SHARE: A French Multicenter Phase III Trial Comparing Accelerated Partial Irradiation Versus Standard or Hypofractionated Whole Breast Irradiation in Breast Cancer Patients at Low Risk of Local Recurrence

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Abstract: The standard treatment for breast cancer patients at low risk of recurrence is based on conservative surgery followed by radiation therapy delivered to the whole breast. The accelerated partial breast irradiation (APBI) concept, developed more than 15 years ago, could be an option in selected patients. However, the ideal patient profile for APBI is still not clearly identified. Recent reports from the American Society for Radiation Oncology (ASTRO) and the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) have suggested selection criteria for "suitable patients" who could receive APBI outside of clinical trials. Currently, there are 6 ongoing phase III trials. All are characterized by a significant heterogeneity regarding inclusion criteria and stratification factors. The French UNICANCER trial (SHARE; ClinicalTrials.gov identifier NCT01247233) will randomize 2,800 patients in 3 arms: APBI (1 week) using 3-dimensional (3D) conformal radiotherapy, standard radiotherapy (6.5 weeks), and hypofractionated radiotherapy (3 weeks). In this article, we review the reported retrospective studies as well as older randomized trials. We will also describe the differences between the 6 ongoing phase III trials and the particularities of the French SHARE trial.

Introduction

The standard treatment for early breast cancer is based on conservative surgery followed by radiation therapy (RT) delivered to the whole breast irradiation (WBI). The recommended total RT dose is 45–50 Gy delivered in 4.5–5 weeks, followed by a 10–16 Gy boost to the tumor bed. Accelerated partial breast irradiation (APBI) offers decreased overall treatment time and several theoretical advantages over WBI, including a decrease in the dose delivered to uninvolved portions of the breast and adjacent organs.

Table 1. Results Published in the Early 2000s in the United States According to APBI Techniques

Institution/Author	N	Median Follow-Up	Rate of Local Recurrences (%)	Good to Excellent Cosmetic Results (%)
Interstitial Brachytherapy				
Ochsner Clinic King et al[30]	84	84	2.5	75
William Beaumont Vicini et al[31]	199	65	2	99
RTOG 95-17 Kuske et al[32]	99	45	3	ND
MammoSite				
Keich et al[33]	70	60	0	86
ASBS Registry Zannis et al[34]	1,403	15	0.1	98
CRT 3D				
William Beaumont Vicini et al[7]	91	24	0	91
New York University Formenti et al[10]	78	28	0	92

ASBS=American Society of Breast Surgeons; CRT 3D=3-dimensional conformal radiotherapy; ND=not determined; RTOG=Radiation Therapy Oncology Group.

In selected populations, taking into account tumor and patient criteria, the APBI concept could be an important option for routine use and improved treatment individualization in the future. Given the interest in APBI, several multicenter, randomized clinical trials have been initiated to compare the effectiveness and safety of APBI compared with WBI. If equivalence between the 2 treatments can be shown, then APBI could be considered as an historic evolution in breast cancer management. However, the ideal patient profile for APBI is still not clearly identified. Recent reports from the American Society for Radiation Oncology (ASTRO) and the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) have suggested selection criteria for "suitable patients" who could receive APBI outside of clinical trials.[1,2]

APBI Nonrandomized Studies

After the first publications of the feasibility of APBI in North America, numerous teams in Europe started their own studies. Although this research has made available an increased amount of data, most results are based on limited follow-up. Table 1 presents some results published by American teams in the beginning of the 2000s. In these studies, the rate of recurrence is limited when rigorous patient selection is applied. In summary, in the postoperative setting, APBI is performed using brachytherapy (BCT) techniques or external beam radiotherapy (EBRT). Intraoperative techniques delivering 1 fraction, either using electrons or x-ray, will not be described here.

Brachytherapy Experiences

BCT can use catheters or other devices (such as MammoSite) implanted during or after surgery. RT delivery in this case is performed in several fractions immediately or a few days after conservative surgery. Thus, one of the most important advantages is that patient selection is based on a perfect knowledge of tumor characteristics.

