The 2018 Assisi Think Tank Meeting on Breast Cancer: International Expert Panel White Paper

Abstract

We report on the second Assisi Think Tank Meeting (ATTM) on breast cancer which was held under the auspices of the European Society for RadioTherapy & Oncology (ESTRO). In discussing in-depth current evidence and practice it was designed to identify grey areas in diverse forms of the disease. It aimed at addressing uncertainties and proposing future trials to improve patient care.

Before the meeting, three key topics were selected: 1) primary systemic therapy, mastectomy, breast reconstruction and post-mastectomy radiation therapy, 2) therapeutic options in ductal carcinoma in situ, and 3) therapy de-escalation in early stage breast cancer. Clinical practice in these areas was investigated by means of an online questionnaire. The time lapse period between the survey and the meeting was used to review the literature and on-going clinical trials. At the ATTM both were discussed in depth and research protocols were proposed.

Keywords: Breast cancer, Radiation therapy, Neoadjuvant chemotherapy, Breast reconstruction, Post-mastectomy radiation therapy, Ductal carcinoma in situ, De-escalating therapy, Hypofractionation, Partial breast irradiation

Highlights

- PMRT may be avoided after PST in some patients with complete pathological response
- When PST transforms cN1 disease to SLN negative, axillary treatment must be defined
- Hypofractionation is an option in patients with immediate breast reconstruction
- Whole breast irradiation can be omitted in selected DCIS patients
- Therapy de-escalation is advisable in low-risk early-stage breast cancer patients

1. INTRODUCTION

The success of the first "Assisi Think Tank Meeting" (ATTM) on Breast Cancer in March 2016, in Assisi, Italy [Aristei et al., 2016], led to the subsequent 3-day “Think Tank Meetings” on rectal [Valentini et al., 2019] and breast cancer in 2017 and 2018 respectively. All were held under the auspices of the European Society for RadioTherapy & Oncology (ESTRO) and were designed to discuss in-depth current practice and identify grey areas in the management of each tumour type. Each aimed at proposing trials to address these uncertainties.

Here we report on the second ATTM on breast cancer. Three key topics were identified for discussion: 1) primary systemic therapy (PST), mastectomy, breast reconstruction and post-mastectomy radiation therapy (PMRT), 2) therapeutic options in ductal carcinoma in situ (DCIS) and 3) therapy de-escalation in early stage breast cancer. The methodology, outcome of discussions, conclusions and study proposals are presented.

2. METHODS

2.1 Pre-meeting work

2.1.1 Identifying grey areas in the 3 selected topics

a) The Scientific Organizers (PP, CA, VV) selected an Expert European Board on the basis of their extensive clinical and research experience in breast cancer and their contributions to guide-line developments. An Executive Committee (MA, LB, CB, CC, IM, BO, OP) was set up.
b) The Scientific Organizers and the Executive Committee prepared a questionnaire on the 3 topics which was distributed to all Expert Board members by Monkey Survey. Under 70% agreement on a treatment option indicated uncertainty i.e. a ‘grey area’ which would be discussed in-depth at the ATTM.

2.1.2 Background study preparation

For each topic Expert Board members set up a working group which included two co-chairs, a secretary and two speakers. They reviewed the literature and summarized the status of on-going clinical research.

2.2 At the Meeting

a) *Day 1* was reserved for the Scientific Organizers and Expert Board. The 3 working groups presented their background study preparation, discussed the grey areas and proposed potential future clinical research.
b) *Day 2* was open to invited physicians who were involved in breast cancer treatment. All participants replied to the questionnaire by means of on-site tele-voting to confirm, or otherwise re-define, the grey areas. After a discussion on current evidence and on-going clinical studies, research proposals were prioritized.
c) *Day 3* the Scientific Organizers and Expert Board summarized the protocol proposals emerging from the first 2 days and selected experts to draw up the protocols and write the present White Paper.

3. RESULTS

3.1 Topic 1- PST, mastectomy, breast reconstruction and PMRT

3.1.1 Summary of current evidence and areas of contention

PST, long the standard of care in locally advanced disease, is now increasingly used in early stage disease. Although PST was not associated with better survival rates than adjuvant chemotherapy, its use in selected patients is justified for response monitoring, with the most responsive tumour subtypes being triple negative and human epidermal growth factor receptor 2- (HER2)-positive. It is also used to predict outcome and increase the number of eligible candidates for breast-conserving surgery (BCS) [Houssami et al., EJC 2012; Cortazar et al., 2014; Bazan et al., 2016; Cain et al., 2017; Gillon et al., 2017].

Although achieving a pathological complete response (pCR) indicates patients with better prognosis [Mamounas et al., 2012; Gillon et al., 2017], there was no consensus on the definition of pCR until 2017 [Sinn et al., 1994; Sataloff et al., 1995; Bear et al., 2003; Green et al. 2005;

Hortobagyi et al., 2017]. It is now defined as the absence of invasive carcinoma in the breast and lymph nodes, independently of DCIS (ypT0/is and pN0).
The following grey areas emerged.

