Two-year Follow-up of Volumetric-modulated Arc Therapy for Treating Internal Mammary Nodes in Locally Advanced Breast Cancer

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Abstract. *Background/Aim:* We evaluated dosimetric and clinical results of volumetric-modulated arc therapy (VMAT) treating internal mammary nodes (IMNs) in patients with locally advanced breast cancer. *Patients and Methods:* Between July 2012 and December 2013, treatment outcomes of 31 patients with stage III breast cancer treated with postoperative radiotherapy including the IMN field using VMAT were analyzed. *Results:* The median follow-up was 25.2 months. VMAT showed good homogeneity and improved conformity. The incidence of lung toxicity of grade 2 or more was 3.2%, and cardiac toxicity was not observed. No patient developed local recurrence. *Conclusion:* VMAT appears safe for the treatment of locally advanced breast cancer including the IMN field.

After randomized trials showed no survival benefit from extended mastectomy including elective internal mammary node (IMN) dissection compared to mastectomy without IMN dissection (1, 2), IMN dissection has rarely been implemented even for patients who have metastases in their IMNs. Since then, radiotherapy (RT) has become the main treatment option for IMN in patients with breast cancer with or without involved IMNs (3).

However, including IMNs within the RT field tends to increase the dose to organs at risk (OAR) (4), hence minimizing the dose to normal organs and tissues while fulfilling the high homogeneity and conformity of treatment plans is a challenging goal. Since the development of Otto's volumetric-modulated arc therapy (VMAT) (5), many studies have attempted to apply VMAT to breast cancer treatment to

improve planning quality and to reduce doses to OAR. Previous studies reported that VMAT achieved better homogeneity and conformity than the conventional technique while the doses to OAR were variable depending on the organs and techniques (6-11). To our knowledge, there are no data reporting the clinical outcomes, including toxicities and local control, after VMAT in patients with breast cancer.

In this study, we retrospectively investigated patients with locally advanced breast cancer who were treated with VMAT including the IMN field following surgery and analyzed dosimetric results as well as clinical outcomes.

Patients and Methods

Patients. Between July 2012 and December 2013, 31 patients with stage III breast cancer treated with postoperative RT including the IMN field using VMAT were included. Eleven patients had metastases in IMNs and seven patients in supraclavicular nodes (SCNs). Every patient signed a written informed consent form before initiation of RT. This study was approved by the Institutional Review Board (EUMC 2015-08-007-001).

Target and OAR delineation and dose prescription. Gross target volumes (GTVs) were unresected metastatic nodes in SCNs or IMNs on pretreatment imaging. The clinical target volume (CTV) included the breast or chest wall, axillary lymph node level II/III, infraclavicular lymph nodes, SCNs and IMNs. IMNs above and at the level of involvement were included in the CTV or first to third intercostal space level for elective irradiation. Planning target volume (PTV) 1 and PTV 2 were generated by adding a 7-10 mm margin around the CTV and GTV respectively and PTV1 was adjusted according to the lung surface and was 3-5 mm inside the skin. The tumor bed was contoured based on surgical clips and scar.

Radiation of 50 Gy in 25 fractions was prescribed to the PTV1 and 60-70 Gy in 25 fractions to the PTV2 using the simultaneously integrated boost (SIB) technique. The dose constraints were V20 less than 35% for the ipsilateral lung and V25 less than 10% for the heart according to QUANTEC (12). Tumor bed boost was delivered with electron with dose of 10 Gy in five fractions separately after completion of VMAT in patients who underwent breast conserving surgery.

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Table I. Patient and tumor characteristics (n=31).

Characteristic	No. of patients
Median age (range), years	48.3 (31-71)
Menopause	
Yes	14
No	17
Stage	
IIIA	12
IIIB	0
IIIC	19
Laterality	
Right	18
Left	13
Location of main mass	
Upper outer	10
Upper inner	7
Lower outer	8
Lower inner	3
Center	3
Multifocality/multicentricity	
Yes	14
No	17
Histologic grade	
1	2
2	14
3	15
Lymph node involvement	
IMN+axilla	11
SCN+axilla	7
Axilla only	13
Lymphovascular invasion	
Positive	18
Negative	13

IMN: Internal mammary lymph node; SCN: supraclavicular lymph node.

