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Review Article

# Omission of postoperative radiation after breast conserving surgery: A progressive paradigm shift towards precision medicine

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A B S T R A C T

Radiation therapy is a standard therapeutic option in the post-operative setting for early breast cancer patients after breast conserving surgery, providing a substantial benefit in reducing the risk of local relapse with a consequent survival gain. Nevertheless, the reduction in the burden related to treatment is becoming crucial in modern oncology for both local and systemic therapies and investigational efforts are being put forward by radiations oncologists to identify a subset of women at very low risk to be potentially omitted from post-operative irradiation after breast conservation. Clinical factors, classical pathological parameters and new predictive scores derived from gene expression and next generation sequencing techniques are being integrated in the quest toward a reliable low-risk profile for breast cancer patients. We herein provide a comprehensive overview on the topic.


**Contents**



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## 1. Introduction

Postoperative whole breast irradiation (WBI) is currently considered as a standard option for most early-stage breast cancer patients (EBC) after breast conserving surgery (BCS) [1]. As shown in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, WBI halves the 10-year rate of any breast cancer recurrence (from 35.0% to 19.3% with an absolute reduction of 15.7%) and reduces the 15-year breast cancer-related mortality by about one sixth (from 25.2% to 21.4% with an absolute reduction of 3.8%) [2]. The addition of a boost dose to the tumor bed provides a further benefit on the risk of local recurrence, with an absolute reduction particularly evident in patients with unfavorable risk factors such as young age (<51 years), high grade tumors and threatened surgical margins [3,4]. The proportional benefit of WBI on both loco-regional relapse and breast cancer mortality is stable among different subsets of women. Conversely, the absolute risk reduction is, to some extent, proportionally affected by factors related to both patient and tumor [3]. Overall, in node negative patients, a subgroup generally at lower risk of disease recurrence, the 10-year rate of any breast cancer recurrence is reduced from 31.0% to 15.6% with an absolute risk reduction of 15.4%, while the 15-year breast cancer-related mortality from 20.5% to 17.2%, with an absolute risk reduction of 3.3% [3]. After stratification of this subgroup of patients according to age, tumor grade, estrogen-receptor status, tamoxifen use and extent of surgical excision, those with a 10-year absolute risk of recurrence at 10 years below 10%, showed an absolute reduction in the 15-year risk of death due to breast cancer of 0.1%. [3]. This observation prompted the need to carefully evaluate and tailor the treatment burden for this subset of patients, particularly the need for adjuvant endocrine therapy and the clinical indication of WBI after BCS. For these patients, the chance to decrease the treatment intensity might be important to avoid unnecessary acute and late toxicity and to optimize resources allocation for healthcare providers [5]. Whether to de-escalate endocrine therapy or radiation still needs further clinical investigation.

To decrease the radiotherapy burden in breast cancer patients several options are available, including the reduction in treatment volumes using partial breast irradiation, the decrease in overall treatment time with accelerated hypofractionation and the refining of radiotherapy delivery techniques (IMRT, VMAT, IGRT, proton therapy) to lower normal tissue dose and to increase the therapeutic index [6–10]. Another option is the complete omission of WBI after BCS, with the administration of adjuvant endocrine therapy, while the avoidance of both RT and hormonal manipulation after BCS is still to be considered as investigational [11]. RT omission after BCS has been explored in several randomized phase III trials, with heterogeneous eligibility criteria, leading to somehow arguable results and consequent confounding interpretations. The adequate selection of patients at very low risk of recurrence is therefore crucial and needs robust clinical evidence. We herein provide a comprehensive review on the omission of WBI after BCS, with a focus on patient- and tumor-related factors to be taken into account for a reliable clinical decision-making process.

## 2. Establishing the role of breast conservation and hormonal therapy

The role of BCS in the setting of EBC has been established in seminal randomized phase III trials performed in the 70–80s in both United States and Europe. The Milan I trial (1973–1980) randomized a total of 701 patients with <2 cm invasive breast cancer and no palpable nodes in the axilla to receive Halsted radical mastectomy vs quadrantectomy + axillary dissection and WBI to the residual breast [12]. At 20-year follow up, the cumulative incidence of ipsilateral breast tumor recurrence (IBTR) was 2.3% in the mastectomy group and 8.8% for breast conservation. No differences in overall survival (OS) were seen (41.2% vs 41.7%) [13]. Similarly, the NSABP B-06 trial (1976–1978) explored the role of local excision with or without radiation in EBC. A total of 1.843 patients with invasive breast cancer ≤4 cm was randomized to receive total mastectomy vs lumpectomy vs lumpectomy + WBI (with axillary dissection) [14]. At 20-years the cumulative incidence of IBTR was 14.3% with lumpectomy and WBI, but no differences were found in terms of disease-free survival (DFS) and OS [15]. Similar conclusions in favor of BCS came out from the European Organization for Research and Treatment of Cancer (EORTC) 10810 and the Danish Breast Cancer Cooperative Group (DBCG)-82TM trials [16,17].