In the literature, there is significant heterogeneity in terms of the surgical margin quality, BCT technique parameters, volume definition, total dose, and dose rate. For example, Poti and colleagues reported a 24% local recurrence rate in 70 patients treated using cobalt 60 sources.[3] This unacceptably high rate can be attributed to the heterogeneity of the patient population as well as to differences in the treatment procedures used in the 27 institutions involved in the study.

Conversely, in a German/Austrian study of 274 patients treated with brachytherapy between 2000 and 2005, the local recurrence rate was only 0.7% after a median follow-up of 32 months (range, 8–68 months).[4] These excellent results can be attributed to a more rigorous patient selection, with tumor size at or less than 30 mm, surgical margins greater than 2 mm, and no macrometastases in the sentinel node. In addition, cosmetic results were considered to be good to excellent in 94% of the patients. These results are similar to those reported

Table 2. 3D CRT Techniques Developed in the United States

Authors	N	Follow-Up	Classification	Dose/Fraction	LR
Taghian et al[12]	61	18 months	pT1 pN0	32 Gy 4 Gy/fraction x2/day	ND
Vicini et al[31]	51	ND	PT1 N0–N+	38.5 Gy 3.85 Gy/fraction x2/day	ND
Formenti et al[10]	47	18 months	pT1 pN0	30 Gy 6 Gy/fraction in 10 day	0%

LR=local recurrence; ND=not determined; 3D CRT=3-dimensional conformal radiotherapy.

previously in the United States with a longer follow-up.[5,6] A report from Vicini and coworkers of the William Beaumont experience showed only 5% recurrences after a median follow-up of 8 years—with no differences in terms of cosmesis—at 6, 24, and 60 months, as compared to a control group treated with standard WBI.[5]

Poti and colleagues also compared 50 Gy WBI to APBI (using either high-dose rate [HDR] BCT delivering 5.2 Gy/7 fractions or 50 Gy/25 fractions, delivered by an electron beam to the tumor bed). After a median follow-up of 30 months, there was no difference in terms of local recurrence, telangiectasia, and fibrosis between the 2 groups.[3]

3D Conformal APBI Experiences

Several teams in the United States developed the use of 3-dimensional conformal radiotherapy (3D CRT) for APBI. Its rapid development is mainly due to the fact that HDR BCT requires experience, a long learning curve, and heavy logistics, with more constraints in everyday practice. In addition, 3D CRT is easier to apply than the other APBI techniques for routine use. In terms of dosimetry, APBI using 3D CRT allows for better optimization and dose distribution, with a reduction in the number of "hot spots" that can induce late skin complications after HDR brachytherapy.[7]

Three modalities of APBI with 3D CRT have been described (Table 2). The William Beaumont group utilizes a sophisticated technique with at least 4 non-coplanar photon beams. This technique allows better dose homogeneity to the PTV but with an important dose to the normal tissue.[7-9] In the technique developed at New York University, the patient assumes a prone position for sparing lung and heart tissue. This technique requires a dedicated treatment table for APBI.[10] The Harvard Medical School technique is simpler and reproducible with 3–4 beams.[11,12] Using this technique, the Boston group has prospectively validated the safety of escalating the dose from 32–40 Gy. A further dose level up to 42 Gy is currently being tested.

APBI French Experience Using BCT and EBRT

In France, 3 teams have developed postoperative APBI in prospective studies using either BCT or EBRT. The Antoine Lacassagne and Gustave Roussy Cancer Centers initiated the GERICO (A French UNICANCER Geriatric Oncology Group) 03 study using HDR interstitial brachytherapy in patients older than 70 years. This study included 42 patients with a very low risk of tumor recurrence. The results were reported at ASTRO 2009.[13]

The Oscar Lambret Cancer Center has published preliminary results on acute toxicity and quality of life after HDR BCT using the MammoSite device, implanted preoperatively in highly selected patients ages 60 years or older. The aim of this study was to test the feasibility of the treatment and performance of this device.[14]

A phase II clinical trial using 3D-conformal APBI was conducted by the Gustave Roussy Institute in collaboration with Massachusetts General Hospital. The main objective was to determine the optimal total dose for 3D-conformal APBI (total dose of 40 Gy or 42 Gy in 10 fractions). This phase II French trial also assessed the feasibility of 3D-conformal APBI using a combination of "en face" electron beam and photon beams.[15-17] As in the US studies, the early cosmetic results and local control in these French experiences are encouraging.