3.1.1.1 Avoiding PMRT after PST

Although there is a general consensus for PMRT in patients with locally advanced disease, mainly if non-operable at diagnosis, or early stage disease not achieving pCR after PST [Chapman et al., 2015; Bazan et al., 2016], the role of PMRT after PST is not supported by evidence from specifically designed randomized trials. Retrospective studies were flawed by selection biases, different initial disease stages (from T1N0 to T3N2-3), surgery (BCS or mastectomy) and systemic therapy regimes. In general, more risk factors were present in patients who received PMRT [Huang et al., 2004; Garg et al., 2004; McGuire et al., 2007; Nagar et al., 2011; Haffty et al., 2019].

Several studies elucidated the clinical, pathological and treatment-related categories of variables in loco-regional relapse (LRR) risk. Clinical risk factors included disease stages III-IV, large tumour size, advanced nodal stage and young age. Poor pathological prognostic factors included lymph-vascular invasion (LVI), extracapsular extension, negative receptor status, triple negative tumour, high Ki-67, 4 or more positive axillary lymph nodes and the extent of the residual tumour burden. Treatment-related risk factors were poor or no response to PST, no supraclavicular irradiation and no tamoxifen administration, which may have indicated patients were receptor negative [Buchholz et al., 2001; Buchholz et al. 2002; Garg et al., 2004; Huang et al., 2005; McGuire et al., 2007; Wright et al., 2013; Bernier et al., 2015; Gillon et al., 2017; Huang et al., 2017; Symmans et al., 2017; Haffty et al., 2019].

In patients with such risk factors, PMRT lowered LRR rates and, in some studies, improved survival [Huang et al., 2004; Garg et al., 2004; McGuire et al., 2007; Nagar et al., 2011; Cortazar et al., 2014; Rusthoven et al., 2016; Ohri et al., 2017; Krug et al., 2019]. A SEER analysis of 2,525 women with pT3N0 breast cancer observed that adding PMRT significantly increased 8-year cause specific survival (85.0% *vs* 82.4%, $p < 0.01$) and overall survival (OS) (76.5% *vs* 61.8%, $p<0.01$) [Johnson et al., 2014]. The National Cancer Database (NCDB) analysis of 3,437 women with pT3N0 breast cancer reported that 48% received PMRT, which was delivered to the chest wall only in 2/3 or to the chest wall and regional lymph nodes in 1/3. The 5-year OS was 91% in patients who received PMRT *vs* 76% in those who did not ($p < 0.001$). The benefit was independent of chemotherapy and/or endocrine therapy (ET) [Cassidy et al., 2017].

Combined analysis of the B-18 and B-27 NSABP studies on mostly stage II patients who did not receive PMRT is worth noting. LRR was infrequent when pCR was achieved, so the results did not support PMRT [Mamounas et al., 2012]. Biases included few patients achieving pCR in the breast and lymph nodes and lack of histological findings on lymph node status at diagnosis. Since other reports [Huang et al., 2004: McGuire et al., 2007; Le Scodan et al., 2012, Shim et al., 2014] confirmed PMRT might be safely omitted in clinical stage II, ypN0-1, with good prognostic features, attempts were made to identify such patients [Bellon et al., 2012; Fowble et al., 2012; Lemanski et al., 2015]. As recommendations were not uniform, doubts persist about which candidates can safely omit PMRT. The ATTM suggested that biomarker assessments before and during PST might improve understanding of breast cancer biology and behaviour.

3.1.1.2 Managing cN1 disease that became ypN0 at sentinel lymph node biopsy

PST was associated with less extensive axillary surgery. When sentinel lymph node (SLN) biopsy reveals histologically confirmed N1 disease at diagnosis that has become stage ypN0 disease after PST, axillary lymph node dissection (ALND) is sometimes no longer performed [Bazan et al., 2016; El Hage Chehade et al., 2016; Cain et al., 2017]. As this new strategy is not evidence-based, it has opened up opportunities for clinical trials investigating fine-tuned axillary therapy (see Table 1). In the absence of evidence, consensus guidelines are emerging, with the contribution of ATTM members (CC, PP) [Gandhi et al.,2019; The American Society of Breast Surgeons, 2019; Burstein et al., 2019], and participation in clinical trials is strongly advised.

3.1.1.3 Internal mammary node irradiation

In patients with indications to PMRT after PST very few data are currently available on internal mammary node (IMN) irradiation [Noh et al., 2014; Haffty et al., 2016; Kim et al., 2015]. IMN irradiation in 284/521 patients with stage II-III breast cancer was associated with a significant improvement in 5-year disease-free survival (DFS) (81.8% *vs* 72.7% without, p = 0.019) and low toxicity rates at a median follow-up of 71 months [Kim et al., 2015]. After adjusting for all potential confounding variables, IMN irradiation was independently associated with improved DFS (p = 0.049), benefitting most N1-2 and triple-negative disease in the inner/central quadrants.

Although prospective studies are warranted, no studies have as yet been specifically designed to assess the effect of IMN irradiation after PST. No information will be forthcoming from current randomized phase III clinical trials (NSABP-B51 and Alliance 11201) as RT is administered to IMNs together with the chest wall, undissected axilla and supraclavicular nodes. In the RaPChem study, IMN irradiation is optional for high-risk patients. Table 1 describes these trials.

