OPTimizing Irradiation through Molecular Assessment of Lymph node (OPTIMAL): a randomized open label trial.

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Abstract
Background
Conservative surgery followed by breast and nodal irradiation is the standard loco-regional treatment for early breast cancer (BC) patients with four or more involved lymph nodes. However, the treatment strategy when fewer nodes are involved remains unclear, especially when lymphadenectomy has not been performed. Sensitive molecular techniques for nodal status assessment such as the OSNA (One-Step Nucleic Acid Amplification) assay can contribute to the definition and standardization of the treatment strategy. Therefore, the OPTIMAL study aims to demonstrate the feasibility of the incidental irradiation of axillary nodes in patients with early-stage BC and limited involvement of the SLN.

Methods
BC patients with conservative surgery and a total tumour load of sentinel lymph nodes assessed with OSNA ranged between 250–15,000 copies/µL will be eligible. Patients will be randomized to receive irradiation on breast, tumour bed, axillary and supraclavicular lymph node areas (intentional arm) or only on breast and tumour bed (incidental arm). All areas, including the internal mammary chain, will be contoured. The mean, median, D5% and D95% doses received in all volumes will be calculated. The primary endpoint is the non-inferiority of incidental irradiation of axillary nodes compared with the intentional irradiation in terms of 5-year disease free survival. Secondary endpoints comprise the comparison of acute and chronic toxicity, loco-regional and distant disease recurrence rates.

Discussion
Standardizing the treatment and diagnosis of BC patients with few nodes affected is crucial due to the lack of consensus on the therapeutic strategies in these patients. Hence, the quantitative score for metastatic burden of SLN provided by OSNA can contribute to improve the discrimination of BC patients with a limited nodal involvement who can benefit from incidental radiation as an adjuvant treatment strategy.

Trial registration
ClinicalTrials.gov, NCT02335957; https://clinicaltrials.gov/ct2/show/NCT02335957

Background
Breast and nodal irradiation in breast cancer (BC) patients have been shown to reduce mortality and disease recurrence [1]. Thus, there is evidence supporting the application of this adjuvant radiotherapy after conservative surgery. In patients with four or more involved lymph nodes (LN), nodal irradiation is also recommended, as it increases patient’s survival rates [2]. This also occurs in patients with other types of locally advanced tumours with LN involvement [3]. A randomized clinical trial carried out by the British Columbia Cancer Agency, showed that the 20-year disease-free survival (DFS) of patients subjected to the combination of chemotherapy and radiation was 13% higher than that of the patients who were treated with chemotherapy alone [4]. Similar results were achieved in the DBCG 82 b&c trial showing a difference of 10% in the 15-year overall survival rate between the treatment combination and chemotherapy alone (39% vs. 29%, respectively) [5]. Furthermore, a study funded by the Canadian Cancer Society determined that adjuvant radiation treatment of patients with more than 3 involved LN led to a decrease in disease recurrence [6]. However, there is no unanimity on the recommendation of radiotherapy when the nodal involvement ranges between 1 and 3 LN [7].

This scenario turned out even more ambiguous since Giuliano et al. demonstrated no significant benefit in loco-regional control with completion of axillary lymph node dissection (ALND) in comparison to no ALND in patients with 1–2 involved LN [8, 9]. On the other hand, AMAROS [10] and OTOSAOR [11] trials demonstrated that nodal irradiation should be regarded as the recommended treatment for patients with few involved LN, instead of ALND. In line with their results, the Canadian trial NCIC-CTG MA20 [6] showed that local irradiation combined with regional irradiation improved the DFS as well as the loco-regional and distant control of the disease in high-risk patients with negative and with positive LN, mostly with 1 to 3 involved LN, while Poortmans et al. [12] demonstrated that the irradiation of the regional nodes in patients with low axillary disease results in an increase of the DFS. Finally, Darby et al. [13] reported that, after breast-conserving surgery, the application of radiotherapy to the breast reduced mortality and the disease recurrence by half while a systematic review, which included more than 20,000 patients from 45 studies, concluded that breast irradiation reduced the loco-regional relapse even in patients without LN involvement [14].
The uncertainty about the proper radiation therapy entails the need for a method that standardizes the choice of treatment and complements the limited diagnostic information [15–17], such as nodal involvement assessment. The OSNA (One-Step Nucleic Acid Amplification) assay provides a quantitative determination of the metastatic burden of the sentinel lymph node (SLN) by measuring the mRNA expression of the tumour marker cytokeratin 19 (CK19) [18]. The OSNA assay not only provides automated and complete intraoperative analyses of the SLN but also standardized and reliable results for SLN metastatic status. The total tumour load (TTL), defined as the sum of the CK19 mRNA copies from all positive SLNs of the patient, entails a quantitative score that integrates both the metastatic burden and the number of SLN affected. The TTL score was proved to be an independent predictor factor of the axillary nodal status, where only 14.7% of patients with TTL beneath 15.000 copies/µl had other positive non-SLN [19]. Recently, the PLUTTO study results also proved its impact on the prognosis of BC patients [20].

