Evaluation of Fractionation Schemes in Breast Cancer Radiotherapy and Dosimetric Study of the Main Organs at Risk

Dissertation Summary of the MSc Thesis in Radiation Protection and Safety

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ABSTRACT: The purpose of this work was to evaluate the impact of different breast cancer radiotherapy regiments on the acceptance of the tolerance criteria of the main organs at risk, the heart and the ipsilateral lung.

In this context, the dosimetric treatment plans of 20 breast cancer patients treated at the Radiotherapy Service of Braga Hospital were analyzed. The treatment planning system was the XiO (Elekta) and the dosimetric treatment plans were performed using 3D-CRT technique (three-dimensional conformal radiation therapy) and the pencil beam algorithm for photon dose calculation.

Two approaches to estimate the equivalence of different radiotherapy schedules have been proposed, the equivalent dose at 2 Gy per fraction model and the biologically effective dose model. These models showed that the hypofractionation course to 42,56 Gy in 16 daily fractions is clinically equivalent to the conventional radiotherapy course to 50 Gy in 25 daily fractions.

Results showed that the tolerance criteria for the organs at risk, the heart and the ipsilateral lung, referring to the hypofractionation course to 42,56 Gy in 16 daily fractions are more restrictive than the tolerance criteria of conventional radiotherapy. This means that if the same setup and the same dose coverage in the planning target-volume are used, the tolerance criteria for the organs at risk of hypofractionation regiment are more difficult to attain.

These results can assist radiation oncologists in the evaluation of radiotherapy prescription doses for breast cancer, in compliance with the principles of radiation protection.

KEY WORDS
External radiotherapy, breast cancer, fractionation, tolerance criteria, organs at risk, radiation protection

1. INTRODUCTION

Early-stage breast cancer patients can benefit from post lumpectomy radiation therapy. It has been shown that post lumpectomy radiotherapy is associated with a promising long- term local control with the same survival outcomes as mastectomy. The current standard management for breast cancer is to treat the whole breast with photon external beam radiotherapy with a total dose of 50 Gy in a fractional dose of 2 Gy, during five working week days (conventional fractionation). Frequently, an additional 10 to 20 Gy dose has been used to boost the tumor excision site, resulting in an overall treatment time of 5 to 7 weeks [1].

The linear-quadratic model suggests that when the α/β ratio of the tumor is the same or less than that of the critical normal tissue, a larger dose per fraction (hypofractionation) with a modest decrease in total dose may be equally or potentially more effective than conventional fractionation. Results in the literature suggest that the α/β ratio of breast cancer is in the range

of 3-5 Gy [2,3]. It is necessary to recognize that the α/β ratio may vary according to the different biological subtypes of breast cancer. An estimate of 4 Gy for α/β ratio has been already reported for the fractionation sensitivity of breast cancer [4]. The low estimated α/β ratio for breast cancer means that it is probably as sensitive to fraction size as is dose-limiting normal tissue, and hypofractionation for breast cancer may actually be advantageous [4,2]

Retrospective studies of hypofractionated radiotherapy in early breast cancer suggest satisfactory outcomes in tumor control and late adverse effects if modest increases in fraction sizes are combined with appropriate downward adjustments to total dose. The first results of a Canadian randomized trial (ONTARIO trial) testing 42,56 Gy in 16 fractions against 50 Gy in 25 fractions are consistent with these findings [5].

Novel radiation therapy techniques can potentially optimize the protection of organs at risk, however heart and lung doses remain important dosimetric surrogates for long term effects and hence influence clinical decision making in adjuvant radiotherapy for breast cancer. Breast cancer radiotherapy influences surrounding healthy tissues and can lead to persistent edema, hyperpigmentation, fibrosis and pneumonitis and more severe late effect like cardiac toxicity and secondary lung cancer [6,7]. The probability of long-term side effects generally depends on the dose per fraction, time interval between fractions, total radiation dose, irradiated volume, dosimetric parameters, cardiotoxicity of concomitant therapies and patient-specific risk factors [7].