3.1.1.4 PMRT target volume contouring and hypofractionation after breast reconstruction

Breast reconstruction, which reduces the patient's psychological discomfort and improves Quality of Life (QoL), has evolved over the years, with different options now being available [Walsh et al., 2014; Aristei et al., 2018; Kaidar-Person et al., 2019]. Although immediate expander/implant is largely used in clinical practice as it is an easier procedure than autologous reconstruction [Jagsi et al., 2014] its irradiation was associated with higher complication rates [Kronowitz et al., 2012; Momoh et al., 2014; Kelley et al., 2014; Jagsi et al., 2016; Poppe et al., 2017]. Technical difficulties were reported in delivering PMRT after reconstruction, as it may lead to sub-optimal target volume coverage and organ at risk (OAR) sparing [Motwani et al., 2006]. More recent data derived from CT-based planning showed no significant differences in dose distribution to OAR, recurrence and survival rates whether the breast implant was present or not [Liljegren et al., 2014; Bjöhle et al., 2019].

After immediate breast reconstruction, contouring guidelines for target volumes in PMRT were lacking until 2019. The target volume frequently included the implant or reconstructed breast itself, with a consequent risk of toxicity. To ensure OAR sparing and reduce toxicity, without compromising target coverage, radiation oncologists, breast surgeons, plastic surgeons and clinical oncologists collaborated in drawing up new ESTRO-ACROP delineation guidelines [Kaidar-Person et al., 2019]. It is to be hoped they will achieve widespread use.

Hypofractionation was reported as successful after mastectomy with no breast reconstruction [Wang et al., 2019]. Even though no randomized data are available on optimal fractionation there are no apparent reasons for avoiding it after modern breast reconstructions [Yarnold et al., 2019] and, in fact, a small increase in its use was reported in the USA [Venigalla et al., 2018].

3.1.2 Current Research Studies

On-going studies on locoregional treatment after PST are reported in Table 1

Currently recruiting patients are 2 randomized U.S. clinical trials: Alliance 11201 and NSABP-B51. In the UK, the ATNEC randomised controlled trial (RCT) is now funded by the National

Institute of Health Research Health Technology and Assessment Programme. In the Netherlands, the RaPChem study is on-going**.**

3.1.3 Proposed Research Strategies

The ATTM proposed examining the role of axillary treatment for clinical T1-2N1 patients with a negative SLN biopsy after PST with stratification for biological subtype. Baseline, pre-PST N1 disease status will be assessed by ultrasound and fine-, core-needle biopsy. Clip insertion or alternative marking will be mandatory. Candidates will be randomised to 1st and 2nd level RT or surgery as axillary treatments *vs* no axillary treatment. Centres will need to decide upfront whether to include axillary levels 3 and 4 and the IMN or not and do this consistently for both treatment arms. The primary endpoint is the 5-year DFS.
A further option might be enrolment of patients in the Indax (Individualized Locoregional Treatment of Initially Biopsy-proven Node-positive Breast Cancer After Primary Systemic Therapy, NCT04281355) protocol which is still under development. After PST, on the basis of the pN stage (as defined by targeted lymph node biopsy and/or SLN biopsy), patients will be enrolled in one of the two experimental arms: pN0 patients will not receive any axillary treatment (RT or ALND), while pN+ patients will receive regional RT, but not ALND.

3.2 Topic 2: Ductal Carcinoma in Situ

3.2.1 Summary of current evidence and areas of contention

The incidence of DCIS has risen from <5% to 20-25% of new diagnoses, due to widespread use of breast cancer population screening programs. Treatment options are mastectomy or BCS followed by whole breast irradiation (WBI). WBI aims at preventing local relapse (LR) which, in 50% of cases, manifests as invasive carcinoma. ET (tamoxifen or aromatase inhibitors) is suitable for selected cases. Grey areas are reported below.

3.2.1.1 Omitting WBI

The efficacy and safety of WBI in DCIS were demonstrated in 4 large randomized studies and in their meta-analysis. With more than 12 years median follow-up they showed significant reductions in LR (either in situ or infiltrating) [Wapnir et al., 2011; Cuzick et al., 2011; Donker et al., 2013; Wärnberg et al., 2014; EBCTCG, Correa et al., 2010]. This benefit was independent of prognostic factors such as age, tumour size and grade, comedonecrosis and surgical margin status [EBCTCG, Correa et al., 2010]. The Ontario Cancer Registry Data confirmed that WBI significantly reduced the 10-year recurrence rate (13% *vs* 20.1% with surgery alone, $p < 0.001$). BCS without WBI did not favour breast preservation because patients later required mastectomy as salvage treatment for LR [Rakovitch et al., 2018]. Although none of the above studies reported any advantage in OS, SEER data (US National Cancer Institute) in a very large series showed that WBI was associated with better OS in patients with high nuclear grade, young age and large-sized tumours [Sagara et al., 2016].

Studies were conducted to define whether WBI could be safely omitted in selected patients. The RTOG 9804 trial randomized women with DCIS and low-risk features (tumours <25 mm in size, low or intermediate grade, free-margins of at least 3 mm and negative post-operative mammogram) to post-operative WBI or not. After a median follow-up of 7 years, LR was significantly lower after RT (6.7% *vs* 0.9%, $p < 0.001$) [McCormick et al., 2015]. The main study bias lay in recruiting a cohort of only 636 patients out of a planned 1,790. A recent update with a 12 year follow-up confirmed that WBI reduced the cumulative incidence of all LR (2.8% vs 11.4%; $p = 0.0001$). Invasive LR was 1.5% after WBI vs 5.8% after BCS alone ($p = 0.016$) [McCormick et al., 2018].

