



Difference of Simultaneous Integrated Boost Technique after Breast Conserving Surgery

Yonca Yahşi Çelen^{1*}, Hazım Orhan Kızılkaya²

¹ Afyonkarahisar Health Sciences University, Department of Radiation Oncology, Afyonkarahisar-Turkey (ORCID:0000-0002-2869-664X)

² Sisli Hamidiye Etfal Training and Research Hospital, Department of Radiation Oncology, İstanbul-Turkey (ORCID: 0000-0001-6946-7539)

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Abstract

Whole breast irradiation after breast conserving surgery (BCS) is the standard treatment for early stage breast cancer. For early-stage breast cancer, breast-conserving surgery and subsequent postoperative radiotherapy are as effective as mastectomy. An early stage 10 breast cancer patient admitted to the Radiation Oncology Clinic of Sisli Hamidiye Etfal Training and Research Hospital was included in the study. The study is a retrospective study and patients were not treated with the plans and techniques used in the studies. In the study, the planning target volume (PTV) and the organs at risk (OAR) planned with Sequential Intensity Modulated Radiotherapy (IMRT) and Simultaneous Integrated Supplement (Boost) Intensity Modulated Radiotherapy (SIB IMRT) techniques in patients who have undergone breast conserving surgery due to breast cancer. It is aimed to be compared dosimetrically. For the study, patients with consecutive IMRT were given 50 Gy / 25 fraction to the whole breast and 10 Gy / 5 fraction to the boost area, while patients with SIB IMRT were given a total of 50.4 Gy / 28 fractions to the entire breast, while additional dose to the boost volume was given 60 Gy / 28 fraction dose. Ipsilateral lung, heart, the minimum and maximum doses of the PTV breast and PTV boost areas and the homogeneity index (HI), conformity index (CI) values were matched with the help of the t - test minitab program.

SIB IMRT technique and Sequential IMRT technique the ipsilateral lung; When the average doses of V5 value for 10 patients are compared, the results are not statistically significant, while the V20 value is statistically significant when the average dose values for 10 patients are compared, it has been demonstrated that SIB IMRT technique can be performed with a lower dose in the ipsilateral lung V20. When the heart average and heart V20 values are compared for the two techniques, the SIB IMRT technique was not statistically significant, and it has no superiority over the Sequential IMRT technique. While dose homogeneity was better with SIB IMRT in whole breasts, there was no difference in boost area homogeneity and whole breast conformity index SIB IMRT technique for decreasing excess normal tissue volumes irradiated, shortening the treatment process, dose reduction in organs at risk, reducing the dose per fraction for the breast and increasing the dose per fraction to the boost area due to the low incidence of acute skin toxicity, standard use in breast protector RT it can be recommended for.

Keywords: Breast cancer, Simultaneous integrated boost, Intensity modulated radiotherapy (IMRT), Breast conserving surgery.

Meme Koruyucu Cerrahi Sonrası (MKC) Simultane İntegre Boost (SIB) Tekniğinin Farklılığı

Öz

Meme koruyucu cerrahi (MKC) sonrası tüm meme ışınlanması erken evre meme kanseri için standart tedavidir. Erken evre meme kanseri için meme koruyucu cerrahi ve ardından postoperatif radyoterapi mastektomi kadar etkilidir. Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi Radyasyon Onkoloji kliniğine başvurmuş erken evre 10 meme kanserli hasta çalışmaya dahil edilmiştir. Çalışma retrospektif bir çalışma olup, hastalar çalışmalarda geçen plan ve tekniklerle tedavi edilmemiştir. Yapılan çalışmada meme kanseri nedeniyle meme

* Corresponding Author: Afyonkarahisar Health Sciences University, Department of Radiation Oncology, Afyonkarahisar-Turkey, ORCID:0000-0002-2869-664X, yoncayahsi@gmail.com

koruyucu cerrahi uygulanmış hastalarda tüm meme ve boost alanına Sekansiyel Yoğunluk Ayarlı Radyoterapi (YART) ve Simultane İntegre ek (Boost) Yoğunluk Ayarlı Radyoterapi (SIB YART) teknikleri ile planlanan hedef alanı (PTV) ve risk altındaki organların (OAR) dozimetrik olarak karşılaştırılması amaçlanmaktadır. Çalışma için ardışık YART kullanılan hastalara tüm memeye 50 Gy/25 fraksiyon ve boost alanına 10 Gy/ 5 fraksiyon, SIB YART kullanılan hastalara da tüm memeye toplam 50,4 Gy/ 28 fraksiyon verilirken aynı zamanda boost hacmine ek doz 60 Gy/ 28 fraksiyon doz verilir. Aynı taraf akciğer, kalp, PTV meme ve PTV boost alanlarının minimum ve maksimum dozları ile Homojenite indeks (HI), konformite indeks (CI) değerleri eşleşmiş veriler için t – testi minitab programı yardımı ile alınan sonuçlar istatistiksel olarak değerlendirilmiştir.

