Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial

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Abstract Background: Accelerated partial breast irradiation (APBI) has been introduced as an alternative treatment method for selected patients with early stage breast cancer (BC). Intensity-modulated radiotherapy (IMRT) has the theoretical advantage of a further increase in dose conformity compared with three-dimensional techniques, with more normal tissue sparing. The aim of this randomised trial is to compare the local recurrence and survival of APBI using the IMRT technique after breast-conserving surgery to conventional whole-breast irradiation (WBI) in early stage BC.

Methods: This study was performed at the University of Florence (Florence, Italy). Women aged more than 40 years affected by early BC, with a maximum pathological tumour size of 25 mm, were randomly assigned in a 1:1 ratio to receive either WBI or APBI using IMRT. Patients in the APBI arm received a total dose of 30 Gy to the tumour bed in five daily fractions. The WBI arm received 50 Gy in 25 fractions, followed by a boost on the tumour bed of 10 Gy in five fractions. The primary end-point was occurrence of ipsilateral breast tumour recurrences (IBTRs); the main analysis was by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NCT02104895.

Findings: A total of 520 patients were randomised (260 to external WBI and 260 to APBI with IMRT) between March 2005 and June 2013. At a median follow-up of 5.0 years (Interquartile Range (IQR) 3.4–7.0), the IBTR rate was 1.5% (three cases) in the APBI group (95% confi-dence interval (CI) 0.1–3.0) and in the WBI group (three cases; 95% CI 0.0–2.8). No significant difference emerged between the two groups (log rank test p = 0.86). We identified seven deaths in the WBI group and only one in the APBI group (p = 0.057). The 5-year overall survival was 96.6% for the WBI group and 99.4% for the APBI group. The APBI group presented signif-icantly better results considering acute (p = 0.0001), late (p = 0.004), and cosmetic outcome (p = 0.045).

Interpretation: To our knowledge, this is the first randomised study using the IMRT technique for APBI delivery. No significant difference in terms of IBTR and overall survival was observed between the two arms. APBI displayed a significantly better toxicity profile.

KEYWORDS Accelerated partial breast irradiation Whole breast irradiation Intensity-modulated radiotherapy IMRT Phase 3 trial

1. Introduction

The standard treatment for early breast cancer (BC) patients is based on breast conservative surgery (BCS) followed by whole-breast irradiation (WBI) [1,2]. The majority of early breast recurrences occur at the site of the original primary tumour, regardless of whether radiotherapy (RT) has been administered or whether the margins are involved [3,4].

Accelerated partial breast irradiation (APBI) has been introduced as an alternative treatment method for selected patients with early stage BC [5]. Potential advantages of APBI include shorter treatment time, improved cosmesis because of the decreased volume of breast tissue treated, and a cost reduction compared with standard fractionation [6]. Recently, many tech-niques have been tested in an attempt to administer adjuvant RT while reducing the burden for patients and RT departments [7,8].

There are currently little randomised controlled trial data confirming that improved homogeneity with simple intensity-modulated radiotherapy (IMRT) decreases late breast tissue toxicity [9].

As the oncology community awaits results from NSABP B-39/RTOG 0413, the largest randomised trial of WBI versus APBI, to provide more conclusive data, many academic and private radiation oncology practices are utilising APBI o protocol [10]. Although the ideal patient profile for APBI is not clearly identified, the American Society for Radiation Oncology (ASTRO) and the Groupe Europe´en de Curiethe´rapie-Euro-pean Society for Therapeutic Radiology and Oncology (GEC-ESTRO) [12] have suggested selection criteria for 'suitable patients' for APBI outside of clinical trials.

We present the results of a randomised trial compar-ing local recurrence and survival of APBI using the IMRT technique after BCS to conventional WBI in early stage BC.

2. Methods

2.1. Study profile and patients

This single-institution study was conceived and per-formed at the Radiation-Oncology Department of Uni-versity of Florence (Florence, Italy).

Between 11th March, 2005, and 18th June, 2013, a randomised phase 3 clinical trial was conducted to com-pare conventional (tangential field) WBI and APBI using the IMRT technique. Eligible patients, as previ-ously described [13], were women aged more than 40 years with early BC (maximum diameter 2.5 cm) suitable for BCS. Enrolled patients had to be able to complete prescribed treatments and to adhere to trial follow up programme. Angiovascular invasion, ductal carcinoma in situ (DCIS), and axillary lymph node posi-tive status were not considered exclusion criteria.

Exclusion criteria were: previously diagnosed solid tumours; left ventricular ejection fraction (LVEF) <50% as measured by echocardiography or a history of active angina, myocardial infarction, or other cardio-vascular disease; forced expiratory volume in 1 s (FEV_1) <1 L/m; extensive intraductal carcinoma; multiple foci cancer; final surgical margins <5 mm; and the absence of surgical clips in tumour bed.

The local Ethics Committee (Azienda Ospedaliero-Universitaria Careggi, Florence, Italy) gave permission to perform the present study, which was conducted according to the Declaration of Helsinki and the Guide-lines for Good Clinical Practice. All patients provided full written informed consent. The trial profile is sum-marised in Fig. 1.

2.2. Randomisation and masking

Patients were randomly assigned to receive either WBI or APBI using IMRT in a 1:1 ratio. Allocation was performed with a computer-generated sequence using a randomly permuted block design, without any stratification of main prognostic factors. The random sequence was kept by an external centre (local Oncolog-ical Centre for Departmental Reference, CORD). The clinicians were required to query it every time an eligible patient had provided written informed consent to deter-mine the allocation arm. Clinicians, investigators and the patients themselves were aware of the arm assignment.