The ECOG-ACRIN E5194 study retrospectively analyzed 665 patients with either low-risk DCIS (as defined above), or high-grade DCIS under 1 cm in size. Despite the size criteria in these two cohorts, median DCIS was only 6 mm, with very wide free margins in 80% of cases. Tamoxifen was non-randomly prescribed to 30% of patients. The risk of developing an ipsilateral breast event (IBE) and an invasive IBE increased through the 12 years of follow-up, without plateauing [Solin et al., 2015]. In conclusion, the ATTM consensus was that none of these studies identified a sub-group of patients who could safely avoid WBI. Many experts were, however, of the view that it might be omitted in selected, well-informed patients after a thorough discussion of its pros and cons.

3.2.1.2 Hypofractionation

As WBI hypofractionation is standard treatment for invasive breast carcinoma (see paragraph 3.3.1.1), there is no reason to presume it would fail in DCIS. Indeed, results of retrospective analyses [Williamson et al., 2010; Wai et al., 2011; Ciervide et al., 2012; Hathout et al., 2013; Lalani et al., 2014; Isfahanian et al., 2017] and a meta-analysis of 4 observational studies with low level evidence, found no difference in LR rates after hypofractionated or standard RT

[Nilsson et al., 2015]. The Danish Breast Cancer Group (DBCG) HYPO trial randomized 1843 patients with early-stage breast cancer, including 248 women with DCIS, to external beam forward planned intensity modulated RT (IMRT) WBI with conventional fractionation *vs* moderate hypofractionation (40 Gy in 15 fractions) with or without sequential boost. Few side effects were reported, with no difference in grade ≥2 breast induration at 3 years post RT (the primary end-point) and the few recurrences were not related to fractionation [Offersen et al., 2017]. At 5 years follow-up, use of boost, 50 Gy/25 fractions, large breast size (> 600 cc CTVp breast) and current smoking impacted significantly on breast induration in univariate and multivariate analyses. Consequently, moderately hypofractionated WBI has become the new standard in DBCG and in most radiation oncology centres worldwide. In 2001 the RTOG 9804 protocol was amended to allow 42.5 Gy in 16 fractions [McCormick et al., 2015]. The updated American Society for Radiation Oncology (ASTRO) guidelines provided only a conditional recommendation for hypofractionation [Smith et al., 2018] while the Royal College of Radiologists recommended hypofractionation also as standard WBI in DCIS [Clinical Oncology, The Royal College of Radiologists, 2019].

3.2.1.3 A role for the boost

To date, the role of a boost to the tumour bed in DCIS has not yet been established, even though several retrospective studies analyzed it, at total doses ranging from 10-20 Gy [Wai et al., 2011; Omlin et al., 2006; Yerushalmi et al., 2006; Jiveliouk et al., 2009; Monteau et al., 2008; Wong et al., 2012; Vidali et al., 2012; Halasz et al., 2012; Meattini et al., 2013; Rakovitch et al., 2013; Kim et al., 2014; Cutuli et al., 2016]. A meta-analysis of observational studies showed a significantly less LR only in patients with close or involved resection margins [Nilsson et al., 2015]. Pooled data from 10 academic institutions in the USA, Canada and France reported that at a median follow-up of over 9 years, boost delivery was associated with significant improvements in ipsilateral-recurrence free survival at 5, 10 and 15 years (97.1% *vs* 96.3%, 94.1% *vs* 92.5% and 91.6% *vs* 88% respectively, p = 0.0389) [Moran et al., 2017]. A French national survey reported a 10-16 Gy boost was delivered after WBI to 530/1658 patients treated in 2014-2015. Factors influencing boost use were nuclear grade and margin status [Cutuli et al., 2019]. Two large randomized trials were designed to assess the role of the boost in DCIS (BONBIS trial NCT00907868 and TROG-NCT00470236). Outcomes are not yet available apart from results on acute toxicities [Bourgier et al., 2019].

3.2.1.4 Accelerated Partial Breast Irradiation

Even though accelerated partial breast irradiation (APBI) is an option in low-risk infiltrating breast carcinoma, its role in DCIS is still being debated. While some retrospective studies reported higher LR rates [Abbott et al., 2013; Leonardi et al., 2019], others showed that APBI was associated with a low LR rate in selected DCIS patients [Benitez et al., 2006; Park et al., 2011; Shah et al., 2012]. Recent ASTRO guidelines recommended APBI for DCIS with the following features: non-palpable DCIS presentation, size < 25mm, low or intermediate grade and free-surgical margins of at least 3 mm but stated intra-operative radiotherapy (IORT) with electrons should not be used in clinical practice [Correa et al., 2017].

