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Radiation-Associated Cardiotoxicity during Breast Cancer Treatment with Ionizing Radiation

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Abstract

Introduction: Breast cancer is the most common cancer in women. The treatment of breast carcinoma has advanced in the last decade and nowadays there are treatment protocols for all stages of the disease. Depending on the histopathology and stage breast cancer is treated with surgery, chemotherapy and radiotherapy. Regarding radiation, the field of irradiation includes the chest wall in patients with mastectomy, or the breast glandular tissue in patients with conserving surgical approaches. It is often treated with radiation therapy with two opposing tangential fields, and when indicated supraclavicular lymph nodes have to be irradiated. In this case an additional anterior field is applied. The tangential as well as the other radiation beams have a potential damaging effect on the healthy surrounding tissues, particularly over the heart in the left breast irradiation and in the lungs as well. **Material and Methods:** The study included 25 patients with left breast carcinoma, all post surgery, treated with radiation therapy, with the Elekta accelerator at our department. For academic purpose the treatment plans were generated following two methods. The first one with two tangential opposite beams plus a supraclavicular beam. In this method the angles of the tangential internal and external create an angle that is equal to 180˚ {310˚ & 130˚}; no further changes were made to the beam geometry. Even though this is not the best option from the dose distribution point of view, it is still the most applied method, probably because of the semplicity of it. For each patient, a second plan was generated using two opposite tangential beams plus the supraclavicular beam. The angles of the internal and external beam were changed from 1˚ to 3˚, depending on the surface of the body, so that the resulting angle was 180˚ ± 3˚ {310˚ ± 3˚ & 130˚ ± 3˚} with the aim to adapt the beam geometry as much as possible to the shape of the thoracic wall and to spare the OAR-s. **Results and Discussion:** The data show that the dose in the organs at risk, in terms of dose percentage, is lower when the angles of the beams are changed with 1˚ - 3˚, compared to the classic method where the internal and external angles equal 180˚. This dose is not only non-negligible but significant; for every angle change from 1˚ to 3˚, there is a significant reduction in the integral dose in the radiated volume, expressed in percentage, up to 5%. **Conclusion:** In most centers, the radiation treatment of breast is realized with two tangential opposite beams, which usually are mirror beams, or in other words, the internal and external beam angles create an angle of 180˚ $\{\alpha + \beta = 180˚\}$. This is a simple method, which provides a good dose distribution, but leaves a relatively high dose in the organs at risk. This study shows the difference in the dose percentage in the heart and lung when the beam angles are changed adapting to the anatomy of the patient. Reducing these doses allows for better overall treatment and less longtime toxicity, particularly for the heart tissues.

Keywords

Radiation, Dose, Brest Cancer, Heart, Gentry Angle

1. Introduction

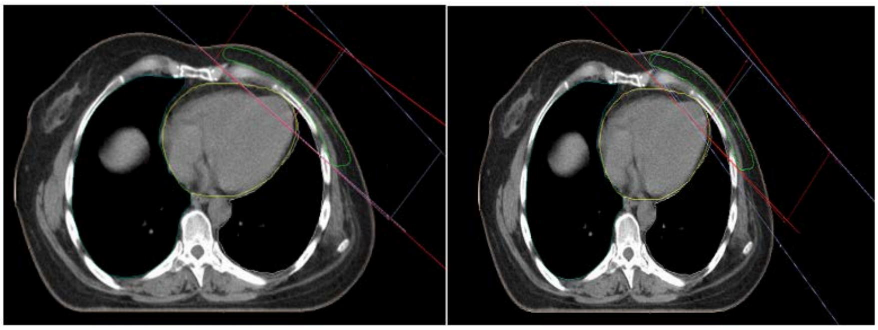
Breast cancer is the most common type of malignancy in women. The treatment process includes irradiation of the breast tissue or chest wall, depending on the type of surgery performed on the patient. In a considerable part, it is necessary to irradiate the supraclavicular region of the affected side. In most centers, the radiation is performed using low-energy photons, and the irradiation field must include the breast area, the surgical cicatrice and the axillary lymph node levels. The treatment plan is generated based on the delineated structures, the target volumes and organs at risk. For left-side breast carcinoma, the critical organs at risk are the heart and the unilateral lung. The damage to the heart occurs because of the localization adjacent to the chest wall, and the affected parts are the left heart chambers, in particular the left descending coronary artery [1]. Radiation-associated cardiotoxicity appears to be delayed typically 10 to 30 years following treatment. Radiation causes fibrosis of all components of the heart and significantly increases the risk of coronary artery disease, cardiomyopathy, valvulopathy, arrhythmias, and pericardial disease.