2.3. Procedures

In our centre, dedicated pathologists performed his-topathological assessment of breast pathology. Oestro-gen receptor (ER) status, progesterone receptor (PgR) status, human epidermal growth factor receptor 2 (HER2) and Ki 67 labelling index were assessed using immunohistochemistry (IHC).

The following well-validated primary antibodies were applied [14] anti-ER, until 2004, clone 1D5 (BioGenex, San Ramon, CA), from 2005 to 2006, clone 6F11 (Ven-tana, Medical Systems, Tucson, Arizona), and from 2007 to present, clone SP1 (Ventana, Medical Systems, Tucson, Arizona); anti-PgR, until 2004, clone 1A6 (BioGenex, San Ramon, CA), from 2005 to 2006, clone 16 (Ventana, Medical Systems, Tucson, Arizona), and from 2007 to present, clone 1E2 (Ventana, Medical Systems, Tucson, Arizona); anti-Ki 67, from 1997 to present, clone Mib-1 (Dako, Golstrup, Denmark); anti-HER2, until 2003, clone TAB 250 (Zymed, San Francisco, CA), from 2004 to present, polyclonal A0485 (Dako, Golstrup, Denmark).

ER, PgR and Ki 67 expression was scored as the per-centage of positive nuclei over the total number of tumour cell nuclei counted. For ER and PgR status, two categories (negative/positive) were considered according to well-established cut-o values [15].

Concerning Ki-67, two categories were used (low/ high) according to a largely adopted cut-o value of 20% [16,17], although the ideal threshold has not been identified yet and varies widely from 1% to 28.6% [18].

HER2 expression was scored according to guidelines for scoring the HercepTest (Dako, Golstrup, Denmark) as follows: 0, no staining or membrane staining in less than 10% of tumour cells; 1+, faint/barely perceptible, incomplete, membrane staining in >10% of tumour cells; 2+, weak to moderate complete membrane staining in >10% of tumour cells; and 3+, strong complete mem-brane staining in >10% of tumour cells. HER2 score 2+ tumours were tested for gene amplification by fluo-rescent in situ hybridisation (FISH). HER2 scores of 0 and 1+ were considered negative. A HER2 score of 3+ and amplified tumours on FISH were considered positive.

The histological types of BC were classified according to the World Health Organisation (WHO) Classification of
Tumours of the Breast published in 2003. The histo-logical grade for individual BCs was determined through the assessment tubule formation, nuclear pleomorphism, and the number of mitotic figures, according to the Elston and Ellis method [19].

Staging was assessed according to the sixth (from 2005 to 2009) and seventh (from 2010 to 2013) editions of the American Joint Committee on Cancer (AJCC) cancer staging manual. We also classified tumours into four molecular subtypes (luminal A, luminal B, HER2 positive and triple negative) using surrogate IHC mark-ers [20].

The surgeons were requested to place clips at the bor-ders of the surgical bed, using a minimum of four clips. Computed tomography (CT) scanning was performed using 0.3 cm thick-slices. The slices extended to com-pletely cover the involved breast, lungs, and a 4-cm mar-gin in the cranial and caudal directions. In both treatment arms, CT was performed within 4 weeks after surgery.

Patients treated with conventional WBI received a total dose of 50 Gy in 25 fractions, followed by a radia-tion boost on a surgical bed of 10 Gy in five fractions, delivered using a direct external electron beam. Tangen-tial field directions were chosen to avoid the contralat-eral breast and to reduce the lung and heart dose. We performed dose-volume histogram analysis for the heart and ipsilateral lung. The organ-at-risk constraints were that 5% of the heart and 20% of the lung were kept to less than 20 Gy. Homogeneity of the dose to the target was controlled by keeping the maximum dose within 53.5 Gy.

In patients assigned to the APBI arm, the clinical tar-get volume (CTV) was drawn with a uniform 1-cm three-dimensional margin around the surgical clips; the CTV was limited to 3 mm from the skin surface. A sec-ond uniform three-dimensional 1-cm margin was added to the CTV to obtain the planning target volume (PTV). The PTV was allowed to extend 4 mm inside the ipsilat-eral lung and was limited to 3 mm from the skin. The ipsilateral and contralateral breast, ipsilateral and con-tralateral lung, heart and spinal cord were contoured as organs at risk.

All of the regions of interest were contoured accord-ing to the International Commission on Radiation Units and Measurements reports 50 and 62 recommendations. No respiratory control was used.

A dose of 30 Gy in five non-consecutive daily frac-tions at 6 Gy/fraction was prescribed (2 weeks of treat-ment). Using the linear quadratic model and assuming an a to b ratio of three, this prescription was equivalent to 54 Gy in a standard 2-Gy fractionation. If the a to b ratio is assumed to be two, the equivalent dose in stan-dard fractionation will be 60 Gy.

The treatment plan was developed using XiO (CMS, Maryland Heights, MO) or Pinnacle [3] (Philips, Amsterdam, The Netherlands) treatment planning sys-tems (TPS). We adopted a standard arrangement of four or five 6 MV X-ray coplanar fields. The IMRT was delivered using a step-and-shoot technique. The average number of segments per plan was 30 (range 28–35).

The following constraints were adopted for plan opti-misation: PTV coverage, 100% of PTV covered by 95% of the prescribed dose (V28.5 = 100%); maximal dose to PTV <105% (31.5 Gy); minimal dose to PTV 28 Gy; uninvolved breast: not >50% received a dose of >50% of the prescribed dose (V15 <50%); ipsilateral lung, not >20% received a dose >10 Gy (V10 <20%); contra-lateral lung, not >10% received a dose >5 Gy (V5 <10%); contralateral breast, maximal dose <1 Gy; and heart, not >10% received a dose >3 Gy (V3 <10%). Homogeneity of the dose to the target was controlled by keeping the maximum dose within 31.5 Gy.