VMAT planning. Eclipse® 10.0 was used for planning. VMAT planning comprised three partial rotations (Arc1, Arc2, and Arc3). In cases involving the right breast, Arc1 was counter-clockwise (CCW) rotation (60°-230°; field size x1=9 cm, x2=4 cm), Arc2 was clockwise (CW) rotation (230°-60°; field size x1=4 cm, x2=9 cm), and Arc3 was the last CCW rotation with a full open field (60°-210°; field size x1=9 cm, x2=9 cm). Corresponding opposite angles were used for left-sided breast cancer.

Dosimetric parameters. The homogeneity index (HI) and the conformity index (CI) of the PTV1 were defined as follows: $HI = [(D_{5\%} - D_{95\%})/D_p] \times 100$, where $D_{5\%}$ and $D_{95\%}$ were the minimum doses delivered to 5% and 95% volume of the PTV, and D_p was the prescribed dose to the breast/chest wall (50 Gy); $CI = (V_{95\%}/PTV) \times 100$, where $V_{95\%}$ represented the volume receiving 95% of the prescribed dose.

Follow-up and toxicity evaluation. Patients were followed-up with breast examination and radiographs every 3 to 12 months according to clinical demand. The Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria and RTOG/the European Organization for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring Schema (13) were used to evaluate acute and late radiation toxicities, respectively.

Statistics. Dosimetric parameters were compared using Student's *t*-test. Kaplan-Meier estimates were used for estimating locoregional control. A *p*-value of less than 0.05 was considered statistically significant. All statistics were performed using the Statistical Package for the Social Sciences software (SPSS) version 18 (SPSS Inc., Chicago, IL, USA).

Table II. Treatments patients received (n=31).

Treatment	No. of patients
Surgery	
BCS	13
MRM	18
Chemotherapy	
Adj CMF x 6	2
Adj AC x 4, T x 4	16
Neo AT x 6	9
Neo AT x 3, Adj AT x 3	2
None	2
Hormonal therapy	
Tamoxifen	16
Aromatase inhibitor	10
None	5
Trastuzumab	
Yes	8
No	23

BCS: Breast-conserving surgery; MRM: modified radical mastectomy; CMF: cyclophosphamide + methotrexate + fluorouracil; AC: doxorubicin + cyclophosphamide; T: Taxol; Neo: neoadjuvant; Adj: adjuvant; Eqv: equivalent dose.

Results

The median follow-up was 25.2 months. The characteristics of the patients and treatments are shown in Tables I and II.

Dosimetric analysis. All dosimetric results are listed in Tables III and IV. Tumor laterality and surgery type did not influence HI. Patients with right-sided breast cancer or treated with breast-conserving surgery had a higher CI than those with left-sided breast cancer or modified radical mastectomy, but the differences were not statistically significant (Tables III and IV).

The average mean heart dose (MHD) in patients overall was 12.1 Gy. The average MHD of those with left-sided breast cancer was 14.3 Gy, which was higher than for those with right-sided breast cancer (10.6 Gy, $p=0.005$). For patients overall, the average mean lung dose (MLD) and V20 of ipsilateral lung were 19.2 Gy and 32.7%, respectively, and mean dose to the contralateral breast was 5.7 Gy and V5 of contralateral breast was 46.7%. No difference in dose to the ipsilateral lung and contralateral breast was found according to tumor laterality and surgery type (Tables III and IV).

Radiation toxicities. Table V shows the results of acute and late radiation toxicities. No patient experienced grade 2 or more acute lung toxicity. Among 11 patients (35.4%) who showed radiological changes of the lung during the follow-up period, only one patient had grade 2 pulmonary effusion in the

Table III. Comparison of dosimetric parameters according to tumor laterality.