Gentry angles depend on the shape of the thorax and the geometric shape of the breast, behind which the heart is located. In most centers, two tangential beams are used to cover the target volume, an internal beam and a secondary external beam, which is usually a mirror beam. Depending on each case, both internal and external tangential fields are primarily used to cover the target volumes, and at the same time to protect the portion of the heart affected by irradiation [2]. The same is true for the lungs, however, a small volume of left lung is practically impossible to avoid due to the beam path which passes through the lung.

Generally, the treatment is considered to be completed if simultaneously the axillary lymph nodes are included in the irradiation fields [3]. Where indicated the supraclavicular region of the affected side is included in the treatment plan. In this case, an additional anterior field is applied. As the irradiation of this region is performed with perpendicular beams, we are faced with some challenges. The first problem is to accurately calculate the resulting dose of irradiation, in the appropriate depth, to avoid the over-dosage of border skin zone [4]. The overdosed border zone is the area where we get contribution from both tangential fields. The second problem is to achieve the appropriate irradiation dose as prescribed by the doctor on the border zone between lungs and thoracal wall. In order to achieve this goal, sometimes segmental beams are used in addition to the adjacent fields, thus over-dosage can be caused due to the presence of more than one beam [5]. In the process of covering the target and sparing the critical organs we risk inhomogeneity and/or inconformity, and the appearance of hot or cold irradiation spots. In this study, we further elaborated on the presence of more than one beam and the involvement of the heart in the irradiation beam [6].

Accepting that we are unable to completely avoid the heart during the radiation, we must take every protective measure to minimize the damage by using the appropriate geometry combined with appropriate selected energy and the irradiation type [7].

An example of breast cancer treatment with photons in a linear accelerator is shown in (**Figure 1**). The treatment is realized with two tangential opposite fields. Compensators are placed in the appropriate positions in a mode to compensate for the longer path of rays in the air. This is the simplest method to generate a treatment plan, especially in post-surgery patients [8]. The Clinic of Oncology in Prishtina is using the Infinity Electa Linear accelerator. The advantage of this machine is the possibility to work with high energies. Furthermore, the photon energies can be selected depending on the depth of the target volume that will be irradiated, within the permitted technical conditions and accessories available in the accelerator [9].



(a) (b)

Figure 1. An example of left breast cancer treatment with Gentry degrees. (a) 310˚ and 130˚, and (b) 310˚ and 135˚.

In this paper, we aim to present in detail the breast cancer treatment from the point of view of risks and toxicity to the heart tissue, as it is the critical organ exposed during the radiation. Also, we take into the consideration the amount of radiation the left lung is exposed to since we cannot avoid it completely.

2. Materials and Methods

The study included 25 patients with carcinoma of the left breast. All patients were previously treated with surgery, total modified mastectomy with axillary dissection and chemotherapy. In all cases, there was clear indication for irradiation of the left supraclavicular region. The working group followed the official protocols of the human resource office for clinical studies. All patients were asked to fill and sign a consent form, and all the personal information regarding, age, gender, diagnosis and treatment remain confidential.

For each patient two treatment plans were generated, using the same delineated volumes and dose prescription. All patients were prescribed the total dose of 41.6 Gy in 16 fractions, with 2.6 Gy of fraction. In principle, the plan was created using two tangential opposite fields, plus an additional anterior beam, to cover the supraclavicular region.

The angle between external and internal fields is approximately 180 to 185 degrees. We realized two types of treatment plans. The first plan was generated with opposite tangential mirror beams, with an angle between internal and external fields of 180˚ {310˚ & 130˚}. No further changes were made on the beam geometry, but we tried to achieve the best possible coverage by changing the beam weight and using compensators. The second plan was also generated with two tangential opposite beams, with an angle between the internal and external beam of 180˚ ± 3˚ {310˚ ± 3˚ & 130˚ ± 3˚}. Opposite fields are angled in a way to create the resultant isodose curves as more as possible similar with curvature of the chest wall.