With some exceptions, the above constraints were also applied to the final dose distribution acceptability criteria. The radiation oncologist was allowed to approve treatment that failed slightly to meet all of the constraints if, for clinical reasons, this was necessary in terms of treatment outcome.

The RT sessions were performed using one of the two linear accelerators in use in our Department for IMRT: an Elekta Precise (Elekta, Crawley, UK), fitted with standard Elekta 80 multileaf collimator leaves, and an Elekta Synergy BM (Elekta AB, Stockholm, Sweden), fitted with a beam modulator multileaf collimator and equipped with on-board cone-beam CT.

The patients were positioned supine on the treatment couch, using a standard breast board and no immobili-sation systems. Patient positioning was verified using a couple of orthogonal portal images (in the case of the Precise linear accelerator) or with kV cone-beam CT before each fraction (in the case of the Synergy linear accelerator). In the latter case, the corrections suggested by the automatic registration between the cone-beam CT and the setup CT, achieved through the Elekta XVI (version 4.5 software), were executed using the 6-degrees of freedom HexaPOD Robotic Treatment Couch (Elekta-Medical Intelligence GmbH, Schwab-munchen, Germany), allowing not only translational but also rotational corrections.

Adjuvant treatments were prescribed following our institute policy during the trial enrolment period. After completion of RT, we followed up all patients monthly for 3 months, every 4 months for 2 years, and every

6 months thereafter. Clinical examination was per-formed at each follow up visit; mammography was annually programmed, and other diagnostic exams were requested only in case of suspect symptoms.

We defined local relapse (true recurrence) as the reap-pearance of the BC in the index quadrant and ipsilateral breast tumours as any new BC diagnosed in other quad-rants of the same breast. The sum of local relapses and new ipsilateral breast tumours was defined as the ipsilat-eral breast tumour recurrence (IBTR). Locoregional tumour recurrence also included any recurrence in the ipsilateral axillary, supraclavicular or internal mammary chain nodal regions. Distant metastases were defined as any recurrence to distant organs (visceral and bone sites).

Treatment tolerance was assessed using the acute radiation morbidity scoring criteria and late radiation morbidity scoring scheme from the Radiation Therapy Oncology Group (RTOG) and the European Organiza-tion for Research and Treatment of Cancer (EORTC) [21]. Cosmetic outcome was scored on the four-category Harvard Breast Cosmesis Scale [22] an excellent cos-metic result score was assigned when the treated breast looked like the contralateral one; a good cosmetic score was assigned for minimal but identifiable radiation e ects of the treated breast; a fair score was used if sig-nificant

radiation e ects were readily observable; a poor score was used for severe sequelae due to radiation e ects. The primary end-point was the IBTR rate. The secondary end-points were overall survival (OS), acute and late side-e ects and cosmetic outcomes.

2.4. Statistical analysis

The study aims to compare the local recurrence at the 5-year follow-up in the APBI and in the WBI arms. Assuming a 5-year IBTR of 3% in the WBI group and equivalence of the two groups if occurrence of IBTR in the APBI group did not exceed 5% (accepted level in most institutions at trial design time), a sample of 245 patients per group provides an 80% statistical power.

The main analysis was by intention-to-treat, includ-ing all randomised patients. We also perform a per-pro-tocol analysis, restricted to patients who received the allocated treatment and satisfied eligibility criteria, thus excluding 14 patients allocated to the APBI arm. Char-acteristics of the patients were compared between groups with an Exact Fisher test or Chi-square for trends, as appropriate. Survival analyses were per-formed in relation to specific events: IBTR, locoregional recurrence (LRR), contralateral BC, distant metastasis (DM) and death. Time to events was measured from the date of diagnosis to the date of the specific event. OS was defined as the time from the diagnosis to time of death or last follow-up (28th February 2014). No loss to follow-up was found. Patients who died before expe-riencing a disease occurrence were considered censored at their dates of death.

Event rates and their 95% confidence intervals (CI) were calculated according to the Kaplan–Meier method. Di erences between groups of patients were evaluated using the log-rank test.

A univariate Cox proportional regression model was used to obtain the hazard ratios (HR) for IBTR and deaths for APBI versus WBI. A multivariable Cox pro-portional regression model was used to identify indepen-dent factors of IBTR among patients treated with APBI using the IMRT technique. All two-sided p values less than 0.05 were considered significant. Statistical analyses were performed using SPSS Statistics software (version 22; SPSS Statistics, IBM Corporation, Armonk, NY, USA). This trial is reg-istered with ClinicalTrials.gov, number NCT02104895.

3. Results

A total of 520 patients were randomised into two groups (260 to WBI and 260 to APBI using the IMRT technique). The main analysis was by intention to treat. We also performed a per protocol analysis, excluding 14 cases allocated to the APBI arm who received WBI because of patient refusal (Fig. 1).

The median follow-up for all patients was 5.0 years (IQR 3.4–7.0); for WBI, 5.3 years (IQR 3.8–7.0); and for APBI with IMRT, 4.8 years (IQR 2.7–7.0).

The main features of the series according to treat-ment group are summarised in Table 1. The majority of enrolled patients had tumour nuclear grade G1-2 (88.9%), positive ER status (95.4%) and negative nodal status (86.2%). Eighteen cases were HER2 positive (3.6%). No patients received adjuvant trastuzumab. No patients received preoperative systemic therapy.

