

**Hypofractionated Boost after Whole Breast Irradiation in Breast Carcinoma: Chronic Toxicity Results and Cosmesis.**

**Running title:** Hypofractionated boost in breast cancer

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## Abstract

**Purpose:** To evaluate the impact of hypofractionated boost after hypofractionated whole breast irradiation in breast carcinoma

**Methods and materials:** Patients after breast conservative surgery were treated all time with hypo-fractionation of 2,67 Gy/day. Whole breast dose was 40.05 Gy followed in case of risk of local relapse by a boost of 16.02 Gy or 8.01 Gy. Acute and chronic toxicity results were evaluated including cosmetic software assisted assesment and objective evaluation of fibrosis parameters (elasticity and hydration) by means a skin tester.

**Results:** An amount of 362 patients were evaluated. Acute toxicities consisted in grade 1 dermatitis in 48.1 %, grade 2 in 44.5 % and grade 3 in 17 patients 4.7 %, respectively. After a median follow-up of 4.5 years, in 308 cases (86.6%) there was no chronic skin or subcutaneous changes. In the first consecutive 50 patients measures with skin tester showed no statistical differences in parameters for skin and subcutaneous fibrosis. Cosmetic results were considered excellent or good in 26% and 62 % respectively.

**Conclusions:** Boost to tumour bed with hypo-fractionated doses is well tolerated and acute and chronic toxicities are mild with good cosmetic results. Objective systems are encouraging methods to assess skin quality and cosmesis.

**Key words:** Breat cancer, Hypofractionation, Toxicity, Cosmesis

## Introduction

Standard treatment for early-stage breast cancer is breast-conserving surgery followed by radiotherapy [1]. The most common radiotherapeutic approach is whole breast irradiation (WBI), 45-50 Gy, 1.8- 2 Gy/day for five weeks followed by a boost to the tumour bed in intermediate and high risk cases with external radiotherapy or brachytherapy [2,3]. Several randomized controlled trials (RCT) [4,5] have been carried out to compare normofractionated with hypofractionated irradiation. Hypofractionation has proven to be equivalent to normofractionation in terms of local control, side effects, and cosmetic results. Long-term results from large, well-designed trials strongly suggest that hypofractionation does not increase chronic toxicity. Given these findings, hypofractionation can now be considered standard treatment in early stage disease [6,7].

Despite the good results, the widespread use of hypofractionation is still far from being completely implemented and some questions are still unsolved [8]. Although some of the aforementioned RCT's administered a normofractionated boost, the use of a hypofractionated boost has not been extensively investigated. The main concern with hypofractionation also for boosting is the potential risk of increased long-term toxicity. In the present study, we evaluated a prospective series of patients who underwent hypofractionated WBI followed by a hypofractionated boost to the tumour bed.

## Methods and materials

Patient inclusion criteria were: conservative surgery, stage I or II, age over 45. Patients were excluded in cases of nodal involvement needing regional irradiation, or a maximum diameter of breast greater than 25 cm. Patients and tumours characteristics are shown in table 1. Mean patient age was 63.3 years. Systemic treatment administered after surgery included hormone therapy (59.7% of patients), chemotherapy (9.7%), or both (22.4%). Patients received adjuvant and concomitant trastuzumab in 4.4 % of cases. All patients underwent a clinical evaluation and signed the informed consent form before inclusion in the study. All patients were treated with opposing tangential fields and in the majority of cases dosimetric optimization was achieved by means of a field in field technique.

The hypofractionated doses were 2.67 Gy per fraction delivered in 15 fractions for a total dose of 40.05 Gy. A boost of 8.01 or 16.02 Gy (at 2.67 Gy/fr) was added according to cumulative risk criteria for local relapse (see Figure 1), assuming biological equivalent dose (BED) tumour values of 80 and 93,4 respectively for  $\alpha/\beta$  values of 4. In the absence of risk factors boost was not administered. Higher doses were administered in cases of close margins (<1mm) or focal margin involvement, extensive or high grade DCIS, or in the presence of two or more risk factors for local relapse. The low boost dose was administered in the remaining cases. Boost was administered by means of photon or electron beams or both.

