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Optimum Treatment Planning Technique Evaluation for Synchronous Bilateral Breast Cancer with Left Side Supraclavicular Lymph Nodes

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ABSTRACT

Introduction: Bilateral breast cancer cases are classified as complex in radiotherapy treatment, especially those with the left side mastectomy and right-side lumpectomy with left side supraclavicular lymph nodes patients. The purpose of this study is to find the optimum treatment planning technique among the three available techniques: 3Dimentional conformal Radiotherapy (3D-CRT), Intensity modulated radiation therapy (IMRT), and Volumetric Modulated Arc Therapu (VMAT).

Material and Methods: Ten Bilateral breast cancer included in this study with left-side mastectomy and right-side lumpectomy with left-side supraclavicular lymph nodes. The patients are delineated by oncologists and prepared for radiation planning by MONACO 5.1 treatment planning system (TPS) with an X-ray photon beam of 6 MV or 10 MV energy using ELEKTA's Agility linear accelerator. The prescribed dose is set at 4005 cCy per 15 fractions. Statistically with anova test among each other.

Results: The treatment with 3D-CRT, IMRT, and VMAT show a significant difference in the results. VMAT gives high dose distribution for the left mastectomy breast and its regional supraclavicular lymph nodes, while the IMRT gives a higher value for the right side breast with lumpectomy. The good homogeneity index is acquired with IMRT, while VMAT gives a better conformity index. The 3D-CRT planning technique lowers the dose to the heart and lunges better than the other techniques.

Conclusion: depending on the patient health and stage, the optimum treatment planning is applied. VMAT and IMRT give effective results than the 3D-CRT.

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Introduction

Synchronous bilateral carcinoma (SBBC) is defined as two or more malignant tumors showed in both breasts in the same times. It's a rare and complex type of tumor. Mastectomy, breast-conserving surgery (BCS), and adjuvant radiotherapy are treatment options for SBBC [1–4]. There are three types of treatment planning techniques used to treat: Three-dimensional conformal radiotherapy (3-DCRT), intensity-modulated radiation therapy (IMRT), and Volumetric-modulated arc therapy (VMAT). Three-dimensional conformal radiotherapy (3-DCRT) treatment planning depends on 3D anatomical information and uses treatment fields that conform as closely as possible to the target volume to deliver adequate dose to the tumor and minimum possible dose to normal tissue [5]. Conventional beam modifiers such as wedges, partial transmission blocks, and/or compensating filters are sometimes used to improve the dose distribution conformality [6] [5]. The IMRT technique defines as the radiation therapy in which a non-uniform fluence is delivered to the patient from any given position of the treatment beam to optimize the composite dose distribution. Its fluence distribution in the plane perpendicular to the incident beam direction is modulated. To that end, the radiation beam is divided into small beam segments, which are in principle deliverable by a multi-leaf collimator (MLC) [5, 7,8]. The VMAT e delivers a rotational cone beam with variable shape and intensity. Its idea came from a delivery plan with a large number of gantry positions. The fluence map of the beam is pre-calculated and decomposed to several

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apertures. These apertures are then delivered at a given gantry position by multiple arcs. It needs more arcs which leads to extended treatment time [9–11]. In VMAT, the MLC leaves must be able to move to their positions within the time required for the gantry to rotate between consecutive gantry positions. When the sampled gantry angles become wider, more difficulties occur in TPS when optimizing the MLC leaves motion constraints [5,8]. This study aims to find the optimum treatment planning technique for the left-side mastectomy and right-side lumpectomy with left-side supraclavicular lymph nodes patients using 3D-CRT, IMRT, and VMAT.

Other studies attempt to find a better technique to treat the SBBC in different methods. Yeona cheo et al, 2019 evaluated the optimal radiotherapy (RT) plan for synchronous bilateral breast cancer (SBBC), especially treatment plans including the regional lymph node (LN) area. Their study include patients with SBBC (5 with small breasts, 5 with large breasts, and 5 who underwent a left total mastectomy). They reported that the modified hybrid plan, using an automatically calculated prescription dose for the right breast and also calculating the background dose from the left breast VMAT plan, showed comparable target coverage to that of the VMAT-only plan and was superior for saving OARs [12].

