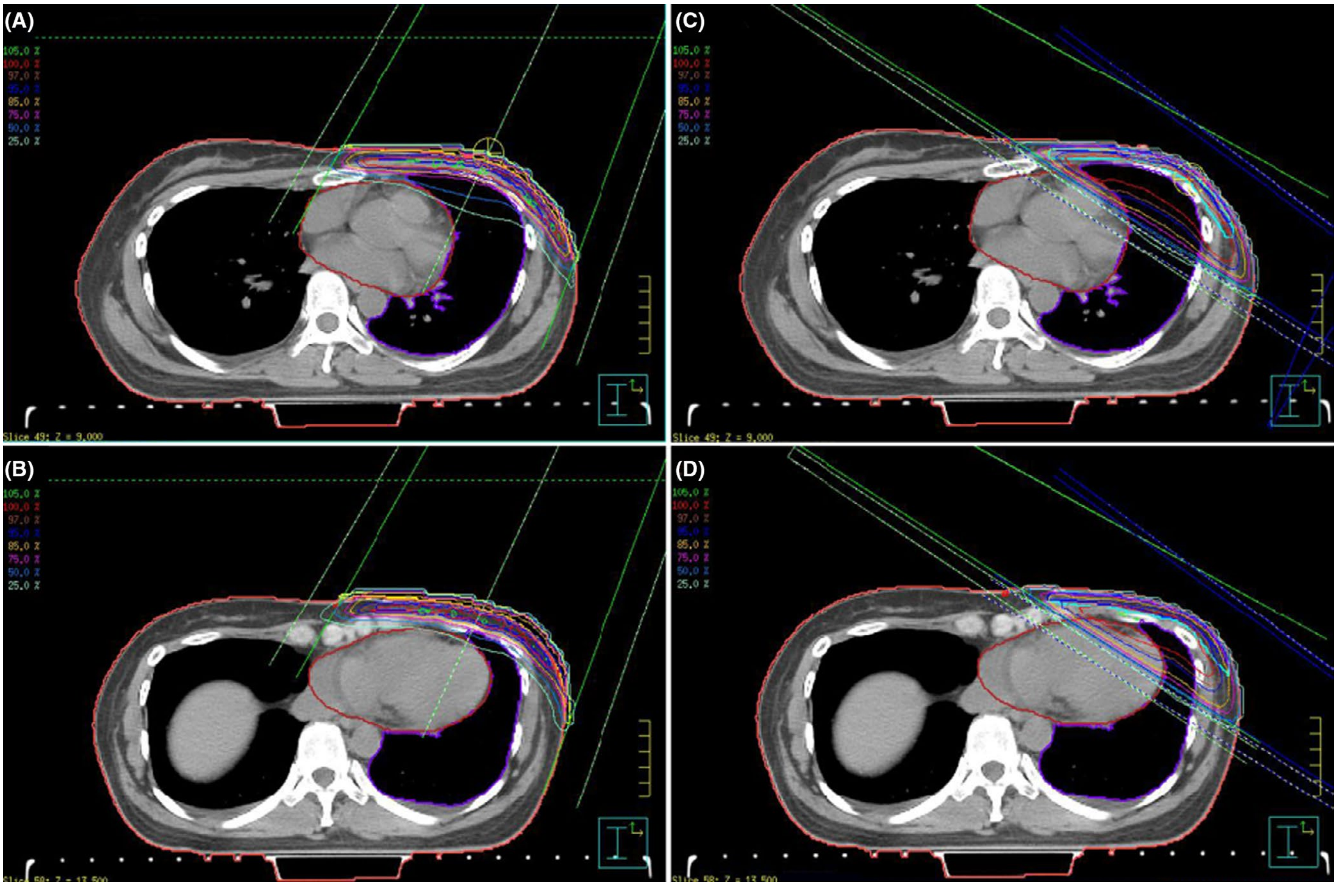

FIGURE 1 A chest wall electron beam plan with patient-tailored bolus (A, B) and a paired tangential plan (C, D) in different axial levels [Color figure can be viewed at wileyonlinelibrary.com]