Phase III Trials Comparing External APBI To Standard WBI

Published Trials

The oldest study comparing external APBI to standard WBI is the Manchester trial, in which 708 patients were treated between 1982 and 1987 and randomized to receive either RT delivering 40–42.5 Gy in 8 fractions over 10 days with a 10 MeV electron beam to the quadrant (APBI arm), or RT (including supraclavicular nodes) delivering 40 Gy in 15 fractions over 21 days using 4 MV-photons (WBI arm). In this trial, no axillary dissections were performed, preoperative and/or postoperative mammograms were not systematically performed, and margins were not evaluated for quality of surgery.[18,19] Despite the high rates of recurrence, particularly in the APBI arm, and the very critical quality of surgery and RT technique, the rate of distant recurrence (distant from the quadrant) was only 5.5%.

Table 3. Comparison of the Ongoing Phase III APBI Trials

Criteria	IMPORT	RAPID	NSABP/B39 RTOG	GEC/ ESTRO	IRMA	TROG	SHARE
Number of arms	2	2	2	2	2	3	3
N	2,100	2,128	>3,000	1,170	3,302	2,094	2,796
Age (years)	>50	>40	>18	>40	>49	>55	≥50 menopausal
Tumor size (mm)	<20	<30	<30	<30	<30	<30	≤20
Number of N+	0	0	0–3N+	0 or 1 micro-metastasis	0–N+	0	0 or pN(i+)
Grade	I–II	I–III	I–III	I–III	I–III	I–II	I–III
Margin size (mm)	>2	Negative*	Negative*	>2 invasive >5 DCIS	>2	>1	Clips + ≥2
Techniques	3D CRT + MI	3D CRT	3D CRT, BCT, and MMS	BCT with HDR and PDR	3D CRT only	3D CRT, MMS, BCT, IORT	3D CRT only
Dose/fraction for APBI arm	–	38.5 Gy/10 fr	3D CRT: 38.5 Gy/10 fr BCT or MMS: 34 Gy/10 fr	HDR: 34 Gy PDR: 50 Gy	38.5 Gy/10 fr	38.5 or 34 Gy in 10 fr	40 Gy/10 fr
Standard arm	50 Gy/25 fr	50 Gy/25 fr	50 Gy/25 fr	50 Gy/25 fr	50 Gy/25 fr	50 Gy/25 fr, 42.5 Gy/16 fr, or 45 Gy/15 fr	50 Gy/25+ 16 fr, 42.5 Gy/16 fr, or 40 Gy/15 fr
Chemotherapy allowed	Yes	Yes	Yes	Yes	Yes	Third arm with TAM or AI without RT	Third arm with TAM or AI with HyF RT

*Margin size not available.

AI=aromatase inhibitors; APBI=accelerated partial breast irradiation; BCT=brachytherapy; CRT=conformal radiotherapy; DCIS=ductal in situ carcinoma; GEC-ESTRO=Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology; HDR=high dose rate; HyF=hypofractionated; IMPORT=Intensity Modulated and Partial Organ Radiotherapy; IRMA=Innovazioni nella Radioterapia della Mammella; IMRT=intensity-modulated RT; IROT=intraoperative radiation therapy; MMS=MammoSite; NSABP=National Surgical Adjuvant Breast and Bowel Project; PDR=pulsed dose rate; RAPID=Randomized Trial of Accelerated Partial Breast Irradiation; TAM=tamoxifen; 3D CRT=3D conformal radiotherapy; TROG=Trans-Tasman Radiation Oncology Group; RT=radiotherapy.

In the study from the National Institute of Oncology of Budapest, Polgár and associates reported similar local control after APBI versus standard WBI in a randomized trial of 258 patients.[20] However, cosmetic results were worse in patients who received APBI using electrons after a median follow-up of 66 months. The authors concluded that these results should be confirmed by further studies.