The maximum dose distribution will be on the breast surface tissue, or closely near the surface, and consequently, the use of different angled geometry would impact the homogeneity of dose distribution, caused by high gradient of resultant dose distribution.

The treatment plans were then compared using the maximal dose, Dmax and mean dose, Dmean, for the target volume, the heart and the left lung.

The integral dose is determined as the product of mean dose, multiplied by the volume of the tissues. There are two key factors we need to consider regarding the volume: 1) the volume of the heart (or the tissue) involved in the irradiation, and 2) the mean dose value of the irradiation. The more we decrease the integral dose, the better results of treatment we will have.

Regarding the integral dose, we must point out that the dosimetric quantity can be of a high value, even if it has to do with low intensity and low energy irradiations which involve a big volume [10]. As a consequence of negligence or some other factors, such irradiations, if not done correctly during the treatment, can become a real problem in the future for the patient and pose real health risks

[11].

It is not difficult to understand that the amount of a tissue damage from radiation is proportional to the difference between the number of died cells and those of recovered one. The cell's recovery rate, on the other side, is a function of absolute number of killed cells. Let us explain this in more details using a numeric example. If the number of killed cells is N, and the recovery capability of health cells is one to two, then the number of healthy cells necessary for normal recovery of damaged N cells, is about 2N. If the number 2N is too high, or is comparable with the total number of such cells to be recovered in the whole tissue volume, then the "help" from healthy cells of the same type, will not be enough for recovery. Between two extreme scenarios cases, *i.e.*, the case of successful total recovery, and the impossibility of recovery, there are many, intermediate cases, which represent a challenge in radiotherapy [12]. It is necessary to find and to choose the above mentioned values, which final product will be the decreasing of the tumor cells number, in parallel with the increase of healthy cells.

3. Results

Table 1 shows the results obtained for all 25 patients. For each patient two treatment plans were generated, using the same delineated volumes and dose prescription. All patients were prescribed the total dose of 41.6 Gy in 16 fractions, with 2.6 Gy per fraction.

Table 1 shows the Dmax and Dmean values, for both treatment plans with tangential fields, *i.e.* $\alpha + \beta = 180^\circ$ and $\alpha + \beta \neq 180^\circ$. The focus of this study is the Dmax and Dmean value, for the heart and lungs in both treatment plans. As it is clearly seen in the table, in cases when the radiation fields are $\alpha + \beta \neq 180^\circ$, the Dmax and Dmean values are much smaller than the values when the radiation fields are $\alpha + \beta = 180^\circ$. This applies to some but not all the patients treated at our clinic. So not always the best treatment plans are when using angles $\alpha + \beta = 180^\circ$. Even the value of Gy and Dmax for breasts treated with angles $\alpha + \beta \neq 180^\circ$ is smaller than that for angles $\alpha + \beta = 180^\circ$. The graphs below show the comparison of the cases according to **Table 1** for angles 310˚ & 130˚ and 310˚ ± 3˚ & 130˚ ± 3˚.

Figure 2 and **Figure 3** show the difference in dose values for both plans. For all patients we have calculated two treatment plans; first plan $\alpha + \beta = 180^\circ$ with two fields and second plan where $\alpha + \beta \neq 180^\circ$ with two fields (α angle is angel 310˚ ± 3˚ and β angle is 130˚ ± 3˚).

In the figure, it can be seen that the Dmax and Dmean values for the breast are within the range of 95% to 107% of the prescribed dose. This means that they are within the D minimum and D maximum values of the total dose of 41.6 Gy. We found that the Dmean for the heart is below 4 Gy. Taking into account that the ALARA principle applies to risk organs, if we compare the graph for Dmean for the heart and lungs, we see that the Dmean values are lower when the $\alpha + \beta \neq 180^\circ$ technique is used, **Figure 2**.

Table 1. Dmax and Dmean values, for both treatment plans with tangential fields, *i.e.* $\alpha + \beta = 180^\circ$ and $\alpha + \beta \neq 180^\circ$.