3.2.1.5 PMRT

PMRT is not routinely considered for DCIS, because long-term LR rates after mastectomy are low, ranging from 0% to 7.5% [Chadha et al., 2012; Shah et al., 2015]. Risk factors for recurrence, usually as infiltrating carcinoma, were positive or close margins, high grade tumours, young age and skin-sparing mastectomy [Chadha et al., 2012; Shah et al., 2015; Timbrell et al., 2017]. In high-grade DCIS, LR rates were 16% at 5 years with resection margins under 2 mm *vs* 2% with margins over 2 mm ($p = 0.035$) [Rashtian et al., 2008]. After a median follow-up of 7.6 years, the LR rate after mastectomy was close to 5% in DCIS patients who presented positive or closed margins and/or high grade tumours or were under 50 years old (n=142) [Childs et al., 2013]. Using the USC/Van Nuys Prognostic Index (VNPI) [Silverstein et al., 2010], Kelley et al reported that for every 100 patients with scores of 10-12 who were treated with mastectomy, 10 patients would relapse after 12 years of follow-up, with 2 or 3 developing distant metastases [Kelley et al., 2011].

3.2.1.6 Genetic assays

The 21-gene Oncotype DX Recurrence Score was recently assessed for evaluating the 10-year LR DCIS risk in 300 patients from the ECOG E5194 trial. Three risk categories were identified: 1) low (Score <39); 2) intermediate (Score = 39-54); 3) high (Score ≥ 55) [Solin et al., 2013]. At 10 years, the LR risk was, respectively, 10.6%, 26.7% and 25.9% for each category. Similar findings were reported in 718 DCIS patients treated with BCS followed by WBI [Rakovitch et al., 2015]. The impact of the Oncotype DX DCIS Score on RT indication after BCS was evaluated in 115 patients. The indication to deliver WBI or not was modified in 31.3% of cases, after the assay result was known [Alvarado et al., 2015a]. However, cost-effectiveness of applying the DCIS assay to all patients needs to be weighed up carefully before any definitive conclusions can be drawn [Raldow et al., 2016].

3.2.2 Current Research Studies

Table 2 lists ongoing trials that focus on RT with or without boost in hypofractionated and conventional schedules in patients with DCIS.
Table 3 lists several ongoing phase II and III studies on APBI, using different techniques and fractionations.
The NSABP B-43 phase III randomized study NCT00769379 is assessing the impact of trastuzumab during RT *vs* RT alone in preventing ipsilateral breast cancer recurrence after BCS [Cobleigh et al., 2013]. The study is active but not recruiting. It was criticized because it could be construed as over-treatment of a non-fatal disease that is sufficiently managed with local treatment and because adding a costly drug to reduce such a small risk was unlikely to be cost-effective [Alvarado et al, 2015b].
Many ongoing trials focus on sparing low-grade DCIS patients from RT. The decision to omit RT in selected cases and the opportunity to share decision-making was investigated in the BRASA study (NCT03375801), which is evaluating the role of an online decisional tool. The Canadian DUCHESS (NCT02766881) is evaluating the role of the DCIS score.
The risks and benefits of active surveillance are being tested in 4 randomized non-inferiority studies with very slow recruitment. Eligibility criteria include low-intermediate risk DCIS, diagnosed by vacuum-assisted core-needle biopsy, in patients aged 40 and over. Patients are randomized to either surveillance (annual mammography for 10 years, with choice of ET), or treatment (surgical excision with or without RT and with or without ET). Progression to higher-grade disease will be treated. The primary outcome is ipsilateral invasive breast cancer free survival [Groen et al., 2017].
"PRECISION" is integrating clinical, pathological, imaging and molecular data from multiple European and American studies in order to develop a risk prediction model for DCIS.
Table 4 includes randomized phase II and III trials investigating the benefit of the boost, its timing, effectiveness and safety.

3.2.3. Proposed Research Strategies

A recent ATTM survey that was sent to radiation oncologists investigated PMRT in DCIS in clinical practice [Montero Luis et al., 2019]. The results led to a multi-centre study for retrospective data analysis. The next step will be a prospective study to identify patients who most benefit from PMRT.

The other proposed study aims at evaluating the role of PBI as sole local treatment in low and intermediate-risk DCIS. Patients will be randomized to receive PBI vs BCS followed by WBI. The working group suggested participating in the following on-going trial that is exploring preoperative APBI schemes in early breast invasive carcinoma and DCIS:
https://clinicaltrials.gov/ct2/show/NCT02482376

3.3 Topic 3: Therapy de-escalation in early stage breast cancer

3.3.1 Summary of current evidence and areas of contention

Early stage, clinically node negative breast cancer is currently managed by BCS followed by WBI [Fisher et al., 2002; Veronesi et al., 2002]. Compared with surgery alone, WBI significantly reduced the absolute risk of any breast recurrence by 15.4% (95% CI 13.2-17.6; $p < 0.00001$) for node negative patients and the 15-year breast cancer related mortality rate by about 3.3% (95% CI 0.8-5.8; $p = 0.005$) [EBCTCG, Darby et al., 2011]. In clinical practice, this modest reduction in mortality is achieved at a cost of several weeks of daily treatments associated with short- and long- term toxicity. Hence the need to investigate therapy de-escalation as reported below. Attention has focused on shortening treatment times and omitting the boost or even WBI.