In 2017, Sung-jin Kim et al., established the intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) treatment plans for synchronous bilateral breast cancer (SBBC) and compare those plans with the previous treatment plans using 3D conformal radiation therapy (3DCRT). The plans were evaluated based on dose-volume histogram analysis. For planning target volumes (PTVs), the mean doses, and the values of V95%, V105%, conformity index, and homogeneity index were reported. For the organs at risk lungs, heart, and liver included. They compared the PTV and organs at risk values of the 3 techniques. Additionally, the independent samples to compare the 2 techniques (IMRT and VMAT) based on the values of Right(Rt.) PTV and left (Lt.) PTV, they found that VMAT is the better [13].

Materials and Methods

This clinical study is a cross-sectional conducted in Baghdad radiotherapy and nuclear medicine and Al-Andalus privet radiotherapy hospital, Baghdad, Iraq from December 2019 to April 2020. The study was approved by the College of Medicine's Institute Review Board (IRB) at Al- Nahrain University.

Female patients diagnosed with synchronous bilateral breast cancer with left side mastectomy and right side lumpectomy with regional left supraclavicular lymph nodes, whether they underwent a surgical procedure, chemotherapy, or both included in this study.

Ten female patients with BBC were diagnosed clinically and by imaging using Ultrasound, Magnetic Resonance Imaging (MRI), and biopsy to have Bilateral Breast Cancer. The Oncologist makes a delineation to the target volumes and organs at risk. The patients prepared for MONACO 5.1 treatment planning system (TPS). They treated with an X-ray photon beam of 6 MV or 10 MV energy using ELEKTA’s Agility linear accelerator from sweden. The prescribed dose set at (4005 cCy per 15 fractions.

Planning Evaluation

The Dose homogeneity and dose conformity used to evaluate the plan and are independent specifications used for the quality of the absorbed dose distribution.

Homogeneity Index

In general, dose homogeneity characterizes the absorbed-dose distribution within the target volume [4, 5, 7].

Several definitions of a homogeneity index have been proposed depending on the radiotherapy modality used. The ICRU in 2010 suggested a new definition for homogeneity index solving the previous known indexes that only deal with the minimum, the maximum dose, or uses reference point doses. The following definition for homogeneity index is suggested [7]:

$$HI = \frac{D2\%-D98\%}{D50\%} \text{[14]} \qquad (1)$$

The HI: homogeneity index, D2 %: is the absorbed dose in 2 % of isodose line, D98 %: is the absorbed dose in 98 % of isodose line, D50 %: is the absorbed dose in 50 % of isodose line

when the HI value is zero, this indicates that the absorbed-dose distribution is almost homogeneous [7].

Conformity Index (CI)

Dose conformity is a characterization for the degree to which the high-dose region conforms to the target volume, usually the PTV. The Conformity Index (CI) is used to evaluate the conformal coverage of the PTV by the isodose volume prescribed in the treatment plan [7,15]:

$$CI = \frac{V_{PTV} \times V_{TV}}{TV_{PV}^2} \text{[39]} \qquad (2)$$

The CI: Conformity Index, V_{TV}: volume of the actual prescribed dose, V_{PTV}: volume of PTV, TV_{PV}: volume of V_{PTV} within V_{TV}, The treatment conformity is said to be achieved the optimum is at CI =1.

Planning Techniques

CRT technique-The ٣D done by using two isocenters for the left and right breasts by adding 4 fields to the patient targets, two fields for each side (left and right breasts) from the midline, and tangential. For supraclavicular lymph nodes, the field’s sets form the anterior and posterior as shown in figure (1)