Ongoing Trials

The worldwide ongoing trials are presented in Table 3. One of the common criteria of these trials is the high number of patients required to demonstrate equivalence between APBI and standard WBI. The most important trial is the National Surgical Adjuvant Breast and Bowel Project (NSABP) B39/ Radiation Therapy Oncology Group (RTOG) 0413, which was opened for accrual in March 2005 for a total of 3,000 patients older than 40 years, with tumors less than 30 mm, and with involvement of 3 or fewer nodes. By June 2006, 1,100 patients had been included. According to the low number of N+ patients included, the sample size was increased to 4,300 patients in 2006. The projected time to reach this accrual goal was thus increased from 2 years and 5 months to 4.6 years.

The GEC/ESTRO trial was activated in 2008. The number of patients required for equivalence was 1,170 patients, with similar criteria as in the RTOG trial. However, only low or HDR brachytherapy was allowed in the APBI arm of this trial.

Two other trials using 3D CRT have been activated in the United Kingdom (IMPORT [Intensity Modulated and Partial Organ Radiotherapy]) with intensity-modulated RT (IMRT) or without IMRT (RAPID OCG [Randomized Trial of Accelerated Partial Breast

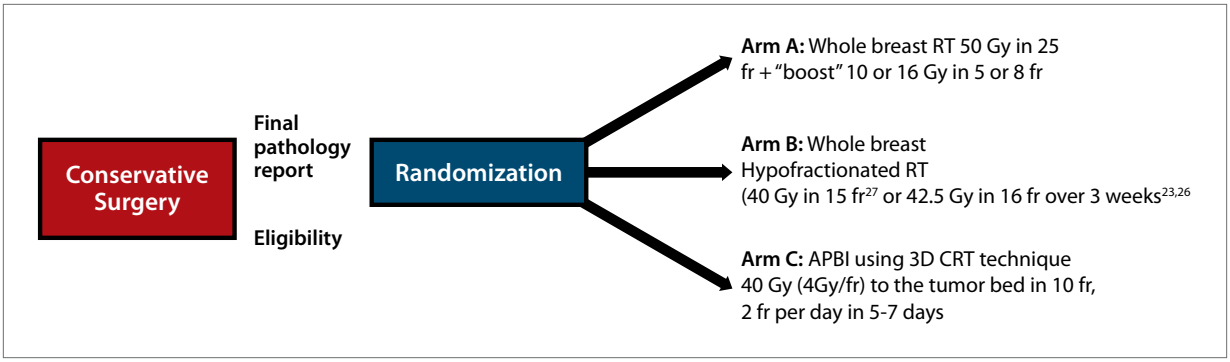

Figure 1. Design of the SHARE trial. APBI=accelerated partial breast irradiation; fr=fractions; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; rt=radiotherapy.

Irradiation from the Ontario Clinical Oncology Group]). These trials will include 2,000 patients each. The Italian trial (IRMA [Innovazioni nella Radioterapia della Mammella]) will use only 3D CRT in both standard WBI and in the APBI arm, delivering 38.5 Gy in 10 fractions. The most recently activated trial is the Australian study of the Trans-Tasman Radiation Oncology Group (TROG). A unique characteristic of this trial is that it will randomize patients into 3 arms: APBI versus standard WBI versus hormonal therapy without RT.

SHARE: French Phase III Trial Proposal

Design and Particularities of the SHARE Trial

The SHARE (Standard or Hypofractionated RT versus APBI for Breast Cancer) trial is designed for postmenopausal women older than 50 years, aims to increase practice homogeneity in France and ensure high-quality criteria for surgery, pathology, and RT in each of the 3 arms. For example, because of the systematic tumor bed remodeling undertaken by the French surgeons, it will not be possible to extrapolate the volume definition and irradiated volumes from the US experiences.[21,22] Another difference is that patients with previous chemotherapy or nodal involvement (1–3 N+) are not allowed to participate, whereas these patients can be included in 5 of the 7 ongoing trials.