The purpose of this work was to evaluate the impact that different radiotherapy schedules for breast cancer treatment have in the fulfillment of the tolerance criteria of the main organs at risk, the heart and ipsilateral lung. In this context, the dosimetric treatment planning data of left-sided breast cancer patients treated at the Radiotherapy Service of Braga Hospital in 2018 were analyzed and treated.

2. MATERIAL AND METHODS

Patient and treatment planning data were collected from the electronic medical records using MOSAIQ (version 2.41, Elekta AB, Stockholm, Sweden) and the Excel database (Microsoft) of the medical physics sector. Collected information included: total number of treated patients; first radiotherapy treatment vs several treatments; location of the tumor. In particular, for breast cancer patients the sample was distributed according to age group and the fractionation treatment schedules used in radiotherapy treatment.

In order to evaluate the potential clinical outcome of the fractionation treatment schedules, was used the linear-quadratic model based biological effectiveness of a given fractionation scheme size is related to the α/β ratio and may be expressed in terms of the biologically effective dose (BED) [3]:

$$BED = D\left(1 + \frac{d}{\alpha/\beta}\right) - K(T - T_d) \qquad (equation\ 1)$$

where D is the total dose delivered during the treatment (expressed in Gy), obtained by multiplying the total number of treatment fractions (n) by the dose per fraction (d); α and β are the radiosensivity coefficients of the linear-quadratic model, expressed in Gy^{-1} e Gy^{-2}, respectively.

This equation also accounts for the repopulation effect correction. This correction must be taken into account for post-operative breast tumors treated with radiotherapy because surgical

resection can leave behind a handful of viable cells which, because they are well vascularized, are capable of rapid growth [4].

As such T is the overall treatment time; T_d is the delay time to onset of accelerated repopulation. An effective doubling time T_{eff} of 26 days to start immediately after surgery is taken from the literature [4,8] and T_d is considered as zero. K (expressed in Gy/day) is the biological dose per day required to compensate for ongoing tumor cell repopulation, calculated based on T_{pot} (potential doubling time) and α (radiosensitivity coefficient):

$K = \frac{ln2}{\alpha\, T_{pot}}$. From the literature T_{pot}=14 days and α=0.08 [9].

BED can be used to equate or compare different fractionation schedules.

A more practical alternative for the clinical oncologist is to convert the BED values to equivalent total doses delivered in 2 Gy fractions, which can then be interpreted according to clinical experience. The 2 Gy equivalent total dose (EQD_2) is given by [3]:

$$EQD_2 = D_1 \frac{{}^{\alpha}/_{\beta} + d_1}{{}^{\alpha}/_{\beta} + d_2} \qquad (equation\ 2)$$

In the other part of this study, 20 female patients treated with adjuvant radiotherapy for left-sided breast cancer were randomly selected from database. This left-sided breast cancer selection was due to the fact that this treatment contributes to higher radiation doses to the heart.

Of these 20 patients, 10 were treated with a conventional radiotherapy course to 50 Gy in 25 daily fractions, and the other 10 patients were treated with a hypofractionation course to 42,56 Gy in 16 daily fractions.

All patients performed a CT scan in the supine position using immobilization support, with both arms above the head.

The delimitation of target-volumes and organs at risk was performed by clinical radiation oncologists using the Eclipse Contouring tool (version 15.5, Varian Medical System). The considered target-volumes were breast CTV (clinical target-volume) and PTV (planning target volume) (PTV = breast CTV + external margin of 5 to 10 mm, excluding a margin of 5 mm from the skin surface). The considered organs at risk were the heart and the ipsilateral lung.

The treatment planning system was the XiO (version 4.62, Elekta AB, Stockholm, Sweden) and the dosimetric treatment plans were performed using: photon energy of 6 MV; 3D-CRT technique (three-dimensional conformal radiation therapy); pencil beam algorithm for photon dose calculation; and Varian 6EX linear accelerator with multileaf collimator.