3.3.1.1 Hypofractionation

Four randomized trials compared a hypofractionated 3-week schedule with a 5-week conventional fractionated schedule, reporting long-term results on local control, toxicity and cosmetic outcomes [Owen et al., 2006; Whelan et al., 2010; Haviland et al., 2013]. The Canadian trial found no differences in adverse effects, cosmetic outcomes, LR and OS [Whelan et al., 2010]. The UK Standardization of Breast Radiotherapy Trialists' Group (START) observed no difference in LR rates while late adverse effects and distant metastases were, surprisingly, reduced with hypofractionation; its benefits were maintained at the 10-year follow-up [Haviland et al., 2016]. Further advantages of hypofractionated schedules were a lower acute toxicity rate (with less dermatitis, pruritus, breast pain, hyperpigmentation and fatigue), better QoL and patient reported outcome measures [Jagsi et al. 2015; Shaitelman et al., 2015; Franco et al., 2018]. Moreover, hypofractionation is cost-effective for patients and healthcare providers, allowing for an optimal allocation of financial and human resources [Lievens et al., 2010; Montero et al., 2014].

Consequently, for early stage invasive breast cancer when the intention is to treat the whole breast without an additional field to cover the regional lymph nodes, ASTRO evidence-based guidelines recommend 40 Gy in 15 fractions or 42.5 Gy in 16 fractions, regardless of age, as long as the breast tissue volume receiving >105% of the prescription dose was minimized [Smith et al., 2018].

In an attempt to shorten the 3-week hypofractionation schedules, maintain the same toxicity profile and effects, UK researchers assessed a 1-week schedule. The FAST trial randomized node negative patients to 28.5 Gy or 30 Gy in 5 daily fractions or 50 Gy in 25 fractions. The 10-year results showed that compared with 50 Gy in 25 fractions, long-term toxicity was similar after the 28.5 Gy schedules, but higher after the 30 Gy schedule. LR rates were similar in all 3 arms [Brunt et al., 2018]. The FAST-Forward phase 3 trial compared 27Gy and 26Gy in 5 fractions in 1-week *vs* 40 Gy in 15 fractions in 3 weeks. Both 1 week schedules were associated with less acute RTOG grade 3 toxicity (9.8% and 5.8% respectively *vs* 13.6% for the 3-week schedule) [Brunt et al., 2016].

3.3.1.2 (A)PBI reduces volumes and may shorten treatment times

(A)PBI schedules are now approved in major guidelines for early stage breast cancer in women aged 50 years and over without poor prognostic features. For example, the updated ASTRO Consensus Statement defined a “suitable” PBI candidate as follows: ≥50 years with unifocal T1N0 ER-positive ductal carcinomas, excision margins of ≥2 mm, no LVI or extensive intraductal component [Correa et al., 2017]. PBI techniques include interstitial and balloon brachytherapy, external beam RT and IORT.

Although several randomized phase 3 trials compared PBI with WBI in low-risk breast cancer patients, diverse techniques, schedules and follow-ups make comparisons challenging. In the Hungarian trial which administered APBI by interstitial brachytherapy to 88 patients and electrons to 40, the 10-year follow-up showed LR rates were 5.1% *vs* 5.9%, ($p = 0.77$) [Polgár et al., 2013]. At the 5 year follow-up, the Groupe Européen Curiethérapie (GEC)-ESTRO trial reported APBI with interstitial brachytherapy was not-inferior to WBI as the cumulative incidence of LR was 0.9% *vs* 1.4% ($p = 0.42$) with a good cosmetic outcome. Although QoL

and toxicity profiles were similar, skin toxicity was better with APBI [Strnad et al., 2016; Schäfer et al., 2018].
In the IMPORT Low Trial patients were randomly assigned to 40 Gy WBI (control), 36 Gy WBI with 40 Gy to the boost area (reduced-dose group), or 40 Gy to the partial breast (partial-breast group) in 15 daily fractions in all arms. The 5-year cumulative incidences of LR were, respectively, 1.1 (95% CI 0·5–2·3), 0.2 (95% CI 0·02–1·2) and 0.5 (95% CI 0·2–1·4) and non-inferiority was confirmed. Moreover, patients reported better breast appearance and less induration with PBI [Coles et al., 2017].
In the Florence trial, 520 women aged > 40 with early breast cancer < 25 mm, were assigned to WBI or APBI delivered by IMRT over 2 weeks (5 fractions on alternate days). After a median follow-up of 5 years, both schedules were associated with 1.5% ipsilateral breast tumour recurrence. The APBI group had significantly lower rates of acute (p=0.0001) and late (p=0.004) toxicities and a better cosmetic outcome (p=0.045) [Livi et al., 2015]. In the health-related QoL investigation responders were mostly in favour of APBI [Meattini et al., 2017].
The NSABP B-39/RTOG 0413 multicentre randomized phase III equivalence study included 4216 patients who received WBI or APBI (delivered with MammoSite single or multi-lumen, Contura, Savi, interstitial brachytherapy or external beam RT). Since eligibility criteria were broad (i.e. stage 0-II; DCIS and invasive tumours; N0 and N1, receptor positive and negative diseases), large heterogeneous groups of patients were recruited. The 10-year cumulative incidence of ipsilateral breast recurrence was 4.6% in the APBI arm *vs* 3.9% in the WBI. Although APBI did not meet the criteria for equivalence to WBI as far as regards local control, it is suggested to be acceptable for well-selected patients on the basis of the very small absolute difference. Furthermore, second cancers and treatment-related toxicities were similar in the two groups, as were the distant disease-free interval, DFS and OS [Vicini et al., 2019].
The RAPID multicentre phase III non inferiority trial randomized 2135 patients to APBI or WBI. The 8-year cumulative rates of ipsilateral breast tumour recurrence were 3.0% in the APBI group *vs* 2.8% in the WBI group. Although acute grade ≥2 radiation-induced toxicity was significantly lower in patients treated with APBI (28% *vs* 45%, p<0·0001), late grade ≥2 toxicity was more common (32% *vs* 13% p<0·0001) as was fair or poor cosmesis at 3 years. These poor outcomes might be related to the APBI treatment schedule (3.85 Gy per fraction, delivered twice daily over 5–8 days; total dose: 38.5 Gy) and volumes [Whelan et al., 2019], as predicted by Yarnold et al. [Yarnold et al., 2011].

