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Incidental axillary irradiation during three-dimensional conformal radiotherapy for breast cancer: which factors can influence this coverage?

Irradiação axilar incidental durante radioterapia conformada tridimensional para câncer de mama: quais fatores podem influenciar essa cobertura?

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ABSTRACT

Objective: To evaluate the percentage of I and II axillary levels receiving 45 Gy during adjuvant radiotherapy for breast cancer and correlate it with anatomical and planning variables. **Methods:** A retrospective study of 51 patients with breast cancer who received adjuvant external radiotherapy in breast or breast bed with tridimensional conformal technique during January 2008 to July 2013. Axillary levels were contoured according to the breast cancer atlas of Radiation Therapy Oncology Group (RTOG). The percentage of each axillary level that received 45 Gy (V45) was reviewed using the dose volume histogram (DVH). This was correlated with the surgery performed, the Clinical Target Volume (CTV), axillary volume, anteroposterior (APD) and laterolateral diameters (LLD) of chest, body mass index (BMI), gantry's angle, distance between the input and output (DIO) of the radiation beam in chest, and patient position (ramp incline, height and angle of the arm). **Results:** The average V45 for level I and II was 44% (0 to 97.2%) and 17.7% (0 to 93.6%). The average dose in 95% of level I was 11.2 Gy (0.14-46.4 Gy) and 5 Gy (0.13-44.4 Gy) in level II. Variables with significant correlation to V45 of level I were the ramp incline (p<0.001) and DIO (p<0.019) and the ramp incline with level II V45(p= 0.004) in multiple univariate analysis. Ramp incline, DIO and LLD correlate with V45 of level I in multivariate analysis (p= 0.012, p= 0.007, p= 0.012, respectively). Patients with BMI>25 received higher doses in level I (p=0.026). **Conclusion:** Axillary coverage with 45 Gy during adjuvant breast irradiation is not adequate but appear to increase with a larger ramp incline and bigger DIO. Dose in Level I increases whith BMI>25 although remains unsatisfactory.

Headings: Radiotherapy; Lymphatic irradiation; Breast neoplasms; Radiotherapy dosage.

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RESUMO

Objetivo: Avaliar a porcentagem dos níveis axilares I e II que receberam 45 Gy durante a radioterapia adjuvante para câncer de mama e correlacioná-la com variáveis anatômicas e de planejamento. **Métodos:** Estudo retrospectivo de 51 pacientes com câncer de mama que receberam radioterapia externa adjuvante na mama ou leito mamário com técnica conformada tridimensional entre janeiro de 2008 e julho de 2013. Os níveis axilares foram contornados de acordo com o atlas de câncer de mama do *Radiation Therapy Oncology Group* (RTOG). A porcentagem de cada nível axilar que recebeu 45 Gy (V45) foi revisada usando o histograma dose-volume (DVH). Isso foi correlacionado com a cirurgia realizada, o volume clínico alvo (CTV), volume axilar, diâmetros anteroposterior (APD) e laterolateral (LLD) do tórax, índice de massa corporal (BMI), ângulo do pórtico, distância entre a entrada e a saída (DIO) do feixe de radiação no peito e posição do paciente (inclinação da rampa, altura e ângulo do braço). **Resultados:** O V45 médio para os níveis I e II foi de 44% (0 a 97,2%) e 17,7% (0 a 93,6%). A dose média em 95% do nível I foi de 11,2 Gy (0,14-46,4 Gy) e 5 Gy (0,13-44,4 Gy) no nível II. As variáveis com correlação significativa com o V45 do nível I foram a inclinação da rampa (p <0,001) e DIO (p <0,019) e a inclinação da rampa com o V45 do nível II (p = 0,004) na análise univariada múltipla. Inclinação da rampa, DIO e LLD correlacionam-se com o V45 do nível I na análise multivariada (p = 0,012, p = 0,007, p = 0,012, respectivamente). Pacientes com IMC> 25 receberam doses mais elevadas no nível I (p = 0,026). **Conclusão:** A cobertura axilar com 45 Gy durante a irradiação adjuvante da mama não é adequada, mas parece aumentar com uma maior inclinação da rampa e maior DIO. A dose no nível I aumenta com IMC> 25, embora permaneça insatisfatória.