In the same period, the benefit of adjuvant endocrine therapy was reported in EBC patients. The NSABP-B14 trial was a randomized, double-blind placebo-controlled trial investigating the role of adjuvant tamoxifen in 2.644 women with invasive breast cancer, negative axillary nodes and positive estrogen receptors (ER) [18]. A significant prolongation in DFS was seen in the tamoxifen group, particularly in younger women (≤49 years), which was maintained at 15 years [18,19]. Moreover, a reduction in breast-cancer mortality was seen in studies as the DBCG 77c trial and the EBCTCG meta-analysis [20,21]. The role of endocrine therapy in reducing the rate of any breast recurrence pushed researchers to test the hypothesis that WBI could be omitted after BCS. The lumpectomy only arm of the NSABP-B06 trial had a high rate of IBTR (27.9% at 5 years and 39.2% at 20 years) [14,15]. But eligibility criteria included tumor up to 4 cm in the largest dimension. Hence, clinical research addressed, at least in some trial, the option to avoid WBI in a patient population harboring smaller tumors.

## 3. First generation of phase III trials investigating WBI omission

The first generation of prospective randomized phase III clinical trials investigated WBI omission after BCS with very broad inclusion criteria and a consequently vague profile of patients at low risk of recurrence [22–32] (Table 1). For example, the Ontario Clinical Oncology Group (OCOG) trial (1984–1989) randomized 837 node negative breast cancer patients, after lumpectomy and axillary lymph node dissection, to receive WBI (416 patients) or no radiation (421 patients) [22]. Tumors were <4 cm in size and resection on free microscopic margins. A dose of 40 Gy in 16 fractions over 3 weeks was given for WBI, followed by a 12.5 Gy boost dose to the tumor bed in 5 fractions. No endocrine therapy was given. After a median observation time of 43 months, the IBTR rate was 5.5% with WBI and 25.7% without [22]. After a median follow up of 91 months, the IBTR rate was 11% with WBI and 35% without, while no difference in OS was seen [23]. Young age (<50 years), tumor size (>2 cm) and poor tumor nuclear grade were found to be predictors of IBTR. Nevertheless, a clearly identified low risk subgroup could not be identified [23].

Other trials explored the option of omitting WBI in the context of an extended surgery to the breast compared to lumpectomy. The Milan III trial (1987–1989) enrolled a total of 567 patients (age: ≤ 70; tumor diameter <25 mm), after quadrantectomy (extensive breast resection including the overlying skin and the underlying fascia) and axillary dissection to receive immediate WBI (294 patients) or no radiation (273 patients). Radiation consisted of 50 Gy in 25 fractions WBI followed by a conventionally fractionated boost up to 10 Gy. Patients having pathological nodal involvement were given adjuvant chemotherapy in case of estrogen receptor negative tumors (96/567; 17%) or tamoxifen if positive (68/567; 12%). Long-term results showed a 10-year crude cumula-

**Table 1**
First generation trials exploring radiotherapy omission after breast conservation in unselected breast cancer patients.

| Author | Years | Pts | Age (yrs) | Surgery | pT stage | pN stage | Size | Adjuv treat | Random | IBTR rate | OS | Median FU (mos) | Factors predicting IBTR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clark et al *OCOG trial* | 1984-1989 | 837 | All | Lump + AD | T1-T2 | N0 | ≤ 4 cm | No | RT vs no RT | 11% vs 35% | 79% vs 76% | 91 | Age (< 50 yrs), size (>2cm) poor tumor grade |
| Veronesi et al *Milan III trial* | 1987-1989 | 567 | ≤ 70 | Quad + AD | T1-T2 | N0 | < 2.5 cm | Tam or CT | RT vs no RT | 5.8% vs 23.5% | 82.4% vs 76.9% | 120 | Age |
| Liljegren et al *Uppsala-Orebro trial* | 1981-1988 | 381 | < 80 | Sector res + AD | T1-T2 | N0 | ≤ 2 cm | No | RT vs no RT | 8.5% vs 24% | 77.5% vs 78% | 120 | Age (< 60 yrs), comedo or lobular histology |
| Fisher B et al *NSABP-B21 trial* | 1989-1998 | 1009 | All | Lump + AD | T1a-T1b | N0 | ≤ 1 cm | Tam on radom | RT + Tam vs RT vs Tam | 2.8% vs 9.3% vs 16.5% | 93% vs 94% vs 93% | 96 | DCis compontent, poor tumor grade |
| Forrest et al *Scottish trial* | 1985-1991 | 585 | ≤ 70 | Lump + AD or AS | T1-T2 | N0 | ≤ 4 cm | Tam or CT | RT vs no RT | 5.8% vs 24.5% | No diff (HR:0.98) | 68 | None |
| Killander et al *SweBCG 91 RT trial* | 1991-1997 | 1187 | < 76 | Sector res + AD | T1-T2 | N0 | < 5 cm | Tam or CT | RT vs no RT | 11.5% vs 23.9% | 71.1% vs 68.4% | 180 | None |
| Holli et al *Finnish trial* | 1990-1995 | 152 | > 40 | Lump + AD | T1 | N0 | < 2 cm | No | RT vs no RT | 7.5% vs 18.1% | 97.1% vs 98.6% CSS | 80 | None |