SIB YART tekniği ile Ardışık YART tekniği aynı taraf akciğer; V5 değerinin 10 hasta için ortalama dozları karşılaştırıldığında sonuçlar istatistiksel olarak anlamlı değilken, V20 değeri 10 hasta için ortalama doz değerleri karşılaştırıldığında istatistiksel olarak anlamlı olup SIB YART tekniği ile aynı taraf akciğer V20’de daha düşük doz ile tedavi gerçekleştirilebileceği ortaya konulmuştur. Kalp ortalama ve kalp V20 değerleri iki teknik için karşılaştırıldığında SIB YART tekniği istatistiksel olarak anlamlı bulunmamış olup, Ardışık YART tekniğine göre herhangi bir üstünlüğü yoktur. Tüm memede doz homojenitesi SIB YART ile daha iyi iken boost alanı homojenitesi ve tüm meme konformite indeksinde fark izlenmedi. Işınlanan fazla normal doku hacimlerini azaltmak, tedavi sürecini kısaltmak, risk altındaki organlarda doz azaltımı, meme için fraksiyon başına düşen dozu azaltmak ve akut cilt toksitesisi insidansının düşük olması nedeniyle boost alanına fraksiyon başına dozu arttırmak için SIB YART tekniği, meme koruyucu RT’de standart kullanım için önerilebilir.

Anahtar Kelimeler: Meme Kanseri, Simultane İntegre Boost, Yoğunluk Ayarlı Radyoterapi (YART), Meme Koruyucu Cerrahi.

1. Introduction

Cancer is of great interest in the scientific world, as it is among the highest causes of death worldwide. According to the report published by the World Health Organization in 2017, there were 8.8 million deaths from cancer worldwide only in 2015 (World Health Organization, 2016). Breast cancer is the second most common type of cancer after lung cancer worldwide (Kozan & Tokgöz 2016). One out of every 4 women diagnosed is breast cancer. It is seen that 44.5% of women diagnosed with breast cancer in our country are between the ages of 50-69 and 40.6% are between the ages of 25-49. The median age of diagnosis was found to be 53 which has the highest incidence of breast cancer compared to 23% of cancers in women in Turkey in cancer-related cause of death in women it is due to the great importance of the first order (Haydaroglu, 2015). In a year, 17,183 women were diagnosed with breast cancer.

On the other hand, despite the increase in the frequency of breast cancer in women in the last 15 years, it is known that there is a decrease in the mortality rate due to this disease (Kanyılmaz et al, 2017). As shown in (Fig. 1.), only 11.5% of breast cancer consists of remote-stage cancer cases.

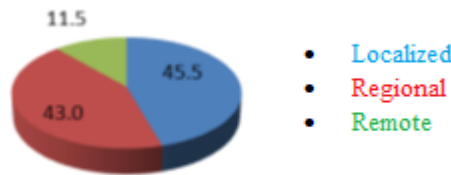


Fig. 1. Percentage distribution of breast cancer stage (Turkey United Database, 2015).

One of the most important risk factors in female cancers such as breast, uterine corpus and ovary is obesity. Cancers caused by obesity mostly affect women. For this reason, when the pattern of obesity related cancers is examined, it is seen that the speed in women is higher than that of men. Half of the diagnosed cases are ductal carcinoma insitu at diagnosis or early stage breast cancer. While treatment was mastectomy for whole breast cancer cases until about 50 years ago, breast conserving surgery and radiotherapy are accepted as standard treatment in early and selected advanced stage cases. The aim of breast-conserving surgery and radiotherapy is to achieve cosmetic success, low local recurrence and accompanying survival equivalent to mastectomy.

Radiotherapy has an important role in multidisciplinary treatment of breast cancer as primary or adjuvant therapy. Radiotherapy is a method used in the treatment of cancer and some benign diseases by using ionizing radiation. The primary goal of radiotherapy is to give the desired dose to the target area by giving the minimum dose to the environmentally critical organs (Chao et al, 2004).

