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ORIGINAL ARTICLE

Is helical tomotherapy-based intensity-modulated radiotherapy feasible and effective in bilateral synchronous breast cancer? A two-center experience

Kemal Ekici[1], Tumay Gokce[2], Ilker Karadogan[2], Aysun Fatma Eraslan[1], Cimen Akcay[2], Oztun Temelli[1], Eda Kaya Pepele[1], Funda Durmus Manalp[2], Caglar Keles[2], Arpaslan Mayadagli[3]

[1]Department of Radiation Oncology, Medical Faculty, Inonu University, Malatya; [2]Department of Radiation Oncology, Ege Private Oncology Radiotherapy Center, Izmir; [3]Bezmi-Alem University, Department of Radiation Oncology, Istanbul, Turkey

Summary

Purpose: *This study describes the early clinical results and dosimetric parameters of intensity-modulated radiation therapy (IMRT) using a tomotherapy device in patients with primary bilateral synchronous breast cancer (PSBBC).*

Methods: *Fourteen patients with bilateral breast cancer were treated with tomotherapy between January 2011 and October 2014. The treatment planning objectives were to cover 95% of the planning target volume using a 95% isodose, with a minimum dose of 90% and a maximum dose of 107%. The organs at risk (OAR), such as the lungs, heart, esophagus and spinal cord, were contoured. Acute toxicity was recorded during and after radiation therapy.*

Results: *The advantages included better treatment conformity with lower dosages to minimize the risk to susceptible organs, such as the lungs, heart and spinal cord. There was improved coverage of the planning target volume, including the regional nodes, without any field junction problems. The median homogeneity index was 0.13 and the median conformity index 1.32. The median V20, V15, V10 and V5 for the total lungs were 18.5, 23.3, 24.2 and 60%, respectively. Skin acute toxicity was grade 1 in 72% and grade 2 in 14% of the patients. Esophageal acute toxicity was grade 1 in 43% of the patients.*

Conclusion: *Tomotherapy delivers treatment that is well-tolerated, with high homogeneity and coverage indexes and the capability to reduce the irradiation dose received by the lungs and heart in PSBBC patients. This technique is therefore feasible and safe for the treatment of bilateral breast cancer.*

Key words: *bilateral breast cancer, intensity modulated radiation therapy, side-effects, tomotherapy*

Introduction

Breast cancer is the most common malignant disease in women in Western countries, where the risk of developing cancer over a lifetime is >10% [1]. However, the occurrence of PSBBC is very rare, accounting for only 1–3% of all breast cancer cases [2]. The histopathologic characteristics and biological behavior of PSBBC are still unclear. It is also not clear whether PSBBC should be considered as a sequential event of a primary tumor or as an independent second primary tumor [3]. There are no clear treatment guidelines for PSBBC, as there are for unilateral breast cancer. Several controversial issues surround PSBBC concerning diagnostic criteria and management policies. Radiotherapy is an important part of the treatment in many breast cancer patients and has a definite

Correspondence to: Kemal Ekici, MD. Department of Radiation Oncology, Faculty of Medicine, Inonu University, 44280, Malatya, Turkey.
Tel: +90 422 341 0660-5603, Fax: +90 422 341 0728, E-mail: drkemal06@hotmail.com
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role in reducing locoregional recurrence, leading to improved recurrence-free survival [4].

The application of radiotherapy in PSBBC is technically difficult because of the proximity to organs like the heart, lungs and esophagus. Modern radiotherapy techniques, such as tomotherapy using image-guided radiotherapy (IGRT) and IMRT, can improve the accuracy of delivery while reducing irradiation to normal tissues. The use of helical tomotherapy, with a rotating gantry around the patient delivering radiation from many angles, is not optimal for irradiation of the breast because, compared with standard tangents, only low doses are delivered to areas of the body that would receive only a scattered dose by conventional radiotherapy [5]. Based on recent literature, this study investigated radiotherapy methods for patients with PSBBC treated with a tomotherapeutic device and the resulting tolerance dosage of the OARs.

Methods

Study design and patients

Between January 2011 and October 2014, 14 patients with PSBBC were evaluated. Nine patients had a bilateral mastectomy and axillary lymph node dissection prior to radiotherapy. Two patients had breast-conserving surgery, and one patient was medically inoperable and treated curatively with radiotherapy. Patients were treated with a helical tomotherapeutic device. Patients with metastatic breast cancer or a previous radiation history of the chest wall due to thoracic malignancy were excluded.