Acute toxicity was assessed weekly during treatment. Follow up was performed at 1, 3, 6, and 12 months post-treatment, and annually thereafter including chronic toxicity assesment via the Radiotherapy Oncology Group (RTOG) criteria scale. Additionally, the first fifty consecutive patients were selected for objective evaluation of chronic skin toxicity. We employed the Multi-Skin-Center® MC-750-B2 probe (CK Electronic, GmbH, Cologne, Germany) to assess erythema, hydration, pigmentation, and skin elasticity. Cosmesis assessment was performed both at subjective and objective levels as follows: Patient cosmesis assessment by the validated 11 item test described by Hoeller [9] (considered the base reference for any comparison with respect to other toxicity and cosmesis results). Moreover, cosmetic outcome was evaluated by a single physician through Harris [10] score. The objective method

consisted of a photographic computer assisted evaluation by means of BCCT-Core 2.0 software (developed by UNESC at Porto University, Portugal), allowing one to obtain an overall evaluation of cosmesis and parameters of shape and symmetry of both breasts [11].

The statistical analysis was performed with SPSS v22 (IBM SPSS, Chicago, IL). Chi-square and exact Fisher tests were employed to evaluate categorical variables. The concordance testing was performed by means of the kappa index. To evaluate differences between quantitative values the Student-T test for related data was employed and the Student T test also for qualitative independent variables.

## Results

A consecutive series of 362 patients who underwent conservative surgery for breast cancer were included in the study. The median follow up period was 4.5 years. Only one case of local relapse was observed and treated with mastectomy. However, 12 deaths occurred, 5 due to metastasis and the remaining 7 due to non-cancer related conditions.

The size of the boost dose was decided according to the risk criteria protocol shown in Figure 1. Low-risk patients (17 cases) received no boost. The 151 intermediate risk patients received 3 doses (up to 48.06 Gy), and the 194 high risk patients received 6 doses of 2.67 Gy (up to 56.07 Gy).

Acute and chronic skin toxicities are shown in Figure 2. There were no cases of treatment interruption due to acute toxicity. A mild dermatitis was observed in the majority of patients. Overall, there were no differences between boost groups. Chronic grade 1 skin toxicity was present in 13.3 % of cases and was superior in the high risk group. Overall, physician cosmesis scoring measured by the Harris scale was considered excellent in 21.6% of cases, good in 71.2%, fair in 6.4% and bad in 0.8%. In the intermediate boost dose group cosmetic results were excellent, good, fair and bad in 11%, 70.4%, 14.4% and 3.7% of cases, respectively, and in the high risk group were quite similar: excellent, good, fair and bad in 23%, 71.3%, 5.3% and 0.8% of cases, respectively.

Multimodal assessment of toxicity and cosmesis in a cohort of 50 patients was carried out at a minimum of 1 year after treatment (range, 1 - 2.11 years; mean, 1.34). Table 2 shows the skin toxicity results of the 50 patient cohort measured with the Multi-Skin-Center® MC-750-B2 tester. Elasticity and erythema measures comparing treated breast to boost area resulted in a lower elasticity ( $p=0.03$ ) and higher erythema rate ( $p=0.01$ ) at boost level. Also these measurements of elasticity and erythema registered by means of the skin tester showed differences between patients with or without chronic toxicity when using the RTOG scale ( $p= 0.047$  and  $p=0.035$  respectively).

