OPTimizing Irradiation through Molecular Assessment of Lymph node (OPTIMAL): a randomized clinical trial

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Abstract

Background and purpose: In breast cancer (BC) patients, the involvement of four or more lymph nodes (LN) is an indication of regional irradiation. The optimal treatment strategy remains unclear when fewer nodes are involved and lymphadenectomy is not performed. We designed a clinical trial to show the non-inferiority of Incidental (INC) compared to intentional (INT) irradiation of axillary nodes in patients with early-stage BC and low burden LN involvement.

Materials and methods: BC patients, cN0 (n = 487) undergoing breast conservation surgery and sentinel node biopsy, with total tumor load assessed by OSNA (One-Step Nucleic Acid Amplification) of 250–15,000 copies mRNA CK19/µL in sentinel LN were randomized to receive INC or INT nodal irradiation. The primary endpoint was 5-year disease-free survival (DFS). Secondary endpoints were locoregional recurrence (LRR), distant recurrence (DR), and acute and chronic toxicity (CT).

Results: Five-years DFS were 93.7% (INC) and 93.8% (INT) (difference 0.1% [95% CI: 5.7%]; non-inferiority p = 0.075). Cumulative Incidences of LRR were 3.5% (INC) and 3.4% (INT) (difference of 0.1% [<4.8%]; p = 0.021), and 5% (INC) and 3.5% (INT) (difference 1.4% [<6.0%]; non-inferiority p = 0.101) for DR. CT was more Incident with INT (26.9%) than with INC (19.2%), though the difference was not statistically significant (HR 1.39 [95% CI: 0.92, 2.10]; p = 0.11).

Conclusion: Intentional does not outperform incidental irradiation by more than 5.7% in terms of 5-year DFS, 4.8% for LRR, and 6% for DR.

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Several trials have shown that radiotherapy increases survival rates in breast cancer (BC) patients and increases disease control when 4 or more involved axillary nodes are present [1–5]. However, there is no consensus on the recommendation of radiotherapy when the nodal involvement ranges between 1 and 3 lymph nodes (LN) [6]. The NCIC-CTG MA20 trial [6] proved that regional nodal irradiation (RNI) improved the disease-free survival (DFS) as well as the locoregional and distant control of the disease in patients with 1 to 3 involved LN, and Poortmans et al. [7,8] demonstrated that the RNI in similar patients increased the DFS. A meta-analysis conducted by Budach et al. [9,10] concluded that additional RNI, including the internal mammary chain, improved overall DFS rates in stage I-III BC patients. In lower-risk patients with 1–2 involved LN, Giuliano et al. demonstrated that axillary lymph node dissection (ALND) provided no significant benefit over no-ALND for the locoregional control [7]. In the same type of...
patients, the AMAROS [11] and OTOASOR [9] trials showed that RNI, rather than ALND, should be the recommended treatment.

Despite all previous evidence on the benefits of radiotherapy, optimal local treatment remains uncertain in patients with low tumor burden, and its choice should be based on a standardized method to complement the limited diagnostic information [12–14], such as nodal involvement. The OSNA (One-Step Nucleic Acid Amplification) assay provides a quantitative measure of the metastatic burden of the sentinel lymph node (SLN) by measuring the mRNA expression of the tumor marker cytokeratin 19 (CK19) [15]. The total tumor load (TTL), defined as the sum of the CK19 mRNA copies from all positive SLNs, was proved to be an independent predictor of the axillary nodal status [16], and a prognosis marker in BC patients [17]. OSNA provides a definitive intraoperative result that allows establishing the pathological staging [16]. This technique is validated and can be used for the LN analysis in BC as well as in other cancers [18–24]. There is sufficient experience published in international guidelines supporting that SLN biopsy is feasible, effective, and safe in most BC clinical scenarios, especially using the OSNA technique for molecular studies [25–27]. The OSNA method is used routinely in Spain and Portugal, where the participating centers in the OPTIMAL study are from.

The OPTIMAL study (OPTimizing Irradiation through Molecular Assessment of Lymph node) was designed to demonstrate the non-inferiority of incidental irradiation of axillary nodes in comparison to intentional irradiation in terms of the 5-year DFS, in patients with early-stage BC cN0 and limited involvement of the SLN with a similar profile to Z011 trial.