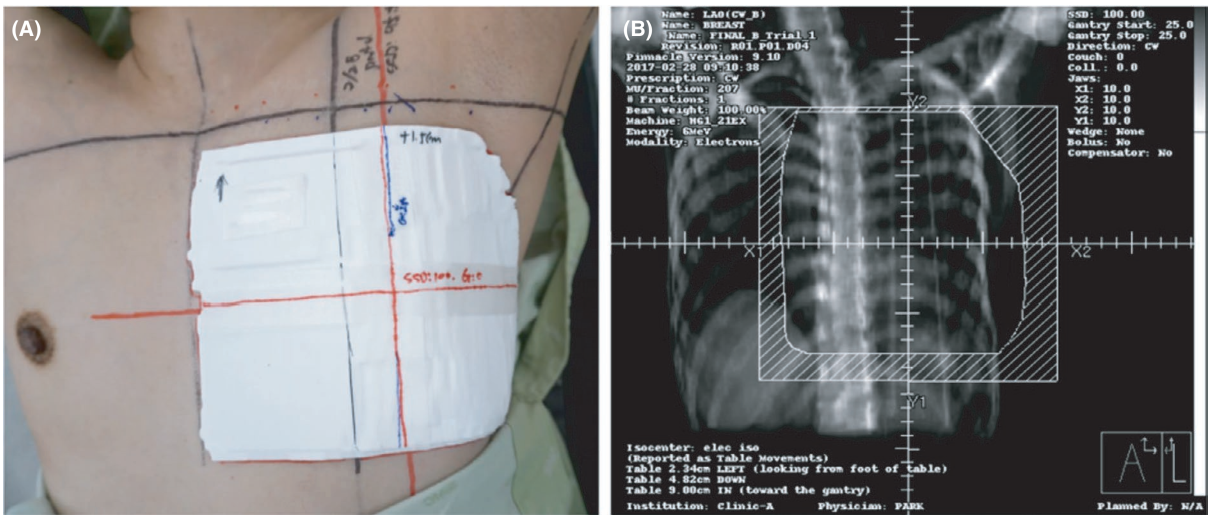

FIGURE 2 Patient-tailored bolus and set up on a patient (A), and portal field of electron beam for chest wall (B) [Color figure can be viewed at wileyonlinelibrary.com]

PTB was 32.63% of left lung volume and much lower than that with the tangential plan.

For target coverage, conformity index (CI) and homogeneity index (HI) were 3.04 and 1.09 with PTB plan, and 6.46 and 1.16 with tangential plan (both $P < 0.001$), which means that the dose distribution of the PTB plan was more confined than that of the tangential plan.

As complication, most patients experienced radiation dermatitis. Grade 2 toxicity occurred in only one patient. Other acute toxicities were not observed. As the late toxicity, four patients visited rehabilitation

TABLE 2 Dosimetric comparison between patient-tailored bolus (PTB) applied electron beam plan and tangential plan

Dosimetric comparison (N = 28)	PTB plan (A) Mean (range)	Conventional plan (B) Mean (range)	(A) − (B)	*P*-value
Target for chest wall				
D_{mean} (Gy)	50.07 (48.33-52.09)	48.11 (44.12-51.56)	1.96	<0.001
D_{max} (Gy)	55.29 (52.76-57.56)	53.05 (51.47-54.81)	2.24	<0.001
D_{min} (Gy)	33.25 (19.10-43.31)	20.72 (0.13-43.51)	12.53	<0.001
CI (V_{95}/V_{CTV})	3.04 (1.94-7.74)	6.46 (1.80-16.71)	−3.42	<0.001
HI (D_{10}/D_{90})	1.09 (1.05-1.36)	1.16 (1.07-1.29)	−0.07	<0.001
Heart				
D_{mean} (Gy)	1.94 (0.68-10.52)	4.33 (1.05-14.12)	−2.39	<0.001
D_{max} (Gy)	34.24 (14.81-52.69)	49.41 (31.60-53.02)	−15.17	<0.001
$V_{2\,Gy}$ (%)	15.65 (0.42-66.13)	25.23 (0.56-56.58)	−9.58	<0.001
$V_{5\,Gy}$ (%)	8.21 (0.26-45.29)	11.04 (0.37-31.33)	−2.83	0.019
$V_{10\,Gy}$ (%)	4.13 (0.17-31.59)	7.74 (0.32-24.79)	−3.61	0.001
$V_{20\,Gy}$ (%)	1.85 (0-19.63)	5.79 (0.05-20.67)	−3.94	<0.001
$V_{30\,Gy}$ (%)	0.69 (0-12.63)	4.64 (0-17.69)	−3.95	<0.001
Left lung				
D_{mean} (Gy)	8.00 (1.11-15.24)	13.46 (7.45-21.79)	−5.46	<0.001
D_{max} (Gy)	50.04 (36.76-55.18)	51.91 (49.39-54.14)	−1.87	0.004
$V_{5\,Gy}$ (%)	32.63 (6.09-56.96)	42.29 (3.91-82.24)	−9.66	<0.001
$V_{10\,Gy}$ (%)	24.85 (3.17-44.50)	34.26 (0.54-67.81)	−9.41	<0.001
$V_{20\,Gy}$ (%)	16.82 (0.81-30.89)	28.45 (0.06-56.88)	−11.63	<0.001
$V_{30\,Gy}$ (%)	11.16 (0.07-22.27)	24.11 (0-49.23)	−12.95	<0.001

clinics due to lymphedema. One patient without any respiratory symptoms showed focal fibrotic changes of peripheral lung parenchyma close to the left CW on chest CT. No cardiac disorder was found.

Median follow-up period was 30 months and the range was 18-43 months. The 3-year progression-free survival and overall survival rates were 82.1% and 100%, repectively. During the follow-up period, there were 9 (32.1%) recurrence and 1 (3.6%) dead events. As patterns of failure, however, no one had CW recurrence in RT field with PTB.