In radiotherapy of breast cancer, prevention of hot and cold dose regions between adjacent areas, establishing adequate dose distribution in perifaric lymphatics, minimum lung, heart and risky organ irradiation, maximum protection of mediastinal tissues, obtaining cosmetically acceptable results can be easily applied and reproducible set. It is aimed to provide up conditions. It has been demonstrated by metaanalysis that radiotherapy (RT) in breast cancer cases has positive effects on disease-free and overall survival when appropriate indications and modern methods are used. The aim of radiotherapy is to maintain the homogeneous target volume and

intact tissues for tumor control, while maintaining the dose distribution required for target volume homogeneous and tumor control. Radiotherapy techniques in cases with breast cancer show differences due to the formation of target volumes at different depths and geometries depending on the anatomical structure of the region to be irradiated. The modern radiotherapy process, which started with the use of mega-voltage therapy equipment, reached a new point with the use of computer technologies in treatment planning and the use of Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) in determining target volumes (Khan, 2003). In modern radiotherapy planning, 3D-dimensional images created in computer environment are created by creating target and critical organ-tissue volumes on the images taken from Computerized Tomography (CT) simulator. An optimal plan is created by reviewing many techniques with planning computers. These are techniques that provide a perfect field combination with linear accelerators and concentric simulation. For this, it has become more important to ensure the stability of the same position in the simulation and treatment of the patient and breast. Radiotherapy treatment techniques can be selected from the most easily applicable technique, and more complex techniques can be selected. For this purpose, Three Dimensional Conformal Radiotherapy 3- DCRT, respiratory controlled RT, static IMRT (field in field) (Hijal et al, 2010, Bantema et al, 2011), dynamic IMRT (Guerrero et al, 2004, Cendales et al, 2012) or volumetrically modulated arc therapy (VMAT) (Nicolini et al, 2009, Scorsetti et al, 2012) can be used.

Intensity modulated radiotherapy (IMRT) is an advanced version of 3D-CRT. By adjusting the dose density in IMRT areas, the target volume can get the most suitable dose, while critical structures can receive less doses than 3D-CRT. The reverse planning technique uses an optimization algorithm that defines the beam parameters required to achieve the best possible solution (Mundt & Roeske 2005). With this algorithm, maximum and minimum dose criteria for target volume and tolerance dose values for risky structures are defined to the system. Therefore, in this method, it is expected that the optimization algorithm will obtain the values entered into the system by entering the desired dose distribution into the system in advance. To achieve this result, the optimization algorithm calculates the ideal bundle weights. With such computer-based radiotherapy techniques, it is possible to achieve near-ideal results in terms of tumor control probability (Tumor Control Probability - TCP) and normal tissue complication probability (Normal Tissue Complication Probability - NTCP) (Webb, 2003). The main purpose of inverse planning is to minimize the total dose received by normal tissues while achieving dose homogeneity at the target. The disadvantage of intensity modulated radiotherapy treatment techniques in breast irradiation is that the scattered dose received by the whole body is higher than 3D-CRT; the main advantage is that V30 doses for the heart and V20 for the lungs are significantly low (ICRU Report 62, 1999).

During optimization, dose-volume lenses are created as a result of the entered criteria. Graphic curves that are desired or close to desired are obtained in terms of target volume and critical structures. After optimization, the dose distribution is calculated with the dose calculation algorithm to convert the plan into true flux by taking the dose calculation parameters such as the yield factor depending on the irradiated area. In other words, the dose distribution desired to be achieved is determined primarily by optimization. This is called "reverse planning" (Mundt & Roeske 2005).

One point to note is that the calculation algorithm can sometimes calculate skin doses lower than their actual value, and this miscalculation may cause skin side effects due to the skin taking high doses. Therefore, the skin contour should be excluded from PTV. IMRT is based on the contour definitions drawn on CT images. Treatment planning system (TPS); By accepting targets and risky organs as fixed structures, it creates a sharp dose gradient around the target and protects the risky organs as much as possible. However, the structures and locations of organs may change because the patient's respiratory movement during treatment changes their target and organ positions. This should be taken into consideration before treatment and "breath hold technique" should be an option for IMRT. If the positions of the target and organ contours in the planning do not match during the treatment, sharp dose gradients originating from IMRT can be a disadvantage. Therefore, patient set-up and immobilization is critical for IMRT. In order to prevent unwanted patient movements, the comfort of the patient in the treatment position is mandatory. In addition, working in harmony with the patient is a key factor for IMRT.

Increasing dose to tumor bed with sequential IMRT reduces local recurrence (Bartelink et al, 2007, Alford et al, 2013) but significantly increases the risk of moderate to severe breast fibrosis by prolonging the treatment (Collette et al, 2008, Van Parijs et al, 2014). Alternatively, using a higher dose per fraction into the tumor bed, SIB IMRT has been shown to be dosimetrically advantageous and very well tolerated in the medium term, particularly for better dose compliance due to shorter treatment time (Bantema Joppe et al, 2012, Van Parijs et al, 2012, Bantema Joppe et al, 2013).

