

# Hypofractionation in Locally Advanced Breast Cancer: “Flash” Scheme



## Hipofraccionamento no Carcinoma Localmente Avançado da Mama: Esquema “Flash”

Marisa PADILHA<sup>1</sup>, Sara GONÇALVES<sup>1</sup>, Carlos FARDILHA<sup>1</sup>, Gilberto MELO<sup>1</sup>, Cristina MIRANDA<sup>1</sup>, Paula ALVES<sup>1</sup>  
*Acta Med Port* 2013 Mar-Apr;26(2):98-101

### ABSTRACT

**Introduction:** Breast cancer is a major cause of death in our country. The Department of Radiation Oncology of Portuguese Institute of Oncology in Coimbra are using a scheme of hypofractionation called “Flash” as a treatment option for elderly patients or low performance status, with locally advanced breast cancer, or with stage IIb or IV, as a neoadjuvant or palliative aim.

**Objectives:** Evaluation of the therapeutic response, for the group of patients selected, who did the hypofractionated scheme, in a retrospective study.

**Methods:** Between January 2006 and December 2008, a total of 83 patients diagnosed with locally advanced breast cancer or with stage IIb or IV, were subjected to breast “Flash”. The radiation dose prescribed was 13Gy in 2 fractions in 3 days (in 23 patients – 27.7%) and 26 Gy in 4 fractions in 5 weeks (60 patients – 72.3%), with 4MV photons, in the sick breast. Global survival was evaluated using the Kaplan-Meier method. Statistical analysis was performed by applying the version 17.0 of SPSS and statistical tests were evaluated at a significance level of 5%.

**Results:** 80 patients (96.4%) who have made breast “Flash” were female, aged between 59 and 93 years and performance status (Karnofsky scale) between 90 and 50%. In 72 patients (86.7%) the histology was invasive ductal carcinoma. Surgery was held in 53% of patients (44) after breast “Flash”, the radical modified mastectomy was the most common surgical technique. The diagnosis of bone metastasis was made in 10 patients (12%), while the global survival rate was 68.7% (57 patients). 10 patients (12%) died because disease progression or persistence. In 50.6% (42 patients) there was no evidence of disease progression and 3.6% (3 patients) showed clinical improvement.

**Conclusions:** The “Breast Flash” is a safe treatment modality, in terms of secondary effects, and a valid therapeutic option for elderly patients or low performance status, with the diagnosis of locally advanced cancer or stage IIb or IV, as neoadjuvant, adjuvant or palliative aim. There is a little risk of relapse or progression in patients with good conditions, so the global survival rate is greater in these cases. There is a little iatrogenesis associated with this type of treatment; just one patient had grade III radiodermatitis.

**Keywords:** Breast Neoplasms/radiotherapy; Dose Fractionation.

### RESUMO

**Introdução:** O carcinoma da mama é uma das principais causas de morte no nosso país. No Serviço de Radioterapia do Instituto Português de Oncologia de Coimbra de Coimbra utilizamos, desde há mais de 30 anos, um esquema de hipofraccionamento de radioterapia, denominado “Flash”, como opção terapêutica em doentes idosos ou com baixo *Performance Status*, portadores de carcinoma da mama localmente avançado ou com estádios IIb ou IV, com intenção neoadjuvante ou paliativa.

**Objetivos:** Avaliar a resposta ao tratamento, nomeadamente sobrevivência global aos três anos, resposta local e toxicidades aguda e crónica, no grupo de doentes seleccionados submetidos a esquema de hipofraccionamento, em estudo retrospectivo.

**Metodologia:** Entre Janeiro de 2006 e Dezembro de 2008, um total de 83 doentes com diagnóstico de Carcinoma da Mama Localmente Avançado ou com estádios IIb ou IV, foi submetido a “Flash” mamário. A dose de radioterapia prescrita foi de 13Gy / 2Fr / 3 dias (em 23 doentes - 27,7%) e 26Gy / 4Fr / 2,5 semanas (em 60 doentes - 72,3%), com fotões de 4 MV, sobre a mama afectada. Foi avaliada sobrevivência global segundo o método de Kaplan-Meier. A análise estatística foi efectuada através da aplicação SPSS, versão 17.0 e os testes estatísticos foram avaliados ao nível de significância de 5%.