A total of 352 (67.7%) patients received adjuvant treatment; 307 (59.0%) patients received exclusive endo-crine therapy, and 8 (1.5%) patients received chemother-apy alone; 25 (4.8%) patients received both treatments. A total of 445 (85.6%) patients had a negative axillary nodal status. Even though it was not an exclusion crite-rion of the trial, we did not enrol patients with 4 or more axillary involved nodes.

The main events identified during the trial follow-up according to the allocated group are summarised in Table 2. At 5-years median follow-up, we recorded six IBTR (5-year event rate 1.5% [95%CI 0.5–2.5]: three sites in the quadrant index (true recurrence) and three in other quadrants. All the IBTR were ER positive, nuclear grade G2, small ductal invasive BC (mean size 9.8 mm).

The mean time to IBTR was 2.9 years (SD 1.3; range 1.0–4.0). The 5-year IBTR rate was 1.5% (three cases) in the APBI group (95% CI 0.1–3.0), within the pre-speci-fied equivalence threshold of 5%, in comparison with that of the WBI group (three cases, 1.4% [95% CI 0.0– 2.8]). No significant di erence emerged between the two groups (log rank test p = 0.86). The HR for the development of IBTR for patients allocated to APBI compared with WBI patients was 1.16 (95% CI 0.23– 5.75; Fig. 2).

Further analyses did not reveal any significant di er-ence between the two groups, according to the 5-year occurrence of local relapse (p = 0.11) and new ipsilateral BC (p = 0.063).

We identified seven axillary nodal recurrences: four in the WBI group and three in the APBI group (p = 0.86). The overall 5-year LRR rate was 1.7% (95% CI 0.6–2.8). The mean to time to LRR was 2.8 years (SD 1.2; range 1.0–4.0).

Contralateral BC occurrence was recorded in 10 patients (5-year event rate 2.5% [95% CI 1.2–3.8]). No significant di erences emerged between the two groups (p = 0.31).

Seven patients developed DM: visceral sites in four cases and visceral plus bone metastases in three cases; the overall 5-year event rate was 1.7% (95% CI 0.6– 2.8). The mean time to DM was 2.9 years (SD 0.7; range

1.5 3.6). No significant di erence between the two groups was found (p = 0.87).

OS at 5 years did not significantly di er between the groups (p = 0.057). We identified eight deaths (5-year event rate 2.1% [95% CI 0.9 3.3]): seven in the WBI group and only one in the APBI group. The 5-year OS rate was 96.6% for the WBI group and 99.4% for APBI group. The risk of dying for APBI patients compared with WBI patients was 0.17 (95% CI 0.02–1.36; Fig. 3).

Among the total deaths, we identified four deaths due to BC progression disease and four due to other causes. No significant di erences emerged between the two groups according to the above-mentioned causes of death (p = 0.40 and p = 0.065, respectively).

Further regression analyses, stratified by selected individual parameters, were performed to find the possi-ble e ect of APBI on IBTR in specific subgroups of patients. No significant results were found (Table 3). The per-protocol analysis resulted in similar findings for all outcomes (Appendix).

Concerning patients treated with APBI, we also attempted to evaluate the individual characteristics asso-ciated with IBTR. Univariate Cox regression models did not present any significant association between selected individual characteristics, such as age, histology, LVI, nuclear grade, pathological tumour and nodal stage, ER, PgR, Ki 67 and HER2 status. Multivariable analysis, including all of the above-mentioned individual features, did not display independent factors of IBTR among patients treated with APBI using IMRT (data not shown). The findings were the same in the per-pro-tocol analysis.

Skin toxicity and physician-rated cosmesis (per pro-tocol analysis) are summarised in Table 4. Concerning acute adverse events, the APBI group displayed signifi-cantly better safety, considering both any grade (p = 0.0001) and grade 2 or higher (p = 0.0001). No grade 3 toxicity was observed in the APBI group. The most frequently observed event was erythema for both arms (any grades; 19.9% in APBI, and 66.5% in WBI arm).

Concerning late side-e ects, only two cases (0.8%) experienced grade 2 toxicity, both in the WBI group (skin fibrosis). No grade 2 or higher toxicity was observed in the APBI group. The most represented event was skin fibrosis in both arms (any grades; 4.5% in the APBI arm and 11.2% in the WBI arm).

In both treatment groups, the cosmetic result was rated as excellent/good for more than 90% of patients. Overall, the APBI group displayed a better outcome compared with the WBI group (p = 0.045).

4. Discussion

Women with small breast tumours treated with APBI with the IMRT technique presented, for the rate of local recurrence of disease, equivalence to that of women trea-ted with postoperative WBI, at a median follow-up of 5 years. There was no evidence of significant di erences regarding the true incidence of recurrence nor new-onset ipsilateral tumours. OS did not di er between the two treatment groups, with the same number of deaths related to BC.

The acute and chronic toxicity and cosmetic outcome of partial breast irradiation was significantly better in comparison with WBI, adding strength to the theoretical advantage for IMRT of further increase in dose conformity compared with other three-dimensional techniques and more normal tissue sparing.

Currently, there are few ongoing phase 3 trials. All are characterised by a significant heterogeneity regard-ing inclusion criteria and stratification factors. To our knowledge, this is the first equivalence controlled ran-domised phase 3 trial comparing WBI with APBI using the IMRT technique (panel).

The standard treatment for BC patients at low risk of recurrence is based on conservative surgery followed by radiation delivered to the whole breast. The APBI con-cept, developed several years ago, could be an option in selected patients. However, the ideal patient profile for APBI is still not clearly identified [23].