In selected cases who receive radiotherapy after breast conserving surgery, additional dose irradiation and breast irradiation are performed simultaneous (simultaneous integrated boost - SIB) (Moamen et al, 2015, Bantema Joppe et al, 2011, Thomas & Fitzgerald 2004). In this technique, the treatment time is shortened. In addition, CTV enables repetitive optimizations to create the limits of homogeneity in the breast. In external dose irradiation after external irradiation of the breast, there is no possibility to obtain the homogeneity created in SIB with the additional dose of electron, photon, IMRT. However, additional dose radiotherapy with brachytherapy can provide SIB-like dose homogeneity. In practice, a total of 5040 cGy from 180 cGy is given in 28 fractions, while the entire breast is given an additional dose to the boost volume and a total of 6000 cGy is given. IMRT + SIB dose definition was made by using the linear quadratic model by calculating the radiobiological equivalent dose of the fraction dose and total dose used in radiotherapy in breast. Normal tissue (α / β): 3 Gy and tumor (α / β): 10 Gy are considered to be comparable to BED values if biological equivalent dose is calculated using IMRT + SIB fractionation and conventional addition (boost) planned LQ model (Fowler, 1989).

2. Material and Method

Sisli Hamidiye Etfal Training and Research Hospital applied to the Radiation Oncology Clinic, retrospectively from the treatment planning system of the early stage 10 breast cancer patient. Using the Computed Tomography (CT) images taken for the treatment

planning of these patients, virtual treatment plans were created by using sequential and SIB Intensity Modulated Radiotherapy technique (IMRT) with 6 MV photon energy in the Eclipse treatment planning system. In the study conducted to investigate the dosimetric difference in tumor and critical organ doses when using IMRT Sequential boost technique and IMRT Simultaneous integrated boost technique, our aim was not to be treated with the plans and techniques used in the studies. is to find the superiority of each other. For the study, patients using consecutive IMRT were given 50 Gy / 25 fraction to the entire breast and 10 Gy / 5 fraction to the boost area, and patients using SIB IMRT were given a total of 50.4 Gy / 28 fractions to the entire breast, while the additional volume was given 60 Gy / 28 fraction dose.

Ipsilateral lung, heart, the minimum and maximum doses of the PTV breast and PTV boost areas and the homogeneity index (HI), conformity index (CI) values were matched with the help of the t - test minitab program.

In the immobilization of the patient whose breast cancer radiotherapy is planned; The anatomical structure of the patient, the anatomical structure of the breast, the position of the arm and body, breathing, weight, RT time length and number of areas play a role. Correct set up is very important in IMRT technique. Patients are placed in the supine position in the midline. The sternum is angled as parallel to the ground as possible. The head is turned in the opposite direction with the appropriate under-head support and, if necessary, a stabilizer is placed under the knee under the hip. The arm on the side to be treated is fixed as high as possible with the arm stabilizers and laid on the CT table. Reference signs are determined on the patient. In this treatment position, 3mm section thickness CT images are taken. The CT images taken are transferred to the treatment planning system (TPS). In the treatment planning system, radiotherapy plan is made on CT images.

However, in some cases it may be necessary to display the tumor more clearly. In such cases, the location of the tumor is determined precisely by evaluating the CT together with the appropriate imaging method, but the radiotherapy plan is again made on CT.

Target volumes, sensitive structures and risky organs are contoured. CTV and PTV are drawn in from 0,5 cm patient contour to protect the skin from high doses. In addition to the standard tangential fields, areas with different gantry angles are used. Dose calculation algorithm is selected, the dose value desired to be given to the target volume is entered into the system, dose calculation is made. The maximum, minimum and average doses, limit volumes, and the priorities of the tissues in planning are introduced to the computerized planning system that will be valid for the target volume and normal tissues. TPS offers the most optimal dose distribution according to the prescribed dose limits. If the optimum dose distribution offered by TPS after the optimization process is not close to the desired dose distribution, the solution of the problem is sought. The beam angles are replaced if necessary. After optimization, dose-volume curves and isodose comparisons are made and the plan is modified if necessary. If the optimum dose distribution offered by TPS is close to the desired dose distribution, the dose is calculated.

Together with the radiation oncologist, the doses taken by the target volume and risky organs are evaluated, the plan is approved after it is found to be suitable for the desired dose distribution. Plan data is transferred to the treatment device and control system and saved. The quality assurance (QA) of the plans is the stage after the plan is approved. Treatment quality controls including MU account are performed. The approved plan is sent to the treatment device, the patient is positioned for treatment. Just before the treatment, kV image is taken to check the accuracy of the set-up position.