**Resultados:** 80 doentes (96,4%) que efectuaram “Flash” mamário eram do género feminino, com idades compreendidas entre os 59 e os 93 anos (idade média 80,72 + 5,87 anos) e *Performance Status* (Karnofsky: 0 - 100) entre 90 e 50%. Em 72 doentes (86,7%) o diagnóstico histológico foi Carcinoma Ductal Invasivo. A cirurgia após a realização do “Flash” Mamário foi realizada em 44 doentes (53%) após evidência de resposta local à radioterapia, sendo a Mastectomia Radical Modificada a técnica cirúrgica mais frequente. Efectuou-se o diagnóstico de metastização óssea em 10 doentes (12%), sendo que a taxa de sobrevivência global foi de 68,7% (57 doentes), em quatro anos. Dez doentes (12%) morreram por progressão da doença ou persistência tumoral. Em 42 doentes (50,6%) não se verificaram evidência ou progressão de doença e três doentes (3,6%) apresentaram melhoria clínica.

**Conclusões:** O “Flash Mamário” é uma modalidade de tratamento segura, relativamente aos efeitos secundários, e opção terapêutica válida para doentes idosos ou com baixo *Performance Status*, com o diagnóstico de carcinoma localmente avançado ou estágio IIb ou IV, a título neoadjuvante ou paliativo. Há menor risco de recidiva/progressão, nos doentes com melhor estado geral, sendo a taxa de sobrevivência global maior nestes casos. Existe pouca iatrogenia associada a este tipo de tratamento, apenas uma doente apresentou radiodermite grau III.

**Palavras-chave:** Neoplasias da Mama/radioterapia; Fraccionamento de Dose.

1 - Serviço de Radioterapia. Instituto Português de Oncologia de Coimbra. Coimbra. Portugal.

Recebido: 29 de Janeiro de 2012 - Aceite: 05 de Março de 2013 | Copyright © Ordem dos Médicos 2013

**INTRODUCTION**

Breast cancer is one of major current health concerns and one of the major causes of death due to cancer in Portugal. In the last few years we have witnessed an increase in incidence and a decrease in mortality associated with this disease due to early diagnosis campaign implementation and to improved treatment efficiency. Radiotherapy, which handles controlled ionizing radiation for therapeutic use, is one of major modalities in cancer treatment.<sup>1</sup>

Radiotherapy dose fractionation appeared in the 1920's and has been used in our Department for 30 years, in the form of a radiotherapy hypofractionation regimen, designed as "Flash", as a therapeutic option for elderly or low-performance status patients with locally advanced or IIb or IV stage breast cancer, as a neoadjuvant or palliative therapy.

Radiobiological models suggest that hypofractionation (higher radiation daily dose in less days) is efficient. This type of fractionation may also improve patient life quality as it implies less hospital attendances when compared to conventional fractionation.<sup>1,3</sup>

In our study, we carried out a retrospective evaluation of local tumor response and year global survival upon radiotherapy with the "Flash" regimen in patients with a diagnosis of locally advanced breast cancer.

**POPULATION AND METHODS**

This study evaluated treatment response to the hypofractionation regimen in patients with locally advanced or stage IIb or IV breast cancer. Our database allowed us to search for patients with locally advanced breast cancer diagnosis between January 2006 and December 2008. Radiotherapy with a hypofractionation regimen was the inclusion criteria. Eighty-three patients

were identified and included in the study. The prescribed radiotherapy dose was of 13Gy / 2Fr / 3 days (BED – 24.7Gy;  $\alpha/\beta = 3$ ) – 6.5Gy every other day (23 patients – 27.7%) and 26Gy / 4Fr / 3weeks (BED – 49.4Gy;  $\alpha/\beta = 3$ ) – 6.5Gy every other day, repeating the same regimen three weeks later (60 patients – 72.3%), with 4MV photon beams directed to the affected area. Two opposed tangent fields were used for dosimetry planning. Forty-four patients underwent surgery (modified or simple radical mastectomy, or tumorectomy - patients with extensive microcalcifications, multicentric tumors or cutaneous oedema upon radiotherapy and chemotherapy underwent mastectomy). Patients with positive hormone receptors underwent hormonal therapy. Acute or late side-effects of radiotherapy were recorded following the European Organization for Research and Treatment of Cancer (EORTC) scale. The Performance Status Karnofsky scale was used. Global survival was evaluated following the Kaplan-Meier method. Statistical analysis used SPSS software, version 17.0 and statistical tests were evaluated with a significance level of 5%.