In summary, the French trial will allow selected patients according to age and low risk of local recurrence parameters. The targeted population consists of the two-thirds of breast cancer patients who receive RT in an adjuvant setting. The trial aims to:

- Evaluate in a subgroup of patients (from 4–5 centers, including about 10% of total number of patients), the impact of magnetic resonance imaging (MRI) on patient selection and the rate of occult disease (multifocality) not detected by standard imaging evaluation, which is considered as an exclusion criteria. To date, only 1 prospective study has been reported. The authors have shown that adding MRI to the standard imaging in preoperative evaluation allows a confirmation of 10% of pathologic invasive carcinoma and multifocality in 28% of the whole population.[23] However, routine use of MRI is not currently recommended for patient selection outside of clinical trials.
- Determine APBI parameters adapted to the surgical procedure in the tumor bed remodeling setting.
- Determine homogeneous criteria for the surgical procedure, as well as minimal requirements and optimal criteria that need to be mentioned in the final pathology report in all 3 arms of the study.
- Optimize the definition of the tumor bed for APBI using 3D CRT.
- Test hypofractionation using 3-week schedules as compared to APBI.
- Evaluate the impact of new molecular classification on local control and predict the risk of locoregional or distant recurrences after APBI by new biological tools. It is a translational study.

Objectives

The trial design is presented in Figure 1. The primary objective is to estimate and compare the rates of local recurrences between the experimental and control arms. The secondary objectives are survival without ipsilateral breast recurrence, survival without nodal regional recurrence, survival without distant recurrence, disease-specific survival, overall survival, rates and type of acute and late toxicities (as assessed by the Common Terminology Criteria for Adverse Events, version 3.0), cosmetic results (according to patient and physician evaluations), quality of life (as assessed by the European Organisation for Research and Treatment of Cancer QLQ-C30) and satisfaction, medico-economic study from surgery to the end of RT, and translational research (optional). The inclusion criteria are listed in Table 4.

Table 4. Inclusion Criteria of the SHARE Trial

- Postmenopausal women aged ≥50 years (stratification: <70 years vs ≥70 years)
- Menopausal status confirmed for ≥12 months (clinically and/or biologically)
- No previous ipsilateral breast and/or mediastinal irradiation
- Pathological confirmation of invasive carcinoma (all types of invasive carcinomas)
- Unifocal tumor confirmed on the pathological specimen
- Pathological tumor size of the carcinoma ≤2 cm (including the in situ component)
- All pathological grades (stratification: HER2 status and hormonal receptors)
- Clear lateral margins confirmed on the final pathology report; the minimal size of the invasive and in situ disease should be 2 mm (≥2 mm)
- pN0 (i+/-) (stratification: pN0 vs pN[i+])
- Chemotherapy and trastuzumab are not allowed; radiotherapy should be started ≥4 weeks and ≤12 weeks after surgery (including the date of second excision for close or involved margins)
- Clips in the tumor bed placed during surgery (4–5 clips)
- Informed and signed consent of the patient

HER2=human epidermal growth factor receptor 2.

Sample Size and Randomization

This noninferiority trial will evaluate the effects of APBI (Arm C: 3D CRT) compared to standard irradiation: classic fractionation (Arm A: 50 Gy/25 fractions/5 weeks) or a hypofractionated schema (Arm B: 40 Gy/15 fractions/3 weeks or 42.5 Gy/16 fractions/3 weeks) on invasive or intraductal ipsilateral intramammary recurrence with a 1:1:2 randomization for arms A, B, and C, respectively, using a minimization algorithm. The noninferiority hazard ratio (HR) margin is estimated at 1.60, under the assumption that the control arm (A+B) will retain one-half of the effect as compared to a treatment group without radiotherapy.[24] This is justified by the results reported by Fisher and coworkers, who reported a cumulative incidence of local recurrence of 10% as compared to 35% after a 12-year follow-up for conservative breast cancer patients with and without radiotherapy.[23] The experimental arm (APBI) will be considered noninferior to the control arms if the upper limit of the 1-sided 95% confidence interval of the HR is less than 1.60 (noninferiority margin). With a 1-sided type I error of 0.025 and 80% power, 144 failures are necessary for the final analysis. One interim analysis is planned after the 72nd failure. This alpha level was chosen for each of the 2 comparisons (C vs A and C vs B). With an estimated failure rate of 4% at 5 years in the control arm, the noninferiority margin of 1.60 corresponds to an absolute failure rate of 6.3% in the experimental arm. With an expected 3-year accrual period and 5 years minimum follow-up, the total study duration is 8 years. With these constraints, it is necessary to include 2,796 patients (699:699:1,398) in 3 years.