	Gentry	310˚ & 130˚						310˚ ± 3˚ & 130˚ ± 3˚					
	Organ	Breast le		Heart		Lung le		Breast le		Heart		Lung le	
	Dose (Gy)	Dmax	Dmean	Dmax	Dmean	Dmax	Datan	Dmax	Dmean	Dmax	Dmean	Dmax	Dmean
Patient number	1	42.8	40	36.7	1.7	39.3	7.7	43.2	40.1	35.9	1.3	36.7	7.7
	2	43.4	40	37.1	2.9	37.7	9.8	43.8	40.12	37	2.6	37.7	9.9
	3	42.3	40	7.5	0.8	37.3	4.3	42.6	40	7.5	0.8	37.2	4.1
	4	43.5	40	36.5	1.5	39.1	5.9	43.6	40	35.4	1.1	39	5.7
	5	44	40.4	38	1.6	38.2	9.5	44.2	40.2	37.6	1.2	38.2	9.6
	6	42.8	40	36.7	1.7	39.3	7.7	43,1	40,4	35.6	1.4	39.1	7.7
	7	43.8	40	27.9	4.6	35.9	7.5	44	41	27.8	3.9	35.7	7.3
	8	41.9	40	33	1.49	34	6.8	42.8	40	32.3	1.2	34	6.7
	9	42,1	40	35.1	3.6	35.2	7.8	43	40	35.1	2.9	34.2	7.5
	10	43	40	33	4.8	36.3	9.6	43	40	31.3	3.8	35.3	9.6
	11	41.8	40	34	4.5	38	7.8	42.8	40	34.6	3.6	38	7.8
	12	42.8	40	36.4	2.2	39	7.6	43.9	40	34.4	1.7	39	7.6
	13	43.8	40	39	3.9	39.6	5.9	44.1	40.4	37.5	2.9	39.1	5.6
	14	43.7	40	34	3.6	39	9.4	44.2	40.4	34.1	2.6	34.2	9.1
	15	42.8	40	38	4.1	38.7	5.8	43.4	40.2	37.2	3.1	38.1	5.7
	16	42.7	40	35.5	3.3	39.2	9	43.8	40.1	34.4	2.8	35.6	8.8
	17	43.2	40	17	1.1	38	6.8	43.9	41	16.6	1	17	1.1
	18	41.5	40	31.9	1.2	37.8	6.6	42.9	40.1	31.5	1	30.1	1.2
	19	43.4	40	31.6	3.8	39	7.1	44.2	41	30.2	2.6	30.6	3.7
	20	43.1	40	27.6	4.6	35.9	8.5	44	40.5	25.8	3.4	27.5	4.5
	21	43	40	35	4.4	39	8.7	43.8	41	34.8	3.5	24.4	4.4
	22	43.1	40	26.9	1.6	36.3	6.1	44.1	40.6	35.9	1	25.6	1.6
	23	43.3	40	38.1	4	37.4	8.9	43.9	40.7	36.7	3.1	35.8	3.4
	24	43.2	40	28.4	4.5	38.4	8.4	44.1	41.3	25.8	3.9	28.4	4.4
	25	43.7	40	32.8	1.3	36	6.4	44.4	40.4	31.5	1	32.1	1.3

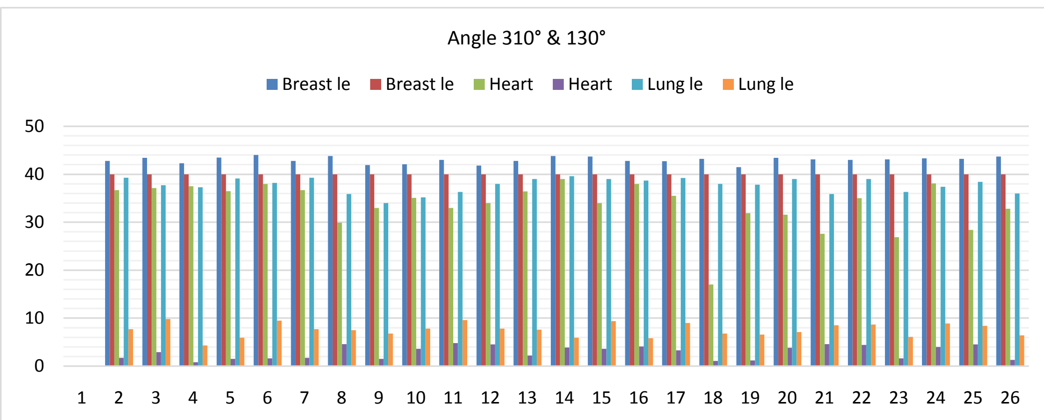


Figure 2. Data for angle 310˚ & 130˚.