**RESULTS**

Our study included 83 patients, from which 80 (96.4%) were female. The average age was  $80.72 \pm 5.87$  ranging between 59 and 93. The *Performance Status* value was between 90 and 50%.

A histological diagnosis of invasive ductal carcinoma was obtained in 72 patients (86.7%). Forty-two (50.6%) patients underwent surgery after having undergone the "Flash" radiotherapy regimen and a radical modified mastectomy was the most common surgical procedure used. Sixty-five patients underwent hormonal therapy and tamoxifen was the most commonly used drug. A diagnosis of bone metastasis has been obtained in 10

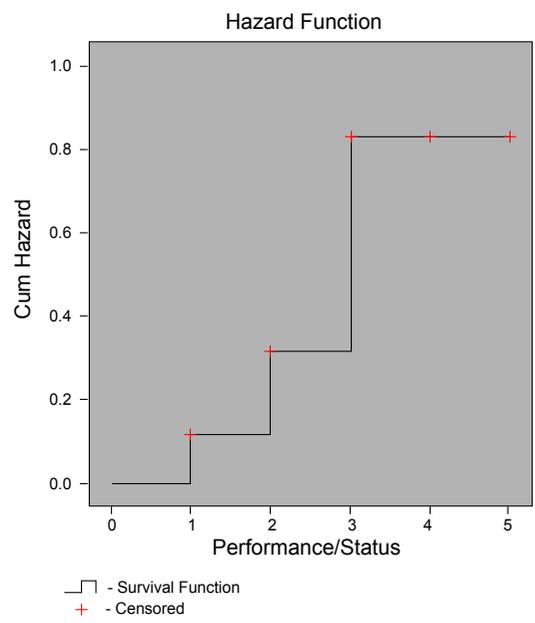


Figure 1 – Global Survival related to *Performance Status*

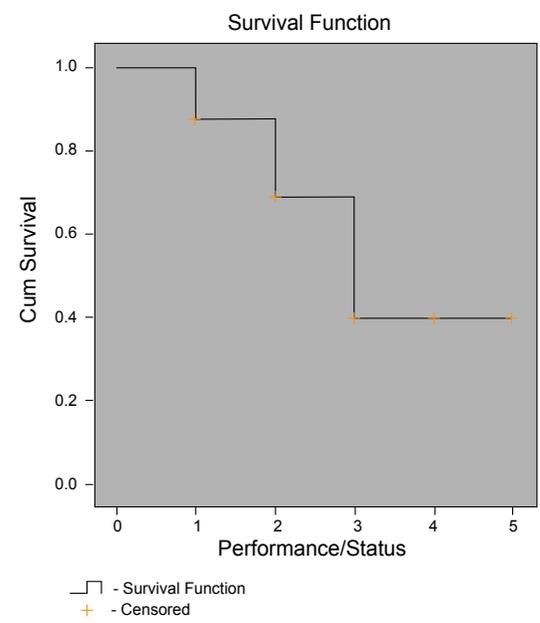


Figure 2 – Risk of disease recurrence or progression according to *Performance Status*.

patients (12%) and the global survival rate was of 68.7% in four years. Ten patients (12%) died due to disease progression or locoregional tumor recurrence. In 42 patients (50.6%) no evidence or progression of the disease was observed and in three patients (3.6%) there was clinical improvement (Fig. 1 and 2).

## DISCUSSION

Locally advanced breast tumors are considered as stage III, although there is no broad consensus regarding which stages should be included in this group.<sup>1</sup>

According with the Cancer American Society data, it is estimated that from the 212,920 patients with a diagnosis of breast cancer, about 12,775 present tumors exceeding 5 cm when diagnosed.<sup>1</sup> Locally advanced breast carcinoma has decreased significantly after a national breast cancer screening campaign has been implemented in Portugal.