In order to evaluate the 3D dose distributions and the dose-volume histograms of the organs at risk, the parameters shown in table 1 were used. These criteria vary according to the type of fractionation regiment used in the radiotherapy treatment.

Table 1. Tolerance criteria [10,11,12]

ORGANS AT RISK	TOLERANCE CRITERIA	
	Conventional Fractionation 50 Gy/25 fractions	**Hypofractionation 42,56 Gy/16 fractions**
Heart	$V_{25Gy} \leq 10\%$ Mean Dose ≤ 5 Gy	$V_{16Gy} \leq 5\%$ Mean Dose ≤ 3,2 Gy
Ipsilateral Lung	$V_{20Gy} \leq 20\%$	$V_{12Gy} \leq 17\%$ $V_{16Gy} \leq 15\%$

After the dosimetric evaluation of the patients' original treatment plans, these plans were converted to the opposite fractionation scheme, that is, plans with a prescribed dose of 50 Gy in 25 fractions were converted to a plan with a prescribed dose of 42,56 Gy in 16 fractions, while plans with a prescribed dose of 42,56 Gy in 16 fractions were converted to a plan with a prescribed dose of 50 Gy in 25 fractions. These new treatment plans are called rescale plans and were not used in the treatment of patients, they only served to perform the dosimetric evaluation using the parameters and tolerance criteria shown in table 1.

The conversion of treatment plans was carried out using the Rescale tool from the XiO planning system, which makes a direct conversion of the doses of the two treatment prescriptions using the same configuration of the treatment fields.

3. RESULTS AND DISCUSSION

A total of 1689 patients were treated at the Radiotherapy Service of Braga Hospital in 2018, 733 female (43.4%) and 956 male (56.6%). 88% of patients (corresponding to 1489) performed radiotherapy for the first time, while 12% (corresponding to 200) were a several radiotherapy treatment.

Main tumors treated are summarized in figures 1, 2 and 3 for both sexes, for males and females, respectively.