Descritores: Radioterapia; Irradiação linfática; Neoplasias da mama; Dosagem de radioterapia.

INTRODUCTION

The interest in verifying incidental irradiation to axillary lymph nodes with tangent fields for breast occurred since the introduction of the sentinel lymph node biopsy at the end of 90's.[1] Several studies evaluated the addition of surgical clips corresponding to axillary lymph nodes in breast radiation fields.[2-5] Krasin et al. (2000) were the first to review this issue in a dosimetric way. They noted that one patient had adequate coverage of axillary level I. In contrast, levels II and III, and internal mammary chain lacked adequate dose for treatment.[6] By that time, in a prospective study, a mean dose of only 6.75 Gy at level I and 1.75 Gy at level II was verified through three-dimensional planning.[7] Reed et al. (2005) later described that the 95% isodose line covered 55% of the levels I and II.[8] Thereafter several studies have tried to improve this coverage using high tangent fields and modified plans with satisfactory results.[5,9-12] When comparing different techniques they found a lesser dose in axilla using Intensity Modulated Radiation Therapy (IMRT).[13,14]

After the publication of ACOSOG Z0011 some hypotheses were developed in an attempt to explain the low regional recurrence in patients with positive sentinel node and no further axillary treatment.[15-16] That include tumors in early stage, adjuvant chemotherapy and hormone therapy, and axillary lymph nodes incidental irradiation.[16] Unfortunately these came down after the publication of a posterior data which evaluated radiation fields used in Z0011 trial. It showed direct lymph node irradiation to supraclavicular fossa, and the use of high tangential fields in a half of analyzed patients.[17] Opposing views argue that even using high tangent fields such nodes would not be adequately treated.[18] Few years after, Donker et al. (2014) trial showed that nodal irradiation and axillary node dissection produce comparable axillary control for patients with tumors ≤ 5cm and positive sentinel node.[19]

The updates of MA 20 and EORTC 22922 trials recently published showed locorregional control benefit with adjuvant radiotherapy to axilla, supraclavicular fossa and internal mammary in patients with early stage breast cancer and 1-3 positive axillary nodes.[20,21]

Due to the extreme relevance and controversy of lymph nodes irradiation in breast cancer, we decided to evaluate the axillary volume receiving 45 Gy during adjuvant radiotherapy for breast cancer in our population and the influence of anatomic or planning variables related to it.

METHODS

This is a retrospective study which include all patients that underwent breast adjuvant radiotherapy with three-dimensional conformal technique in our institution during the period of January 2008 to July 2013. We exclude those who had axillary or supraclavicular fossa irradiation, T4b tumors, patients treated without standard immobilization or high tangent fields. Delivered dose to breast or chest wall were 50.4 Gy in 1.8 Gy daily fractions, 5 days per week, by 6MV Linac. We used Eclipse™ Treatment Planning System (Varian-Palo Alto) with pencil beam algorithm for contouring and planning. The chosen treatment plan was the one with the best coverage, of Clinical Target Volume (CTV), at least 95% of CTV receiving 95% of treatment dose (D95=95%), delineated according to Radiation Therapy Oncology Group (RTOG) atlas[22] and that respected normal tissue constrains (Table 1). The dose gradient should be between 95% and 107% of the prescribed dose.

Axillary levels I and II were contoured posteriorly treatment using appropriated software in the simulation computed tomography (CT), also according to RTOG breast cancer atlas by a radiation oncology resident and supervised by two staffs. Then the percentage volume of each level that received 45 Gy (V45) was analyzed as the dose delivered to 95% (D95) of axillary volume. Boost was not considered for these analyses because of the short sample. We collected information about tumor (stage and histology), patient (age, weight, height), position during the radiotherapy (ramp incline, height and angle of the arm) and previous treatment (surgery performed) in patient records. CTV and axillary levels' volume, anteroposterior diameter (APD) and laterolateral diameter (LLD) of patient's chest, gantry angulation, distance between the input and output (DIO) of the radiation beam in the chest were obtained from the planning software. The staging system used was AJCC 2007. All patients used a ramp for immobilization with the ipsilateral arm to the committed breast abducted as much as tolerable and flexed 90 degrees. The LLD and APD were measured in the largest diameter of the chest in axial plan and DIO in the axial slice of isocenter. We also measured the amount of lung inside the field (perpendicular line between the field border and thoracic wall in axial slice).