Pts: patients; yrs: years; Adjuv treat: adjuvant treatment; IBTR: ipsilateral breast tumor recurrence; OS: overall survival; FU: follow up; mos: months; Lump: lumpectomy; AD: axillary dissection; Quad; quadrantectomy; res: resection; Tam: tamoxifen; CT: chemotherapy; RT: radiotherapy; diff: difference; CSS: cancer specific survival.

tive incidence of 23.5% with WBI vs 5.8% without. No difference in OS was detected at 10 years [24,25]. Age was found to be a significant factor affecting the rate of IBTR [25]. The Uppsala-Orebro Breast Cancer Study Group Trial (1981–1988) randomized, a total of 381 stage I breast cancer patients (aged <80, with a unifocal node negative tumor sized ≤2 cm), after standardized sector resection (dissection of the breast gland up to its peripheral aspects in the plane of Scarpa's fascia, included in the specimen, and down to the pectoralis muscle) and axillary dissection, to receive (184 patients) or not (197 patients) WBI, consisting of 54 Gy/27 fractions with no boost to the surgical bed [26,27]. No adjuvant endocrine therapy was given. The IBTR rate were 2.9% in the WBI arm and 7.6% in the no radiation arm at 3 years, 3.3% vs 18.4% at 5 years and 8.5% vs 24.0% at 10 years [27–29]. No difference in OS was seen at 10 years. Patients aged >60 years, without comedo or lobular cancer or without the mammographic appearance of a stellate lesion with microcalcification were found at low risk of recurrence (<6% at 5 years) [30].

Tumors size was taken into account in both the Milan III and Uppsala-Orebro trials in which patients were accrued if having tumors sized <25 mm and ≤20 mm, respectively. Another study accounting for tumor dimension is the NSABP B-21 trial (1989–1998), which enrolled a total of 1.009 patients, with a diagnosis of invasive breast tumor ≤1 cm, negative axillary nodes and free tumor margins after lumpectomy and axillary dissection [31]. Patients were randomized to receive adjuvant tamoxifen only for 5 years (336 patients), WBI (50 Gy/25 fractions over 5 weeks + b oost as per center's policy) and placebo (336 patients) or WBI + tamoxifen (337 patients). At 8 years, the cumulative incidence of IBTR was 16.5% with exclusive tamoxifen, 9.3% with WBI only and 2.8% with WBI and tamoxifen. The advantage in reducing IBTR for WBI was observed regardless of ER status. Patients treated with tamoxifen (with or without WBI) had a lower rate of contralateral breast cancer (HR: 0.45; 95%). No difference in OS was seen [31]. Tumors arising within a radial scar, those of tubular histology or with no poor tumor grade or ductal carcinoma in situ component were found to be at lower risk [32].

The role of adjuvant endocrine therapy as a subsidiary to WBI was investigated also in the Scottish trial (1985–1991), which randomized 585 patients (age: <70 years, with invasive breast cancer ≤4 cm, node negative and no fixation of primary tumor) after local excision and either axillary sampling (3–4 nodes) or clearance (levels I-III), to receive postoperative WBI (291 patients) or no further local treatment (294 patients) [33]. All subjects were given adjuvant systemic treatment with oral tamoxifen in case of ER positive tumors or 6 cycles chemotherapy for negative cases. At a median follow up time of 5.7 years, IBTR rate was 5.8% after WBI and 24.5% with no radiation. No differences in OS were seen. The advantage of WBI in terms of IBTR rate was seen irrespective of ER status [33].

In the aforementioned trials, the population of patients included was widely heterogeneous, selected mainly by tumor size, unifocality, negative axillary nodes and free-resection margins after BCS. Age was not used as a selection criterion and hence no focus on an elder population was addressed. The same consideration can be made for hormonal receptor status whose evaluation was yet to be completely established at the time. A trial with strict selection criteria was the Finnish study which enrolled patients with unifocal tumor sized <2 cm, well-or moderately-differentiated (G1-G2), with positive progesterone receptor (PgR) and no extensive intraductal component [34]. The broad spectrum of patient, tumor and treatment characteristics allowed for subset analyses to extrapolate factors predictive of local relapse and patient subgroups at low risk. Age, tumor size, poor differentiation grade, histology were identified, but a clear low risk profile was hardly identified.