Our trial demonstrated a very low rate of IBTR, with only six events at the 5-year median follow-up (1.4% ver-sus 1.5%; p = 0.86), largely below the pre-specified 5% di erence and less than reported in the literature in early BC patients undergoing WBI.

The relatively short mean time to IBTR of 2.9 years, among our predominately low risk factors population, is probably due to the small number of events and, defi-nitely, to the short follow-up.

In the TARGIT phase 3 trial [24], intraoperative irra-diation resulted in much the same proportions of having local recurrence as with conventional radiotherapy at 4 years (1.2% versus 0.95%), but at 5 years, local recur-rence was significantly greater in the TARGIT group (3.3% versus 1.3%; p = 0.042) [25].

The ELIOT trial randomised 1305 women with early BC, suitable for BCS to receive either external WBI or intraoperative radiotherapy with electrons. After a medium follow-up of 5.8 years (IQR 4.1–7.7), 35 patients in the intraoperative radiotherapy group and four patients in the external radiotherapy group had experienced IBTR (p < 0.0001). The 5-year event rate for IBTR was 4.4% (95% CI 2.7–6.1) in the intraoper-ative radiotherapy group and 0.4% (95% CI 0.0–1.0) in the external radiotherapy group (HR 9.3; 95% CI 3.3–26.3). These data confirm the need for longer fol-low-up and highlight the importance of proper selec-tion of patients. Failure of local control was partly attributable to ipsilateral events in sites other than the index quadrant, which have a long mean time to relapse, and partly to recurrences around the original tumour [8].

APBI with IMRT was characterised by the same occurrence rates of distant metastases and disease-related deaths, without a significant di erence at the 5-year median follow-up. Overall, our phase 3 trial indicated a very low rate of events at the 5-year median follow-up, confirming the great development and e cacy of current BC screening and treatment. At the same time, it underlines once again the importance of longer follow-up in addition to an appropriate selection of patient candidates for APBI.

The small numbers of IBRT recorded suggest as, prob-ably, some highly selected patients do not need radiother-apy. To design perspective trials with no adjuvant radiation control arm would be an interesting challenge.

The analysis of BASO II trial, a 2 2 clinical trial of factorial design with or without RT and with or without tamoxifen, evaluated the absolute levels of local recur-rences achieved by the treatments in a large and well-defined subgroup of women with excellent prognosis tumours undergoing BCS. The actuarial rate of local failures at 10 years was of 22% without either adjuvant therapy, 8% for the addition of RT alone, 8% for the addition of tamoxifen, and 2% when both treatments were applied [26]. Following randomisation to RT or no RT, no significant di erence was seen in numbers of deaths, whether from BC (4% versus 5% at ten years, respectively) or non-BC deaths (6% in both cases) [27]. These results added strength to the concept that some patients might not require RT, but probably at least the same number does not require any endocrine ther-apy since, although well tolerated by most patients, can cause significant side-e ects.

Fourteen patients (2.7%) initially allocated in the APBI arm did not receive the randomisation treatment. Therefore, we also performed a per-protocol analysis, which confirmed the findings of the intention-to-treat approach (Appendix).

Overall, APBI with IMRT resulted in less toxicity compared with WBI, and it produced significantly less adverse acute and late skin toxicity and an excellent cos- metic outcome. This approach enormously increased patients' treatment acceptance.

There are four published phase 2 trials concerning APBI using the IMRT technique exclusively that report a good outcome in terms of skin toxicity profile and con-trasting results in terms of cosmetic outcome. In all cases, the used fractionation schedule was 3.85 Gy per fraction delivered twice daily for a total dose of 38.5 Gy [28–31].

In particular, our study revealed an absolutely satis-fying late toxicity profile. At a 5-year median follow-up, we assessed almost 80% of enrolled patients at more than 36 months from the end of radiation. Significantly higher late toxicity was observed in the WBI arm. The most represented late skin adverse event was grade 1–2 fibrosis (11.2% in WBI, 4.5% in APBI arm), and no grade 3 toxicity was recorded in either arm.

Cosmesis assessment confirmed the substantial safety of APBI delivered using the IMRT technique; the APBI arm displayed a slightly but significantly bet-ter overall cosmetic outcome. The few published small-series phase 2 trials using exclusively IMRT for APBI delivery are in agreement with our satisfactory results in terms of skin toxicity and cosmetic outcome, with the excellent-good rate ranging between 92.2% and 97% [28–31].

The only negative experience in terms of cosmesis was reported by Liss and colleagues [31]; although only 3.3% of patients had grade 2 fibrosis, a progressive cosmetic decline was observed, with 26.7% of cases having a fair to poor result. The RAPID trial [32], a large prospective randomised trial using APBI delivered using external 3-dimensional conformal radiotherapy (3DCRT), also dis-played adverse cosmesis at 3 years (35% in APBI, 17% in WBI; $p < 0.001$).

Some possible causes of this unexpected poor out-come may be the high volume of breast receiving 50% of the prescribed dose observed in patients who had fair/poor cosmesis. Another possible explanation could be that a twice-daily schedule used in these studies may have a greater biological e ect due to incomplete recovery [33].

The larger number of adverse events in terms of cos-mesis reported in the RAPID trial compared to our study, should be also related to the large sample size and the extremely accurate cosmetic assessment of the Canadian study (nurse, patients, and physicians' evaluation).

However, our results suggest that we are most likely allowing a su cient recovery time, prescribing five non-consecutive fractions, and keeping the homolateral breast V15 far below the protocol constraint of 50%. Basically the safety outcome appears to be related both to the fractionation and total prescribed dose and to the delivery technique. The good dose homogeneity and sparing of the uninvolved homolateral breast obtainable with IMRT might indeed have favourable influence on the occurrence of adverse events.