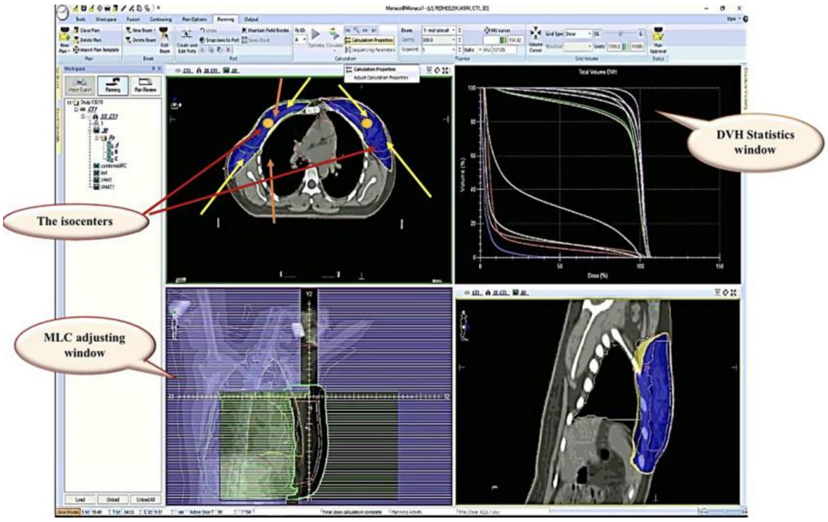

Figure 1. The 3D Treatment Planning Technique

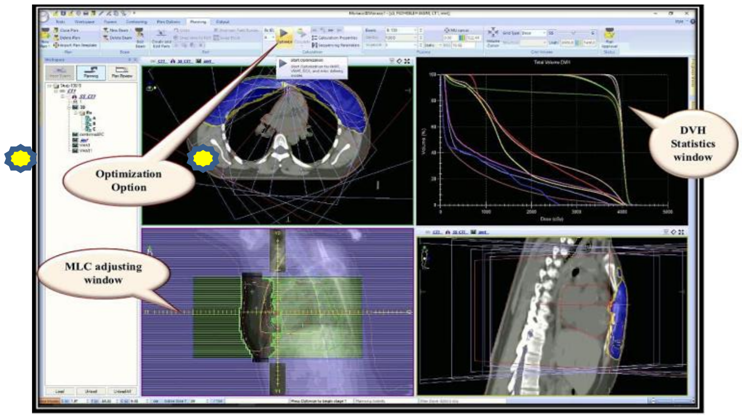

Figure 2. The IMRT Treatment Planning Technique

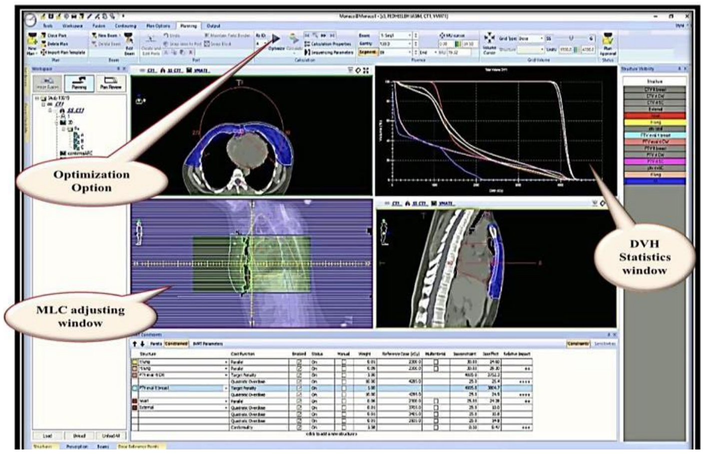

Figure 3. The VMAT Treatment Planning Technique

For the IMRT technique, the isocenter is placed in the middle of the two breasts just below the sternum, as pointed as illustrated in figure (2). Nine radiation beams are setting at angle ranging from 240^0 to 130^0 rotation around the patient the distance between each beam is 20 degrees.

For VMAT, the isocenter is also positioned just below the sternum as the same as IMRT. One beam contains 2 partial arcs as shown in figure (3). The VMAT constraints sets for PTV and OARs.

Planning Evaluation

Evaluation of planning done by the Oncologist firstly on dose distribution for target and OARs by reading the statistic to all patients for each technique and check if it needs to be edited. Then recording the data used in this study, such as CH, HI, and dose statistics .

Statistical Analysis

Data analysis was carried out using the available statistical package of Statistical Packages for Social Sciences- version 24 (SPSS-24). Data were presented in simple measures of mean, standard deviation. The significance of the difference of different means (quantitative data) was tested using one way ANOVA test for the difference between three means. Statistical significance was considered whenever the p-value was equal or less than 0.05

Results

The results of the left side mastectomy and right-side lumpectomy with left side supraclavicular lymph nodes patients who were treated with the three radiation planning techniques 3D-CRT, IMRT, and VMAT are presented with statistical analysis for the minimum dose (V90%, V95%) and maximum dose (V105%, V110%) to the planning target volume (PTV), homogeneity and conformity indexes, and organs at risk (heart and lungs) to know which of the treatment technique is better to treat the SBBC.

