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SURGICAL BREAST CLIPPING FOR DELIMITATION OF RADIOTHERAPY DOSE IN BREAST CANCER

Clipping de mama cirúrgico para delimitação de dose radioterápica no câncer de mama

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ABSTRACT

Objective: To evaluate the benefit of radiotherapy planning, involving the use of surgical clips in conservative treatment of early-stage breast cancer. **Methods**: Retrospective cohort. Twelve (12) breast cancer female patients were retrospectively evaluated. These women had undergone breast-conserving treatment in which the tumor bed had been demarcated with titanium 200 surgical clips to guide breast boost radiotherapy. Volumes were calculated. Radiotherapy planning in the same patient with boost dose guided by metal clips was compared to planning guided by surgical scar or by imaging tests prior to surgical treatment. **Results**: A reduction of 36.7% in total volume of the irradiated breast (p=0.022), a reduction of 55.7% in boost volume (p=0.001), a reduction of 35.9% (p=0.001) in the breast volume receiving the prescribed boost dose and a reduction of 4.5% (p=0.014) in the maximum dose applied to the lung were shown. **Conclusions**: Clip placement in surgical bed following conservative treatment for breast cancer determined a reduction of 36.7% in irradiated breast volume and use of a lower dose of irradiation.

KEYWORDS: Breast cancer; surgical clips; radiotherapy.

RESUMO

Objetivo: Avaliar o benefício do planejamento radioterápico, envolvendo o uso de clipes cirúrgicos em tratamento conservador de estágio inicial de câncer de mama. **Métodos:** coorte retrospectiva. Doze (12) pacientes do sexo feminino com câncer de mama foram avaliadas retrospectivamente. Estas mulheres foram submetidas a tratamento conservador da mama em que o leito do tumor foi demarcado com grampos cirúrgicos de titânio 200 para orientar a radioterapia de mama. Os volumes foram calculados. O planejamento de radioterapia no mesmo paciente com dose de reforço guiada por clipes metálicos foi comparado ao planejamento guiado por cicatriz cirúrgica ou por exames de imagem antes do tratamento cirúrgico. **Resultados:** Foram observadas uma redução de 36,7% no volume total da mama irradiada (p = 0,022), uma redução de 55,7% no volume do reforço (p = 0,001), uma redução de 35,9% (p = 0,001) no volume mamário recebendo a dose de reforço prescrita e uma redução de 4,5% (p = 0,014) na dose máxima aplicada ao pulmão. **Conclusões:** A colocação do clipe no leito cirúrgico após tratamento conservador para câncer de mama determinou uma redução de 36,7% no volume mamário irradiado e o uso de menor dose de irradiação.

PALAVRAS-CHAVE: Câncer de mama; instrumentos cirúrgicos; radioterapia.

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INTRODUCTION

Breast-conserving treatment for breast cancer is based on surgical excision and axillary management followed by radiation therapy delivered to the remaining breast with or without the inclusion of lymph node chain regions and drainage areas[1].

Radiotherapy includes the whole breast, generally associated with a boost dose to the tumor bed aimed at reducing the probability of local disease recurrence. A boost to the tumor bed is used since it is the site of most local recurrences. Furthermore, greater control may be obtained with the boost dose in the quadrant initially affected by the tumor[2,3].

With modern radiotherapy techniques, including Tridimensional Conformal Radiation Therapy (3D-CRT) or Intensity-modulated RadiationTtherapy (IMRT), it is possible to adequately protect healthy adjacent organs: heart, lungs, esophagus, spinal cord and skin with a more uniform dose distribution, reducing acute and chronic toxicity related to treatment[2,3].

The most widely used boost plan is generated using the surgical scar. However, this method is subject to geographical planning errors resulting in inadequate coverage of the excision cavity, especially in immediate breast reconstruction for conservative treatment. In these cases, oncoplastic techniques determine breast remodeling. The surgical scar is not necessarily on the initially affected quadrant, making it difficult to establish whether the parenchymal margin that will receive the boost dose is still in the quadrant's projection in question[2,3].

Another way to determine boost location is by visualizing metal clips placed during surgery to better delimitate boost volume in the previous tumor site[4].

The current study assessed the benefit of radiotherapy planning, which involved surgical clip placement in the conservative treatment of early-stage breast cancer.

PATIENTS AND METHODS

Twelve breast cancer patients undergoing conservative treatment were retrospectively evaluated. The tumor bed of these patients had been demarcated with titanium 200 surgical clips to guide breast boost radiotherapy.