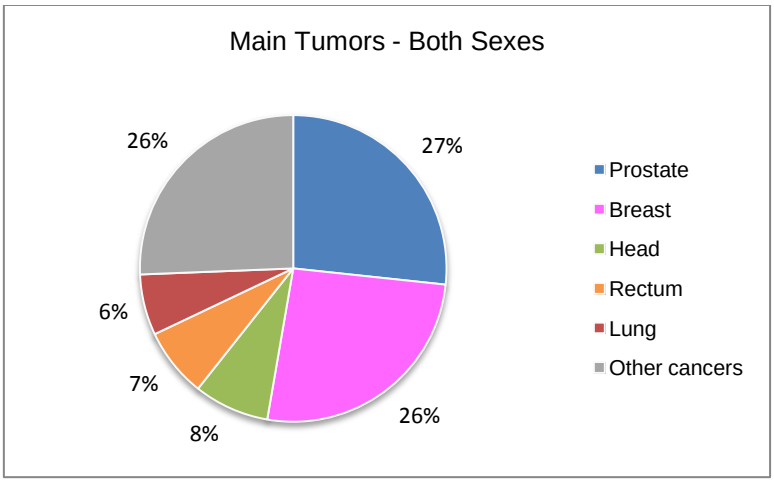

Figure 1. Number of new cases and tumor location for both sexes

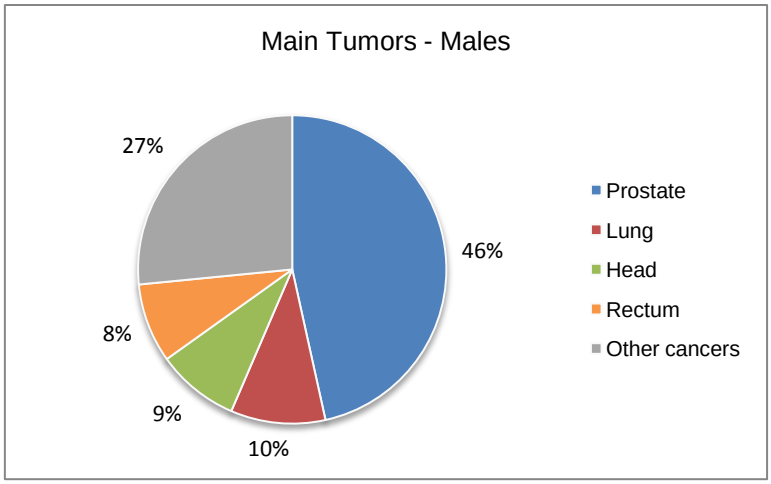

Figure 2. Number of new cases and tumor location for males

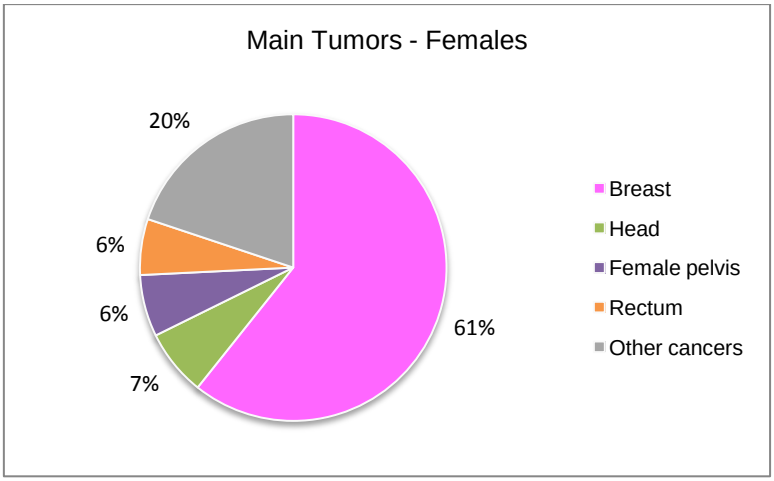

Figure 3. Number of new cases and tumor location for females

A total of 393 patients treated with breast radiotherapy, 391 females (99.5%) and 2 males (0.5%). Of these, 207 patients treated the left-sided breast (52.7%), 183 the right-sided breast (46.6%) and 3 both breasts simultaneously (0.7%). Median age at time of radiotherapy was 59 years (range: 28–96).

Patients belonging to the age group 45-54 years are those who have a greater representation in the sample (29%). Next are the patients belonging to the age group 55-64 years and 65-74 years, respectively, where each group represents 22% of the sample. The age group 18-34 years is the one with the lowest representation in the sample (2%).

The most frequent fractionation schemes were the conventional fractionation course to 50 Gy in 25 daily fractions (n = 232) and the hypofractionation course to 42.56 Gy in 16 daily fractions (n = 139). The conventional fractionation has an average radiotherapy time of 33 days, while the hypofractionation course has an average duration of 22 days. The reduction in radiotherapy time could allow for an increased in installed capacity and, consequently, expand the access, reducing costs.

In Table 2, BED calculation are shown for either breast cancer or normal tissues (fibrosis and erythema), for both conventional and hypofractionation schemes. The BED calculation for breast tumor shown in the first column includes the appropriate correction for repopulation. For the normal tissues no correction for repopulation was assessed.

Table 2. BED calculations

Fractionations Schemes	BED (Gy) Tumor control α/β = 4 Gy	BED (Gy) Late Fibrosis α/β = 2,5 Gy	BED (Gy) Erythema α/β = 8 Gy
Conventional 50 Gy/25 fractions	54,6	90	62,5
Hypofractionation 42,56 Gy/16 fractions	57,3	87,8	56,7

The value of the α/β ratio used for tumor control was 4 Gy. Analyzing the results for BED values of the tumor control, it is possible to verify that the BED value for the hypofractionation scheme is 57,3 Gy, which is slightly higher than the BED value for the conventional fractionation scheme, which is 54,6 Gy. According to this calculation, the BED value for the hypofractionated scheme favors increased tumor control.