The overall score with photographic software correlated better to patient cosmetic satisfaction than subjective physician evaluation using the Harris scale (Correlation coefficient 0.36 vs 0.26;  $p=0,016$ ). The morphologic values on BCCT-CORE software assessment that best correlated with asymmetry perceived by the patient were the BCE (*Breast Compliance Evaluation*;  $p=0,018$ ), pBRA (*proportion Breast Retraction Assessment*;  $p=0,021$ ) and pUNR (*proportion Upward Nipple Retraction*;  $p=0,023$ ). There was also a correlation between physician evaluated RTOG toxicity score and overall software cosmetic values ( $p=0,041$ ).

Despite volumes and diameter of breast and also boost volume showed no influence on overall cosmesis scores by means of the three evaluations, there was a significant statistic correlation between boost volume and any toxicity according RTOG score (ROC curve, Figure 3). The absolute value of boost volume cut off for chronic toxicity risk

was 55 cc. Also, this value of boost volume was highly correlated with the presence of telangiectasia ( $p=0,000$ ) and skin fibrosis ( $p=0,021$ ).

## Discussion

Radiotherapy schedules to treat breast cancer are continually being refined and improved. Because the main objective of most hypofractionation studies resides in treating the whole breast, the choice of boost technique and doses has received less attention and remain unanswered. As a result, even though hypofractionation is fast becoming the standard approach to WBI, there is a huge variability in schedules applied to boost after whole breast hypofractionated irradiation. The major studies that have evaluated a boost after hypofractionated WBI are those carried out by the Royal Marsden Hospital, in which 14 Gy fractionated at 2 Gy per session was administered [12] and the START A and B studies, which evaluated a boost of 10 Gy. The aforementioned trials used a normofractionated boost after adjuvant radiotherapy. Fear of toxicity, particularly late toxicity, had prevented the widespread use of hypofractionated boost. Several groups had tested alternative schedules of boost after WBI: four doses of 2.5 Gy [13] or three doses of 3 Gy [14] with electrons, a single dose of 8 Gy with electrons [15] or a single dose of 12 Gy with electron intraoperative therapy [16], with similar rates of acute and chronic toxicities. Karasawa et al [17] performed a regimen that was very similar to ours administering 3 doses of boost at the same hypofractionated schedule of 2.7 Gy per session compared to normofractionated WBI and boost, achieving equivalent efficacy and less acute skin reaction after hypofractionation. A more recent approach consists of a boost given concomitantly as proposed by Meei Teh et al [18]. They carried out a prospective study in 15 patients who received 42.4 Gy of WBI with a concomitant boost of 10.08 Gy delivered in 16 fractions, showing low rate of skin toxicities.

As hypofractionation schedules become more common, it is important to consider the radiobiological aspects of hypofractionation due to its implications for tumour response and tolerance in healthy tissues. The main studies of daily hypofractionation [19] suggest that we should assume an estimated  $\alpha/\beta$  value for breast tumour of around 4 and that doses per fraction should not exceed 3.1 Gy in order to avoid increasing chronic toxicity. Qi et al. [20] performed a statistical modelling to establish radiobiological equivalencies between a standard schedule (25 sessions, 2 Gy/fraction) and diverse altered fractionations (Table 3), concluding that hypofractionation results in lower BED to the organs at risk (OAR). In fact, comparing our hypofractionated schedule to the standard 2 Gy per fraction with 16 Gy boost [21], results in a lower BED for tumor (93.4 vs 99;  $\alpha/\beta=4$ ) and lower BED for acute (70.95 vs 79.2;  $\alpha/\beta=10$ ) and chronic toxicity (105.84 vs 110;  $\alpha/\beta=3$ ).

In our study, we observed no relevant acute or chronic toxicity (Figure 2). Assessment of skin toxicity is difficult and normally involves the use of subjective scales such as the RTOG [22] scale or the National Cancer Institute Common Toxicity Criteria (CTC) [23] or visual photographic evaluation. In the present study, we used the same objective system—the Multi-Skin-CenterMC-750-B2 probe—that we used in previous RCT comparing accelerated partial breast irradiation (APBI) to WBI [24].