This was evident in the SweBCG 91 RT trial (1991–1997), where 1.187 patients with T1-T2 N0 M0 disease were randomized, after sector resection and axillary dissection, to receive (593 patients) or not (594 patients) WBI (48–54 Gy in 24–27 fractions over 5 weeks) [35]. Adjuvant tamoxifen or CMF chemotherapy were prescribed in stage II patients. At 5-years, the cumulative incidence of IBTR was 14% for patients having WBI omitted and 4% for those receiving radiation, while at 15.6 years, it was 23.9% and 11.5% respectively [35,36]. Recurrence-free survival was lower for patients not receiving WBI (51.7% vs 60.4%), while OS did not significantly differ. In this trial the 15-year cumulative incidence of IBTR in patients not receiving radiation ranged from 16.7% to 28%, depending on age, tumor size, hormonal receptor status and diagnostic methods. In low-risk patients, aged >64 years, with a primary tumor sized <21 mm and having positive ER and PgR, the cumulative reduction in IBTR rates following WBI was higher

**Table 2**
Trials investigating the omission of radiotherapy in patients selected by clinical and pathological characteristics.

| Author | Years | Pts | Age | Surgery | pT stage | pN stage | HR status | Size | Margins | Other factors | Random | LR rate | OS | Median FU (mos) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hughes et al<br>*CALGB 9343* | 1994-<br>1999 | 636 | ≥ 70 | Lump or WE +<br>AD or AS | T1 | N0 | ER + | ≤ 2cm | No tumor<br>on ink | NR | TAM+RT vs TAM | 2% vs 9% | 67% vs 66% | 154 |
| Fyles et al<br>*Toronto-BC trial* | 1992-<br>2000 | 769 | ≥ 50 | BCS + AD | T1-T2 | N0 | NA | < 5 cm | No tumor<br>on ink | NR | TAM+RT vs TAM | 3.5% vs 17.6% | 93.2% vs 92.8% | 96 |
| Kunkler et al<br>*PRIME II trial* | 2003-<br>2009 | 1326 | ≥ 65 | BCS + AD<br>or AS or SLNB | T1-T2 | N0 | ER/PgR + | < 3cm | ≥ 1 mm | G3 or LVI+ allowed<br>(not both) | TAM/AI + RT vs TAM/AI | 1.3% vs 4.1% | 93.9% vs 93.9% | 60 |
| Blamey et al<br>*BASO II trial* | 1992-<br>2000 | 1135 | < 70 | WE +<br>AD or AS | T1 | N0 | ER/PgR + | < 2cm | No tumor<br>on ink | G1 only or fav. hist.<br>LVI+ not allowed | BCS only vs BCS + RT<br>vs BCS + TAM vs<br>BCS + RT + TAM | 10.2% (pts not receving RT)<br>3.9% (pts receiving RT)<br>11.7% (pts not receiving TAM)<br>4.2% (pts receiving TAM) | NR | 121 |
| Potter et al<br>*ABCSG trial 8A* | 1996-<br>2004 | 869 | All | Lump or WE<br>or QUAD + AD | T1-T2 | N0 | ER/PgR + | ≤ 3cm | R0 res | G3 not allowed | TAM/AI + RT vs TAM/AI | 0.4% vs 5.1% | 97.9% vs 94.5% | 53.8 |
| Winzer et al<br>*GBCSG trial* | 1991-<br>1998 | 361 | 45-75 | BCS + AD | T1 | N0 | ER/PgR + | ≤ 2cm | R0 res | G3, LVI +, EIC<br>not allowed | BCS only vs BCS + RT<br>vs BCS + TAM vs<br>BCS + RT + TAM | 29% (BCS)<br>4% (BCS + RT)<br>2.5% (BCS + TAM)<br>3.2% (BCS + RT + TAM) | NR | 71 |
| Tinterri et al<br>*RT 55-75 trial* | 2001-<br>2005 | 749 | 55-75 | QUAD + SLNB<br>or AD | T1-T2 | ≤ 3 nodes<br>involved | ER/PgR +<br>ER/PgR - | < 2.5 cm | R0 res | G3 allowed<br>LVI + or EIC<br>not allowed | RT vs no RT | 3.4% vs 4.4% | 81.4% vs 83.7% | 108 |

Pts: patients; HR: hormonal receptor; LR: local relapse; OS: overall survival; FU: follow up; mos: months; Lump: lumpectomy; WE: wide excision; AD: axillary dissection; AS: axillary sampling; BCS: breast conserving surgery; SLNB: sentinel lymphnode biopsy; NA: not available; ER: estrogen receptor; PgR: progesteron receptor; NR: not reported; fav. hist.: favourable histology; res: resection; fa LVI: limphovascular invasion; EIC: extensive intraductal component; TAM: tamoxifen; RT: radiotherapy; AI: aromatase inhibitor.

than in the whole cohort (IBRT: 25.9% for no WBI arm vs 5.3% for the radiation arm) [36].

Clinical features of breast cancer at diagnosis still represent major prognostic factors for EBC. However, it is clear nowadays that they could not represent anymore the only assessed factors to correctly stratify patients for the risk of relapse and allocate them to the most appropriate and tailored treatment approach.

## 4. Phase III trials investigating selective WBI omission in patients at low risk

Trials of second generation tried to create a more reliable profile of EBC patients at low risk of recurrence, with a systematic use of age thresholds, hormonal receptor status and other factors such as tumor grade, lymph vascular extension, extensive intraductal component, for precise allocation [37–46] (Table 2). Pre-established selection criteria allowed for a better targeting of the patient population but at the same time narrowed the chance to perform robust subset analyses.