According to the literature, breast fibrosis (late effect) is associated with an α/β ratio of 2,5 Gy, while erythema (acute effect) is associated with an α/β ratio of 8 Gy [8]. The obtained results show that the BED values calculated for normal tissues using the hypofractionated treatment scheme are lower than the values obtained in the conventional treatment scheme. These results favor the use of hypofractionated scheme, as it causes less side effects to healthy breast tissues.

The results presented in table 2 are in agreement with the results presented by the Canadian study by Whelan TJ et al. (ONTARIO trial) [5], both with regard to tumor control and the expected effects on healthy breast tissues. Results of this trial demonstrate that a shorter fractionation schedule of 42,5 Gy in 16 fractions over 22 days is as effective as the more traditional schedule of 50 Gy in 25 fractions over 33 days in terms of preventing recurrence of breast cancer. The rates of local recurrence at 5 years were low and similar in both treatment arms. Regarding normal tissues, the results of the Canadian study demonstrated that the incidence of late radiation toxicity on skin and subcutaneous tissue was uncommon in both treatment regimes, although patients treated with hypofractionation radiotherapy fared about 5% better. Given that most of the toxic effects of radiation therapy would be expected by 5 years, further differences between groups in skin and subcutaneous tissue toxicity are unlikely to occur with longer follow-up.

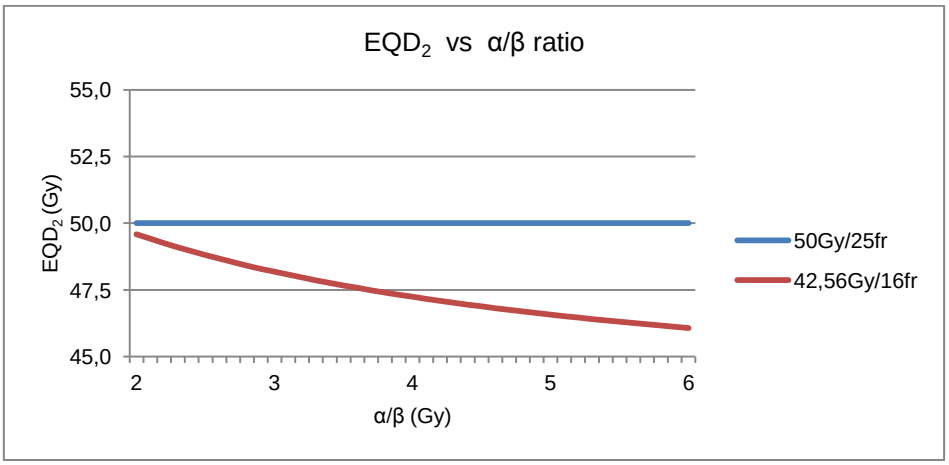

Figure 4. EQD_2 values as a function of the α/β ratio

In figure 4, EQD_2 calculation are shown for both conventional and hypofractionation schemes.

The calculation of the dose equivalent to 2 Gy per fraction allows for the estimation of the equivalence of the two fractionation schemes used in radiotherapy treatments.

According to the results presented in figure 4, it is possible to verify that the lower the value of the α/β ratio, more equivalent are the two fractionation schemes. That is, for an α/β = 2 Gy, the EQD_2 value of the hypofractionation scheme is 49,6 Gy, this value being the closest to the 50 Gy value, corresponding to the conventional fractionation scheme.