An advantage of IMRT is that, when compared with conformal techniques, IMRT produces optimal dosimet-ric results and allows an easier and less time-consuming treatment delivery. To obtain a high conformity, 3DCRT needs the usage of multiple non-coplanar beams, often multiple beam energies or a combination of photons and electrons. Although Michalski and col-leagues [34] suggested prudence when attempting to use an inverse treatment plan for APBI delivery because of breathing motion, Bortfeld and colleagues [35] studied the e ect of intra-fraction motion on IMRT dose deliv-ery and concluded the main e ect of organ motion in IMRT is an averaging of the dose distribution, which is the same as for treatments with conventional beams.

From the point of view of the planning time, IMRT is overall more time consuming when compared to a stan-dard tangential fields technique. Conversely, the large di usion of inverse planning techniques, the calculation speed of modern treatment planning systems, and the possibility of using plan templates,

speeds up the process of IMRT planning. Concerning quality assurance (QA), in a centre which already implemented IMRT technique, a comprehensive QA programme involving both specific controls on linear accelerators and on patients is already applied. So the resources necessary to implement APBI would not have implications for the applicability of the technique.

Finally, APBI appears to represent a cost-e ective method compared with WBI to deliver adjuvant radia-tion therapy following BCS, regardless of the APBI technique employed [36].

However a consideration should be made regarding the introduction of hypofractionated regimens which widely replaced the 50 Gy in 25 fractions, thus partially reducing the benefits of APBI in terms of treatment time spending [37–39].

In conclusion, though currently waiting for the final results of the NSABP/RTOG phase 3 trial, the largest trial that should help to define the characteristics of suit-ability for APBI, our trial demonstrated excellent results in terms of safety, with a very low rate of local recur-rences. APBI using the IMRT technique with the admin-istration of 30 Gy in five non-consecutive fractions should be part of the multidisciplinary discussion to o er a tailored treatment for the patient.

5. Panel: Research in context

5.1. Systematic review

As far as we are aware, six randomised trials of intra-operative or external APBI have been reported up to now, and only four trials published results concerning treatment e ectiveness. Dodwell and colleagues [40], between 1986 and 1990, randomised women to receive conventional WBI or APBI by a variety of techniques; due to problematic enrolment, the trial closed prema-turely before the recruitment target. In addition, the Christie Hospital trial [41], with 708 patients random-ised from 1982 to 1987, failed to prove the e ectiveness of this approach for local control.

The TARGIT study, a phase 3 trial using intraoper-ative irradiation, reported a 5-year local recurrence rate significantly greater for the experimental arm (3.3% in APBI, 1.3% in WBI; $p = 0\ 042$) [25]. The ELIOT trial randomised 1305 women with early BC, suitable for BCS to receive either external WBI or intraoperative radiotherapy with electrons. After a medium follow-up of 5 8 years, the intraoperative radiotherapy arm dis-played a higher rate of IBTR ($p < 0.0001$). The 5-year event rate for IBTR was 4.4% in the intraoperative radiotherapy group and 0.4% in the external radiother-apy group [8].

To determine whether APBI is equivalent to or better than conventional or hypofractionated WBI after breast conservation therapy for early stage BC, a Cochrane Review has been recently published [42]. Due to the low quality of evidence, there were no clear findings of a di erence for the outcomes of overall survival (HR 0.99; 95% CI 0.83–1.18), distant metastasis-free survival (HR 1.02; 95% CI 0.81–1.28) and relapse-free survival (HR 0.99; 95% CI 0.53–1.85).

There are no published clinical data comparing 3DCRT versus IMRT APBI techniques, and IMRT is not allowed in the current NSABP B-39/RTOG 0413 trial.

5.2. Interpretation

To our knowledge, this is the first controlled random-ised phase 3 study using exclusively the IMRT technique for APBI (30 Gy in five non-consecutive 6 Gy fractions). No significant di erence in terms of IBTR was demon-strated between the two arms. APBI using IMRT dis-played a significantly better acute and late toxicity and cosmetic outcome profile compared with WBI, at the 5-year median follow-up.

The eligibility criteria of our study were simple and limited, based on age, tumour size and status of surgical margins. These criteria were most likely adequate at the time of the study design but are

currently limited by the knowledge of the importance of clinical and pathologi-cal factors critical to the selection of patients for APBI. Our phase 3 trial revealed a very low rate of local failure at 5-years median follow-up, confirming the great devel-opment and e cacy of current BC screening and treat-ment. At the same time, it underlines once again the importance of the need for an appropriate selection of patients for APBI.

The sample size of this single-centre trial was chosen in order to have an 80% statistical power. This fact,
together with the low number of events, indicates that our study results should be interpreted with caution; longer follow-up is strongly required.

However, the results of our study may help clini-cians in the selection of women candidates for APBI delivered with an e ective technique, characterised by a safe toxicity profile, from the perspective of improv-ing the compliance and, consequently, patients' quality of life.

Contributors

L.L., I.M., G.S., L.M. contributed to the conception and design of the study. L.L., I.M., C.D.C, V.S. were responsible for randomisation and data collection. C.S. analysed the data. S.B. was responsible for patho-logical evaluation of surgical specimens. L.O., D.C., L.S., M.F. were responsible for surgery. L.L., I.M., G.S., F.P., P.B. were responsible for radiotherapy. L.M., S.P. were responsible for medical physics. JN was responsible for radiology. I.M., L.M., G.S., S.P. wrote the first draft of the manuscript. All authors pro-vided feedback, revised the draft critically, and gave final approval to submit for publication. L.L., I.M., C.S., G.S. had full access to all of the data and were responsible for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest statement

None declared.