The results of dose distribution for the three techniques are presented as how much of the Vx (volume) receiving X (amount) of dose in cGy as summarized in table 1. For the dose delivered to 90% of the PTV, it was found that there is a highly significant difference in the three techniques for both sides (left and right PTV) and also a significant difference for supraclavicular lymph nodes (SC). The better technique for the left and supraclavicular lymph nodes was VMAT, then IMRT, and finally 3D. While the priority of dose distribution for the right PTV is given to the IMRT, VMAT comes next, and finally the 3D.

The dose at V95% of the PTV shows a highly significant difference for both right PTV, left PTV, and the supraclavicular. It can be noticed that the IMRT shows a good dose distribution for the right and supraclavicular, then the VMAT and after that the 3D. But for the left PTV, the VMAT comes first followed by IMRT and 3D, respectively.

The results of the maximum dose delivered to the V105% of the PTV for the right PTV and the supraclavicular shows a significant difference for the three techniques but not a significant for left PTV. For left PTV and supraclavicular, the VMAT shows the higher results of dose delivery, 3D comes next ad finally the IMRT. While for the right PTV (SC), the VMAT gives a higher result, then the IMRT and 3D.

It was noticed that there is no significant difference among the three techniques for the dose reached 110% of the volume for left and right PTVs. The higher results showed with the 3D technique, followed by VMAT and IMRT. While for the supraclavicular, they show a highly significant difference when the VMAT gives the high results, and no dose reached this volume for IMRT and 3D.

Right and left PTVs had a significant difference in their HI and CI while the left Supraclavicular Lymph nodes are not (SC) as explained in table 2. IMRT shows a better homogeneity for left, right PTVs and left supraclavicular lymph nodes, then VMAT, and finally 3D.

VMAT gives a better result for left and right PTVs followed by IMRT and 3D, in terms of the conformity index. While for the left supraclavicular lymph nodes, the 3D shows good conformity followed by IMRT and VMAT with equal mean values.

Table 1. Minimum and Maximum Dose for the PTV of the Left Side Mastectomy and Right-Side Lumpectomy with Left side Supraclavicular Lymph nodes with VMAT, IMRT, and 3D radiation therapy techniques

		3D	IMRT	VMAT	p-value
LT PTV	V90 (%)	77.54 ± 9.12	99.38 ± 0.20	99.48 ± 0.20	< 0.00001*
	V95 (%)	60.81 ± 11.37	95.36 ± 0.60	95.90 ± 1.33	< 0.00001*
	V105 (%)	9.57 ± 13.86	5.08 ± 5.10	13.91 ± 4.65	0.130707
	V110 (%)	5.43 ± 10.87	0.016 ± 0.020	0.33 ± 0.18	0.140375
RT PTV	V90 (%)	85.10 ± 6.57	99.59 ± 0.21	99.35 ± 0.52	< 0.00001*
	V95 (%)	66.10 ± 11.83	97.18 ± 1.13	96.52 ± 1.97	< 0.00001*
	V105 (%)	3.75 ± 4.03	5.51 ± 5.96	19.61 ± 2.59	< 0.00001*
	V110 (%)	1.00 ± 2.00	0.012 ± 0.019	0.64 ± 0.27	0.209113
LT SC	V90 (%)	87.53 ± 10.76	99.54 ± 0.59	99.92 ± 0.10	0.000241*
	V95 (%)	79.49 ± 16.66	97.81 ± 0.73	95.94 ± 2.80	0.000713*
	V105 (%)	3.75 ± 4.39	2.07 ± 4.03	7.68 ± 3.67	0.019773*
	V110 (%)	0 ± 0	0 ± 0	0.15 ± 0.13	0.000175*

*Significant Difference at *p-value* Level 0.05 with One Way ANOVA Test.