In the Cancer and Leukemia Group B (CALGB) 9343 trial (1994–1999), a total of 636 patients were randomized after lumpectomy or wide local excision and axillary sampling or dissection to receive adjuvant tamoxifen alone (319 patients) or tamoxifen + WBI (317 patients) [37]. Eligibility criteria included women aged ≥70 years with stage I invasive breast cancer (cT1N0M0) with positive ER. WBI was delivered up to 45 Gy in 25 fractions over 5 weeks, including level I-II axillary nodes. A sequential electron boost of 14 Gy in 7 fractions was given. Tamoxifen was administered for 5 years [37]. At 5-years, the rate of IBTR was 1% in the group submitted to WBI and tamoxifen and 4% in the tamoxifen alone group, while at a median follow up of 12.6 years it was 2% and 9%, respectively [37,38]. At 154 months, the time to loco-regional recurrence was longer for the WBI + tamoxifen group, while OS did not significantly differ. No subgroup analysis was performed [38].

In the Toronto and British Columbia trial (1992–2000), a total of 769 patients was randomized after BCS and axillary dissection, sampling or clinical assessment, to receive adjuvant tamoxifen alone (386 patients) or tamoxifen + WBI (383 patients) [39]. Inclusion criteria comprised women aged ≥50 years with a node negative invasive breast cancer sized <5 cm (T1-T2 stage). Axillary dissection or sentinel lymph node biopsy were performed except in women older than 65 years, who were considered eligible also if staged negative on the axilla with clinical criteria. WBI was delivered with a hypofractionated schedule of 40 Gy in 16 fractions over 3–4 weeks, followed by a 12.5 Gy/5 fractions boost to the tumor bed. Adjuvant tamoxifen was given for 5 years. Five-year IBTR rate was 7.7% in the group receiving exclusive tamoxifen and 0.6% in the group submitted to WBI and tamoxifen. At 8 years, the rates increased to 17.6% and 3.5%, respectively [39]. The addition of WBI to tamoxifen significantly improved 5-year DFS compared to tamoxifen alone (91% vs 84%). Five-year OS was not significantly different [39].

In the PRIME II trial (2003–2009), a total of 1.326 patients was randomized after BCS and pathological axillary staging (sentinel lymph node biopsy, four-node lower axillary node sampling, axillary dissection) to receive WBI (658 patients) or no further local treatment (668 patients) on top of planned adjuvant endocrine therapy [40]. Eligibility criteria included women aged 65 years or more with EBC at low risk of local recurrence (cT1-T2N0 tumor sized ≤3 cm with clear resection margins and hormonal receptor expression). Patients with grade 3 tumors or lympho-vascular invasion were allowed but not those with both risk factors. Radiation was given to the whole breast up to 40–50 Gy in 15–25 fractions over 3–5 weeks. A boost to the tumor bed was allowed with electrons or iridium implants up to 10–15 Gy. After a median follow up of 60 months, IBTR rate was 1.3% in patients submitted to WBI and 4.1% in those who were not. No difference in OS was observed. The absolute risk reduction with the addition of WBI was 2.9% at 5 years. No risk factors predictive for local recurrence were found (tumor size or grade, age, margin status, LVI+, ER status). The only variable predictive of IBRT was the omission of WBI (HR: 4.87) [40].

The British Association of Surgical Oncology (BASO) II study was a randomized clinical trial with a 2 × 2 factorial design evaluating the effect of the addition of WBI or tamoxifen or both in EBC after wide local excision on free margins and axillary sampling or clearance [41]. Patient profile was chosen according to the Nottingham Prognostic Index which stratifies risk groups in different prognostic categories [42]. Eligibility criteria included patients <70 years of age with node negative invasive breast cancer sized ≤20 mm, with histological grade 1 or specific good prognosis histology (mucinous, papillary, tubular, cribriform) and no evidence of lymphovascular invasion. The four available treatment arms included BCS only, BCS + WBI, BCS + tamoxifen or BCS + WBI + tamoxifen. At a median observation time of 121 months, the cumulative incidence of IBTR was 10.2% for patients not receiving radiation (BCS only and BCS + tamoxifen group), 3.9% for those receiving radiotherapy (BCS + WBI and BCS + WBI + tamoxifen groups), 11.7% for those not receiving tamoxifen (BCS and BCS + WBI groups) and 4.2% for patients receiving tamoxifen (BCS + tamoxifen and BCS + WBI + tamoxifen groups). The annual rate of IBTR was 0.4% in patients receiving WBI or tamoxifen, 1.2% and 1.3% in those having WBI or tamoxifen omitted, respectively. The risk of local recurrence was reduced by the addition of WBI (HR: 0.37) or tamoxifen (HR: 0.33). The use of both WBI and tamoxifen was associated to a non-significant improvement in OS [41].