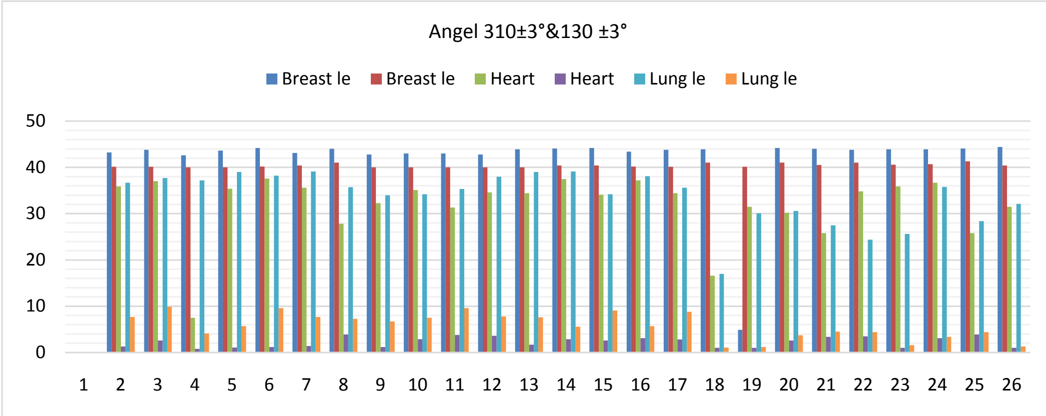


Figure 3. Data for angle 310˚ ± 3˚ & 130˚ ± 3˚.

General discussions: From the experience at our clinic, and many clinics abroad, and as indicated by the data, reducing the irradiation volume of heart and lung in terms of percentage dose from the angled tangential internal and external fields, ($\alpha + \beta = 180˚$), is not only non-negligible but is significant. For every angle change from 1˚ to 3˚, there is a reduction of radiation volume of the integral dose up to 5%. There are objective limitations on the gentry value, limitations conditioned by SSD and the opposite breast. The internal angle, α can be changed between 300˚ to 315˚. If the angle is higher than 315˚, the irradiation beam will penetrate the entire heart and lung structures. If the angle is lower than 300˚, the intended irradiation volume will be irradiated with low radiation dose and the opposing breast will be radiated unnecessarily. We are faced with the similar physical limitations for the β angle. The external beam must be between 120˚ and 135˚, because both the patient's body, especially the arm, and the couch do not allow other angles.

The amount of the heart volume involved into the radiation beam depends from individual anatomical characteristics and is highly variable, however in the majority of cases it is between 7% to 10%; when this volume is multiplied by the mean organ dose, the result is a completely non tolerable integral dose. Choosing a better irradiation geometry can improve the results and offer better heart protection. We follow similar calculations for the lungs but have to consider that we are dealing with a different density compared to that of the heart. Due to the presence of the air inside the lungs sometimes we get the wrong impression that the integral dose is tolerable. This is numerically true, but we should take into account the air inside the lungs which creates heterogeneities and cause secondary radiations which are difficult to quantify. Another reason is that the radiosensitivity of lung tissues is significantly higher than that of heart muscle.

4. Conclusions

This study demonstrated that the method of two opposed tangential fields for breast cancer treatment in linacs is the simplest. Applying this method in daily practice raises the issue of irradiation volumes of organs at risk, left lung and heart, which are relatively high and which require accurate calculations.

We demonstrated that the use of angled beams, internal and external, which create an angle of 180˚, even with a few degrees of convexity, would improve significantly the treatment, reducing the part of heart muscle involved in radiation beams.

The same attention and care must be observed for the lungs on both sides.

It is of paramount importance to calculate the gap between the two adjacent fields, depending on the depth of the volume to be irradiated.

Similar attention must be paid to the adjacent apposed fields to calculate the necessary gap to provide a uniform dose in mid-depth of the gap itself.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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