The project was approved by Research Ethic Committee (number 623.105) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis

We correlated all the variables with V45 of axillary levels I and II using Pearson correlation for numerical variables and the Mann-Whitney test for categorical variables and then we performed multivariate analysis (Pillai Screening, Wilks Lambda, Hotelling Screening, Roy's Largest Root Test). We used t-test to compare axillary dose of each levels between different groups of Body Mass Index (BMI<25 and BMI≥25) as the WHO classification for normal versus overweight/obese[24] using univariate analysis. Significance was established when *p*<0.05.

Table 1. Normal tissue constrains.

Organs at risk	Volume (%)	Dose (Gy)
Lungs	< 20	20
Heart	< 10	25
Esophagus	< 50	35
Spinal cord	punctual	45

Institutional constraints based on QUANTEC. (Marks LB, Yorke ED, Jackson A et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010 Mar 1;73: S10-9)[23].

RESULTS

During the period analyzed, 365 patients had undergone adjuvant radiotherapy for breast cancer at our institution. Sixty-nine were treated with 3D-CRT. Of them, 17 were excluded by drainage irradiation and one for utilizing another immobilization device. Fifty-one patients were included.

Patients, tumor and planning characteristics are presented in Tables 2, 3 and 4.

Lumpectomy was done in 96% and modified radical mastectomy in 4%. Most of the patients (53%) were submitted to sentinel node biopsy with a median of two nodes dissected. Sixteen (31.4%) had axillary dissection (average of 11 nodes) and eight (15.6%) had intact axilla by the time of adjuvant radiotherapy.

The median CTV volume was 602cm³ (166.4-1228.3cm³), median axillary level I volume was 42cm³ (15.2-91.4cm³) and 18cm³ (8.3-34.6cm³) for level II. The average axillary volume was 52, 60 and 70cm³ for patients with axillary dissection, sentinel node biopsy and intact axilla respectively. Twenty-nine (57%) patients were overweight (BMI≥25), twelve had normal BMI (BMI<25) and 10 were obese (BMI>30). The median axillary volume in these groups was 61.6, 49.3 and 70.2cm³, respectively. V45 for level I was in average 44% (0 to 97%) and for level II was 17.7% (0 to 93.6%).

The median D95 of axillary level I was 11.2 Gy (0.14-46.4 Gy) and level II was 5 Gy (0.13-44.4 Gy).

Arm's angle was -20 degrees in 84% of the cases. Median lung inside the radiation field was 2.3cm (0.9-4.0cm).

Statistical results are shown in Tables 5, 6, 7 and 8. We could see a significant relation between ramp incline and levels I and II V45 ($p<0.001$ and $p=0.004$), and also between DIO and level I V45 ($p=0.02$) in univariate analysis. In multivariate analysis DIO, ramp incline and LLD had significant correlation ($p=0.036$, $p=0.045$ and $p=0.007$, respectively) with level I. Level I V45 increased in patients with BMI≥25 ($p=0.026$) in univariate analysis.

Table 2. Patients' characteristics.

Variable	Median	Variation
Age	56 y	33 – 81 y
Weight	67 kg	45 – 100 kg
Height	158 cm	141 – 170 cm
BMI	27	17 - 38
APD	22 cm	18 – 26 cm
LLD	33 cm	29 – 39 cm

Table 3. Tumors' characteristics.

Histopathology	N	%
Invasive Ductal Carcinoma	38	74.5
Ductal Carcinoma In Situ	9	17.6
Invasive Lobular Carcinoma	2	3.9
Mucinous Carcinoma	1	2
Tubular Carcinoma	1	2
Breast side		
Right	29	57
Left	22	43
Stage		
0	9	17.7
IA	20	39.2
IIA	12	23.5
IIB	5	9.8
IIIA	2	3.9
IIIB	1	2
Relapse	2	3.9

Table 4. Planning characteristics.

Variable	Median	Variation
Ramp incline	25 degrees	18-35 degrees
Arm's height	3	1 - 6
DIO	22 cm	17-26 cm

Table 5. Correlation (Pearson) between numeric variables and level I and II V45.