In this generation of trials the option of WBI omission was addressed to a population selected by patient characteristics such as age (≥65 or ≥ 70 as in the PRIME II and CALGB 9343 trials), and tumor features such as size (T1 or favorable T2 tumors, except for the Toronto and British Columbia trial), hormonal receptor status (positive in most of the studies) and other histologic charcteristics such as tumor grade, lymph vascular invasion and extensive intraductal component (Table 2). Subset analysis, such as the one performed in the PRIME II trial, were not able to identify predictive factors for IBTR in this selected setting of patients [40]. The addition of either WBI or tamoxifen after BCS lowers the local recurrence rate, with comparable effects as seen in the BASO II and German Breast Cancer Study Group trials [41,44]. Combining WBI and Tamoxifen has addictive effect in preventing IBTR '[37,39]. No influence on OS was detected in any trial by the addition of WBI.

There is a growing burden of knowledge concerning the impact of tumor's biology on disease outcome. Phenotypical biology signature might not be able to overcome the impact on prognosis of clinical features, but should be strongly integrated in the decision making process, in order to avoid over- or under-treatment and to implement personalized radiotherapy approaches.

## 5. Prospective trials using biomarker-based approaches to identify low risk patients

Different molecular subtypes of breast cancer can be identified through gene expression profiling and next generation sequencing techniques. This can help identifying specific clinical behaviors and different responses to therapy [47,48]. Approaches such as immunohistochemistry (IHC) can provide parameters for major intrinsic biologic subtype determination. This can be enriched with information predicting patient's risk for local and distant relapse [3,49]. Liu et al recently performed an analysis on patients accrued in the Toronto-British Columbia trial, using a 6-IHC marker subtyping panel to explore the predictive ability of intrinsic subtyping with respect to the benefit of WBI and to identify a subgroup of patients at low-risk of local recurrence [50]. Luminal subtypes were shown to have a lower benefit if submitted to WBI (HR: 0.4 for Luminal A-like and 0.51 for Luminal B-like) when compared to high-risk subtypes (Luminal HER2 positive, HER-enriched, basal like and triple-negative non-basal type). In a targeted evaluation on low-risk patients (over 60 years of age, tumors below 2 cm in size and Grade 1–2) with Luminal A subtype, the 10-year IBTR rate was 3.1% vs 11.8% for high-risk patients [50].

Tumor subtyping assessed through IHC, genomic expression or signature assays is a promising strategy to identify a subgroup of low-risk women to whom spare radiotherapy after BCS. Different studies are presently investigating this approach (Table 3).

The IDEA (Individualized Decisions for Endocrine Therapy) trial (NCT02400190) is a multicentric prospective single-arm observational study (University of Michigan Cancer Center) assessing loco-regional relapse rate after BCS in post-menopausal women (age:50–69), planned to undergo post-operative endocrine therapy (either tamoxifen or aromatase inhibitors) [51]. Inclusion criteria comprise unifocal disease, stage cT1 N0 M0 with negative axilla, excision margins ≥2 mm, hormonal receptor positive and HER2 negative. The study relies on a gene expression signature based on the 21-gene recurrence score assay *Oncotype*DX (Genomic Health Inc, Redwood City, CA), able to estimate the risk of loco-regional recurrence in node negative, ER positive breast cancer patients [52]. The threshold score used is ≤18 for patients to be classified as low-risk. Five-year loco-regional recurrence rate is the primary endpoint. Pattern of failure, type of salvage therapy for local relapse, distant metastases and breast-cancer specific and overall survival will be collected up to 10-year follow-up [51].

The PRECISION (Profiling Early Breast Cancer for Radiotherapy Omission) trial is a non-randomized phase II trial (Dana Farber Cancer Institute-NCT02653755), evaluating the omission of WBI after lumpectomy in breast cancer patients (aged 50–75) deemed at favorable-risk and receiving adjuvant endocrine therapy [53]. Inclusion criteria comprise unifocality, size ≤2 cm, node negativity after assessment of the axilla, ER and PgR positivity, HER2 negativity and grade 1–2. Patients aged <50 are excluded because considered as having a different natural history, as premenopausal women, and harboring different histologic and biologic tumor characteristics. Patients over 75 are excluded because of typical logistic challenges during follow up and competing causes of death. The trial relies on Prosigna Breast Cancer Assay (NanoString Technologies Inc., Seattle, WA) for gene expression profiling using PAM50 gene signature. This test measures the transcriptional profile of 50 classifier genes to generate a clinically validated score for the 10-year risk of distant recurrence (ROR) [54]. The primary endpoint of the study is 5-year local–regional recurrence rate in the ipsilateral breast or regional lymph-nodes. Patients stratified as intermediate- or high-risk will undergo WBI. For those categorized as low-risk, WBI will be omitted, but endocrine therapy will be offered. Secondary endpoints are recurrence-free, disease-free and overall survival. A total of 1380 patients are planned for accrual [53].