Another controversial issue is the cosmesis evaluation. Initially performed by direct evaluation of photographs, no standardized method exists to carry out this evaluation [25]. Computer assisted evaluation tools allow more reproducible and less time consuming assessment [26] of morphologic changes in breast appearance, colour and surgical scar assessment and allows to give an overall score [10] that, according to our results, compares better with the patient's opinion of the cosmesis result. Experience with BCCT-core software utilized also in the Young Boost

Trial has shown that some morphological parameters correlate with patient cosmesis score but also with other subjective findings like firmness [27].

Despite the good results seen in our study and in others, it is essential to be aware of the risks involved when using hypofractionated schedules so, as emphasized by several authors, when there were necessary, IMRT or field in field optimization should be utilized [28]. Given that hypofractionated and normofractionated breast radiotherapy are essentially equivalent in terms of efficacy and toxicity [29], it is evident that by shortening the treatment length of treatment with hypofractionation can improve the efficiency of a radiotherapy department. Conventional irradiation schedules consisting of 50 Gy plus a boost of 16 Gy administered in 33 fractions, are equivalent to 11-21 hypofractionated doses (depending on the sequence and fractionation used). Thus, hypofractionation can potentially decrease the workload of radiotherapy treatment units by 45% allowing for substantial time saving. Moreover, patients would benefit from fewer treatments while the increased efficiency in resource utilization could lower costs by up to 24% [30]. The significant improvement in patients' quality of life associated with this schedule also constitutes another benefit.

**Conclusions**

Hypofractionated irradiation in breast cancer is now considered standard treatment after breast-conserving surgery. Longer follow up is needed to fully assess its impact on chronic toxicity when applied also as a boost after WBI. Cosmetic results also seem good. The use of quantitative skin toxicity measuring systems could be useful to provide a more objective approach to compare different hypofractionation schedules and doses.

Figure legends

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Figure 1. Criteria used to define risk group and dose prescription.

Figure 2. Percentages of chronic toxicities after hypofractionated WBI plus boost among boost groups.

Figure 3. Receiver operation characteristic (ROC) curve and associated area for boost volume as predictor for any chronic toxicity.

Statements:

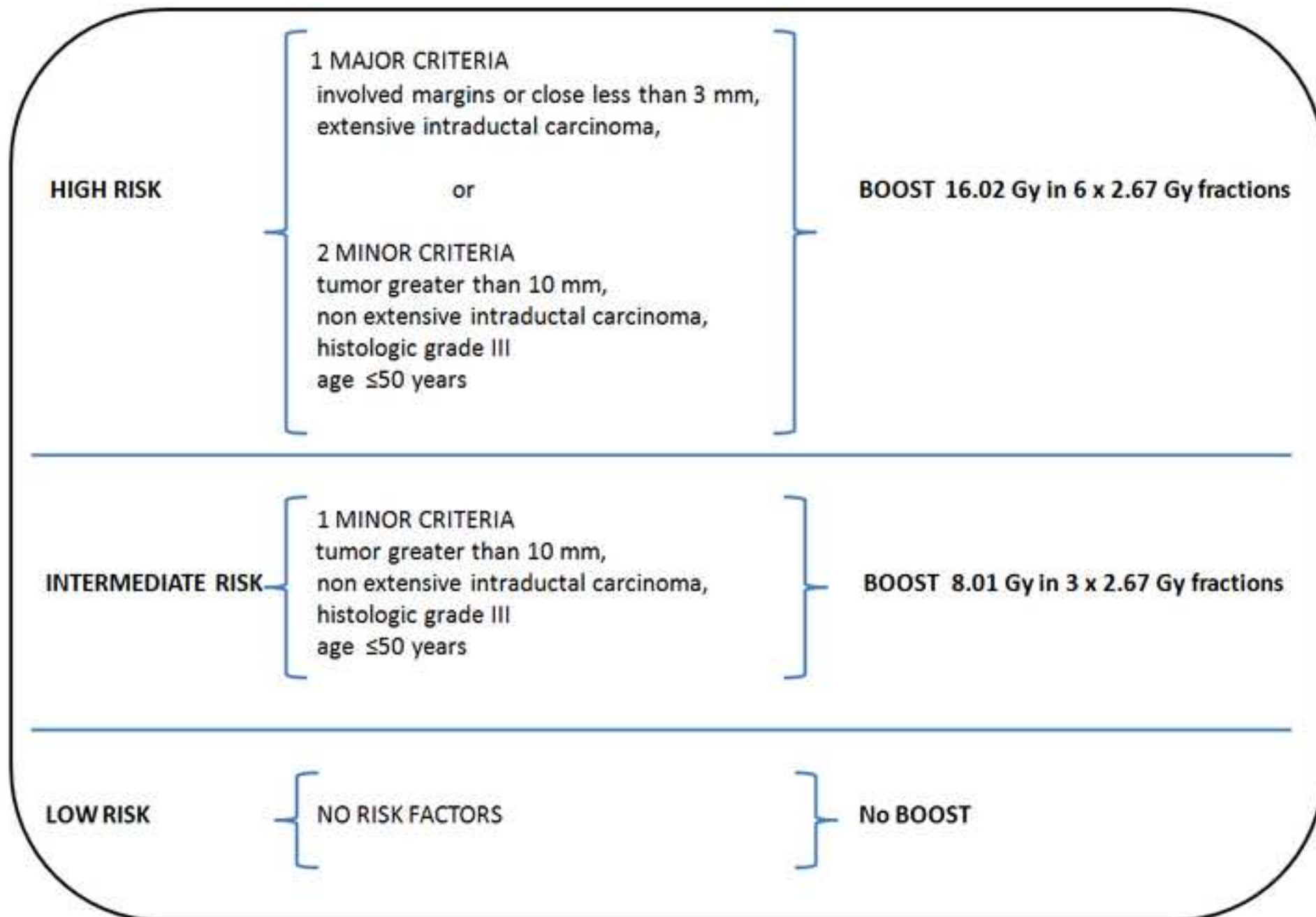
- 1.- All patients included had signed a informed consent
- 2.- The research involving human participants included in the study has respected the Declaration of Helsinki regarding the ethical principles of human experimentation
- 3.- Conflict of Interest statement: all the authors declare that they have no conflict of interest.