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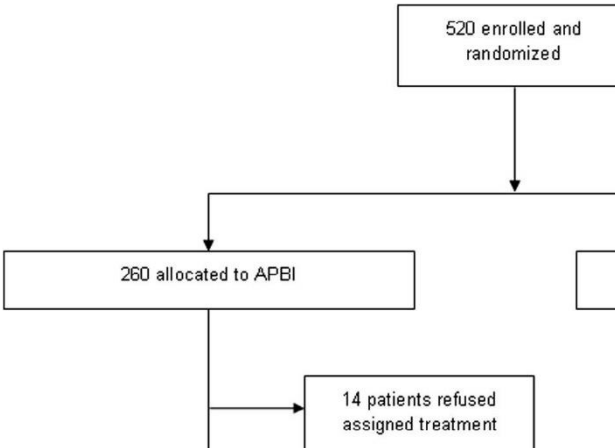

Fig. 1. Trial profile

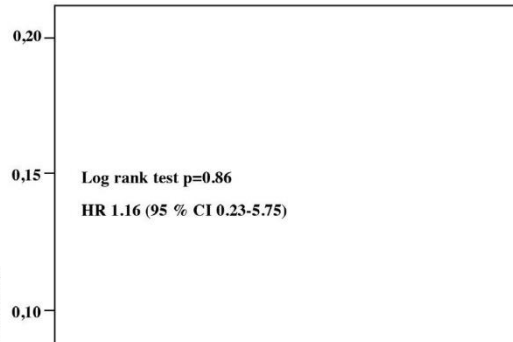

Fig 2. Cumulative incidence of ipsilateral breast tumour recurrence (intention-to-treat population).

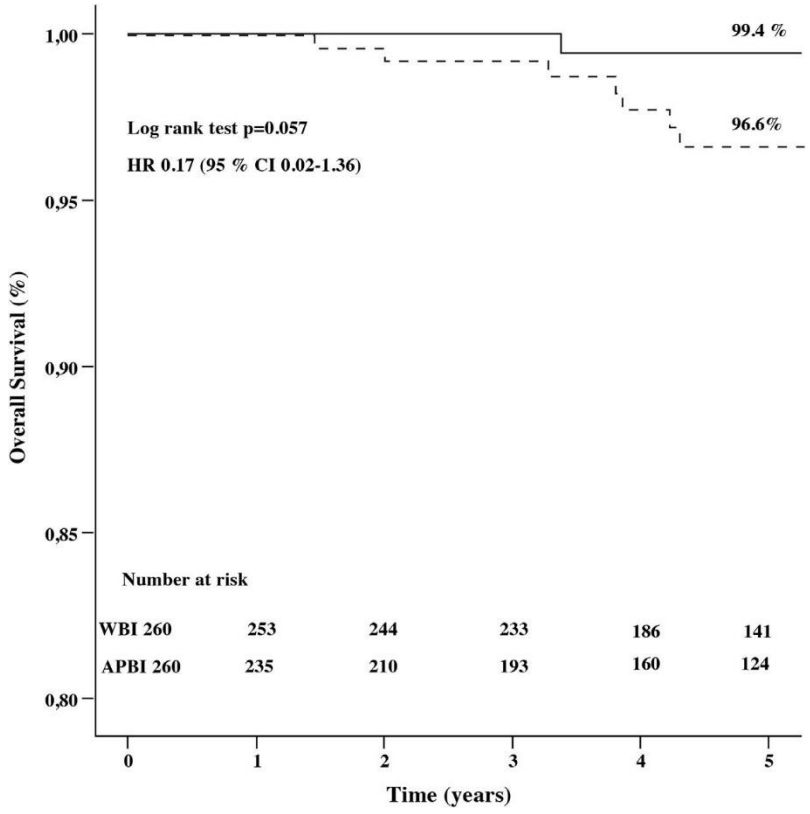

Fig. 3. Overall survival (intention-to-treat population).

table 1
Features of patients according to allocated group (intention-to-treat population).

	Whole breast		Partial breast	
	N	%	N	%
Age				
<50	45	17.3	41	15.8
51–59	76	29.2	61	23.5
60–69	81	31.2	99	38.1
P70	58	22.3	59	22.6
Quadrant				
Upper outer	123	47.3	118	45.4
Upper inner	26	10.0	26	10.0
Upper central	63	24.2	69	26.5
Lower outer	14	5.4	17	6.5
Lower inner	16	6.2	9	3.5
Lower central	13	5.0	14	5.4
Subareolar	5	1.9	7	2.7
Histology				
Ductal carcinoma in situ	32	12.3	23	8.8
Ductal invasive	153	58.8	146	56.2
Lobular invasive	29	11.2	21	8.1
Ductal and lobular invasive	18	6.9	15	5.8
Other	28	10.8	55	21.1
Lymph vascular invasion				
Absence	229	88.1	241	92.7
Presence	31	11.9	19	7.3
Tumour nuclear grade				
G1	103	39.6	124	47.7
G2	124	47.7	110	42.3
G3	33	12.7	26	10.0
Pathological tumour stage				
pTis	32	12.3	23	8.8
pT1a	18	6.9	28	10.8
pT1b	88	33.8	98	37.7
pT1c	107	41.2	97	37.3
pT2	15	5.8	14	5.4
Number of positive nodes				
None	213	81.9	232	89.2
1–3	33	12.7	19	7.3
No axillary nodal dissection	14	5.4	9	3.5
Oestrogen receptor				
Negative	11	4.2	12	4.6
Positive	249	95.8	248	95.4
Progesterone receptor				
Negative	25	9.6	28	10.8
Positive	235	90.4	232	89.2
Ki-67 proliferative index*				
<20%	174	72.2	193	79.4
P20%	67	27.8	50	20.6
HER2 status<				
Negative	216	94.4	232	97.5
Positive	13	5.6	6	2.5
Molecular subtype				
Luminal A	151	72.6	169	79.3
Luminal B	42	20.2	33	15.6
HER2 positive (non-luminal)	13	6.2	6	2.8
Triple negative	2	1.0	5	2.3
Adjuvant treatment				
None	75	28.8	93	35.8
Endocrine therapy exclusive	162	62.3	155	59.6
Chemotherapy exclusive	3	1.2	5	1.9
Endocrine and chemotherapy	20	7.7	7	2.7
ASTRO class				
Suitable	113	43.5	133	51.2
Cautionary	79	30.4	74	28.5
Unsuitable	68	26.1	53	20.3
ESTRO class				
Low risk	166	63.8	190	73.1
Intermediate risk	47	18.1	41	15.8
High risk	47	18.1	29	11.1