Table 2. Homogeneity and Conformity Indexes of the Left Side Mastectomy and Right-Side Lumpectomy with Left side Supraclavicular Lymph nodes with VMAT, IMRT, and 3D radiation therapy techniques

		3D	IMRT	VMAT	p-value
LT PTV	HI	0.74 ± 0.23	0.12 ± 0.02	0.13 ± 0.01	< .00001*
	CI	0.18 ± 0.12	0.28 ± 0.05	0.30 ± 0.07	0.00016*
RT PTV	HI	1.37 ± 1.76	0.10 ± 0.01	0.14 ± 0.02	0.024582*
	CI	0.28 ± 0.07	0.43 ± 0.08	0.45 ± 0.08	0.0001*
LT SC	HI	2.15 ± 3.46	0.09 ± 0.009	0.11 ± 0.1	0.067027
	CI	0.16 ± 0.22	0.06 ± 0.01	0.06 ± 0.01	0.20202*

*Significant Difference at *p-value* Level 0.05 with One Way ANOVA Test.

Table 3. Organs at Risk (OAR) Sparing for Left Side Mastectomy and Right-Side Lumpectomy with Left side Supraclavicular Lymph nodes with VMAT, IMRT, and 3D radiation therapy techniques.

		3D	IMRT	VMAT	p-value
Heart	Mean (cGy)	755.72 ± 239.40	1647.44 ± 219.64	1797.58 ± 131.97	< 0.00001*
Lung	Lt Mean (cGy)	1233.76 ± 334.85	1876.38 ± 240.23	1979.6 ± 285.98	< 0.00001*
	Lt $V_{2000\ cGy}$	29.38 ± 9.13	38.23 ± 5.59	40.75 ± 9.20	0.00043*
	Rt Mean (cGy)	581.58 ± 302.66	1663.56 ± 209.31	1868.14 ± 216.76	< 0.00001*
	Rt $V_{2000\ cGy}$	12.41 ± 4.70	28.00 ± 5.77	35.31 ± 9.16	< 0.00001*

*Significant Difference at *p-value* Level 0.05 with One Way ANOVA Test

The OAR sparing values presented in this part as $D_{n\%}$ and V_m as dose-volume metrics. The terms studied included in this study are the mean dose to the heart, the mean dose for each lung, and the volume that received 2000 cGy of the sparing dose. The results of the heart and lungs are summarized in table 3 where there was a significant difference between the calculated doses among the three techniques. 3D planning techniques show a to lower the dose to OAR at all terms, then IMRT and VMAT respectively.

Discussion

The optimal techniques in planning for treating the bilateral breast cancer with regional lymph nodes, specifically the left side mastectomy and right-side lumpectomy with left side supraclavicular lymph nodes were investigated. The main reason for making the SBBC cases hard is that the large volume needs to be irradiated, especially with the lymph nodes. This leads to a large amount of radiation exposure to organs at risk such as the heart and lungs. The treatment planning technique that we could say is better than the other is the one that gives the higher dose to the target volume or PTV and lowers the dose as much as possible to the organ at risk, whatever group is included in this study.

Generally, for our results for patients with left-side mastectomy and right-side lumpectomy with left side supraclavicular lymph nodes, VMAT show an acceptable coverage that considered to the PTV and conformity index the IMRT or 3D-CRT. In terms of homogeneity, the IMRT had superior then VMAT and 3D. While the 3D in most groups gives a lower dose that reached the heart and exceeds 16 Gy for the left lung with both IMRT and VMAT techniques and with VMAT only for the right lung. IMRT technique is intermediate for all terms.

The 3D-CRT planning technique had an advantage for lowering the dose to OARs for SBBC; because of its characteristics, it has limitations such as inadequate coverage for the PTV, poor homogeneity, and conformity due to an increase of cold spot regions. These limitations occur because of an overlap area laying between the PTV and OARs. During the planning, the physicist tries to protect the OAR by close or minimize the field using the multileaf collimators (MLCs), and he reaches his protection, but this will lower the dose given to the PTV.

The composition of the beams in IMRT treatment planning for SBBC makes a difference in the results. When we use 10 beams (fields) or more, it gives a better result, or we can say near the ideal for OARs or target of the tumor, but this will increase the treatment time, which is not comfortable for the patient. We can acquire almost an ideal dose distribution because of VMAT arc rotation around the target with precise adjustment for treating the SBBC.

Donovan et al. 2008 [16] investigated the efficiency of the IMRT treatment planning technique for breast cancer radiotherapy. They agreed with our results when they found an acceptable coverage for PTV, good dose homogeneity, and protection to OARs.