	All (n=31)	Right breast (n=18)	Left breast (n=13)	
	Mean (95% CI)			p-Value
Homogeneity index	17.4 (9.0-31.6)	17.1 (9.0-31.6)	17.7 (10.8-31.1)	0.759
Conformity index	82.5 (39.1-98.5)	85.2 (67.2-97.5)	78.7 (39.1-98.5)	0.270
Heart				
MHD (Gy)	12.1 (5.3-20.3)	10.6 (5.3-13.9)	14.3 (9.3-20.3)	0.005
V10 (%)	48.6 (6.3-98.4)	42.3 (6.3-70.0)	57.4 (22.6-98.4)	0.824
V20 (%)	13.7 (0.0-37.2)	7.5 (0.0-15.9)	22.2 (9.4-37.2)	0.088
V25 (%)	7.9 (0.0-24.6)	3.4 (0.0-8.6)	14.0 (5.6-24.6)	<0.001
V30 (%)	4.6 (0.0-14.0)	1.6 (0.0-4.7)	8.8 (3.5-14.0)	<0.001
V40 (%)	1.5 (0.0-6.0)	0.4 (0.0-1.4)	2.6 (0.8-6.0)	<0.001
Ipsilateral lung				
MLD (Gy)	19.2 (13.4-21.8)	19.4 (13.4-21.8)	19.0 (16.7-21.3)	0.521
V5 (%)	96.8 (84.3-100.0)	97.9 (90.0-100.0)	95.1 (84.3-100.0)	0.131
V10 (%)	74.1 (46.0-94.6)	75.9 (46.0-94.6)	71.8 (57.1-83.9)	0.349
V20 (%)	32.7 (21.0-41.3)	33.3 (21.0-41.3)	32.0 (26.4-38.3)	0.427
V40 (%)	11.4 (1.4-19.7)	10.9 (1.4-15.9)	12.1 (8.5-19.7)	0.360
Contralateral breast				
MBD (Gy)	5.7 (2.0-9.5)	5.4 (0.0-7.6)	6.1 (3.2-9.5)	0.068
V5(%)	46.7 (5.8-10.0)	42.2 (5.8-74.1)	52.9 (12.2-100.0)	0.177

CI: Confidence interval; MHD: mean heart dose; MLD: mean lung dose; MBD: mean contralateral breast dose.

Table IV. Comparison of dosimetric parameters according to surgery.

	All (n=31)	BCS (n=13)	MRM (n=18)	
	Mean (95% CI)			p-Value
Homogeneity index	17.4 (9.0-31.6)	16.4 (9.0-31.6)	18.1 (10.8-31.1)	0.394
Conformity index	82.5 (39.1-98.5)	87.5 (75.9-98.5)	78.4 (39.1-94.0)	0.062
Heart				
MHD (Gy)	12.1 (5.3-20.3)	11.6 (8.6-16.7)	12.6 (5.2-20.3)	0.478
V10 (%)	48.6 (6.3-98.4)	43.9 (22.6-64.4)	52.4 (6.3-98.4)	0.274
V20 (%)	13.7 (0.0-37.2)	12.2 (0.4-31.6)	14.9 (0.0-37.2)	0.494
V25 (%)	7.9 (0.0-24.6)	7.2 (0.0-21.1)	8.4 (0.0-24.6)	0.650
V30 (%)	4.6 (0.0-14.0)	4.3 (0.0-13.4)	4.8 (0.0-14.0)	0.795
V40 (%)	1.5 (0.0-6.0)	1.3 (0.0-6.0)	1.7 (0.0-3.9)	0.713
Ipsilateral lung				
MLD (Gy)	19.2 (13.4-21.8)	18.8 (13.4-21.7)	19.6 (18.2-21.8)	0.236
V5 (%)	96.8 (84.3-100.0)	96.1 (85.8-100.0)	97.3 (84.3-100.0)	0.520
V10 (%)	74.1 (46.0-94.6)	73.3 (46.0-92.6)	74.9 (63.8-94.6)	0.720
V20 (%)	32.7 (21.0-41.3)	31.9 (21.0-41.3)	33.4 (28.2-37.5)	0.391
V40 (%)	11.4 (1.4-19.7)	10.4 (1.4-15.1)	12.3 (6.6-19.7)	0.119
Contralateral breast				
MBD (Gy)	5.7 (2.0-9.5)	6.0 (3.9-9.5)	5.4 (2.0-8.6)	0.160
V5(%)	46.7 (5.8-10.0)	51.9 (14.3-100.0)	42.4 (5.8-74.3)	0.226

CI: Confidence interval; BCS: breast-conserving surgery; MRM: modified radical mastectomy; MHD: mean heart dose; MLD: mean lung dose; MBD: mean contralateral breast dose.

ipsilateral lung 150 days after beginning RT. The median time to development late lung toxicities of any grade was 6.9 months. The incidence of grade 2 acute dermatitis was 19.4 % and severe dermatitis did not develop in any patients. There was no cardiac toxicity observed during the follow-up period.