Therefore, the OPTIMAL study (OPTimizing Irradiation through Molecular Assessment of Lymph node) aims to demonstrate the non-inferiority of incidental irradiation of axillary nodes compared with the intentional irradiation in terms of 5-year DFS of patients with early-stage BC and limited involvement of the SLN according to the OSNA quantitative score.

**Methods / Design**

**Study Design**

The OPTIMAL study is an open-label multicentre and international trial (NCT02335957) conducted in over 40 sites from Spain, Portugal, and Italy. Eligible patients will be randomized with a 1:1 allocation ratio to receive irradiation on breast, tumour bed, axillary and supraclavicular lymph node areas (intentional arm) or only on breast and tumour bed (incidental arm), as depicted in Fig. 1. Randomization by blocking within centres to minimize imbalance of treatments among centres will be conducted through the online randomization software RANDI2 (www.dkfz.de; Heidelberg University) embedded in the electronic case record form (eCRF). All patients will have to provide their Informed Consent prior to the inclusion in the study.

BC, breast cancer; CK19, cytokeratin 19 mRNA, messenger ribonucleic acid; SLN, sentinel lymph
node; TTL, total tumour load

Eligibility Criteria

Inclusion Criteria
Female invasive ductal breast cancer patients
Older than 18 years old
Previous treatment with breast-conserving surgery without axillary lymphadenectomy
OSNA assayed SLN with a TTL within the 250-15,000 copies/µL range
≥70% grade in the Karnofsky Performance Scale Index
Written and signed Informed Consent

Exclusion Criteria
Other types of breast cancer
Bilateral breast cancer
Male breast cancer patients
Patients who underwent a mastectomy or ipsilateral dissection of axillary LN
Having received previous thoracic irradiation
Systemic neoadjuvant therapy prior to surgery
Contraindications to radiotherapy such as pregnancy or serious collagen disease.
Other Neoplasms and or any associated sever comorbidities that may interfere with the study

Endpoints

Primary Endpoint
The primary endpoint is the non-inferiority of incidental irradiation of axillary nodes in contrast to intentional irradiation, in terms of the 5-year DFS of patients diagnosed with early-stage breast cancer with limited involvement of the SLN treated with breast-conservative surgery without axillary lymphadenectomy.

Secondary Endpoints
The secondary endpoints established were the following:

Loco-regional tumour recurrence in the two treatment arms within the 5-year follow-up period.
Distant tumour recurrence in the two treatment arms within the 5-year follow-up period.
Acute toxicity induced by either the incidental or intentional radiation treatment.
Chronic toxicity induced by either the incidental or intentional radiation treatment.
Total irradiation dose (Gy) received in axillary levels I-III, supraclavicular fossa, and internal mammary chain volumes in the incidental arm.

Radiation procedure

Volume Delineation
All nodal areas from axillary levels I-III, the supraclavicular fossa and the internal mammary chain must be contoured in all patients regardless of the assigned arm following the guidelines of the Radiation Therapy Oncology Group [21].

Treatment Planning
The treatment planning must be carried out on a 3D system with correction tissue heterogeneity and
matrix resolution of 2.5 mm. Techniques in the supine position are allowed and the prone position is not permitted.

High or modified tangential, AP/PA, 3D conformal, and field in field techniques as well as intensity modulated radiation therapy or volumetric modulated arc therapy are allowed.

Breast: The treatment must be performed with a 6MV-15MV photon. The isocentre must be located within the planning target volume of the breast in the incidental arm but it may be located outside of the intentional arm. In order to minimize the dose in the lung and heart, the use of tangential beams over the entire breast volume is recommended.