3. Results and Discussion

In the study, patients undergoing breast conserving surgery with the diagnosis of breast cancer, target area (PTV) and the organs at risk (PTV) planned with Sequential Intensity Modulated Radiotherapy (IMRT) and Simultaneous Integrated Supplement (Boost) Intensity Modulated Radiotherapy (SIB IMRT) techniques OAR) was dosimetrically compared.

SIB IMRT technique and Sequential IMRT technique the ipsilateral lung; The doses of V5 value for 10 patients were compared using the minitab program and the paired t test. In order to perform Paired T - test on 10 patients included in the study, the normality test was applied to see if the data fit the normal distribution is shown in (Fig. 2.) As the result of the test ($p > 0.05$), 10 patient data are suitable for normal distribution (*Table 1.*)

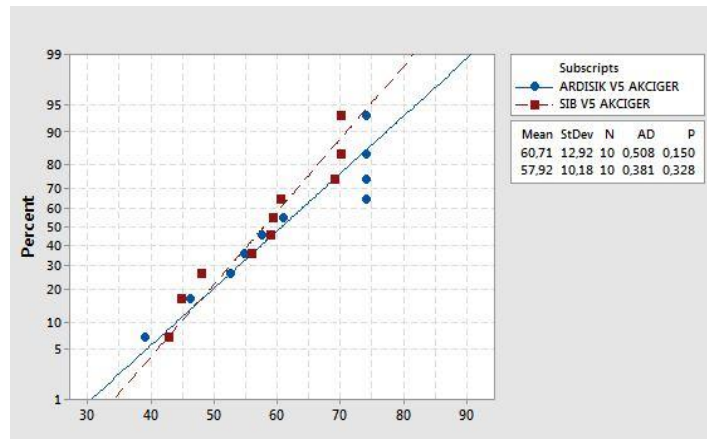


Fig. 2. Normality test results.

Table 1. Minitab V5 ipsilateral lung test result paired T-test and CI: SIB V5 Lung; Sequential V5 Lung descriptive statistics.

Sample	N	Mean	StDev	SE Mean
SIB V5 Lung	10	57,92	10,18	3,22
Sequential V5 Lung	10	60,71	12,92	4,08

Mean	StDev	SE Mean	95% Upper Bound for μ difference
-2,79	5,50	1,74	0,40

T-Value	P-Value
-1,60	0,072

μ difference: mean of (SIB V5 Lung- Sequential V5 Lung)

Since Table 1 is the result of the test ($p > 0.05$), the SIB IMRT technique was not found statistically significant and has no superiority over the Sequential IMRT technique.

SIB IMRT technique and Sequential IMRT technique ipsilateral lung; Doses of V20 values for 10 patients were compared using the minitab program and the paired t test. In order to perform Paired T - test to 10 patients included in the study, the normality test was applied to see if the data fit the normal distribution is shown in (Fig. 3.) Since the test result ($p > 0.05$), the data of 10 patients are suitable for normal distribution (Table 2.).

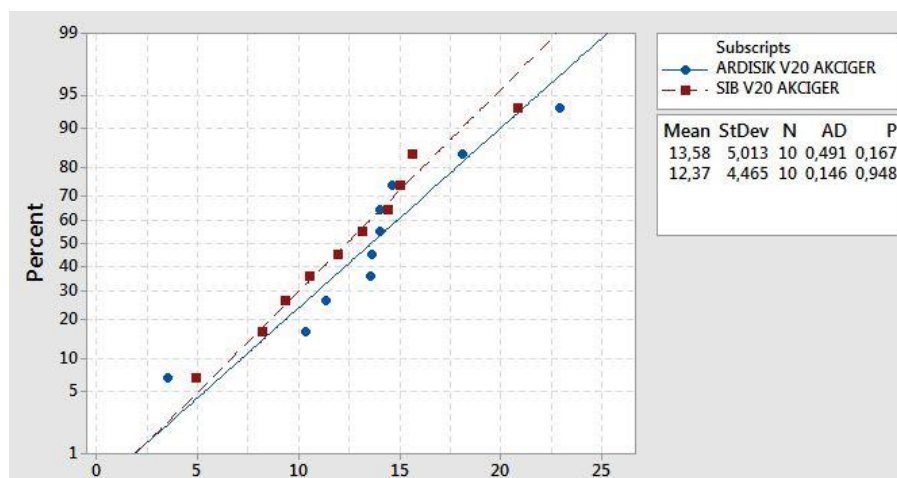


Fig. 3. Normality test result.

Table 2. Minitab V20 ipsilateral lung test result paired T-Test and CI: SIB V20 SIB V20 Lung; Sequential V20 Lung descriptive statistics.