The volumes were calculated and the treatment planning in the same patient with radiation boost guided by metal clips was compared to the treatment planning guided by surgical scar or imaging tests prior to surgical treatment.

All treatment planning was done by the same radiation therapist and medical physicist.

Radiotherapy was performed with the patient in the supine position. The breast was immobilized with the hand placed beneath the head ipsilateral to the tumor and face turned towards the contralateral side. Indexed breast boards were used, offering greater reproducibility of patient positioning.

Computed tomography images were acquired with the patient immobilized and in treatment position. These images were sent to a planning system. In all tomography slices, target-volumes were delineated, along with volumes of healthy surrounding organs (organs at risk) to be spared. Thus, the chest wall, external breast contour, lung volume and cardiac silhouette could be perfectly visualized. This systematic approach can improve target-volume coverage and minimize radiation dose to organs at risk.

A two-field tangentially-opposed photon beam technique was used, with the purpose of obtaining a homogeneous distribution in the whole target volume.

Treatment was performed with a 3-D conformal teletherapy technique in an ELEKTA SYNERGY linear accelerator, at a dose of 50Gy in 25 fractions and a supplemental (boost) dose of 10Gy in 5 fractions delivered to the surgical bed, with clip placement and a margin of 2 cm.

The following clinical boundaries were used for treatment:

- Medial limit: midline;
- Lateral limit: mid-axillary line or 1 cm beyond the volume of palpable breast tissue;
- Lower limit: 2 cm below the inframammary sulcus;
- Upper limit: second intercostal space or head of the clavicle;
- Lung depth: 1.5 to 2 cm.

Taking into consideration the described limits, treatment targets and organs at risk were delimited:

- Clinical Target Volume (CTV): the whole breast present, plus the supraclavicular fossa and axilla when indicated.
- Planning Target Volume (PTV): is the CTV plus a margin that considers errors of positioning and variations resulting from internal movement.
- Organs at risk: lungs, heart, esophagus and spinal cord.

Variables were organized in Excel spreadsheets and analyzed in the SPSS software, version 20.0. Variables were described by tables, graphs, means and standard deviations. The Kolmogorov-Smirnov test was used to obtain data normality. To compare the means between using surgical clips and not using them in the tumor bed, Student's t-test was used at a significance level of 5%.

RESULTS

The main demographic characteristics are described in Table 1.

For a comparative analysis, the current study was divided into two groups:

- Group 1: represents treatment planning without clip placement
- Group 2: planning with clips.

In both groups, the following variables were analyzed:

- "A" represents the total volume of irradiated breast minus the boost volume in cm3;
- "B" represents the boost volume in cm3;

- "C" breast volume receiving the prescribed boost dose;
- "D" represents the maximum lung dose.

Tables with variable data (A, B, C and D) were constructed for 12 patients per group.

Through IBM SPSS Statistics 20 software, using Student's t-test the variables between both groups were compared and the p-value for each one resulted from this comparison, as shown in Table 2.

Assessment of variable A: total volume of irradiated breast minus boost volume in cm^3, a reduction of 36.7 % was shown in group 2 when clips were placed in the breast.

The graph above shows a $p<0.001$ for variable B (boost volume in cm^3) in both groups. Group 2 had a decrease of 55.7 % in boost volume (Figure 1).

Variable C (breast volume receiving the prescribed boost dose) is represented in the graph above, with $p=0.001$ (Figure 2),

Table 1. Main demographic characteristics.

Topics	Radiotherapy and Chemotherapy	Neo Chemotherapy	Radiotherapy Only
Number of patients	7	4	1
Age at surgery (years)			
Mean	59,5	49,5	51
Range	44 to 75	36 to 63	51 to 51
Sides			
Right	4	3	1
Left	3	1	0
Tumor stage			
T1	5	1	1
T2	2	1	0
T3	0	1	0
T4	0	1	0
Stage N			
N0	4	0	1
N1	3	3	0
N2	0	1	0
N3	0	0	0
Tumor type			
CDI	6	4	0
CDIS	0	0	1
CLI	1	0	0
Number of clips			
mean	4	4	4
range	3 to 5	3 to 5	4 to 4
IHC			
ER+ PR+ HER2+	1	2	0
ER+ PR+ HER2-	5	1	0
ER- PR- HER2+	0	0	1
ER+ PR- HER2-	1	0	0
ER- PR- HER2-	0	1	0
Time between surgery and treatment (days)			
Mean	151	74,5	37
Range	41–261	42–107	37–37

CDI: invasive ductal carcinoma; CDIS: in situ ductal carcinoma; CLI: invasive lobular carcinoma; ER: estrogen receptor; PR: progesterone receptor; HER2: HER2 receptor; +: positive; -: negative showing a significant difference in the irradiated breast volume with the prescribed boost dose between both groups. Group 2 had a mean decrease of 35.9% in irradiated volume with prescribed boost dose.