Tumour bed: Mini-tangential photon fields or simple electron fields, including a combination of energies, can be used. Brachytherapy or intraoperative irradiation are also allowed as long as the contribution of the dose to the nodal areas can be calculated. The use of boluses can be considered if needed.

Nodal areas: In the intentional arm, the treatment planning must be optimized to ensure the prescribed dose to the nodal areas, except the internal mammary chain, minimizing the dose at the organs at risk. In the incidental arm, the treatment planning for nodal areas will not be performed.

A non-planned gap of up 3 days is acceptable. Longer non-planned interruptions should be compensated by hyperfractionation of the daily normal dose.

Dose Prescription

All doses prescribed will follow the International Commission on Radiation Units and Measurements guidelines. A minimum of 95% of the volume must receive at least 95% of the prescribed dose. Less than 5% of the volume may receive a dose of 105% and less than 2% should receive a dose of 107%, with a maximum global dose of 110%. The dose in the breast must be 50.0 Gy by 25 fractions of 2.0 Gy in 5 weeks or through hypofractionated schedules as 40.05 Gy in 15 fractions of 2.67 Gy for 3 weeks. In the tumour bed, the schedule and total dose are left to the criterion of the centre. In nodal areas, the intentional irradiation to the breast and tumour bed will be calculated. Limiting doses for the organs at risk must be: i) ipsilateral lung: V20 less than 25%; and ii) heart: V20 less than 10% and V40 less than 5%.

Radiotherapy Verification

Verification methods will be conducted in both arms. Treatment verification is required at the first treatment fraction and allowed on the three first fractions. The verification must be performed using electronic portal images of the treatment beam; either with MV or kV. Orthogonal images or cone-beam images can be used on the verification of the isocentre. Weekly control will be performed, and systematic daily control is also permitted.
Follow-up

Patients will be followed for up to 5 years after the intervention according to the visit schedule detailed in Table 1. In each visit, physical examination and recurrence assessment will be performed. An image assessment will be requested every year after the intervention. Reasons for discontinuing follow-up must be reported.

Table 1
Schedule of visits and assessments (dots) that will be performed during the 5-year follow-up period.

| Post-Intervention (Year) | 1 | 2 | 3 | 4 | 5 |
|--------------------------|---|---|---|---|---|
| Post-Intervention (Month) | 1 | 3 | 6 | 9 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 |
| Acute Toxicity           | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Physical Exam            | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Image evaluation of local recurrence | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Survival and disease recurrence | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Chronic Toxicity (Continuous Recording) |       |       |       |       |       |       |       |       |       |       |       |       |
| Co-medication, (Adjuvant) (Continuous Recording) |       |       |       |       |       |       |       |       |       |       |       |       |

Data collection and analysis

Data Collection

Study data will be recorded in an eCRF (OpenClinica®, LLC). The demographic and clinical data requested is depicted in Table 2. Acute and chronic toxicity will be recorded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) [22] criteria. Specific follow-up outcomes will be assessed and registered during the visits scheduled as stated in Table 1.
Table 2
Data collected in the electronic case record form.

| Panel in eCRF | Data recorded                                      |
|---------------|---------------------------------------------------|
| Informed Consent | Date                                               |
| I/E criteria  | Yes; Not                                           |
| Demographic data | Age at inclusion; Menstrual State                 |
| Comorbidities | If yes: specify                                    |
| Cancer Histology and Receptors, SLN OSNA | Tumour grade; Tumour size (maximum diameter); P53 (%) ; Ki67 (%) ; Lymphovascular infiltration; Ductal Ca in situ; % Estrogenic receptors; % Progesterone receptors; HER2 receptor status; OSNA TTL of SLN |
| Type of surgery | Tumour surgery; date; Margins                      |
| Image evaluation of local recurrence | Technique; Local recurrence (if yes: Maximum diameter) |
| Randomization | Treatment randomly allocated; Randomization date    |
| Physical Examination | Palpable breast tumour (if yes: size, skin infiltration, inflammatory carcinoma, satellite lesions); Palpable axillary nodes (if yes: size); Palpable supraclavicular nodes (if yes: size); Node staging |
| Radiotherapy intervention | Patient completed the allocated treatment (if no: main reason); Start date; End date; Treatment gaps (if yes, reason); Dose per volume (Mean; Median; D95; D5; Volume) in breast, tumour bed, supraclavicular and axillary levels I-III, and Internal mammary chain |
| Previous medication (Adjuvant therapy) | Drug; Start date; Stop date                        |
| Co-medication (Adjuvant therapy) | Drug; Start date; Stop date                        |
| Survival and disease recurrence | Date of follow-up visit (If not performed, reason); Local recurrence; Regional recurrence (if yes: nodal level); Distant recurrence (if yes: organ); Vital status (if dead: date and cause) |
| Toxicity, acute and chronic | CTCAE term; Grade; Start date; Stop date; Status (recovered w/o sequels; death) |