In these trials there was basically no disadvantage in terms of local control, with interpretation difficulties due to differences in the statistical designs (non-inferiority margins) [Coles et al, 2019].

Given the results of the NSABP B-39/RTOG 0413 and the RAPID trials, the 2019 St. Gallen Panel did not broadly endorse APBI, suggesting that it may be appropriate for carefully selected, low-risk patients, as defined by international guidelines [Burstein et al., 2019]. Although the 2018 ATTM was held when only the RAPID preliminary results were available [Olivotto et al., 2013], the panelists were in favour of other external beam (A)PBI schedules, such as in the IMPORT Low [Coles et al., 2017] or in the Florence [Livi et al., 2015] trials. Late toxicity needs, however, further investigation and personal communication suggests waiting for IRMA trial results later this year.

IORT was initially tested in the ELIOT trial using electron beams to administer 21Gy. At a median follow-up of 5.8 years, the 5-year ipsilateral breast recurrence rates were 0.4 % for WBI and 4.4% for IORT (1.4% luminal A, 4.9% luminal B, 5.9% HER2+, non-luminal, and 18.9% triple negative) [Veronesi et al., 2013]. The main bias of the study was patient selection. In fact, IORT with electrons seems feasible in the luminal A subtype, as already reported in the ASTRO recommendation. The TARGIT trial used low-energy x-rays (50 KV maximum; Intrabeam®) for APBI with 20 Gy delivered to the tumour bed surface which dropped to 5-7 Gy at approximately 1 cm depth. At a median follow-up of 29 months, the 5-year risk for LR was 3.3 % for TARGIT *vs* 1.3 % for WBI [Vaidya et al., 2014]. IORT with Intrabeam® cannot be assessed as a feasible de-escalation strategy.

3.3.1.2 Boost Omission

In the Lyon trial boost omission was associated with a rise in LR (at 5 years 4.5% *vs* 3.6%; p = 0.044) and less grade 1 telangiectasia (5.9 % vs 12.4%), without significant differences in cosmesis [Romestaing et al., 1997]. The EORTC "boost *vs* no boost trial" (22881/10882) revealed that boost had no significant effect on long-term OS, although it improved local control. The risk of moderate to severe boost-related fibrosis rose from 1.6% to 4.4 % at 10 years. Since young patients benefitted most from boost [Bartelink et al., 2007], it can safely be avoided in most patients over 60 years of age, at low-risk of relapse i.e. with tumours <3cm in size, negative surgical margins, positive hormone status and no extensive intra-ductal component. On the other hand, according to the GEC-ESTRO Breast Cancer Working Group, boost can be omitted in low-risk patients aged at least 50 years old, with unicentric and/or unifocal disease, clear surgical margins of at least 2 mm and no axillary lymph node invasion. Otherwise boost is mandatory [Polo et al., 2017].

3.3.1.4 Avoiding RT

Experts now focus on identifying, mainly by means of predictive biomarkers, a very low-risk group whereby risks and benefits can be discussed and an informed decision made with the patient.

In "low-risk" patients aged ≥65-70 years, with small (<2 cm), receptor-positive tumours and node-negative axilla, local excision and adjuvant ET with or without RT were compared in some clinical randomized trials [Potter et al., 2007; Hughes et al., 2013; Blamey et al., 2013; Kunkler et al., 2015]. All showed that avoiding RT led to only slightly increased risks in terms of local control and made no difference to OS, suggesting RT can be safely omitted in selected low-risk patients. In the BASO trial the same average annual LR rate of 0.8%, was observed in patients who received RT or ET [Blamey et al., 2013], suggesting that ET might be omitted as well, provided that RT is given.

Likewise, in an evaluation of the NCDB (2010-2014), equivalent 5-year OS rates were reported in elderly women with T1N0 hormone-receptor positive, HER2 negative breast cancer who received either adjuvant RT or adjuvant ET (Buszek et al., 2019]. On the other hand, 5-year OS improved in elderly, early-stage, hormone receptor-positive HER2 negative breast cancer patients who also received postoperative RT associated with adjuvant ET [Herskovic et al., 2018]. However limitations inherent to retrospective database studies suggest these findings should be validated in prospective randomized trials.

A report based on the SEER database showed that RT delivery after BCS was significantly varying according to molecular subtype in patients aged over 70 years, with T1N0M0 breast cancer. Patients between 70-74 years old, with ER negative/HER2 negative status and high-grade disease were more likely to receive adjuvant RT which was associated with improved breast cancer specific survival in ER+/HER2- and ER-/HER2- patients [Haque et al., 2017].