Sample	N	Mean	StDev	SE Mean
SIB V20 Lung	10	12,37	4,46	1,41
Sequential V20 Lung	10	13,58	5,01	1,59

Mean	StDev	SE Mean	95% Upper Bound for $\mu_{\text{difference}}$
-1,209	1,955	0,618	-0,076

T-Value	P-Value
-1,96	0,041

$\mu_{\text{difference}}$: mean of (SIB V20 Lung- Sequential V20 Lung)

As a result of Table 2 test ($p < 0.05$), it was revealed that the ipsilateral lung V20 value was statistically significant when comparing the average dose values for 10 patients, and with the SIB IMRT technique, a lower dose treatment could be performed in the ipsilateral lung V20. SIB IMRT technique and Sequential IMRT technique were compared for 10 patients with heart average and heart V20 values using the minitab program and paired t test. In order to perform Paired T - test on 10 patients included in the study, the normality test was applied to see if the data fit the normal distribution and shown in (Fig. 4.) Since the result of the test ($p > 0.05$), the data of 10 patients are suitable for normal distribution (Table 3.).

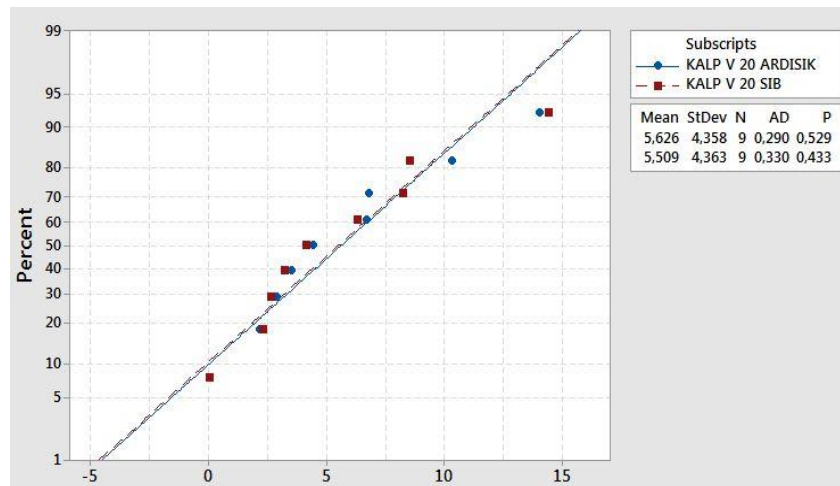


Fig. 4. Normality test result.

Table 3. Minitab V20 heart test result paired T-test and CI: Heart V20 SIB; Heart V20 Sequential descriptive statistics.

Sample	N	Mean	StDev	SE Mean
Heart V20 SIB	10	5,51	4,11	1,30
Heart V 20 Sequential	10	5,80	4,15	1,31

Mean	StDev	SE Mean	95% Upper Bound for $\mu_{\text{difference}}$
-0,295	1,110	0,351	0,348

T-Value	P-Value
-0,84	0,211

$\mu_{\text{difference}}$: mean of (Heart V 20 SIB - HeartV 20 Sequential)

As a result of Table 3 test ($p > 0.05$), when the mean and heart V20 values were compared for the two techniques, the SIB IMRT technique was not statistically significant, and it did not have any superiority over the Sequential IMRT technique.

The target volume (PTV) planned with both planning techniques received the desired dose as shown in (Fig. 5.) Dose homogeneity of the whole breast is better with the SIB IMRT technique. No statistically significant difference was observed in dose-volume comparisons and conformity index values of other risk organs.

It is aimed to compare the target volume and risk organs with the successive IMRT (Intensity Modulated Radiation Therapy) in (Fig. 6.) and SIB (Simultaneous Integrated Boost) techniques in (Fig. 7.) IMRT SIB technique can be recommended as adjuvant radiotherapy method in early breast cancer due to the shortening of the general treatment period, dose reduction in the organs at risk and high homogeneity and conformational advantages (Cuzick et al, 1994).

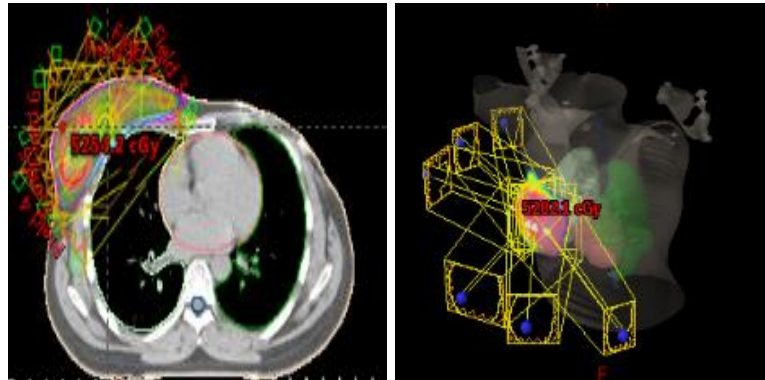


Fig. 5. Treatment areas of breast cancer patients planned with Imrt technique.