A total of 1400 patients (250 recurrence events) must be recruited to show the non-inferiority of the experimental arm (incidental irradiation) with a 80% of statistical power when we assume a 5-year recurrence rate of 15% in the control intervention (intentional irradiation) [8], a 5% non-inferiority margin, a yearly dropout rate of 5%, and a fixed sample design. Despite the short follow-up period, the large number of patients to be included in the study will preserve the statistical significance of the survival rates and will be enough to evaluate differences in the toxicity rates.

Statistical analysis
Two sets of patients will be analysed: the intention-to-treat (ITT) group, which includes all randomized patients, to describe the baseline clinic-pathological patients’ characteristics; and the per-protocol subset, which includes patients who finish the intervention treatment as planned with all dosimetry data completed, for the endpoint. A descriptive analysis will be carried out reporting absolute and relative frequencies for all variables recorded and stratified by treatment group. Two analyses of the primary endpoint (disease-free survival rate) will be conducted. The confirmatory analyses will be carried out using a non-inferiority long-rank test in the ITT set of patients, which includes all
randomized patients regardless of whether the treatment or follow-up are accomplished. A secondary explanatory analysis will be conducted in the per-protocol subgroup, which will include patients who will have finished the intervention treatment with all dosimetry data completed, by an adjusted Cox regression model using the covariates: centre, age at inclusion, tumour size, hormone receptor status, Her2 receptor status, and OSNA results. With regards to the secondary endpoints: the outcomes of loco-regional and distant recurrence will be analysed using the Cox approach, this time in the ITT set. Acute toxicity will be analysed by a chi-squared test comparing frequencies in both treatment groups. Chronic toxicity will be analysed by using Kaplan Meier curves and comparing them by a standard log-rank test. Interim analyses are planned when 85 events and 169 events will be reached.

**Current Status of the Trial**

From February 2015 to February 2020, a total of 451 patients have been recruited (224 in the intentional arm and 227 in the incidental arm). Out of the 329 (73%) have completed the radiation treatment and acute toxicity events have been reported in 319 cases. At present, a total of 48 chronic toxicity and 13 recurrence events have been reported.

**Discussion**

Nowadays, nodal irradiation is conducted in early BC patients with 2 or fewer affected LN instead lymphadenectomy although it is unclear whether local specific treatment is required in these patients. This uncertainty arises from that current studies do not clearly describe the radiation volumes used as adjuvant treatment. Some physicians advocate that the breast of these patients should be treated with high or modified tangents [23]. Therefore, although it is not stated as LN irradiation, the axillary levels I and II are being irradiated. Accordingly, more than 70% of patients who had not undergone lymphadenectomy received LN radiation and even 19% received unallowed supraclavicular irradiation in the study conducted by Giuliano and col. [24]. In consequence, studies that specifically evaluate the incidental and intentional doses are necessary. Thus, the OPTIMAL trial was designed to outline an evidence-based strategy for the treatment of BC patients with limited nodal involvement by determining the non-inferiority of incidental radiation of the axillary nodes in comparison with
intentional radiation. The ESTRO (European SocieTy for Radiotherapy and Oncology) meeting in Assisi stated the importance of further investigations on regional lymph node treatment and highlighted the design and expected results of the OPTIMAL, SENOMA, and POSTNOC studies, all of them focused on the treatment of patients with limited axillary disease [25].