Materials and methods

Design

We designed a multicentric, international, open-label, parallel-group randomized clinical trial to compare two modalities of radiotherapy in BC patients with limited axillary lymph node involvement, treated with breast conservation surgery (BCS) without lymphadenectomy. The trial protocol was cleared by the Ethics Review Boards of participating centers and approved by the Health Authorities, and was registered in ClinicalTrials.gov, NCT02335957 [28]. Informed consent was obtained for all the included patients, and their privacy rights were always observed.

Radiation Oncology Departments of hospitals in Spain, Portugal, and Italy were invited to participate if they performed conformal 3D or intensity-modulated dosimetric computation and agreed to the radiotherapy protocol. All these centers use the OSNA method routinely for the evaluation of the axillary LN in BC patients.

Subjects of study

Patients with breast infiltrating ductal carcinoma in stages T1 or T2 and cN0, treated with BCS (tumorectomy or quadrantectomy) without lymphadenectomy were eligible if they were 18 years or older, had SLN assessed by OSNA, with TTL in the range of 250 – 15,000 copies/μL, a Karnofsky Index ≥70% and consented to participate. Exclusion criteria were: other types of BC or bilateral BC, males, mastectomy or axillary homolateral LN dissection, previous thoracic radiotherapy, neoadjuvant therapies, contraindications for radiotherapy (pregnancy, severe collagen diseases), and other neoplasms or severe associated comorbidities that could interfere with the study evaluations.

After surgery and at first radiotherapy consultation, enrolled patients randomly received either intentional (INT) or Incidental (INC) irradiation of lymphatic node areas, with a 1:1 allocation ratio, stratifying by the center. A centralized web-based tool was used to allocate treatments to the enrolled patients and keep the randomization concealed.

Radiotherapy planning

All nodal areas from axillary levels I–III, the supravacular fossa, and the internal mammary chain should be contoured in all patients regardless of the assigned arm, following the guidelines of the Radiation Therapy Oncology Group [29]. Radiotherapy was performed on each arm as follows:

- Intentional irradiation of LN: Patients received a total dose of 50 Gy in the whole breast and nodal areas (axillary I, II, III, and supravacular) with optimization of the technique, in daily fractions of 2 Gy and 5 fractions/week for 5 weeks.
- Incidental irradiation of LN: Patients received the same total dose to the whole breast, but not aimed at nodal areas.

In both treatment arms, further tumor bed boost was allowed according to the investigator criteria when dose contribution to the nodal areas could be calculated. The internal mammary chain was not intentionally irradiated in either of the two treatment arms. Nodal contours were hidden in the incidental arm to avoid radiation-planning bias. Doses received to each LN level were measured in both groups. More details on the radiotherapy protocol and other design issues have been previously reported [30].

Outcomes

The pre-specified primary endpoint was the 5-years DFS (5-y DFS), defined as the time from randomization to any BC-related event (including local, regional, or distant recurrence or death from BC) or end of follow-up, whichever occurred first. Patients that died due to other causes were censored at the death date. Pre-specified secondary endpoints were locoregional recurrence (LRR; local: in treated breast, regional: in the ipsilateral axilla or supravacular fossa), distant recurrence (DR: affection of other organs outside the breast, ipsilateral axilla or supravacular fossa), acute and chronic toxicity assessed by a selected subset of the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) [31], and total irradiation dose (Gy) received in axillary levels I, II and III, supravacular fossa, and internal mammary chain volumes, at the end of radiotherapy.

Statistical analysis

The trial was sized to show that INC is non-inferior to INT, with a non-inferiority margin of 1.373 for the hazard ratio, assuming 5-year DFS of 0.85 and 0.80 for INT and INC, respectively. Since two interim analyses were planned using the Hwang-Shih-DeCani alpha spending function to keep the global significance level at 5%, a maximum sample size of 1422 patients was anticipated to provide 80% power. However, the trial was prematurely terminated due to low recruitment before the first interim analysis, and therefore a single (final) analysis was done at the usual 5% significance level.

Data are described as mean (SD), median [IQR], or n (%), as appropriate. Analyses were conducted by intention-to-treat (ITT), on all randomized patients meeting the selection criteria and having at least one follow-up assessment. For the primary outcome (DFS), a secondary “per-protocol” analysis was also performed on patients who had complete radiotherapy data. The planned analysis based on the hazard ratio (HR) was considered inappropriate for several reasons: first, because 5-y DFS in both treatment groups were higher than the values assumed to determine the pre-specified non-inferiority margin for the HR; second, because the
proportional hazards assumption was questionable for efficacy outcomes (DFS, LRR, and DR); and third, because a heavy loss of power was expected since the trial was prematurely terminated before reaching the planned sample size. For these reasons, we compared DFS, LRR, and DR at five years using the Kaplan-Meier (KM) estimates and corresponding standard errors in a non-inferiority (one-sided) z-test, for a non-inferiority margin of 5%, and reported the one-sided 95% confidence interval (CI) for the between-groups difference. The frequency of acute toxicity was compared by a chi-square test. KM estimates of the chronic toxicity incidence were compared by a standard log-rank test and a two-sided 95% CI was computed for the hazard ratio (HR). All analyses were conducted with the R language, version 4.0.4 for Windows [32].