4 | DISCUSSION

To reduce the radiation dose to OAR while delivering a sufficient dose to target, various techniques for PMRT such as deep inspiration breath hold, prone position technique, intensity-modulated radiation therapy (IMRT), and proton therapy have been applied. Of these techniques, IMRT is a relatively new technique with the benefit of uniform dose distribution.[6] However, it has the disadvantage of a larger low-dose area, which has the possibility of increasing the risk of contralateral breast cancer or a secondary cancer.[7] Another technique proposed to protect OAR is proton therapy. However, the number of clinics with proton therapy is limited and its current cost-effectiveness has been reported to be inappropriate for use in breast cancer patients.[8]

Electron beam, which has a shorter penetration length than photon beam, has traditionally been used for RT to a relatively superficial target. Because of this physical property, some centers have used EBT for PMRT.[9] However, EBT has a limitation of dose distribution. The round-shaped CW slopes laterally and the surface after mastectomy has often nonuniform scars. Also, the CW itself consists of biomaterials with various densities, such as ribs, muscles, and adipose tissue. To overcome these flaws, an appropriate bolus has been considered. The commercial bolus is a gelatinous sheet of equal thickness and it is difficult to regulate dose distribution. Moreover, it induces air gaps on unusually convex or concave surfaces such as an uneven scarred lesion. There are some reports of cases treated using a customized bolus.[9] However, this approach could not be widely used because of laborious and time-consuming process.

To combine the advantages of EB and customized bolus, our center started applying PTB applied EBT for PMRT using 3D-printing techniques. In the dosimetric comparison, the PTB plan reduced the mean heart dose by 2.39 Gy, and theoretically might prevent 17.0% of the increase in coronary heart disease after RT.[3] For the left lung, the volume irradiated at 5 and 20 Gy was at safe levels with both plans, but the late protective effect indicated that the PTB plan decreased low dose as well as high-dose exposures. Especially, the PTB plans including IMN area (Figure 3) showed obviously superior dose distribution than tangential plans.

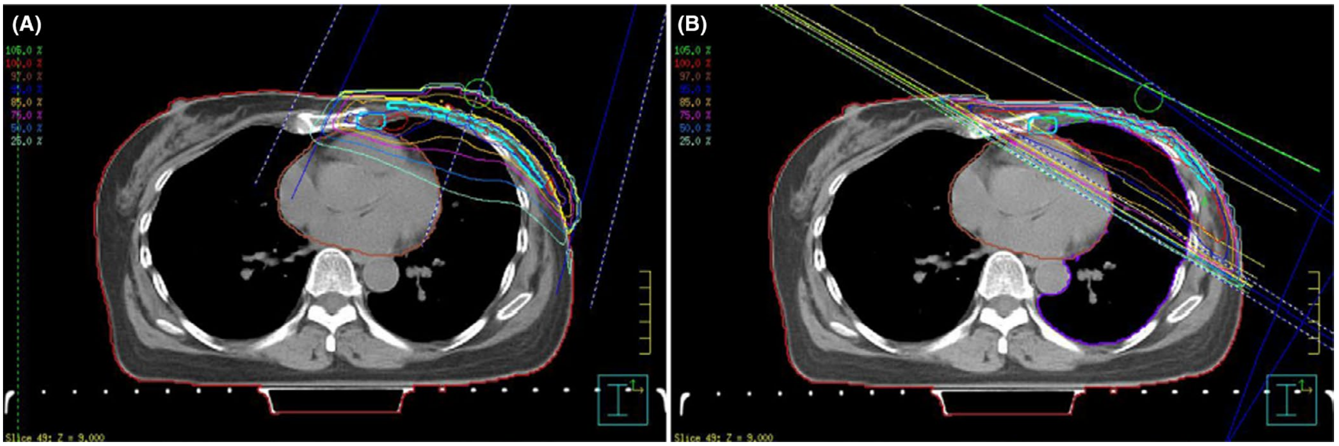

FIGURE 3 A electron beam plan with IMN irradiation using patient-tailored bolus (A) and a paired wide tangential plan (B) [Color figure can be viewed at wileyonlinelibrary.com]

With EBT, which is physically less skin sparing than photon beam, skin toxicity is a concern. Furthermore, the bolus itself increases the surface dose. Previous studies reported the rate of acute skin toxicity from EBT for PMRT was similar to or not much higher than that with conventional therapy.[9,10] In this study, similarly, there was severe acute skin toxicity. However, late skin complications such as fibrosis or telangiectasia were reported more often with EBT than photon beam.[11] It is therefore necessary to follow-up on the long-term radiation toxicities after EBT. Nevertheless, PTB might be beneficial for high-dose irradiation to skin or scar area of CW. In our center, patients who have positive resection margin at skin or strong lymphovascular invasion are strongly considered for treatment using PTB.

In conclusion, PTB applied EBT as PMRT is expected to be effective for left breast cancer with reduced risk of cardiac disease and lung morbidity although a larger number of patients and longer durations of follow-ups are needed to verify clinical or cosmetic results of this therapy.

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How to cite this article: Yang K, Park W, Ju SG, et al. Heart-sparing radiotherapy with three-dimensional printing technology after mastectomy for patients with left breast cancer. *Breast J*. 2019;25:682–686. https://doi.org/10.1111/tbj.13304