In the OPTIMAL trial, the SLN status and the limited LN involvement is determined according to the OSNA quantitative molecular assay [18]. At the time of the study design, few studies with regards to OSNA performance had been reported. Nowadays, its contribution to the improvement of BC patient staging and prognosis has been widely reported [26]. In fact, LN assessment with OSNA assay and the evaluation of the TTL as a quantitative score of the metastatic burden of the patients is recommended for the management of BC patients in the SESPMA (Spanish Society of Senology and Breast Pathology) and the NICE (National Institute for Health and Care Excellence) guidelines [27–29]. This technique provides quick and standarized results at in-house diagnostic laboratories, which prompts the patient’s diagnosis and treatment tailoring, since central laboratories are not required for a reliable LN assessment.

In conclusion, standardizing the treatment and diagnosis of BC patients with few nodes affected is crucial due to the lack of consensus on the proper therapeutic strategy for these patients. Hence, the quantitative score for metastatic burden provided by OSNA assay can contribute to improving the discrimination of BC patients with a limited nodal involvement who can benefit from incidental radiation as an adjuvant treatment strategy.

**Abbreviations**

ALND
Axillary lymph node dissection
AP/PA
Anterior-posterior/posterior-anterior
BC
Breast cancer
CK19
Cytokeratine 19
CTCAE
Common Terminology Criteria for Adverse Events
DFS
Disease free survival
eCRF
Electronic case report form
ESTRO
European Society for Radiotherapy and Oncology
ITT
Intention-to-treat
LN
Lymph node
mRNA
messenger ribonucleic acid
NICE
National Institute for Health and Care Excellence
OSNA
One-Step Nucleic Acid Amplification
SESPM
Spanish Society of Senology and Breast Pathology
SLN
Sentinel lymph node
TTL
Total tumour load

Declarations

Ethics approval and consent to participate

The study will be conducted in accordance with the Declaration of Helsinki - Ethical Principles for Medical Research Involving of Human Subjects and guidelines for Good Clinical Practice. The Spanish Agency of Medicines and Medical Devices evaluated and classified the study. The study has been approved by the Institution Research Board of each centre.

Consent for publication

Not applicable.

Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available due to confidentiality reasons but are available from the corresponding author on reasonable request.

**Competing interests**

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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The sponsor GICOR (Grupo Investigación Clínica en Oncología-Radioterapia), non-profit research organization, is responsible for ensuring compliance with legal regulations and study management.

GICOR has the final responsibility for publication.

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**Authors' contributions**

Study conception and designed: MA. Study data monitoring: XS. Manuscript conception and writing: MA and XS. All authors read and approved the final manuscript.

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References

1. Abe O, Abe R, Enomoto K, Kikuchi K, Koyama H, Masuda H, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. Lancet. 2005;366:2087–106.

2. Recht A, Comen EA, Fine RE, Fleming GF, Hardenbergh PH, Ho AY, et al. Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. Pract Radiat Oncol. 2016;6:e219–34.

3. Dalela D, Santiago-Jiménez M, Yousefi K, Karnes RJ, Ross AE, Den RB, et al. Genomic classifier augments the role of pathological features in identifying optimal candidates for adjuvant radiation therapy in patients with prostate cancer: Development and internal validation of a multivariable prognostic model. J Clin Oncol. 2017;35:1982–90.

4. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005;97:116–26.

5. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international
consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol. 2007;82:247–53.

6. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015;373:307–16.

7. Xie L, Higginson DS, Marks LB. Elective Regional Nodal Irradiation in Patients With Early-Stage Breast Cancer. Semin Radiat Oncol. Elsevier Inc.; 2011;21:66–78.

8. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis. Jama. 2011;305:569–75.

9. Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch a M, et al. Locoregional Recurrence after Sentinel Lymph Node Dissection with or without Axillary Dissection in Patients with Sentinel Lymph Node Metastases: The American College of Surgeons Oncology Group Z0011 Randomized Trial. Ann Surg. 2010;252:426–33.

10. Straver ME, Meijnen P, Van Tienhoven G, Van De Velde CJH, Mansel RE, Bogaerts J, et al. Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial. Ann Surg Oncol. 2010;17:1854–61.

11. Sávolt PG, Polgár C, Udvarhelyi N, Rubovszky G, Kovács E, et al. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla – Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. Eur J Surg Oncol. 2017;43:672–9.

12. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015;373:317–27.
13. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10 801 women in 17 randomised trials. Lancet. Elsevier Ltd; 2011;378:1707–16.