Based on this information and according to the results presented, it can be concluded that the hypofractionation course to 42,56 Gy in 16 fractions is a good candidate for the treatment of breast cancer, as this tumor has low α/β ratio values in relation to other types of tumors, where the typical value is around 10 Gy. For this reason, for the values of the α/β ratio presented, the EQD_2 curve of the hypofractioned scheme approaches the curve of the conventional treatment scheme, which indicates that the two treatment schemes are clinically equivalent.

Results obtained in the dosimetric analysis of the treatment plans are shown in tables 3 and 4.

Starting by analyzing the results presented in table 3, it is possible to observe that for all original treatment plans with a conventional fractionation regiment, all dosimetric parameters evaluated meet the tolerance criteria of the respective organs at risk.

The same is not verified when these plans were converted to a 42,56 Gy hypofractionation scheme in 16 fractions. In this case, several dosimetric parameters exceed the tolerance criteria. For the heart, 60% of the sample does not meet the criteria (plans 1, 3, 5, 6, 9 and 10), and for the lung, 40% of the sample does not meet the criteria (plans 1, 4, 8 and 9).

Regarding the results presented in table 4, it is possible to observe that, with the exception of plan 13, all the other original treatment plans composed of a hypofractionation scheme of 42,56 Gy in 16 fractions, fulfill all the tolerance criteria. In the case of plan 13, the dosimetric parameter for the lung exceeds the tolerance criteria, that is, V_{12Gy} = 17,7% and V_{16Gy} = 15,6%.

When converting the original plans shown in table 4 to a conventional 50 Gy fractionation scheme in 25 fractions, all dosimetric parameters for both heart and ipsilateral lung meet the respective criteria.

Obtained results showed that the tolerance criteria for the organs at risk, the heart and the ipsilateral lung, referring to the hypofractionation course to 42,56 Gy in 16 daily fractions, are more restrictive than the tolerance criteria of conventional radiotherapy. This means that if the same setup and the same dose coverage in the planning target-volume are used, the tolerance criteria for the organs at risk of hypofractionation regiment are more difficult to attain.

Table 3. Results of the dosimetric evaluation. The original treatment plans has a prescribed dose of 50 Gy in 25 fractions and the rescale plans has a prescribed dose of 42,56 Gy in 16 fractions.

Plan ID	Heart				Ipsilateral Lung		
	Original Treatment Plan **50 Gy/25 fractions**		Rescale Plan **42,56 Gy/16 fractions**		Original Treatment Plan **50 Gy/25 fractions**	Rescale Plan **42,56 Gy/16 fractions**	
	$V_{25Gy} \leq 10\%$	**$D_{mean} \leq 5Gy$**	**$V_{16Gy} \leq 5\%$**	**$D_{mean} \leq 3{,}2Gy$**	**$V_{20Gy} \leq 20\%$**	**$V_{12Gy} \leq 17\%$**	**$V_{16Gy} \leq 15\%$**
1	7,1	5,0	8,2	4,3	16,8	19,1	17,2
2	2,5	2,4	3,2	2,0	12,3	14,7	12,8
3	5,3	4,2	6,3	3,6	15,0	17,0	15,0
4	0,6	1,7	0,9	1,5	16,8	19,6	17,3
5	4,9	4,1	6,0	3,5	8,6	10,4	8,9
6	7,4	4,9	9,1	4,2	13,2	15,7	13,7
7	3,0	3,3	3,8	2,8	8,2	9,9	8,4
8	3,1	3,1	4,0	2,6	20,0	22,9	20,7
9	5,5	4,3	6,8	3,6	17,4	19,9	17,8
10	5,4	4,2	6,4	3,6	10,0	11,3	10,2

Table 4. Results of the dosimetric evaluation. The original treatment plans has a prescribed dose of 42,56 Gy in 16 fractions and the rescale plans has a prescribed dose of 50 Gy in 25 fractions.