Finally, patients with BRCA1/2 pathogenic variants were less likely to receive RT after BCS, perhaps because of concerns that RT was associated with increased cancer risks or more toxic effects which were, however, not observed elsewhere [Kurian, et al. JAMA Oncol 2020]. Therefore, RT was omitted after BCS not only in low-risk, elderly patients but also, unjustified, when concerns arose about RT-related risks. Research is needed to confirm these results in other pathogenic variant carriers and evaluate long-term outcomes.

3.3.2 Current Research Studies

Many on-going trials, as described in Table 5, are evaluating diverse RT schedules in association with different boost timing and administration modalities.
Other studies on de-escalation [Bhattacharya et al, 2018] are reported below:
Four new studies were initiated to clarify the impact of tumour and patient characteristics, and genetic tissue profiles especially in early stage breast cancer patients over 50 years old.
The IDEA (Individualized Decisions for Endocrine Therapy) trial is a multi-centre, prospective, single-arm observational study on LRR after BCS, in a selected population of post-menopausal women (aged 50–69) with low-risk tumours. All will receive adjuvant ET. Risk will be stratified by gene expression profiling, as determined by the OncotypeDX, a 21-gene recurrence score assay (Genomic Health Inc., Redwood City, CA).
The PRECISION (Profiling Early Breast Cancer for Radiotherapy Omission) trial is a non-randomized phase II trial, that is expected to complete accrual in 2020. It will evaluate whether WBI can be avoided after lumpectomy in favorable-risk breast cancer patients (aged 50–75) receiving adjuvant ET. Risk was stratified by the Prosigna Breast Cancer Assay (NanoString Technologies Inc., Seattle, WA) which provides gene expression profiling of the PAM50 gene signature.
The UK PRIMETIME trial is a prospective biomarker-directed case-cohort study targeting women aged ≥ 60, with T1N0M0 grade 1 or 2, positive hormonal receptors and HER2 negative tumours. WBI will be omitted in informed, 'very low risk' patients as determined by the IHC4+ C biomarker [Kirwan et al., 2016].
The Dutch TOP-1 Trial (Tailored treatment in Old (elderly) Patients) is a prospective cohort study for breast cancer patients aged 70 years or over. Patients will be recruited within 3 months of BCS if they display the following eligibility criteria: tumour size <1 cm and grade 1-2 or tumour size <1-2 cm and grade 1, ER > 50%, HER2-negative, SLN negative or with isolated tumour cell clusters (ITC), R0 resection. ET and RT will be omitted. Like the BRASA study, the TOP-1 study avails of an online tool that decides whether RT should be administered or not.
Two RCT are testing RT omission in selected patients with the 5-year invasive LRR as primary endpoint. The EXPERT trial (EXamining PErsonalized Radiation Therapy for low-risk breast cancer), was initiated in 2017 by the Australian New Zealand breast cancer group in collaboration with Breast International Group (BIG) and International Breast Cancer Study Group (IBCSG) and Trans Tasman Radiation Group (TROG). It is recruiting patients ≥ 50 years

old, pT1N0, estrogen receptor positive, HER2 negative, PAM 50 with ROR ≤60 and no tumour on ink. Patients will be randomized to RT + ET and ET alone. Target accrual is 1170 patients. The DBCG RT Natural trial, NCT 03646955, was initiated in 2018. Eligible patients are at least 60 years old, with non-lobular carcinoma pT1N0, ≥ 10% estrogen receptor positive, HER2 negative, grade 1-2, margins ≥2mm. 926 patients will be randomized to external beam PBI 40 Gy/15 fractions *vs* no RT. ET and zoledronic acid will be prescribed, independently of arm. The trial is open for participation from outside Denmark.

3.3.3 Proposed research strategy

A multi-centre study is expected to be activated in 2020. Entitled "ExclUsive endocRine therapy Or Partial breast irradiation for women aged ≥70 years with luminal-A early stage breast cancer (EUROPA). A randomized phase II-III controlled trial comparing Health Related Quality of Life by Patient Reported Outcome Measures", it will include patients ≥70 years, with invasive pT1 (<2cm), cN0 or pN0 (i+) Luminal-A at immunohistochemistry (ER+ and PgR+, HER2 negative, Ki67<20%) breast cancer. They will be randomized to APBI starting after 4-12 weeks after surgery *vs* ET for 5-10 years according to national guidelines and local policy, using QoL as the primary endpoint. Since the ATTM experts are of the opinion this trial investigates an interesting therapeutic approach that could impact on daily practice, they advise enrolling patients in it as soon as it is activated.

4. Conclusions

This white paper confirms the validity of the original ATTM approach in exploring different areas of breast cancer. Its in-depth analysis of the state of the art and on-going studies reveals grey areas and controversies, generates problem-solving approaches and envisages the future of RT. It is be hoped this ATTM white paper will aid multidisciplinary groups in adopting new strategies and conducting clinical trials in the search to improve patient care.

Acknowledgements: The authors thank all other ATTM Expert European Board members: Lorenzo Falcinelli, Fabio Marazzi, Nadia Pasinetti, Vincenzo Tombolini

Conflict of interest: The authors declare that they have no conflict of interest. Dr. Charlotte Coles is supported by the Cambridge National Institute of Health Research Biomedical Research Centre. Dr Ugur Selek is an Accuray Advisory Board.

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