Representation of variable D (maximum lung dose) in the graph above (Figure 3), with a p=0.014. However, there is a considerable difference between both groups, although the difference between the maximum lung dose in percentage is not great (4.5%). In the same group, there is probably not much difference between maximum doses, resulting in a small standard deviation. Another factor contributing to this significance is that 100% of this study's patients received a higher dose in group 1.

DISCUSSION

Boost radiotherapy of the tumoral bed is a major tool in local control of breast malignancies following conservative treatment. Four randomized studies have currently demonstrated a significant increase in disease-free survival after the use of boost radiotherapy in patients with negative margins undergoing conservative surgeries[5-10].

Table 2. Student's t-test results for comparison of the means according to selected variables.

Variables	Groups	N	Mean	P
A	1	12	643.11	0.022
	2	12	879.34	
B	1	12	424.28	0.001
	2	12	187.99	
C	1	12	517.18	0.001
	2	12	331.26	
D	1	12	60.44	0.014
	2	12	57.74	

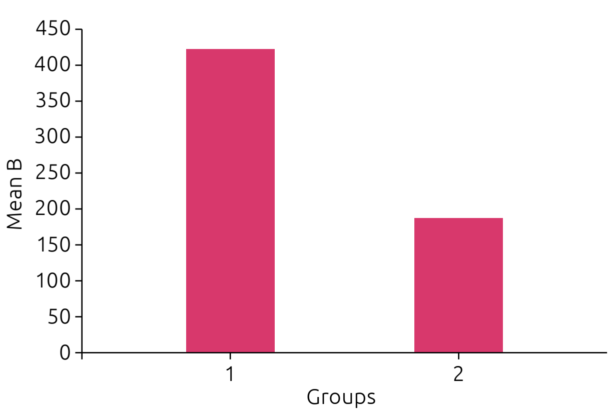

Figure 1. Comparison between means of variable "B".

For a successful radiation boost, adequate tumor bed location is necessary. However, the more frequent use of oncoplastic techniques makes locating the tumor bed more difficult in patients undergoing reconstructive surgery. Traditional reference points such as the surgical scar, seroma's position and tumor location in previous exams may be insufficient in these patients[11].

Breast radiation treatment uses a total teletherapy dose of 50 Gy in 25 daily fractions of 2.0 Gy, 5 days a week[12]. Other treatment regimens, such as hypofractionation, may be considered but should be decided by the medical team. A boost dose to the tumor bed is frequently recommended, using external beam radiation. Brachytherapy may also be used. Randomized studies have demonstrated a significant improvement in local control with a boost dose when compared to whole breast radiation only. The addition of a 10–20 Gy boost dose may decrease local recurrence rates by 50%[13]. The absolute benefits of using a boost dose are more notable in younger women and is indicated in all patients younger than 50 years. Other factors to consider for boost indication are: close margins (affected or unknown), tumors with high local aggressiveness and presence of more than 25% of ductal carcinoma ***in situ*** (DCIS) in surgical specimen. In older women, in the lack of risk factors for local recurrence, the omission of a boost dose may be considered.

In a North-American study, it was observed that only 57% of treatment target volumes coincided when different radiologists

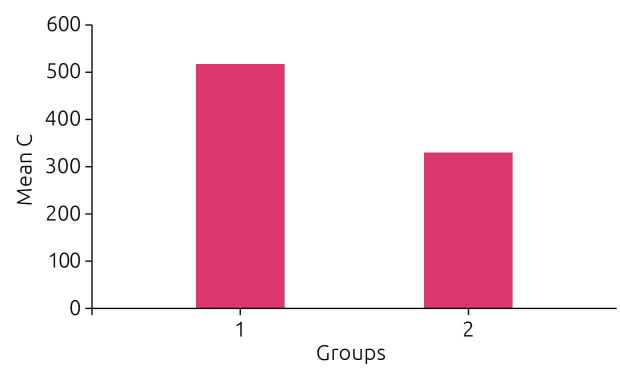

Figure 2. Comparison between means of variable "C".