Treatment in Arms A and B

Radiation therapy of the whole breast Patients in Arms A and B will receive radiation of the whole breast.

Delay between surgery and RT RT should be started within 12 weeks after the last surgery. Treatment is performed using a linear accelerator delivering at least 4 MV photons. IMRT is not allowed.

CT scan simulation CT scan is systematically performed, with slices spaced at 4 mm or less, followed by digital reconstruction. Organ at risk delineation should concern the contralateral breast, lungs, heart, liver, spinal cord, and thyroid.

Target volume definition The breast clinical target volume (CTV1) includes the whole breast up to the whole of the pectoralis fascia. The surgical clips are included in the CTV1. Conversely, the pectoral muscle, the ribs, the lung, the heart, and the first 5 mm from the skin surface should be excluded from the CTV1. PTV1 corresponds to CTV1 + 1–1.5 cm margin for respiratory motion (internal margin) and a "setup margin." PTV1 is irradiated at a dose of 50 Gy (or equivalent dose for hypofractionated schedules), with 2 tangential fields.

The boost volume is PTV2 in arm A. It should be defined clinically and according to the surgical clips, breast remodeling, and seroma visible on the CT scan. A margin of 1–2 cm should be added. The pectoral muscle, the ribs, the lung, the heart, and the first 5 mm from the skin surface should be excluded from CTV2. PTV2 results from CTV plus 1–2 cm.

Dose prescription (Arm A) A total of 50 Gy is delivered in 25 fractions: 1 fraction of 2 Gy per day, 5 days a week according to the International Commission on Radiation Units & Measurements 62 prescription. In this arm, the boost of 10–16 Gy is delivered in 5–8 fractions. The boost, using electrons, photons, or the mixed beams technique, is started after completion of the 50 Gy without interruption. The choice of technique is left to local policy. However, a brachytherapy boost is not allowed in this arm of the study, and no nodal irradiation is allowed.

Dose prescription (Arm B) The main point is that in both schedules, the total dose is delivered in 3 weeks. The Canadian schedule described by Whelan and colleagues delivers 42.5 Gy in 16 fractions (2.65 Gy/f, 5 f/week).[25,26] The UK schedule, reported in the START (Standardisation of Breast Radiotherapy) B trial, delivers 40 Gy in 15 fractions (2.66 Gy/fractions, 5 fractions/week).[27] Nodal and boost RT are not allowed. The decision to omit the boost in the hypofractionated arm is based on the fact that in both the Canadian and the START trials, no boost was delivered. After more than 10 years of follow-up in the Canadian trial, there was no difference between the standard and hypofractionated schemes. There are no data available for a hypofractionated schedule of a dose equivalent of up to 45–50 Gy plus boost.

Dosimetry and constraints A positioning system is used during simulation and treatment to optimize reproducibility. The prone position technique is not allowed. Virtual simulation is recommended for 3D reconstruction of the target volumes and organs at risk. The "hot spot" zones must be limited to minimal values. The reference isodose is chosen by the radiation oncologist for coverage of 90–95% of the PTV by the prescribed dose. The heterogeneity of the dose should not exceed 10% in the PTV. Field-in-field planning is recommended, particularly in large breasts. In all cases, heart and lung constraints are recommended. The mean dose to the heart (for right side tumors) should be at or less than 5 Gy. This level corresponds to the 1% mortality risk from heart toxicity.[28] The use of heart block is possible. The ipsilateral lung distance is 2 cm or less. Furthermore, 20% of the ipsilateral lung should not receive more than 20 Gy (the mean ipsilateral lung dose is ≤7.5 Gy).

Arm C (3D CRT): Accelerated Partial Breast Irradiation

Delay between surgery and RT RT should be started within 12 weeks after the last surgery. Treatment is performed using a linear accelerator delivering photons of 4 MV or more. IMRT is not allowed.