Results
From February 2015 to April 2021, 489 patients were assessed for eligibility. In April 2021, the trial was prematurely terminated due to low recruitment, and follow-up was stopped in August 2021. Two patients not meeting all selection criteria were excluded before randomization. Four hundred eighty-seven patients were assessed with the R language, version 4.0.4 for Windows [32].

Radiotherapy data were completed in the 427 out of 442 (96.6%) patients (INT: 220/222 or 96.4%, INC: 222/222 or 96.8%). Fifteen patients were excluded from the “per-protocol” analysis due to incomplete data. Table 2 summarizes the irradiated volumes without remarkable differences between groups. In the INT arm, 64.1% of patients received a boost, and in the INC arm, 60.8%. Table 3 shows the mean (SD) irradiation dose received per volume. In the INC arm, the mean doses received at level III and supraclavicular fossa were negligible, but those received at axillary levels I and II were 31.3 Gy and 20.3 Gy, respectively. In the INT arm, the internal mammary chain received slightly superior doses because the intentional irradiation of axillary levels III and supraclavicular volumes may include Incidentally part of mammary chain volume.

The median follow-up time was 3.7 years (with a range from 78 days to more than 6 years). During the follow-up, twenty-five events were reported in 16 patients (INC:10, INT:6). There were five deaths due to BC (INC:4, INT:1), four cases of local recurrence (INC:2, INT:2), five cases of regional recurrence (INC:3, INT:2), and eleven cases of distant recurrence (INC:8, INT:3).

Fig. 1 shows the KM estimates of the DFS by irradiation modality. The DFS at 5-years were 93.7% and 93.8% in the INC and INT irradiation groups respectively, with a difference of 0.1% (one-sided 95% CI: <5.7%; non-inferiority p = 0.075). Results were very similar when the analysis was conducted “per-protocol” on the 427 patients: 5-y DFS were 93.5% and 93.7% in INC and INT treatment groups respectively, with a difference of 0.2% (one-sided 95% CI: <5.9%; non-inferiority p = 0.082).

| Table 1 | Baseline characteristics of patients. LVI: lymphovascular invasion; ER: estrogen receptors; PR: progesterone receptors; OSNA: One-Step Nucleic acid Amplification; TTL: Total Tumor Load; SLN: Sentinel Lymph Node. |
|---|---|
| Age, mean (SD) | 56 (10) |
| Menstrual status, n (%) | 51 (25.5) |
| Pre-menopause | 52 (23.6%) |
| Peri-menopause | 19 (8.6%) |
| Post-menopause | 149 (67.7%) |
| Tumor grade, n(%) | 56 (25.7%) |
| G1 | 127 (57.7%) |
| G2 | 33 (15.0%) |
| Unknown | 3 (1.4%) |
| Tumor size, median [IQR] | 160.0 [11.5, 20.0] |
| LVI, n(%) | 50 (22.7%) |
| Ductal Ca in situ, n (%) | 140 (63.3%) |
| ER (%) cells, median [IQR] | 95.0 [90.0;100] |
| PR (%) cells, median [IQR] | 80.0 [20.0;98.0] |
| Her2receptor positive, n (%) | 20 (9.0%) |
| OSNA TTL of SLN (copies/mL), median [IQR] | 1155 [420,3525] |
| Surgery, n (%) | 148 (67.3%) |
| Tumorectomy | 72 (32.7%) |
| Surgery margins, n (%) | 14 (6.3%) |
| Positive | 206 (93.6%) |
| Negative | 56 (25.3%) |
| Comorbidities, n (%) | 150 (68.2%) |
| Adjuvant treatments (any), n (%) | 37 (16.8%) |
| Chemotherapy-based (any) | 25 (11.4%) |
| Anthracyclines and related substances | 49 (22.3%) |
| Combinations of antineoplastic agents | 49 (22.3%) |
| Nitrogen mustard analogues (Cyclophosphamide) | 20 (9.1%) |
| Pyrimidine analogues (FU) | 65 (29.5%) |
| Taxanes | 63 (28.4%) |
| Endocrine-based (any) | 30 (13.6%) |
| Anti-estrogens | 56 (25.5%) |
| Aromatase inhibitors | 50 (4.5%) |
| Targeted therapy (any) | 21 (6.6%) |
| Monoclonal antibodies | 31 (14.0%) |