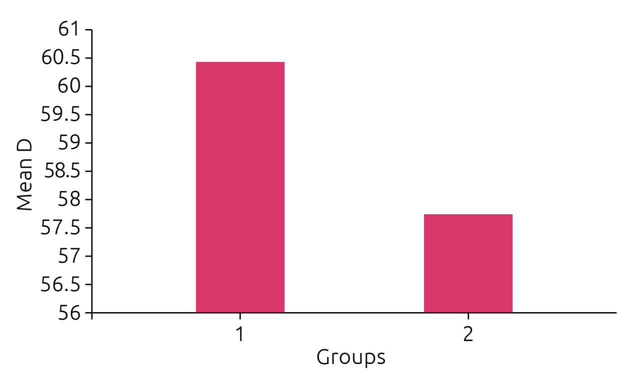

Figure 3. Comparison between mean of variable "D".

did radiotherapy planning in cases where the tumor bed was difficult to define[14]. An alternative method to this problem is the use of surgical clips to mark tumor bed. It has demonstrated good results in some studies, although a consensus does not exist among health professionals[15-22].

A North-American study involving 30 patients concluded that when clinical data was used to delineate treatment area, 49% of the tumor bed received less than 90% of the planned radiation dose. When clips were used, all patients received more than 90% of boost radiation. While treatment area is lost, healthy breast tissue is unnecessarily irradiated[17]. In our study, a reduction of 37.6% in irradiated breast area minus boost volume was observed following clip placement (p=0.022).

Concomitantly, a reduction of 55.7% in the boost volume prescribed (p=0.001) and increase in the area receiving the planned dose (517.18 × 331.23 cm3) (p=0.001) were also observed. With a smaller area of irradiated breast tissue, the ipsilateral lung received a lower dose. Lung dose decreased by around 4.5 % (p=0.014). These values corroborate the hypothesis that surgical clip placement in tumor bed allows a more accurate treatment with fewer side-effects.

In the literature, there is still no definition of the required number of clips. Nevertheless, the use of a minimum of three clips is recommended for demarcating the surgical area[22]. However, in wide surgical excisions, it is prudent to place a minimum of 5 clips to delineate the 4 radial beds and tumor bed depth[21].

CONCLUSION

Clip placement in the surgical bed following breast-conserving treatment for breast cancer determined a reduction of 36.7% in the irradiated breast volume. There was also a reduction in the total boost volume and amount of irradiated lung tissue, thus enabling a more effective treatment and reducing side effects.