14. Van Wely BJ, Teerenstra S, Schinagl DAX, Aufenacker TJ, De Wilt JHW, Strobbe LJA. Systematic review of the effect of external beam radiation therapy to the breast on axillary recurrence after negative sentinel lymph node biopsy. Br J Surg. 2011;98:326–33.

15. Setton J, Cody H, Tan L, Morrow M, Hudis C, Catalano J, et al. Radiation field design and regional control in sentinel lymph node-positive breast cancer patients with omission of axillary dissection. Cancer. 2012;118:1994–2003.

16. Haffty BGB, Hunt KKK, Harris JRJ, Buchholz T a. Positive sentinel nodes without axillary dissection- implications for the radiation oncologist. J Clin Oncol. 2011;29:4479–81.

17. Bayo E, Herruzo I, Arenas M, Algara M. Consensus on the regional lymph nodes irradiation in breast cancer. Clin Transl Oncol. 2013;15:766–73.

18. Tsujimoto M, Nakabayashi K, Yoshidome K, Kaneko T, Iwase T, Akiyama F, et al. One-step nucleic acid amplification for intraoperative detection of lymph node metastasis in breast cancer patients. Clin Cancer Res. 2007;13:4807–16.

19. Peg V, Espinosa-Bravo M, Vieites B, Vilardell F, Antúnez JR, De Salas MS, et al. Intraoperative molecular analysis of total tumor load in sentinel lymph node: A new predictor of axillary status in early breast cancer patients. Breast Cancer Res Treat. 2013;139:87–93.

20. Peg V, Sansano I, Vieites B, Bernet L, Cano R, Córdoba A, et al. Role of total tumour load of sentinel lymph node on survival in early breast cancer patients. The Breast.
21. Li XA, Ph D, Tai A, Ph D, Arthur DW, Buchholz TA, et al. Variability of target and normal structure delineation for breast cancer radiotherapy: an RTOG Multi-Institutional and Multiobserver Study [Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definitions]. Int J Radiat Oncol Biol Phys. 2009;73:944–51.

22. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.0. 2010; Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

23. Gebhardt BJ, Thomas J, Horne ZD, Champ CE, Ahrendt GM, Diego E, et al. Standardization of nodal radiation therapy through changes to a breast cancer clinical pathway throughout a large, integrated cancer center network. Pract Radiat Oncol. 2018;8:4–12.

24. Jagsi R, Chadha M, Moni J, Ballman K, Laurie F, Buchholz TA, et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. J Clin Oncol. 2014;32:3600–6.

25. Aristei C, Kaidar-Person O, Arenas M, Coles C, Offersen BV, Bourgier C, et al. The 2016 Assisi Think Tank Meeting on breast cancer: white paper. Breast Cancer Res Treat. 2016;160:211–21.

26. Chaudhry A, Williams S, Cook J, Jenkins M, Sohail M, Calder C, et al. The real-time intra-operative evaluation of sentinel lymph nodes in breast cancer patients using One Step Nucleic Acid Amplification (OSNA) and implications for clinical decision-making. Eur J Cancer Surg Elsevier Ltd. 2014;40:150–7.

27. Bernet L, Piñero A, Vidal-Sicart S, Peg V, Giménez J, Algara M, et al. Consenso sobre la biopsia selectiva del ganglio centinela en el cáncer de mama. Revisión 2013 de la Sociedad Española de Senología y Patología Mamaria. Rev Esp Patol. 2014;47:22–32.

28. National Institute for Health and Clinical Excellence. Intraoperative tests (RD-100i
OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer. Diagnostics guidance [DG8] [Internet]. 2013. Available from: http://www.nice.org.uk/nicemedia/live/14247/64810/64810.pdf.

29. Szabatura AH, Pharm D, Seung AH, Pharm D, Freml JM, Pharm D, et al. Early and Locally Advanced Breast Cancer. Natl Inst Heal Clin Excell. 2019;1–32.

Figures
Early-BC patients
with limited SLN involvement
(TTL: 250-15,000 CK19 mRNA copies/µL)

Eligibility Assessment

Randomization
1:1 allocation

Intervention

Arm A: Intentional nodal radiation
breast, tumour bed, axillary I-III
and supraclavicular areas

Arm B: Incidental nodal radiation
breast and tumour bed

Total Dose (50 Gy)

5-year Follow-up

Disease-free survival
Acute and chronic toxicity
Loco-regional and distant recurrence

Figure 1
OPTIMAL-I study design.