Plan ID	Heart				Ipsilateral Lung		
	Original Treatment Plan **42,56 Gy/16 fractions**		Rescale Plan **50 Gy/25 fractions**		Original Treatment Plan **42,56 Gy/16 fractions**		Rescale Plan **50 Gy/25 fractions**
	$V_{16Gy} \leq 5\%$	**$D_{mean} \leq 3{,}2Gy$**	**$V_{25Gy} \leq 10\%$**	**$D_{mean} \leq 5Gy$**	**$V_{12Gy} \leq 17\%$**	**$V_{16Gy} \leq 15\%$**	**$V_{20Gy} \leq 20\%$**
11	4,1	2,5	3,3	2,9	16,6	14,6	14,2
12	4,9	3,1	4,0	3,6	12,8	11,3	10,9
13	1,8	1,5	1,1	1,8	17,7	15,6	15,1
14	5,0	2,8	3,9	3,3	17,0	15,0	14,8
15	4,9	2,8	3,8	3,3	13,8	11,6	11,0
16	0,9	1,3	0,5	1,6	14,4	12,5	12,1
17	2,8	2,0	2,3	2,3	15,1	13,2	12,8
18	3,8	2,2	3,1	2,6	11,1	9,8	9,5
19	4,9	2,7	4,1	3,2	15,5	13,9	13,6
20	4,4	2,8	3,6	3,3	11,4	10,4	10,2

4. CONCLUSIONS

Breast cancer is the second most common cancer worldwide, and the tumor that has the highest incidence in women.

In this work it was possible to verify that in the study sample, referring to patients who performed radiotherapy treatment at Braga Hospital in 2018, breast cancer was the one that had a higher prevalence in female patients, representing 61% of all the cases. Patients aged 45-54 years were those who had a greater representation in the sample (29%).

According to the results, 60% of the radiotherapy treatment plans were carried out with a conventional fractionation course to 50 Gy in 25 fractions, while the remaining 40% were carried out with a hypofractionation scheme, the most used being 42,56 Gy in 16 fractions.

The low value of the α/β ratio for breast cancer, currently estimated at 4 Gy, means that probably the tumor tissue is as sensitive to the dose delivered per fraction as the normal tissue that limits the dose, which indicates that hypofractionation can be advantageous in breast cancer radiotherapy treatments.

Comparing the conventional fractionation course to 50 Gy in 25 fractions with the hypofractionation course to 42,56 Gy in 16 fractions, by calculating the BED and EQD_2 it was possible to verify that the two regimens are clinically equivalent, with hypofractionation increasing tumor control, providing less late toxicity.

Another advantage of using hypofractionation radiotherapy is related to the fact that these treatments have a shorter duration, which allows to treat a larger number of patients, improve their quality of life as they finish treatment faster and still reduce the associated costs.

With regard to the dosimetric study performed, dosimetric parameters commonly used in clinical practice were analyzed, which play a role as clinical predictors of toxicity to the organs at risk.

Through the obtained results it was possible to conclude that the tolerance criteria, for the heart and the lung, referring to the hypofractionation course to 42,56 Gy in 16 fractions are more restrictive than the tolerance criteria of the conventional radiotherapy. That is, when the plans treated with the conventional scheme were converted to the hypofractionation scheme, 60% of the sample does not meet the tolerance criteria for heart, while 40% does not meet the tolerance criteria for lung. This result means that using the same setup and obtaining the same dose coverage in the planning target-volume, the tolerance criteria for the organs at risk of hypofractionation regiment are more difficult to accomplish.

The dosimetric study was carried out on the treatment plans for single left-sided breast, since this treatment contributes to higher doses in the heart compared to right-sided breast treatments. However, when we evaluate breast treatment plans where it is also necessary to irradiate the axillary region, the supraclavicular region or the internal mammary chain, the doses received, namely by the lung, increase considerably. Thus, in these treatment plans it is more difficult to meet the tolerance criteria of the organs at risk for hypofractionation regiments.

These results can assist radiation oncologists in the evaluation of radiotherapy prescription doses for breast cancer, in compliance with the principles of radiation protection.

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