Local control. No patients experienced locoregional recurrence.

Discussion

Since VMAT has been used for treatment of breast cancer, many reported the dosimetric outcome of VMAT in comparison to 3-dimensional conformal RT, however, to our knowledge there are no reported clinical results of VMAT, this is the first study reporting the clinical outcomes of VMAT in patients with breast cancer.

Before using VMAT to treat IMN, we had treated patients with locally advanced breast cancer including the IMN with forward intensity-modulated radiation therapy combined with photon-electron (PE-fIMRT) with a field-in-field technique. The weak point of PE-fIMRT was a cold triangle at the matching boundary between the tangential photon beam and the electron beam. If a tumor is in the inner quadrants, the risk of IMN metastasis is higher than for outer tumors (13) and IMN treatment is more likely to be recommended. Ironically, in this situation, the tumor bed would be located in the cold triangle. In addition, patients with IMN metastasis where surgery does not have any role, boost to IMN metastases is needed but it is very difficult to accomplish with great homogeneity and conformity. In order to overcome these problems, VMAT planning has been attempted in our institution since July 2012.

The main concern about the use of VMAT for breast cancer treatment was doses to OAR. In contrast to previous studies, VMAT did not lower OAR doses in our study compared to our previous experience. The main reason for high OAR doses might be the difference in clinical situations. For elective irradiation of IMNs, only the first to third intercostal space levels are included usually, however, in the present study, patients with metastasis of IMN lower than the third intercostal space were not uncommon, hence use of an increasing RT dose to the heart as well as the lungs. In particular, VMAT resulted in a large lung volume receiving a low to moderate RT dose as shown in Tables III and IV.

Nevertheless, radiation toxicities were not remarkable. Contrary to previous results which showed that V5 or V10 are predictors of symptomatic radiation pneumonitis in patients with lung cancer (14-16), only one patient experienced clinically significant pulmonary toxicity despite a high V5 and V10 in our study. We assume that the differences in the patient populations, including performance status and chemotherapy regimen, have produced different consequences. As a result,

Table V. Radiation toxicities (n=31).

Toxicity	Acute, n (%)	Late, n (%)
Lung		
Grade 1	0	10 (32.2)
Grade 2	0	1 (3.2%)
Grade 3-4	0	0
Skin		
Grade 2	6 (19%)	0
Grade 3-4	0	0
Heart		
Any grade	0	0

treating IMN with VMAT seems safe in regard to acute and late pulmonary toxicity. No cardiac toxicity has been observed during the follow-up period, however, since RT-induced cardiac toxicities can develop even decades after radiation exposure (17, 18), a longer follow-up is mandatory in order to fully evaluate RT-induced cardiac toxicities. Radiation exposure to the contralateral breast can interrupt the treatment of metachronous contralateral breast cancer or generate secondary breast cancer. Considering the incidence of metachronous cancer and the safe outcome after re-irradiation (19, 20), and very low possibility of second malignancy after radiation exposure (21), we think benefit from VMAT could outweigh its harm.

The rationale by which we treated patients with locally advanced breast cancer with VMAT, despite the relative high doses to the OAR, was improved homogeneity and conformity of target volumes. In this study, more than half of the patients had gross disease in IMNs or SCNs and the majority of patients had a large number of axillary nodal metastases with tumor located in inner quadrants, suggesting high possibility of developing IMN metastases. Compared to our historical experience of PE-fIMRT, VMAT gave better HI and CI when treating internal mammary chain with GTV. It is well known that local control is related to overall survival in breast cancer (22, 23), therefore efforts to control locoregional disease with an appropriate RT dose is important. Although we cannot conclude whether improved homogeneity and conformity led to better local control and eventually better survival in this study, local control has been excellent so far.

In conclusion, VMAT yielded good homogeneity and conformity when treating IMN in patients with locally advanced breast cancer. High OAR doses did not lead to clinical toxicities and no severe cardiac and lung toxicities were observed at 2 years follow-up. Long-term follow-up is needed to assess the benefit and harm of VMAT and careful patient selection is necessary in choosing VMAT as RT technique.

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