Volume delineation

All patients were immobilized using an individualized thoracic Alpha Cradle (Orange City, Lowa 5/04/USA) with both arms stretched above the head. Radiopaque wires were located on the patients' skin on computed tomography (CT) simulation to define the scars and field edges and to provide a clinical margin around the palpable breast tissue. Patients underwent CT scans from the lower neck to the mid abdomen at 3-mm-slice spaces. Images were imported into the VoLO® treatment planning system (Accuray Inc., Sunnyvale, CA, USA). In breast-conserving surgery, the breast clinical target volume (CTV) was delineated within the area covered by the radiopaque wires marking palpable breast, including tissue within the limits of the standard whole breast irradiation, according to the protocol of the Radiation Therapy Oncology Group 0413 [6]. Breast CTV excluded skin and any non-breast structures deeper than the pectoralis muscle. The breast planning treatment volume (PTV) was generated by adding a tridimensional margin of 5 mm around the breast CTV. For the boost volume, a lumpectomy cavity was defined based on presurgical, clinical and radiological information, surgical clips, seroma and all other surgically-induced changes considered to be part of the lumpectomy cavity. The boost PTV was defined by adding a tridimensional margin of 5 mm beyond the

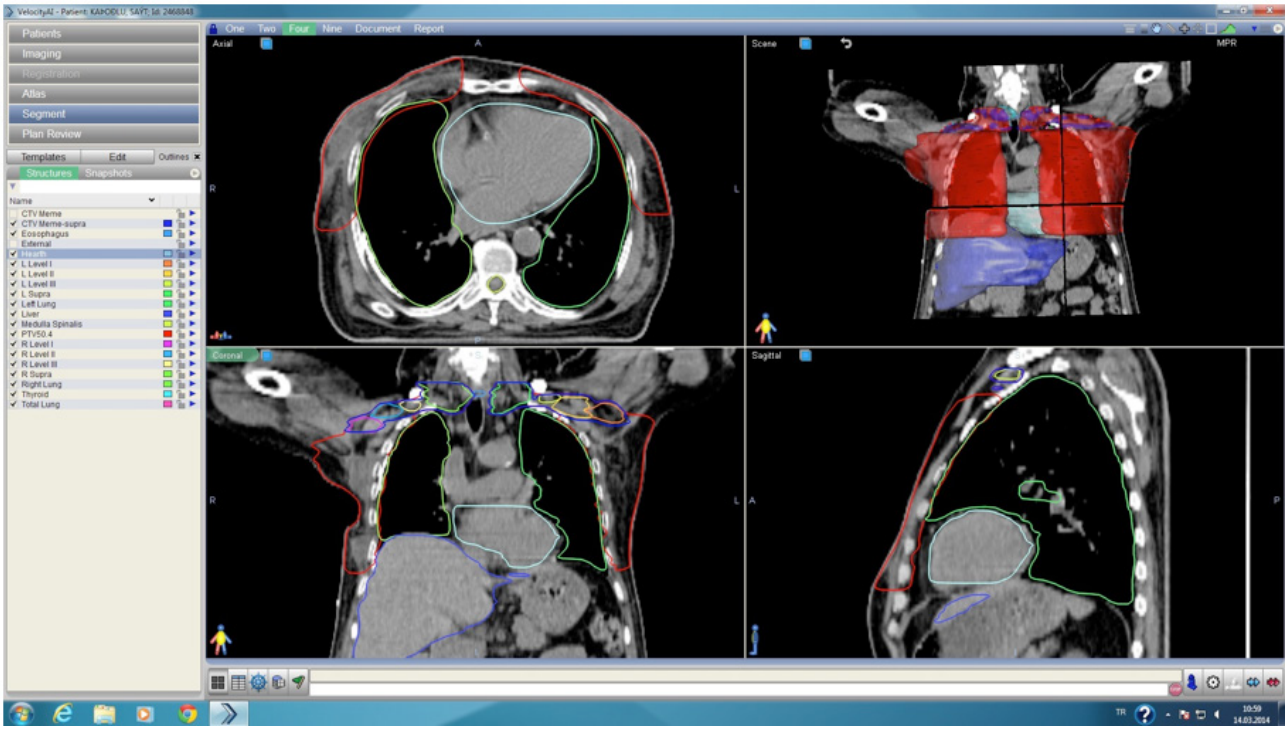

Figure 1. Images of axial, coronal and sagittal plans of a patient.

boost CTV. Both boost and breast PTV were restricted to a depth of 3 mm under the skin surface [7]. In patients with a mastectomy, PTV was defined by addition of the chest wall, including the pectoralis muscles, chest wall muscles and ribs, and including the rib pleural interface. The lungs, heart and esophagus were delineated according to the RTOG 0413 protocol [6].