HER2, human epidermal growth factor receptor 2; ASTRO, American Society for Radiation Oncology; ESTRO, European Society for Therapeutic Radiology and Oncology.

A total of 260 patients were assigned to whole breast irradiation and 260 to partial breast irradiation.

* n = 241 for whole breast, n = 243 for partial breast.

< n = 229 for whole breast, n = 238 for partial breast.

n = 208 for whole breast, n = 213 for partial breast irradiation.

Table 2
5-year event rate according to allocated group (intention-to-treat population).

	Total	Whole breast (n = 260)		Partial breast (n = 260)		Log-rank p value
		N	%	N	%	
Ipsilateral breast tumour recurrence	6	3	1.4	3	1.5	0.86
Local relapse	3	3	1.4	0	0	0.11
New ipsilateral breast cancer (BC)	3	0	0	3	1.5	0.063
Locoregional tumour recurrence	7	4	1.9	3	1.5	0.86
Contralateral breast tumour	10	7	3.2	3	1.6	0.31
Distant metastasis*	7	4	1.8	3	1.5	0.87
Total deaths	8	7	3.4	1	0.6	0.057
Breast cancer	4	3	1.6	1	0.6	0.40
Other cause	4	4	1.8	0	0	0.065

* As first or secondary event.

Table 3
Ipsilateral breast tumour recurrence by subgroup (univariate analysis), intention-to-treat population.

	Whole breast	Partial breast	HR (95% confidence interval (CI))	Log-rank p value
Overall	3/260	3/260	1.16 (0.23–5.75)	0.86
Age				
<50	1/45	1/41	1.52 (0.96–24.23)	0.77
51–59	0/76	1/61	–	–
60–69	1/81	0/99	–	–
P70	1/58	1/59	1.07 (0.07–17.08)	0.96
Lymph vascular invasion				
Absence	3/229	3/241	1.11 (0.23–5.52)	0.90
Presence	0/31	0/19	–	
Tumour nuclear grade				
G1	0/103	2/124	–	–
G2	2/124	0/110	–	–
G3	1/33	1/26	1.43 (0.09–22.92)	0.80
Pathological tumour stage				
pTis	0/32	0/23	–	–
pT1a	1/18	0/28	–	–
pT1b	0/88	2/98	–	–
pT1c	1/107	1/97	1.32 (0.08–21.23)	0.84
pT2	1/15	0/14	–	–
Number of positive nodes				
None	2/213	2/232	1.08 (0.15–7.70)	0.94
1–3	0/33	1/19	–	–
No axillary nodal dissection	0/14	0/9	–	–
Oestrogen receptor				
Negative	1/11	0/12	–	–
Positive	2/249	3/248	1.79 (0.80–10.69)	0.53
Progesterone receptor				
Negative	1/25	1/28	0.91 (0.06–14.48)	0.94
Positive	2/235	2/232	1.23 (0.17–8.75)	0.84
Ki 67 proliferative index				
<20	1/174	3/193	3.13 (0.33–30.1)	0.32
P20	2/67	0/50	–	–
HER2 status				
Negative	2/216	3/232	1.13 (0.16–8.02)	0.90
Positive	1/13	0/6	–	–

HER2, human epidermal growth factor receptor 2.

Table 4
Acute/late skin toxicity and physician-rated cosmesis (per-protocol analysis).

	Whole breast (n = 260)		Partial breast (n = 246)		Overall p value*
	N	%	N	%	
Acute skin toxicity					
None	87	33.5	197	80.1	
Yes, any Grade	173	66.5	49	19.9	0.0001
None	87	33.5	197	80.1	
Grade 1	75	28.8	44	17.9	
Grade 2	81	31.2	5	2.0	
Grade 3	17	6.5	0	0	
Grade 4	0	0	0	0	0.0001
Grade 0–1	162	62.3	241	98.0	
Grade P2	98	37.7	5	2.0	0.0001
Late skin toxicity					
None	231	88.8	235	95.5	
Yes, any Grade	29	11.2	11	4.5	0.004
None	231	88.8	235	95.5	
Grade 1	27	10.4	11	4.5	
Grade 2	2	0.8	0	0	
Grade 3	0	0	0	0	
Grade 4	0	0	0	0	0.015
Grade 0–1	258	99.2	246	100.0	
Grade P2	2	0.8	0	0	0.26
Physician-rated cosmesis					
Excellent	233	89.6	234	95.1	
Good	25	9.6	12	4.9	
Fair	2	0.8	0	0	
Poor	0	0	0	0	0.045

Bold values reached the statistical significance p-value < 0.05.
* p-Value from Chi-square test.