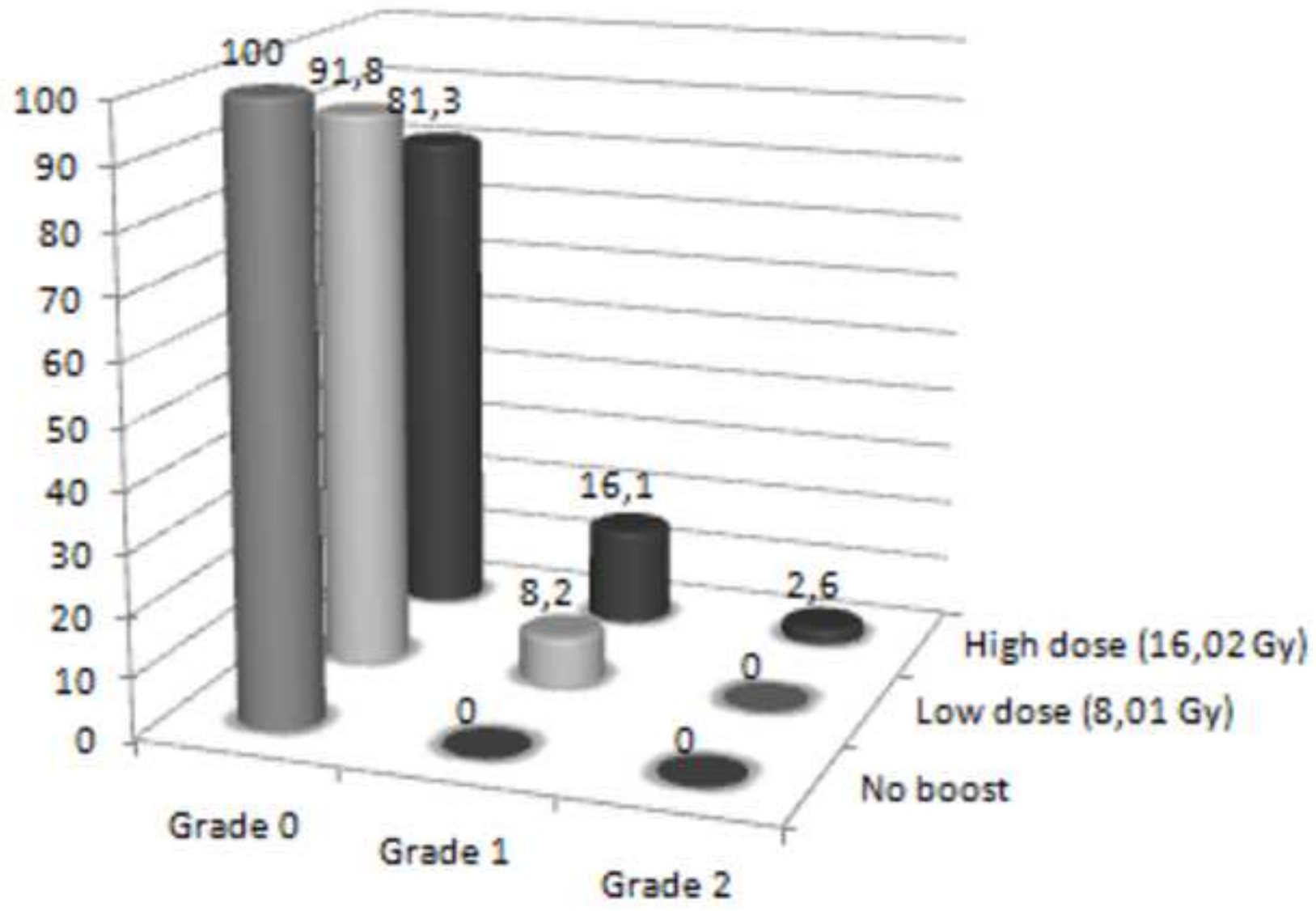
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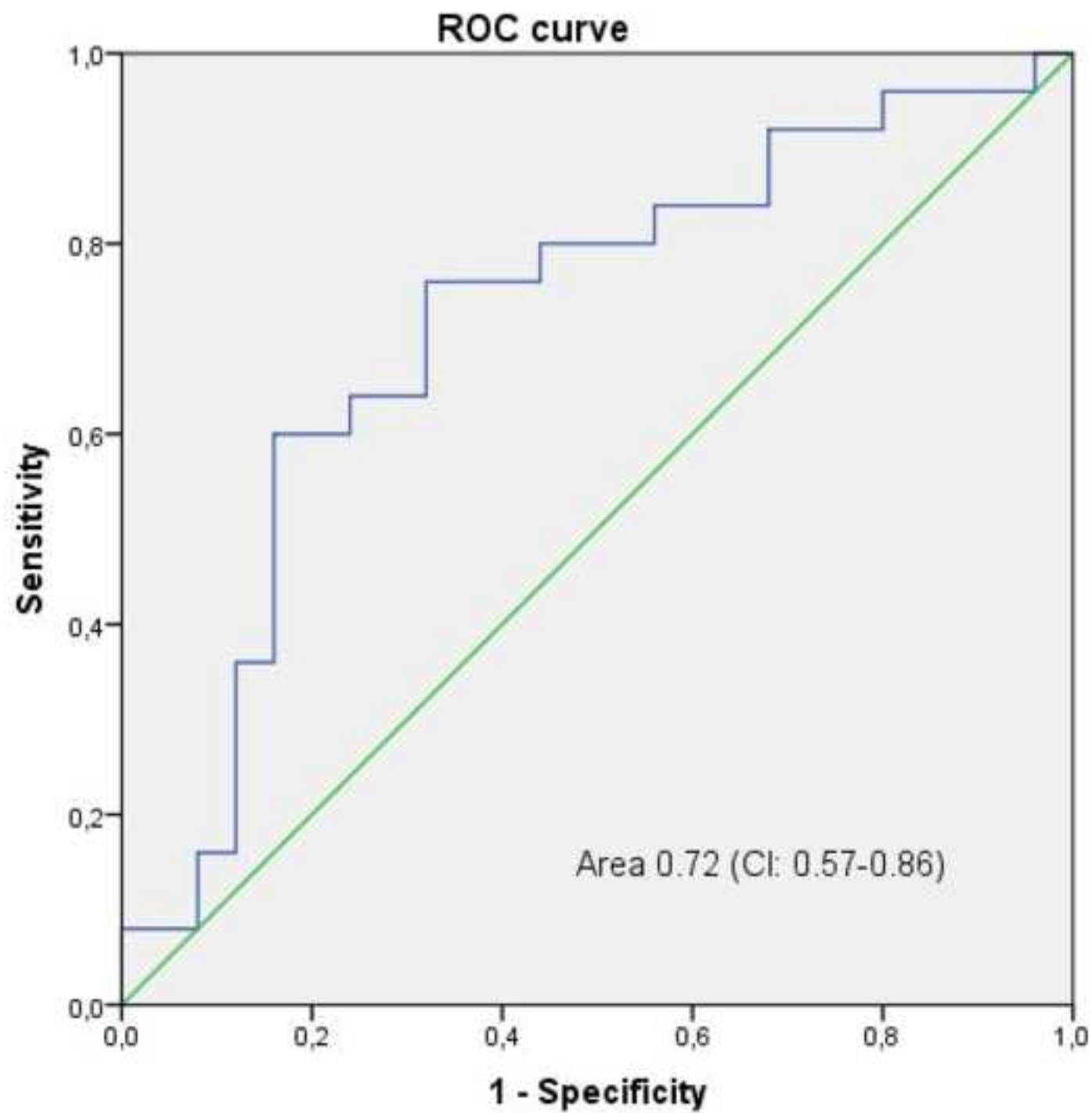