*Adjuvant treatment with chemotherapy, endocrine or targeted therapy alone or in combination.

| Table 2 | Contour volumes. |
|---|---|
| Breast (cc), mean (SD) | 750.4 (411.8) |
| LRR, incidental irradiation (N = 222) | 772.3 (385.5) |
| Tumor bed (cc), mean (SD) | 109.7 (227.9) |
| LRR, intentional irradiation (N = 220) | 148.4 (268.2) |
| Supraclavicular (cc), mean (SD) | 31.1 (23.7) |
| LVI, incidental irradiation (N = 222) | 33.1 (32.6) |
| Axillary level 1 (cc), mean (SD) | 54.9 (43.3) |
| LVI, intentional irradiation (N = 220) | 54.2 (40.4) |
| Axillary level 2 (cc), mean (SD) | 30.8 (22.2) |
| LVI, incidental irradiation (N = 222) | 32.8 (26.6) |
| Axillary level 3 (cc), mean (SD) | 24.5 (20.9) |
| LVR, incidental irradiation (N = 222) | 25.7 (23.9) |
| Internal mammary chain (cc), mean (SD) | 21.7 (30.3) |
| LVR, intentional irradiation (N = 220) | 24.5 (47.5) |

LRR was observed in nine patients (INT:4, INC:5). The KM estimates of the 5-years Incidence of LRR were 3.5% and 3.4% in the INC and INT irradiation groups respectively, for a difference of 0.1% (one-sided 95% CI: <4.8%; non-inferiority p = 0.021). DR
occurred in 11 patients (INT:3, INC:8), and the KM estimates of the 5-years Incidence were 5% and 3.5% in the INC and INT irradiation groups respectively, with a difference of 1.4% (one-sided 95% CI: <6.0%; non-inferiority p = 0.101).

Acute toxicity events were reported in 191 (86.8%) of INT vs 199 (89.6%) of INC patients (chi-square test, p = 0.55). Most acute toxicity events (see Table 4) were mild or moderate (CTCAE grades 1 or 2). Grade 3 dermatitis radiation occurred in 13 (5.86%) of INC vs 20 (9.4%) of INT arm patients, skin hyperpigmentation in one incidental case, and skin ulceration in one intentional case.

Table 3
Mean dose received by volume. *Referred to patients that received “boost”, 141 and 135 patients in the intentional and incidental irradiation groups, respectively.

| Event                          | Intentional irradiation (N = 220) | Incidental irradiation (N = 222) |
|-------------------------------|-----------------------------|----------------------------------|
| Breast (Gy), mean (SD)        | 49.8 (4.8)                  | 50.2 (4.7)                       |
| Tumor bed (Gy), mean (SD)*    | 59.4 (6.64)                 | 59.6 (6.62)                      |
| Axillary level 1 (Gy), mean   | 48.0 (4.6)                  | 31.3 (13.4)                      |
| (SD)                          |                             |                                  |
| Axillary level 2 (Gy), mean   | 47.5 (6.0)                  | 20.3 (15.3)                      |
| (SD)                          |                             |                                  |
| Axillary level 3 (Gy), mean   | 47.6 (7.6)                  | 9.1 (11.2)                       |
| (SD)                          |                             |                                  |
| Supraclavicular (Gy), mean    | 50.0 (8.4)                  | 1.0 (8.4)                        |
| (SD)                          |                             |                                  |
| Internal mammary chain (Gy),  | 24.3 (14.6)                 | 19.8 (13.2)                      |
| mean (SD)                     |                             |                                  |

Discussion

This study shows that the estimated advantage of RNI in early BC patients cN0 with low TTL assayed by OSNA (<15000) has a low impact on LRR and DFS at a median follow-up of 3.7 years. Nodal irradiation has shown benefits in several trials [5,7,9,10,33], concluding that ALND could be substituted by RNI [29]. The authors of these studies were aware of some overtreated patients [34], and the need to irradiate in cases with low LN involvement has always been doubted [35]. For this reason, several trials have been conducted [36,37]. Our trial was designed to verify whether INC irradiation was sufficient or whether complete radiotherapy of all node levels was necessary.