Nicolini et al. 2009 [17] nearly agreed with our results. They used Eclipse TPS belonged to Varian linac to compare IMRT and VMAT techniques for the treatment of SBBC. They showed good coverage for PTV equally with both techniques, but we found that some groups had better coverage for VMAT and others for IMRT. The difference is attributed to using different dose calculations, MLC compositions, device configuration, and optimization algorithms. Also, Nicolini used 2 arcs for VMAT while we used two partial arcs.

Yusoff et al. 2012 [18] mainly disagreed with our results, and they reported their comparative study for SBBC between 3D-CRT and IMRT treatment plans. They found that PTV coverage was the same in both techniques, whereas the IMRT was better for protecting the OAR. The disagreement occurs because of using mixed radiation from electron and photon beams in their treatment planning.

Pasler et al. 2015 [19] agreed with our study for VMAT. They studied the VMAT planning technique for the patients of left breast cancer with lymph nodes using 2 partial arcs and found an advantage for the target coverage and better HI, CI with accepted OARs protection.

Sung Jin Kim et al. 2017 [13] strongly agreed with the results of this study. They compared the three treatment planning techniques 3D-CRT, IMRT, and VMAT using MONACO TPS for SBBC patients found out that the 3D-CRT had a lower PTV coverage, HI, CI, and low dose to OARs, which is similar to our findings. Also, they stated that IMRT and VMAT decrease the cold spots better than the 3D-CRT and they were acquiring better dose distribution for PTV. Furthermore, good dose conformity and homogeneity. The hot spots confirm that VMAT and IMRT had a higher value than the 3D-CRT as we also found.

Karthick et al. 2017 [20] demonstrated the synchronous bilateral breast cancer with a 3D-CRT treatment planning technique using a mono iso-center for six female patients. They acquired good homogeneity and conformity indexes and good protection to OAR. They study the total PTV [PTV for the tumor of both breasts and related lymph nodes) and had a good dose distribution, but we don't know if they used other techniques that included what they could find in our study, so our results disagree with Karthick et al. in this part. Also, they used a mono iso-center while we used two isocenters in the 3D-CRT planning technique. Furthermore, they use Eclipse TPS from Varian, which has a different calculation method from the Monte Carlo algorithm used in Monaco TPS. This research agreed with our study in the OARs production part because of MLC controlling in 3D-CRT techniques.

Darby et al. 2013 published that ischemic heart disease also increased when the mean dose to the heart increased [21]. There was no limited dose for heart published (according to our knowledge), so we should lower the dose as much as possibly achievable. Lungs are also infected with a high dose of radiation, causing diseases such as pneumonitis. Several studies suggested that the mean dose reached to the lung or so-called mean lung dose (MLD) should range from 6 – 16 Gy without regional lymph nodes [13,17,22,23] and with regional lymph nodes [12].

In this study, we noticed that VMAT treatment planning technique gives better dose coverage for synchronous bilateral breast cancer. If we look for the technique that gives us a homogenous dose distribution, IMRT is the most recommended technique. When the protection of organs at risk is chosen as priority to SBBC treatment, the 3D-CRT technique is the better choice.

We noticed that SBBC had its entity, unlike other cancer types treated with radiation treatment planning techniques. The advanced techniques are produced to increase dose at target and reduce the dose to organs at risk, but with SBBC, things work differently. It may not be necessary to be applied for all cases deals with radiation. They may give homogenous high dose distribution, but they damage the OARs such as heart and lung, especially for ischemic heart disease patients or those with pulmonary dysfunction.

Conclusion

We investigated the most complicated cases in radiotherapy with a large targted volume to test the three common treatment planning techniques 3D-CRT, IMRT, and VMAT, to find the optimum one to treat the synchronous bilateral breast cancer. Mostly, VMAT gives optimum dose coverage, homogeneity, and conformity indexes for left-sided PTV, while the right side is optimum with the IMRT technique. The 3D-CRT technique is optimum to choose to protect the OARs. The final decision is taken depending on the treated case situation. Because there were no guidelines for treating such cases, this study was done to help physicists and oncologists suggest some of the guidelines and use them as a resource for treating the SBBC patients. Depending on the patient health and stage, the optimum treatment planning technique in this study is recommended to be applied. This research indicates using an optimum treatment planning technique for each group of SBBC to get good quality and morbidity of life for these patients.

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