Table 1. Clinical and pathological characteristics.

|                        |                                | N   | %    |
|------------------------|--------------------------------|-----|------|
| Menopause              | Yes                            | 331 | 91.4 |
|                        | No                             | 31  | 8.6  |
| Type of surgery        | Tumorectomy                    | 335 | 92.5 |
|                        | Quadrantectomy                 | 27  | 7.5  |
| Systemic treatments    | Hormone therapy                | 216 | 59.7 |
|                        | Chemotherapy                   | 35  | 9.7  |
|                        | Hormone therapy + chemotherapy | 81  | 22.4 |
|                        | Trastuzumab + chemotherapy     | 16  | 4.4  |
|                        | No systemic treatment          | 14  | 3.8  |
| T                      | T1                             | 264 | 78.5 |
|                        | T2                             | 78  | 21.5 |
| N                      | N0                             | 309 | 85.4 |
|                        | N0i+                           | 4   | 1.1  |
|                        | N1mic                          | 12  | 3.4  |
|                        | N1                             | 36  | 9.9  |
| Histology              | CDI                            | 308 | 85.1 |
|                        | CLI                            | 32  | 8.8  |
|                        | Other                          | 22  | 6.1  |
| Margins                | Negative                       | 241 | 66.6 |
|                        | Close                          | 109 | 30.1 |
|                        | Involved                       | 12  | 3.3  |
| Intraductal presence   | Yes                            | 191 | 52.8 |
|                        | No                             | 171 | 47.2 |
| Estrogen receptors     | Positive                       | 306 | 84.5 |
|                        | Negative                       | 49  | 13.5 |
|                        | Unknown                        | 7   | 1.9  |
| Progesterone receptors | Positive                       | 268 | 74   |
|                        | Negative                       | 86  | 23.8 |
|                        | Unknown                        | 8   | 2.2  |
| Her2neu                | Positive                       | 27  | 7.5  |
|                        | Negative                       | 309 | 85.4 |
|                        | Unknown                        | 26  | 7.2  |
| Risk group             | Low                            | 17  | 4.8  |
|                        | Intermediate                   | 146 | 41   |
|                        | High                           | 193 | 54.2 |