REFERENCES

1. National Comprehensive Cancer Network. Breast cancer Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2003 Apr;1(2):148-88. http://doi.org/10.6004/jnccn.2003.0016
2. Marta GN, Hanna SA, Martella E, Silva JLF, Carvalho HA. Câncer de mama estádio inicial e radioterapia: atualização. Rev Assoc Med Bras. 2011;57(4):468-74. http://dx.doi.org/10.1590/S0104-42302011000400024
3. Pirlamarla A, Ferro A, Yue NJ, Haffty BG, Goyal S. Optimization of surgical clip placement for breast-conservation therapy. Pract Radiat Oncol. 2014;4(3):153-9. http://dx.doi.org/10.1016/j.prro.2013.07.013
4. Kovner F, Agay R, Merimsky O, Stadler J, Klausner J, Inbar M. Clips and scar as the guidelines for breast radiation boost after lumpectomy. Eur J Surg Oncol. 1999;25(5):483-6. https://doi.org/10.1053/ejso.1999.0683
5. Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, Barillot I, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med. 2001;345(19):1378-87. https://doi.org/10.1056/NEJMoa010874
6. Bartelink H, Horiot JC, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, et al. Impact of a higher radiation dose onlocal control and survival in breast-conserving therapy of early breastcancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol. 2007;25(22):3259-65. https://doi.org/10.1200/JCO.2007.11.4991
7. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-yearfollow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16(1):47-56. https://doi.org/10.1016/S1470-2045(14)71156-8
8. Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X, Ardiet JM, et al. Role of a 10-Gy boost in the conservative treatmentof early breast cancer: results of a randomized clinical trial in Lyon, France. J Clin Oncol. 1997;15(3):963-8. https://doi.org/10.1200/JCO.1997.15.3.963
9. Polgár C, Fodor J, Orosz Z, Major T, Takácsi-Nagy Z, Mangel LC, et al. Electron and high-dose-rate brachytherapy boost in the conservative treatment of stage I-II breast cancer first results of the randomized Budapest boost trial. Strahlenther Onkol. 2002;178(11):615-23. https://doi.org/10.1007/s00066-002-1053-1
10. Tessier E, Héry M, Ramaioli A, et al. Boost in conservative treatment:6 years results of randomized trial (Abstr 345). Breast Cancer Res Treat. 1998;50:203-335. https://doi.org/10.1023/B:BREA.0000013524.28746.0d
11. Marta GN. A importância da utilização de clips cirúrgicos na delimitação do volume de tratamento do reforço de dose no planejamento radioterápico. Rev Bras Mastologia. 2016;26(4):186-9. https://doi.org/10.5327/Z201600040009RBM
12. Hunter MA, McFall TA, Hehr KA. Breast-conserving surgery for primary breast cancer: Necessity for surgical clips to define the tumor bed for radiation planning. Radiology. 1996;200:281-2. https://doi.org/10.1148/radiology.200.1.8657928
13. Coles CE, Wilson CB, Cumming J, Benson JR, Forouhi P, Wilkinson JS, et al. Titanium clip placement to allow accurate tumour bed localisation following breast conserving surgery – audit on behalf of the IMPORT trial management group. Eur J Surg Oncol. 2009;35:578-82. https://doi.org/10.1016/j.ejso.2008.09.005
14. Landis DM, Luo W, Song J, Bellon JR, Punglia RS, Wong JS, et al. Variability among breast radiation oncologists in delineation of the postsurgical lumpectomy cavity. Int J Radiat Oncol Biol Phys. 2007;67(5):1299-308. https://doi.org/10.1016/j.ijrobp.2006.11.026

15. Kirova YM, Fournier-Bidoz N, Servois V, Laki F, Pollet GA, Salmon R, et al. How to boost the breast tumor bed? A multidisciplinary approach in eight steps. Int J Radiat Oncol Biol Phys. 2008;72(2):494-500. https://doi.org/10.1016/j.ijrobp.2007.12.059

16. Goldberg H, Prosnitz RG, Olson JA, Marks LB. Definition of Post lumpectomy tumor bed for radiotherapy boost field planning: CT versus surgical clips. Int J Radiat Oncol Biol Phys. 2005;63(1):209-13. https://doi.org/10.1016/j.ijrobp.2005.01.044

17. Benda RK, Yasuda G, Sethi A, Gabram SG, Hinerman RW, Mendenhall NP. Breast boost: are we missing the target? Cancer. 2003;97(4):905-9. https://doi.org/10.1002/cncr.11142

18. Pezner RD, Tan MC, Clancy SL, Chen YJ, Joseph T, Vora NL. Radiation therapy for breast cancer patients who undergo oncoplastic surgery: localization of the tumor bed for the local boost. Am J Clin Oncol. 2013;36(6):535-9. https://doi.org/10.1097/COC.0b013e318256efba

19. Kirova YM, Castro Pena P, Hijal T, Fournier-Bidoz N, Laki F, Sigal-Zafrani B, et al. Improving the definition of tumor bed boost with the use of surgical clips and image registration in breast cancer patients. Int J Radiat Oncol Biol Phys. 2010;78(5):1352-5. https://doi.org/10.1016/j.ijrobp.2009.10.049

20. Furet E, Peurien D, Fournier-Bidoz N, Servois V, Reyal F, Fourquet A, et al. Plastic surgery for breast conservation therapy: how todefine the volume of the tumor bed for the boost? Eur J Surg Oncol. 2014;40(7):830-4. https://doi.org/10.1016/j.ejso.2014.03.009

21. Kirby AN, Jena R, Harris EJ, Evans PM, Crowley C, Gregory DL, et al. Tumour bed delineation for partial breast/breast boost radiotherapy: what is the optimal number of implanted markers? Radiother Oncol. 2013;106(2):231-5. https://doi.org/10.1016/j.radonc.2013.02.003

22. Belkacémi Y, Fourquet A, Cutuli B, Bourgier C, Hery M, Ganem G, et al. Radiotherapy for invasive breast cancer: guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. Crit Rev Oncol Hematol. 2011;79(2):91-102. https://doi.org/10.1016/j.critrevonc.2010.06.002