	N	Median	V45 level I Univariate *p*	V45 Level I Multivariate *p*	V45 level II Univariate *p*	V45 Level II Multivariate *p*
APD	51	22cm	0.169 *p*=0.24	0.239 *p*=0.628	0.084 *p*=0.6	1.279 *p*=0.265
LLD	51	33cm	-0,076 *p*=0.59	8.245* *p*=0.007	-0,011 *p*=0.94	2.546 *p*=0.119
Ramp incline	51	20cm	.551* *p*<0.001	6.934* *p*=0.012	0.4* *p*=0.004	1.667 *p*=0.205
Level I Volume	51	42cm³	0.133 *p*=0.35	1.151 *p*=0.290	0.146 *p*=0.3	0.255 *p*=0.616
Level II Volume	51	18cm³	0.082 *p*=0.56	1.160 *p*=0.288	0.216 (NS) *p*=0.13	0.045 *p*=0.834
CTV Volume	51	602cm³	0.171 *p*=0.23	0.365 *p*=0.549	0.179 *p*=0.2	0.087 *p*=0.770
DIO	51	22cm	.326* *p*=0.02	6.922* *p*=0.012	0.240 *p*=0.09	3.974 *p*=0.053
Lung	51	2,3cm	0.058 *p*=0.7	4.027 *p*=0.052	-0.090 *p*=0.53	3.315 *p*=0.077

* significant correlation at 0.05

Table 6. Correlation between surgery and level I and II V45.

		Lumpectomy	Mastectomy	Mann-Whitney test (p)
		N = 42	N = 9	
	Mean	43.2	48.3	
level I V45	Median	42.9	46.7	0.67
	Standard deviation	25.2	31.8	
	Mean	17.5	18.4	
level II V45	Median	4.3	7.1	0.78
	Standard deviation	26.1	29.9	

Table 7. Correlation between BMI and levels I and II V45.

BMI	Level I V45 median (variation)	p	Level II V45 median (variation)	p
BMI>25 (n=39)	48% (0-97)	0.09	20% (0-94)	0.25
IBMI<25 (n=12)	33% (8-62)		15% (8-23)	

Table 8. Correlation between BMI and levels I and II D95.

BMI	Level I V45 median	p	Level II V45 median	p
BMI>25 (n= 39)	13.44%	0.026*	5,74%	0.36
IBMI<25 (n= 12)	3.78%		2.75%	

* p<0.05.

DISCUSSION

In the present study, we analyzed the volume of axillary level I and II who received 45 Gy incidentally during adjuvant breast cancer radiotherapy.

The average axillary volume in our study was 42cm³ for level I and 18cm³ for level II. Krasin et al. (2000) obtained similar results with an average of 50cm³ for level I and 23cm³ for level II.[6] Another study showed an average of 68cm³ for level I and 25cm³ for level II.[13] RTOG atlas was not used by these authors as a guide, what may have led to discrepancies in the axillary volume. We also observed a volume variation according to axillary surgical approach and BMI. Patient with intact axilla and BMI above 30 had higher axillary volume.

Most studies evaluating incidental axillary dose concluded that the dose delivered to the levels I and II during adjuvant radiotherapy was not therapeutic.[6-11,21] In the present study an average of 44% of level I volume and 17% of level II received 45 Gy. Krasin et al. (2000) reported that 95% of the prescribed dose covered 50% of axillary volume[6] and others reported 55%.[8]

In comparison with another data of patients treated in prone position only 13% of level I and 0% of levels II and III received 45 Gy.[25] Other one compared axillary dose between patients in prone and supine position noting that 90% of the prescribed dose reach 21% and 50% of level I volume, respectively.[26]

In relation to axillary coverage, our results showed a large individual variation. Seven (14%) patients in this study received 45 Gy over 80% of the level I axillary volume, including one with adequate coverage (V45=97%). Likewise, this occurred in four patients for level II. When evaluating individual factors and those related to treatment that could be associated with higher axillary coverage, we found that the DIO, ramp incline and LLD had significant correlation. Such findings have not been previously described in the literature. When trying to establish a cut-off for the first two variables over which more than 50% of each level volume receives 45 Gy using the ROC curve, the value that came over to DIO was 21.9cm with a relative risk 5.9, and 21.5 degrees for ramp incline. However, they were not good predictors (sensitivity of 0.75 and specificity 0.64 for DIO and 0.75 and 0.710 for ramp incline, respectively).