CT scan simulation CT scan is systematically performed, with slices spaced at 2 mm, followed by digital reconstruction. Organ at risk delineation should concern the contralateral breast, lungs, heart, liver, spinal cord, and thyroid.

Volume definition After tumor removal, the surgeon will remodel the tumor bed using several remodelling surgical techniques that will not allow for any residual cavity. The delineation of CTV includes the tumor bed as defined by the clips position and, sometimes, with the small quantity of seroma in the initial tumor site. The PTV corresponds to the CTV plus a margin of 1.5–2 cm. The 5 mm below the skin surface and pectoralis should be excluded from the PTV. The delineation technique and target volume have been reported elsewhere.[21,22]

Treatment modality Mixed modality using photons/electrons to minimize the dose received to the lungs is strongly encouraged.[29] Any combination of photon beams of energy at or exceeding 4 MV, with the addition of 1 electron beam (that accounts for ≤20% of the dose), may be used to provide the dosimetric requirements of homogeneity to treat adequately the PTV. The technique used in the SHARE trial is adopted from the one described by Taghian and associates, including mini-tangents plus en-face electrons.[12] This APBI technique, in which the electron beam contribution should be 20% or less of the dose, was used by the Institut Gustave-Roussy team in a phase II study.[15,16] Preliminary results of acute toxicity have been reported.[17] A positioning system is used during simulation and before all fractions twice a day to optimize reproducibility. The technique utilizing the prone position technique is not allowed. Virtual simulation is recommended for 3D reconstruction of the target volumes and organs at risk.

Dose prescription A total dose of 40 Gy in 10 fractions (4 Gy per fraction) is delivered over 5 treatment days for 1 week overall, as described elsewhere.[15-17] The minimum interval between fractions needs to be at least 6 hours. Treatment may be started on any day of the week for a total duration of 7 days (including the weekend) between the first and the last fraction.

Dosimetry and constraints The total dose is prescribed on the reference isodose (100%). The "hot spot" zones must be limited to minimal values with a maximum dose of 105%. Ninety-five percent of the total dose should cover 90% of the PTV. Thus, the minimal dose in 90% of the PTV should be 38 Gy. For the non-target breast-tissue volume, V20 Gy should be less than 50%. The heart volume receiving 20 Gy, 10 Gy, and 5 Gy should be, respectively, less than 0.5%, 1%, and 4%. The use of heart block is possible. The ipsilateral lung volume receiving 20 Gy, 10 Gy, and 5 Gy should be, respectively, less than 1.3%, 5.7%, and 8%.

Endocrine Therapy

The decision on the type and duration of endocrine therapy for hormone-positive patients is left to the treating center's local policy. The total duration should not exceed 5 years. Tamoxifen (20 mg/day) or any aromatase inhibitor is possible as upfront hormonal therapy for 5 years. Sequential treatment using tamoxifen first (for 2–3 years), then aromatase inhibitors (exemestane [Aromasin, Pfizer], anastrozole [Arimidex, AstraZeneca], or letrozole [Femara,

Novartis]) is also allowed in this trial. All of these hormonal treatments can be given concomitantly with RT except tamoxifen, which should be started after RT completion.

Conclusion

The SHARE French trial is 1 of the 7 ongoing non-inferiority APBI phase III studies in the world. Randomization concerns only patients with a low risk of recurrence who will not need chemotherapy or trastuzumab (Herceptin, Genentech). In addition to developing the APBI nationally and promoting the importance of the learning curve for a given technique, we aimed to ensure, in France, very high quality and homogeneity at the various steps of the treatment given at a dose of 40 Gy in 10 fractions. Our protocol was constructed from Massachusetts General Hospital and Institut Gustave-Roussy experiences, based on clinical experience from phase I and II trials. Furthermore, the SHARE trial is a 3-arm study including hypofractionated schemes using either the Canadian or the UK START schedules. This design allows the possibility of a comparison of APBI to standard treatment (all ongoing trials), hypofractionation (SHARE), and nonirradiation (as planned in the TROG trial).

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