The EXPERT (Examining PErsonalised Radiation Therapy for Low-risk Early Breast Cancer) trial, run by the Breast Cancer Trial Group in Australia and New Zealand, with inclusion criteria similar to the PRECISION trial, will employ Prosigna in order to identify low-risk breast cancer patients (over 50 years of age, having Stage I, ER positive, HER2 negative disease). Interestingly, the trial is designed as a randomised phase III trial [54].

Two other ongoing studies are using IHC to identify breast cancer subtypes. Particularly, the so called IHC4 + clinical factors is a refined immunohistochemical assessment strategy combining protein expression of ER and PgR, HER2 and Ki-67% with clinic-pathological features to characterize the risk of recurrence for each patient [55]. In the TransATAC translational study, ancillary to the ATAC (Arimidex, Tamoxifen Alone or Combined) trial, IHC4 + clinical factors was able to provide information about prognosis for post-menopausal women undergoing endocrine therapy [56].

The LUMINA study, a multicentric single-arm prospective cohort trial (Ontario Clinical Oncology Group-OCOG), investigates the hypothesis that IHC4 + clinical factors may be able to identify low-risk patients [57]. The trial evaluates the risk of IBTR after BCS and sentinel lymph node biopsy/axillary dissection in women

**Table 3**
New generation trials including those based on biomarker-based patient selection.

| Study | Design | Country | Pts | Age | Surgery | Axillary staging | HT | Stage | Margins | Biology | Selection Test | Category | Primary end-point |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IDEA | Observational study | USA | 200 | 50-69 | BCS | SLNB or AD | Yes | I (cT1N0M0) | $\geq$ 2 mm | ER+ve<br>PgR+ve<br>HER2 -ve | Oncotype-DX | Score $\leq$ 18 | 5-year LRR rate |
| PRECISION | Phase II trial | USA | 1380 | 50-75 | BCS | SLNB or AD | Yes | I (cT1N0M0) | No ink on tumor | ER+ve<br>PgR+ve<br>HER2 -ve<br>G1-G2 | Prosigna | Low risk | 5-year LRR rate |
| LUMINA | Cohort trial | Canada | 500 | $\geq$ 55 | BCS | SLNB or AD | Yes | I (cT1N0M0) | $\geq$ 1 mm | ER+ve<br>PgR+ve<br>HER2 -ve<br>Ki-67<13.25% | IHC4 + clinical factors | Low risk | 5-year IBTR rate |
| PRIMITIME | Case cohort study | UK | 2400 | $\geq$ 60 | BCS | SLNB | Yes | I (cT1N0M0) | No ink on tumor | ER+ve<br>PgR+ve<br>HER2 -ve<br>G1-G2<br>Ki-67 testing | IHC4 + clinical factors | Very low risk | 5-year IBTR rate |
| EXPERT | Phase III RCT comparator WBI | AUS-NZ | 1170 | $\geq$ 50 | BCS | SLNB | Yes | I (cT1N0M0) | No ink on tumor | ER+ve<br>PgR+ve<br>HER2 -ve<br>G1-G2 | Prosigna | Low risk | 5-year IBTR rate |
| TOP-1 | Cohort study | The Nehterlands | 800 | $\geq$ 70 | BCS | SLNB | No | I (cT1N0M0) | No ink on tumor | G1-G2 if sized < 1 cm<br>G1 if sized 1-2 cm<br>ER > 50%<br>HER -ve | None | Low risk | 5-year IBTR rate |
| NATURAL | Phase III RCT comparator PBI | Denmark | 926 | $\geq$ 60 | BCS | SLNB or AD | No | I (cT1N0M0) | $\geq$ 2 mm | G1-G2<br>ER > 50%<br>HER -ve | None | Low risk | 10-year IBTR rate |

Pts: patients; HT: hormonal therapy; RCT: randomized controlled trial; WBI; whole breast irradiation; PBI: partial breast irradiation; BCS: breast conserving surgery; SLNB: sentinel lymphnode biopsy; AD: axillary dissection; ER: estrogen receptor; PgR: progesteron receptor; HER2: Human Epidermal groeth factor Receptor −2; IHC: immuno-histochemistry + clinical 4; IBTR: ipsilateral breast tumor recurrence; LRR: local–regional relapse.

over 55 years of age submitted to adjuvant endocrine therapy (tamoxifen or aromatase inhibitors). The low-risk population (5- and 10-year IBTR rates < 5% and < 10%, respectively) characteristics are: negative axilla, Luminal A-like subtype (ER $\geq$ 1%, PgR > 20%, HER2 negative, Ki-67 < 13.25%), size $\leq$ 2 cm, excision margins $\geq$ 1 mm, with ductal, tubular, mucinous, non-lobular histology, no high tumor grade (Grade 3) nor lymph vascular invasion or extensive intraductal component. Five-year rate of IBTR (recurrent, invasive or in-situ cancer in the ipsilateral breast, histologically proven) is the primary endpoint of the study. Secondary endpoints are recurrence free interval, 5-year event free survival and overall survival. Up to 500 patients are planned for enrollment [57].