Supraclavicular lymph nodes included the medial and lateral supraclavicular nodes corresponding to levels IV and Vb of the Robbins classification [8]. Axillary lymph nodes included surgical levels I (lateral, pectoralis and subcapsular nodes), II (central axillary nodes) and III (apical axillary nodes), as defined by the inferior border of the pectoralis major and the inferolateral and superomedial edges of the pectoralis minor [9]. Internal mammary lymph nodes were delineated following the trajectory of the mammary vessels, usually from the superior aspect of the medial first rib to the superior aspect of the fourth rib. Delineation of the nodal areas was according to published guidelines [10].

Fractionation, total doses and volume indications

In mastectomized patients, the target volumes were treated with a dose of 50–50.4 Gy in 25–28 fractions. In breast-conserving surgery, the tumor bed was boosted sequentially (8–10 Gy/4–5 fractions). One inoperable patient was treated with a total dose of 66 Gy.

Tomotherapy volumes included the whole chest wall in the majority of patients, as well as the supraclavicular nodes, axillary nodes and internal mammary nodes when indicated. In patients with breast-conserving surgery, a boost dose was administered (Figure 1).

Tomotherapy

A virtual blocking structure was created to avoid irradiation to OARs (posterior incidences in bilateral breast cancer). The helical tomotherapy parameter definitions were between 2.5 and 5 cm for the field size and 0.18–0.3 for pitch, with a planning modulation factor of 2.5–3.5. All treatments included a delivery quality assurance prior to treatment initiation. The OARs such as the lungs, spinal cord, esophagus and heart were contoured. For the PTV, the objectives were to cover at least 95% of the PTV with a 95% isodose, to include a minimum PTV dose of 90% and a maximum dose of 107%. For the OARs, the planning objectives were maximal doses of 45 Gy for the spinal cord, V40<30%, V50<20% for the esophagus, V60<33%, V40<50% for the heart, V20<25%, V15<20% and V5<50% for both lungs. These planning objectives for the OARs were uniform for all patients and were established following the strictest constraint recommendations to assure the lowest possible dose delivered to normal tissues.

All treatments were delivered through a 6 megavolt (MV) photon helical tomotherapy Hi-Art II system unit (TomoTherapy, Inc., Madison, WI, USA). Patients were positioned by aligning the lasers in the treatment room with marks made on the patients' skin. Megavoltage images of the entire length of the PTV were acquired before each fraction and then co-registered with the planning images based on soft tissues and bones. The patient setup before treatment was verified by the system software and the radiation therapist. Patient setup deviations were detected in the medial-lateral, cranial-caudal and anterior-posterior directions. Rotational deviations in the cranial-caudal axis (roll), anterior-posterior axis (pitch) and medial-lateral axis (yaw) were also identified. Daily setup corrections for non-rotational deviations and roll were performed for all patients; rotational deviations for pitch and yaw were taken into account only when subjectively considered to be important.

Follow-up

Follow-up by clinical examinations was performed weekly during the entire treatment, followed by every 3 months during the first year and every 6 months during the second year after treatment. Clinical characteristics and follow-up information were collected from the clinical charts; acute toxicity (up to 4 weeks after finishing treatment) was recorded according to the Common Terminology Criteria for Adverse Events v. 3.0 (CTCAE) [11]. Dose volume histograms for PTV for the lungs, heart, esophagus and spinal cord were recorded from dosimetric charts. The homogeneity index was calculated by dividing the maximal PTV dose by the prescription dose; the coverage index was calculated by dividing the minimum PTV dose by the prescription dose. The conformity index was calculated by dividing the PTV volume by the irradiated volume. These indexes were calculated according to the recommendations established for evaluating tomotherapy treatment plans [12].

Results

Patient characteristics are summarized in Table 1. All patients in this study had bilateral breast cancer, and their irradiation was very difficult using a conventional device. For this reason, these patients were treated with a tomotherapeutic IMRT system. The patient median age was 40 years (range 34–85).

Most patients had received adjuvant chemotherapy associated with mastectomy and axillary lymph node dissection, with more than 10 lymph nodes excised in most patients. One patient was inoperable. Adjuvant hormonotherapy was used in all patients with positive hormone receptors.