In the group of locally advanced breast tumors there are patients with resectable and non-resectable tumors. These tumors should have a multidisciplinary approach (chemotherapy, hormonal therapy, surgery, radiotherapy) considering the specificity of each case.<sup>1</sup>

In locally advanced tumors, with no surgical conditions for neoadjuvant systemic therapy, radiotherapy may be used preoperatively or as a definitive locoregional treatment. In elderly or low performance status patients, the total time interval for a breast-oriented radiotherapy is approximately of five weeks, when a 2Gy/day conventional fractionation is used, with a possible negative impact on patient's life quality.<sup>2,3</sup> The hypofractionation has showed the same biological efficacy on the tumor, without adding any toxicity to the healthy tissues and with less total treatment time. These fractionation regimens, using higher fraction doses than in conventional regimens, may present equal efficacy.<sup>3,4</sup>

Results of three recent studies comparing the conventional fractionation with hypofractionation have been published. In the study by Timothy Whelan *et al.*, a comparison between two fractionation regimens has been made, three weeks of treatment (42.5Gy / 16 fractions) *versus* five weeks (50Gy / 25 fractions), with a 10-year follow-up. The authors concluded that the hypofractionation is not inferior to the conventional regimen in patients who underwent tumorectomy due to a breast invasive carcinoma, with tumor-free surgical margins and absence of lymph metastasis.<sup>4</sup> The

results of the studies START Trial A and B, where two hypofractionation regimens have been compared with the conventional fractionation regimen, were in agreement with the hypothesis that hypofractionation is equally safe and effective as the conventional fractionation, in particular concerning the locoregional tumor control and the late effects on healthy tissues; breast cancer cells, as well as late responding normal tissue cells, show a similar response to the fraction doses.<sup>5,6</sup> The studies START showed a strong evidence in favour of hypofractionation, with a potential for less adverse effects on surrounding tissues.<sup>6</sup>

Adel Courdi *et al.* showed that a hypofractionation radiotherapy regimen (five 6.5Gy fractions, once a week, in a total of 32.5Gy, followed by an additional 6.5Gy dose applied to the tumor, in one to three fractions) resulted in an acceptable toxicity, beyond obtaining adequate local control. This regimen may be proposed to patients for whom daily treatments would be difficult due to advanced age or comorbidities.<sup>7</sup>

Baillet *et al* carried out a comparative study between two fractionation regimens, 45Gy in 25 fractions over 33 days vs. 23Gy in four fractions over 17 days, in patients with breast cancer. They concluded that there was no significant differences between both fractionation schemes in what concerned complication rates and side-effects.<sup>8</sup>

## CONCLUSION

The *Breast Flash* regimen is a safe treatment modality and a valid therapy for elderly or low-performance status patients with a diagnosis of locally advanced carcinoma, as a neoadjuvant or palliative therapy. There is a lower risk of recurrence/progression in patients with better health conditions, with an increased global survival in these patients. There are few adverse effects related to this type of treatment. The results of this study have major implications on radiotherapy practice, with a life quality benefit for these patients.

## CONFLICT OF INTERESTS

The authors declare that there was no conflict of interests regarding the writing of this manuscript.

## FINANCIAL SOURCES

There were no external financial sources in the writing of this manuscript.

## REFERENCES

- Halperin EA, Perez CA, Brady LW. Breast cancer: locally advanced and recurrent disease, postmastectomy radiation, and systemic therapies. In: Perez and Brady's Principles and Practice of Radiation Oncology. Philadelphia: Lippincott Williams & Wilkins; 2008. p.1292- 317.
- Chargari C, Kirova YM, Laki F, Savignoni A, Dorval T, Dendale R, et al. The impact of loco-regional treatment in elderly breast cancer patients: Hypo-fractionated exclusive radiotherapy, single institution long-term results. *Breast*. 2010;19:413-16.
- Loredana M. Altered fractionation in radiotherapy: From radiobiological rationale to therapeutic gain. *Cancer Treat Rev*. 2010;36:606-14.
- Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med*. 2010;362:6:513-20.
- Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bliss JM, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol*. 2008;9:331-41.
- Hopwood P, Haviland JS, Sumo G, Mills J, Bliss JM, Yarnold JR, et al.

- Comparison of patient-reported breast, arm, and, shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *Lancet Oncol.* 2010;11:231-40.
7. Courdi A, Ortholan C, Hannoun-Lévi JM, Ferrero JM, Largillier R, Balu-Maestro C, et al. Long-term results of hypofractionated radiotherapy and hormonal therapy without surgery for breast cancer in elderly patients. *Radiother Oncol.* 2006;79:156-61.
8. Baillet F, Housset M, Maylin C, Boisserie G, Bettahar R, Delanian S, et al. The use of a specific hypofractionated radiation therapy regimen *versus* classical fractionation in the treatment of breast cancer: a randomized study of 230 patients. *Int J Radiat Oncol Biol Phys.* 1990;19:1131-3.