In the United Kingdom, the PRIMETIME trial, a prospective biomarker-directed case-cohort study plans to enroll 2400 women aged $\geq$60, with T1N0M0 tumors having positive hormonal receptors, negative HER2, and Grade 1–2 [58]. After BCS, sentinel lymph node biopsy and central testing of Ki-67, patients are planned to be scored according to IHC4 + clinical factors with a dedicated calculation algorithm. Those stratified in the ‘very low risk’ category, will be spared WBI. Complementary endocrine therapy will be given for 5 years. Primary endpoint is IBTR at 5 years [58].

The future of precision medicine should be based on the integration of clinical features (patient- and disease-related) with biomarkers and gene-signatures. An interesting example is the genomic-adjusted radiation dose (GARD) score, which employs the gene-expression-based radiosensitivity index and the linear quadratic model to determine the therapeutic effect of radiotherapy. This score showed also to be an independent predictor of radiotherapy-specific outcomes and to be able to estimate the probability for both relapse- and distant metastasis-free survival [59].

However, the cost-effectiveness and the reliability of this multimodal assessment will be a major concern to be carefully evaluated within clinical trials and in clinical practice eventually.

## 6. Selective omission of endocrine therapy for patients treated with BCS and radiation

A high variability in terms of prescription of adjuvant endocrine therapy after BCS (with or without WBI) can be found in daily practice, with some clinicians prescribing endocrine therapy whenever ER positivity is present and others tailoring the indication carefully evaluating the potential benefit in reducing failure rates compared to the acute and late treatment-related toxicity profile. The use of hormonal manipulation affects the risk of recurrence at any site, including local relapses, and thus affects the absolute benefit of WBI after BCS. The knowledge on the toxicity profile of hormonal manipulation is well-established, since side effects of endocrine therapy could significantly impact long term health-related quality of life (HRQoL) of potentially frail patients [60].

For a patient population at low-risk of relapse, a de-escalation of the treatment package may include the omission of endocrine therapy, instead of WBI, after BCS or even the omission of both the treatment approaches. Robust data on these options are lacking and prospective clinical studies are strongly demanded.

The clinical question whether this subset of patients really needs adjuvant hormonal therapy is still pending. In this sense, a few trials are being initiated to fulfill this gap.

In the Netherlands, the TOP-1 clinical trial is investigating the option to omit WBI in a group of EBC patients not receiving adjuvant endocrine therapy. Although the HRQoL is assessed, the primary endpoint of the study is local relapse rate [61]. Similarly, the ongoing Danish Natural trial is evaluating if omission of WBI in very low risk EBC may provide patients with an equivalent local control of disease [62].

To our knowledge, the only trial combining a unique primary endpoint – such as HRQoL – with a cost-effective biomarker assessment (luminal A-like tumor based on IHC) is the phase 2–3 EUROPA trial (NCT04134598). This study will explore the role of exclusive partial breast irradiation vs exclusive endocrine-therapy after BCS for EBC women aged ≥ 70 with luminal A-like disease to determine which of these options may be better in terms of quality of life [63].

## 7. Conclusions

The challenge to identify the most suitable subset of EBC patient that can have WBI omitted after BCS is still ongoing. Probably, a comprehensive integration of features related to patient (age, comorbid conditions, life expectancy) and tumor, including either classical factors (size, hormonal receptor status, grade of differentiation and intrinsic subtyping) and genetic and molecular features, may enhance our ability to properly identify patients at low-risk of recurrence. New generation trials will, supposedly, help in answering this question. Nevertheless, the ideal treatment package for this potential low-risk patient subgroup still deserves investigation. Omission of WBI with no adjuvant endocrine treatment after BCS may consistently increase IBTR rate even in patients with this recurrence profile. Avoiding radiation in low-risk patients undergoing adjuvant endocrine therapy needs careful consideration as well. Endocrine therapy may be associated with an increased risk for osteoporosis with skeletal related events, cardiovascular disease, sexual dysfunction and even neurocognitive effects [64]. Adjunctively, the impact of endocrine therapy on OS in post-menopausal patients has yet to be confirmed with even compliance to treatment being rather unpredictable, as only 35–60% of women accomplish a full 5-year adjuvant program [65]. Treatment safety and quality of life should also be considered as crucial clinical endpoints and, hence, the need for adjuvant systemic therapy in low-risk EBC may be debatable. Overall, the side-effects of adjuvant systemic therapy may outweigh those of WBI, especially considering that hypofractionation, accelerated partial breast irradiation and refined delivery techniques have consistently decreased the radiation-burden in breast cancer patients [66–69]. Composite endpoints evaluating not only IBTR rate and OS but also the toxicity profile of treatments, patient quality of life, psychosocial issues, and cost-effectiveness would be indicated to better tailor the clinical decision-making process in low-risk EBC patients [70]. A cautionary statement should finally be pointed out, whenever considering the omission of a well-established and effective treatment option, as the recent data on surgery omission in case of complete response after primary systemic therapy in breast cancer patients do confirm [71].

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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