The median PTV was 2070 cc (range 934–3114). PTV homogeneity and conformity indexes exhibited median values of 0.13 and 1.32, respectively. The median V20 for the lungs was 18.5 (range 6.9–25.5). V15 < 35% and V10 < 60% for

Table 1. Patient characteristics (N=14)

Characteristics	*N*	*%*
Gender		
Male	1	7
Female	13	93
Age (years)		
≤65	10	71
>65	4	29
Surgery		
Mastectomy	6	43
Breast conserving	7	50
Inoperable	1	7
Nodal intervention		
Axillary dissection	8	57
Sentinel node biopsy	5	36
None	1	7
Chemotherapy		
No	1	7
Yes	13	93
Hormonotherapy		
No	0	0
Yes	14	100
Clinical stage R (L)		
I	4 (5)	29 (36)
IIA	5 (3)	36 (21)
IIB	1 (3)	7 (21)
IIIA	3 (1)	21 (7)
IIIB	1 (2)	7 (14)
IIIC	-	-

R: Right, L: Left

Table 2. Dosimetric parameters (N=14)

Parameters	*Median (range)*
HI	0.13 (0.03–1.15)
HI for boost*	0.06 (0.02–0.1)
CI	1.32 (1.15–1.78)
CI for boost*	1.80 (1.32–2.12)
Dynamic jaws 2.5 (5)**	10 (4)
V20 total lungs (%)	18.51 (6.90–25.50)
V15 total lungs (%)	23.30 (11.01–34.30)
V10 total lungs (%)	24.25 (22.04–59.53)
V5 total lungs (%)	59.90 (38.96–78.20)
V55 esophagus (%)	0.33 (0–4.71)
V25 heart (%)	6.0 (0–13.03)
V40 heart (%)	0.68 (0–2.50)
Dmax spinal cord (Gy)	23.91 (11.02–40.74)
Dmax esophagus (Gy)	43.14 (8.28–67.54)
Dmax heart (Gy)	44.23 (36.10–52.15)
Treatment duration (sec)	507 (225–1200)

*Nine patients received the boost plan, **first for 2.5 jaws, second for 5 jaws, HI: homogeneity index, CI: conformity index, sec: second

the lungs were achieved in all patients. Maximal doses for the spinal cord and esophagus were < 45 and 60 Gy, respectively, in all cases (Table 2). Treatment-related acute toxicity was limited to grade 2 for the skin and grade 1 for the esophagus (Table 3).

Discussion

PSBBC are thought to be independent tumors rather than secondary to metastatic spread from a primary lesion. Their characteristics imply that these independent tumors arise due to the presence of intra-ductal components and different histologies or grades of differentiation between the tumors [2,13]. In a study of chromosomal abnormalities in patients with bilateral breast cancer, the majority of contralateral tumors arose independently of the primary tumor. It is estimated that 5-10% of all breast cancers are hereditary, half of which are related to a germ-line mutation in BRCA1 or BRCA2. Women with BRCA mutations are at risk of bilateral breast cancer, and bilateral disease increases the likelihood of identification of a mutation. Genetic testing for BRCA1 or BRCA2 was not carried out in this study [14].

Conventional radiotherapy techniques for the treatment of breast cancer have produced impressive locoregional control and overall survival rates, with little change in the methods used over the years. With advances in imaging, treatment planning and delivery, new radiotherapy techniques are available that should offer advantages while maintaining high rates of local control and overall survival. IMRT represents one of the most important technological advances in radiotherapy since the advent of the linear accelerator. It is an evolving field showing significant potential for improving radiotherapy in many patient groups, and tomotherapy is probably the most sophisticated form of IMRT used in clinical practice today [5,15].

Difficulties in treatment planning for PSBBC vary. Because the PTV is large with a wide irradiation field size, the lungs and heart might be exposed to relatively high doses of radiation. The following aspects have been considered: the status of the heart and heart disease induced by radiotherapy, including (a) acute injuries (e.g. pericarditis) and (b) late effects (e.g. congestive heart failure, ischemia, coronary artery disease and myocardial infarction) [16].