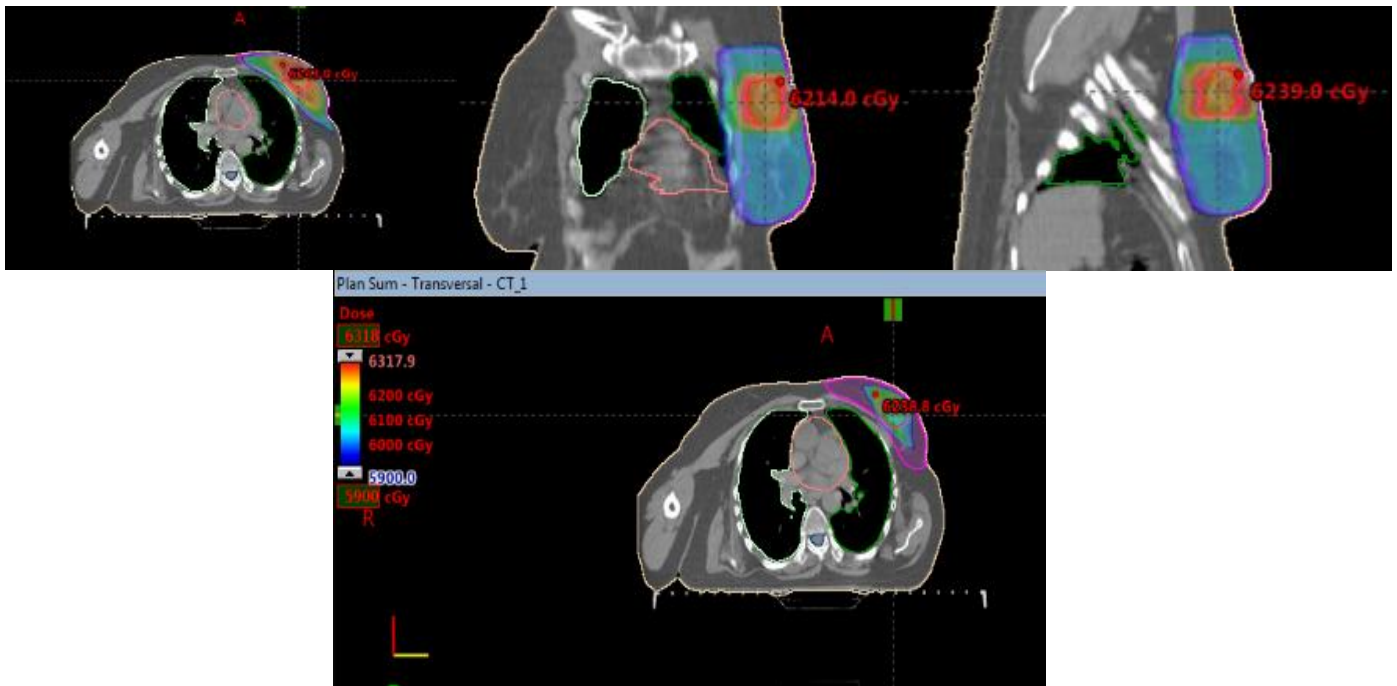


Fig. 6. IMRT with Sequential Boost.