Another important finding was that patients with BMI>25 received significant higher dose at level I in our study (p=0.026). Similar data conducted at MD Anderson Cancer Center with patients in prone position showed similar correlation. Obese patients received higher dose at level I.[26] Although, this dose remained sub-therapeutic. Another study also attempted to correlate treatment variables (gantry's angle, field's size, collimator's angle) with incidental axillary dose but had negative outcome.[7] Russo et al. (2011) showed an increase in axillary dose in patients with bilateral expanders.[27] This could be explained by a lower gantry angulation to save the contra- lateral breast and could be associated with an increased DIO, which correlated significantly with V45 in our study. Dully to the absence of a significant gantry's angles variation between our patients, this could not be correlate with axillary coverage. Also the small number of mastectomy (17.6%) interfere in the evaluation between surgery procedure and axillary coverage.

Another factor that could also be related to increase axillary coverage would be the CTV volume. Russo et al. (2011) reported that this coverage increases with the expander's volume in patients with bilateral reconstruction.[27] But, we found no correlation between CTV volume and the V45.

In general, we observed that the anteroinferior region of level I was covered by 45 Gy isodose line. The same occurred with the level II in most cases. We cannot say that this region corresponds to sentinel lymph node area in our study because of the lack of identification. Belkacemi et al. (2014) described clips corresponding to sentinel lymph node area exactly at this location.[10] According to what was shown by Rabinovitch et al. (2008), the sentinel node was at the level of the fourth thoracic vertebral body and below the clavicle, near the *m. latissimus dorsi*.[3]

Regarding dose in axilla, we observed that 95% of level I received an average dose of 11.2 Gy and level II 5 Gy. Others showed that 95% of axillary levels I, II and III received 66, 44 and 31% of the prescribed dose,[9] which are much higher than ours. In other way, lower doses were also observed as 5 to 6.75 Gy for level I and 1 to 1.75 Gy for level II.[7,10] Our small sample may have impacted a more detailed analysis of the variables. The fact it is a retrospective study did not impact the results in our opinion because the variables were well documented. Maybe in a prospective study professionals involved in the planning could represent a bias.

Speculating why DIO, LLD and BMI had a positive correlation with V45, we think that chest anatomy and volume has an import role in this effect. 84.6% of patients with overweight or obesity had DIO≥21 in comparison to 25% of patients with normal BMI. Also 88.5% and 92.6% of patients with LLD and APD over the median (33cm and 22cm, respectively) had DIO≥21.

Although we did not find correlation with CTV volume and V45 in multivariate analysis, 91.6% of patients with CTV volume over the median (602cm^3) had DIO≥21. Therefore, we think that DIO has a better correlation with chest format and volume than the others variables isolated. Assuming that axilla is in posterior position in comparison to breast the inclusion of this region in the field will depend on patient anatomy. Ramp incline also depends of patients' chest format. Patients which a thinner chest will need higher inclination.

We conclude that less than a half of level I axillary volume receives therapeutic dose incidentally during adjuvant radiotherapy for breast cancer using 3DCRT. Considering whole axilla, low dose is delivered during treatment. Ramp incline, DIO and LLD had a positive correlation with V45 of level I in multivariate analysis, as BMI also had with level I. Even with individual variations, in the majority of cases, the radiation dose is not therapeutic.

AUTHOR'S CONTRIBUTION

Lícia Moreira Medeiros Araújo: Collection and assembly of data, Data analysis and interpretation, Manuscript writing.

Vinicius Fernandes Araújo: Collection and assembly of data.

Rodrigo Souza Dias: Collection and assembly of data, Conception and design, Final approval of manuscript.

Adelmo José Giordani: Conception and design, Provision of study materials or patient.

Roberto Araújo Segreto: Conception and design, Final approval of manuscript.

Helena Regina Comodo Segreto: Conception and design, Data analysis and interpretation, Final approval of manuscript, Manuscript writing.

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