Table 3. Patient side effects and tomotherapy characteristics (N=14)

Variable	*Variable levels*	*No.*
Radiotherapy treatment volume	Chest wall	5
	Breast	9
	Axillary nodes	12
	Supraclavicular nodes	12
	Internal mammary chain	1
Boost	No boost	5
	Phase	8
	SIB*	1
Radiotherapy duration (days)	<35	1
	36–49	10
	>49	3
Skin acute toxicity	None	2
	Grade 1	10
	Grade 2	2
Esophageal acute toxicity	None	8
	Grade 1	6

*simultaneous integrated boost

The side effects of breast radiotherapy include lung and cardiac toxicity, lymphedema, brachial plexopathy, soft tissue fibrosis and cosmetic sequelae, as well as secondary malignancies. Patients accepting adjuvant radiotherapy should be counselled on the potential benefits of local treatment and the side effects, including late toxicity, particularly since many patients have a good long-term prognosis. IMRT must be evaluated alongside these considerations [5].

Although modern radiotherapy techniques such as three-dimensional conformal radiation therapy (3D-CRT) have improved, symptomatic radiation-induced pneumo¬nitis occurs in 1–10% of irradiated patients with breast cancer. Investigational studies to reduce the radiation dosage to the lungs using IMRT have been conducted. There are obvious dosimetric differences between IMRT and 3D-CRT, and several studies have analyzed the dosimetric parameters of IMRT and 3D-CRT for entire breast irradiation in early-stage breast cancer patients [17]. IMRT improved the avoidance of radiation to the heart, lung, and axillary regions while promoting PTV coverage. Tomotherapy could also attain fine PTV coverage and spare the OARs compared with 3D-CRT in breast cancer patients [18,19].

The $V20_{Gy}$ of the lungs is highly associated with radiation pneumonitis and is usually used for dose constraints and evaluation of treatment plans. The median $V20_{Gy}$ in our patients was 18.5 Gy.

As reported for conventional IMRT in a recent study, there were no grade 3 or greater acute kidney toxicities, and grade 2 toxicity was similar to that reported in other patients treated with conventional IMRT. A significant reduction in acute grade 2 or worse dermatitis, edema, and hyperpigmentation occurred with IMRT compared with conventional wedge-based radiotherapy. There was a trend towards reduced acute grade 3 or greater dermatitis (6 vs 1%, p=0.09) in favor of IMRT. Chronic grade 2 or worse breast edema was significantly reduced with IMRT compared with conventional wedge-based radiotherapy. No difference was found in cosmesis scores between the two groups [12]. The use of IMRT in the treatment of the whole breast resulted in a significant decrease in acute dermatitis, edema, and hyperpigmentation and a reduction in the development of chronic breast edema compared with conventional wedge-based radiotherapy [20].

Sas-Korczyńska et al. [21] reported that IMRT reduced the mean heart dose com¬pared with 3D-CRT. Previous research indicated that if the heart dose was >30 Gy, there was a risk of coronary heart disease, whereas a mean heart dose < 26 Gy significantly reduced the risk of pericarditis. IMRT reduced the cardiac high dose area and long-term cardiac complications. Compared with 3D-CRT tomotherapy IMRT also tended to reduce the mean heart dose. Late cardiac mortality has been associated with non-conformal radiotherapy due to the considerably high radiation doses received by the heart. The use of modern treatment techniques has been associated with a decline in cardiac radiation doses and a consequen-

tial decrease in cardiac mortality. Chemotherapy also contributes to cardiac toxicity. Cardiac dysfunction ranged from 4–7% in metastatic patients treated with trastuzumab alone and rose to 27% when treated with concomitant trastuzumab, anthracycline and cyclophosphamide [22].

It must also be borne in mind that the use of IMRT also results in the delivery of radiation to normal tissues outside of the breast that would typically not have been irradiated. The long-term effects of irradiating these normal tissues is not known, however, because patients with breast cancer generally enjoy long survival, they may be at risk of developing secondary malignancies or other late complications [23].

Volumetric intensity-modulated arc therapy (VMAT) has a shorter treatment time than that of tomotherapy IMRT; VMAT treatment reduced treatment time by 74% The average measured treatment time was 3.0±0.1 min for MVAT [24]. In this study, the patient median treatment duration was 507 sec for helical tomotherapy.

In conclusion, in cases where there are difficulties in treatment planning techniques using conventional radiation therapy systems, tomotherapy IMRT systems can provide convenient radiotherapy planning for bilateral breast cancer patients. In breast cancer, tomotherapy can deliver well-tolerated treatment with high homogeneity and coverage indexes capable of sparing the OARs in patients with bilateral breast cancer, and can reduce the risk of cardiac toxicity derived from chemotherapy, or preexisting cardiac or pulmonary diseases. Further clinical studies into the use of tomotherapy are required to evaluate any late toxicities and the risk of secondary malignancies.

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