Table 2. Mean values of skin parameter measures using the Multi-Skin-Center® MC-750-B2.

| <b>Parameter</b>                        | <b>Boost area</b>  | <b>Other quadrants,<br/>ipsilateral breast</b> | <b>Contralateral breast</b> |
|---|--------------------|--|-----------------------------|
| <b>Elasticity (%)</b>                   | 73.1 ( $\pm$ 10)   | 78 ( $\pm$ 7.2)                                | 83.2 ( $\pm$ 5.3)           |
| <b>Erythema (L*a*b index)</b>           | 26.2 ( $\pm$ 7)    | 24.9 ( $\pm$ 9.9)                              | 21.3 ( $\pm$ 5.2)           |
| <b>Melanin (% , manufacturer index)</b> | 5.1 ( $\pm$ 5.5)   | 4.9 ( $\pm$ 5.2)                               | 3.4 ( $\pm$ 4.1)            |
| <b>Hydration (g/h·m<sup>2</sup>)</b>    | 36.4 ( $\pm$ 10.3) | 38.5 ( $\pm$ 8.9)                              | 40.8 ( $\pm$ 9.5)           |

Table 3. Comparison of biologically equivalent doses (BED) for several fractionation schedules.

| <b>Schedule</b>  | <b>Fractionation,<br/>breast<br/>irradiation</b> | <b>Boost<br/>fractionation</b> | <b>Total N° of<br/>fractions</b> | <b>BED<br/>tumour<br/>(<math>\alpha/\beta=4</math>)</b> | <b>BED<br/>Acute effects<br/>(<math>\alpha/\beta=10</math>)</b> | <b>BED chronic<br/>toxicity<br/>(<math>\alpha/\beta=3</math>)</b> |
|--|--|--------------------------------|----------------------------------|---|---|---|
| Conventional   | 2x25   | -                              | 25                               | 75  | 60  | 83.33   |
| Canadian   | 2.66x16  | -                              | 16                               | 70.76   | 53.8  | 80.2  |
| Conventional + boost                                   | 2x25   | 2x8                            | 33                               | 99  | 79.2  | 110   |
| START A Exp. arm 1                                     | 3x13   | 2x5                            | 18                               | 83.25   | 62.7  | 94.7  |
| START A Exp. arm 2                                     | 3.2x13   | 2x5                            | 18                               | 89.8  | 66.9  | 85.9  |
| START B  | 2.67x15  | 2x5                            | 20                               | 81.7  | 62.7  | 92.3  |
| Normofractionated +<br>concomitant boost               | 1.8x28   | 2.3 – 2.4x28                   | 28                               | 93.4 – 97.4   | 76 – 79.3   | 103 – 107.5   |
| Hypofractionated +<br>concomitant boost<br>(RTOG 1005) | 2.67x15  | 3.2x15                         | 15                               | 80  | 60.8  | 90.7  |
| Present study<br>(short boost)                         | 2.67x15  | 2.67x3                         | 18                               | 80  | 60.81   | 90.72   |
| Present study<br>( long boost)                         | 2.67x15  | 2.67x6                         | 21                               | 93.4  | 70.95   | 105.84  |