Our trial was prematurely terminated because the recruitment rate was much lower than expected. Reasons for low recruitment are the increase in the frequency of primary systemic treatment due to better clinical and ultrasound diagnostic as well as the impact of the COVID-19 pandemic. The consequent loss of power in the analysis of DFS was partially compensated by an incidence of disease progression events lower than assumed in the sample size determination and, therefore, more extreme 5y DFS values. In any case, our results show that the outperformance of INT over INC irradiation is no more than 5.7% in terms of 5-y DFS and provides evidence of non-inferiority of the INC irradiation in terms of LRR for the pre-specified non-inferiority margin of 5% (p = 0.021).

Comparison with relevant findings from other published studies is difficult because most of them do not clearly describe the radiotherapy volumes used as adjuvant treatment. Previous studies have reached conflicting conclusions on the need for axillary treatment in BC patients. While some have shown that even low axillary burden implies a worse prognosis [38] and that local treatment, whether ALND or radiotherapy, improves survival [39–41], others have concluded that RNI is not necessary [42–44]. Also, a metaanalysis found that level III and supraclavicular fossa irradiation does not improve survival [45]. However, this discrepancy might be explained by the exact volumes and doses received at each level, mainly from incidental irradiation, which is often not reported in radiotherapy studies [46]. It is known that these are not negligible and can be responsible for good results in study arms without regional treatment [47], particularly when the so-called “high tangents” are used to treat patients with low burden positive nodes or without specific contouring of low axilla (levels I and II). It must also be weighed considering that in the Z011 trial, a considerable proportion (19%) of patients received intentional irradiation to supraclavicular as reported in the revision of radiotherapy fields inside the trial by Jaggi et al. [48]. As stated by ESTRO guidelines [49] and other studies [50] careful delineation of volumes and levels at risk is recommended. In our study, the doses received at low axillary levels in the INC irradiation arm were important, and we hypothesize that this is probably the case in other studies. Consequently, in patients with TTL < 15000 copies mRNA CK19/µL, exclusive radiotherapy of axillary levels I and II would be the most useful.
appropriate, as suggested by several authors [51–53], to gradually de-escalate axillary treatment as advised [54].

Precision oncology needs new development in pathology management, including technologies for LN analysis such as OSNA. Numerous validation studies have compared this technology with conventional techniques (haematoxylin and eosin staining and immunohistochemistry), obtaining sensitivity, specificity, and area under the ROC curve results of 0.90, 0.96, and 0.98, respectively [55]. Furthermore, OSNA is the only one that currently allows the analysis of the whole SLN, which is considered the procedure of choice for the pathological study of the SLN [56–58]. OSNA has also been introduced into clinical usage for intraoperative SLN metastasis detection [59] and has demonstrated how TTL is considered a prognostic factor [17,60]. With the advantage of standardization, reliability, and repetitiveness, molecular diagnostic techniques for intra-operative detection of SLN involvement can help clinicians make the right decisions about optimal treatment indications.

Our study has several important limitations derived from its premature cancellation. First, the consequent loss of power might be the reason why we failed to show non-inferiority in terms of 5-y DFS for the pre-specified margin of 5%. Second, the median follow-up length was 3.7 years, with less than 100 patients per group followed for more than 3 years (see Fig. 1). Third, some randomized patients had to be excluded from the analysis due to a lack of follow-up data, and post-randomization exclusions can be a source of bias. However, the number of these exclusions was not significantly different in the two intervention groups (Chi-square test $p = 0.25$), making them less likely to be a source of bias. In light of these limitations, our results should be considered with caution and confirmed by future studies with longer follow-ups.

Conclusions

This trial failed to show non-inferiority of the incidental irradiation compared to intentional irradiation of axillary nodes for the pre-specified non-inferiority margin of 5% in terms of 5-years DFS. However, the estimated advantage of intentional irradiation is no higher than 5.7%. In terms of LRR, incidental irradiation was not inferior to intentional irradiation, which outperformed the former by no more than 4.8%. Acute toxicity was similar in both irradiation modalities, but data suggested a potential higher incidence of chronic toxicity in the case of intentional irradiation.

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Conflict of Interest Statement

Dr. Algara has received consulting honoraria from Sysmex and Aristo and speaking honoraria from Siemens and Roche; the rest of authors declare that they have no competing interests.
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