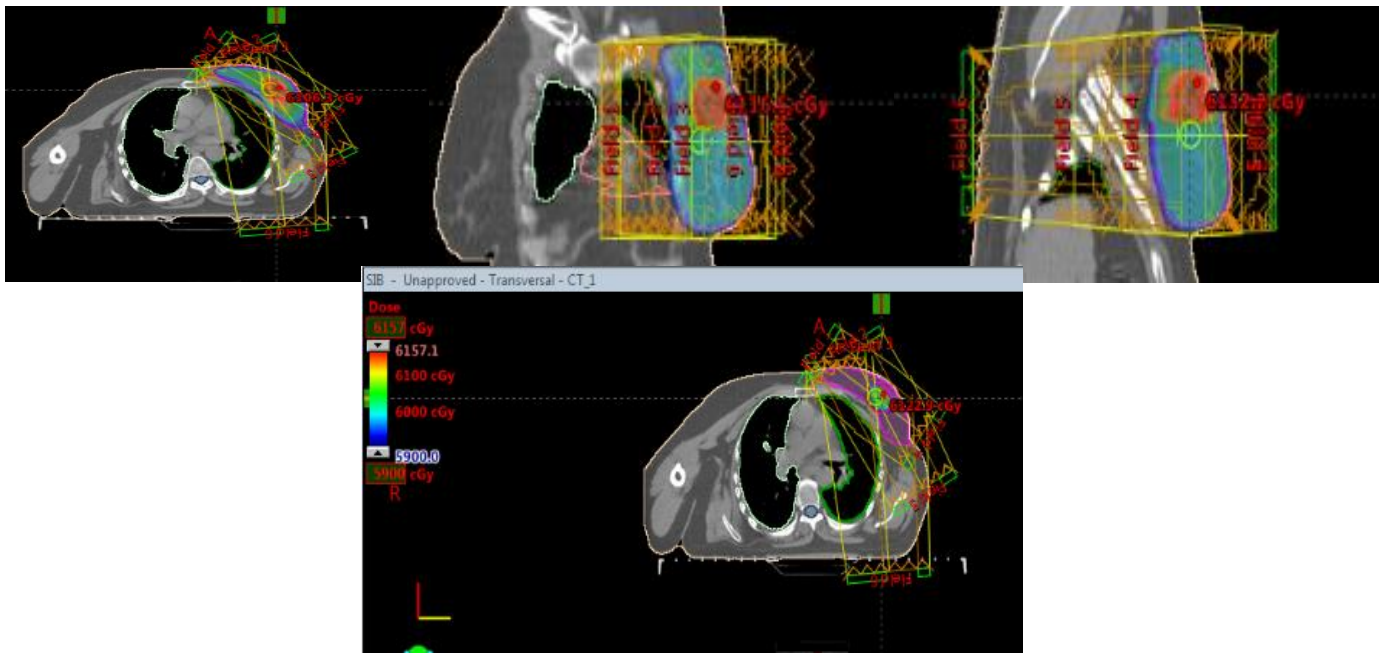


Fig. 7. IMRT with SIB.

It is evaluated by looking at the maximum and minimum doses of PTV, whether the defined dose covers the target, as well as the dose (D5) taken by 5% of the PTV (D95) and the doses taken by 95% (D5). D5 here represents the maximum dose and D95 represents the minimum dose. When the formula below is evaluated, it is seen that lower homogeneity index (HI) values provide a more homogeneous dose distribution on the target. Ideally, the value of HI is 0. The D50 in the formula is the dose taken by 50% of the target (Claus et al, 2002).

$$HI = ((D5-D95) / D50)$$

According to ICRU 62, the conformity index is found by dividing the treated volume by the entire PTV volume (ICRU Report 62, 1999).

$$CI = \text{Treated volume} / \text{PTV}$$

According to ICRU 83, the conformity index is found by dividing the PTV volume, which is surrounded by the determined reference dose, by the entire PTV volume. Ideally, the conformity index (CI) value is 1. Because the reference dose is expected to surround the entire PTV [31].

$$CI = \text{PTV volume} / \text{PTV that takes 95\% of the defined dose}$$

Dose homogeneity in the whole breast was better with SIB IMRT planning, but there was no difference in the boost area homogeneity and the whole breast conformity index. SIB IMRT technique was found to be statistically significant and lower in the ipsilateral lung V20 value. While dose homogeneity was better with SIB IMRT in whole breast, there was no difference in boost area homogeneity and whole breast conformity index. IMRT SIB technique for decreasing excess normal tissue volumes irradiated, shortening the treatment process, dose reduction in organs at risk, reducing the dose per fraction for the breast and increasing the dose per fraction to the boost area due to the low incidence of acute skin toxicity, standard use in breast protector RT it can be recommended for.

4. Conclusions and Recommendations

The IMRT SIB technique is recommended as adjuvant radiotherapy in early-stage breast cancer due to shortened overall treatment time, target coverage and dose reduction in organs at risk, and high homogeneity and fitness benefits. Van der Laan et al. in their work, SIB techniques outperform the sequential technique. Dose analysis shows greater compliance spillage into the ipsilateral breast tissue other than the support volume. Although the PTV chest is also lower than the PTV increase, it has to take a dose. In the sequential reinforcement technique, the dose to the surrounding breast tissue is undesirable and SIB dose to the surrounding breast tissue is required when required. For the SIB technique, no extra margin around the PTV supplement is required to achieve target coverage. The better homogeneity index of the IMRT SIB technique and low lung doses is advantageous due to the decrease in the total fraction number. In the selection of patient treatment method, we recommend the selection by considering these advantages. (Moamen et al, 2016, Sedlmayer et al, 1994, Wan Der Laan et al, 2007).

The results of the sequential IMRT and SIB IMRT comparisons are consistent with the literature information.

5. Acknowledge

Our work has been done within the framework of academic ethical principles and the ethics committee permission has been obtained under the number 1322.

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