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Critical Reviews in Oncology / Hematology 177 (2022) 103774

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Ways to improve breast cancer patients' management and clinical outcome: The 2020 Assisi Think Tank Meeting

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ARTICLE INFO

Keywords:
Breast cancer
Radiation therapy
De-escalating therapy

ABSTRACT

We report on the third Assisi Think Tank Meeting (ATTM) on breast cancer, a brainstorming project which involved European radiation and clinical oncologists who were dedicated to breast cancer research and treatment. Held on February 2020, the ATTM aimed at identifying key clinical questions in current clinical practice

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https://doi.org/10.1016/j.critrevonc.2022.103774
Received 8 June 2021; Received in revised form 19 July 2022; Accepted 29 July 2022
Available online 30 July 2022

Stereotactic radiation therapy
Oligometastatic disease
BCRA-mutated patients
Contralateral breast cancer prevention

and "grey" areas requiring research to improve management and outcomes. Before the meeting, three key topics were selected: 1) managing patients with frailty due to either age and/or multi-morbidity; 2) stereotactic radiation therapy and systemic therapy in the management of oligometastatic disease; 3) contralateral breast tumour prevention in BCRA-mutated patients. Clinical practice in these areas was investigated by means of an online questionnaire. In the lapse period between the survey and the meeting, the working groups reviewed data, on-going studies and the clinical challenges which were then discussed in-depth and subjected to intense brainstorming during the meeting; research protocols were also proposed. Methodology, outcome of discussions, conclusions and study proposals are summarized in the present paper. In conclusion, this report presents an in-depth analysis of the state of the art, grey areas and controversies in breast cancer radiation therapy and discusses how to confront them in the absence of evidence-based data to guide clinical decision-making.

1. Introduction

The "Assisi Think Tank Meeting" (ATTM), a brainstorming project on breast cancer, was first launched in 2016 (Aristei et al., 2016); it involves European radiation and clinical oncologists who are dedicated to breast cancer research and treatment and is endorsed by the European Society for RadioTherapy & Oncology (ESTRO) and by the Italian Association of Radiotherapy and Clinical Oncology (Associazione Italiana di Radioterapia e Oncologia clinica - AIRO).

The ATTM aims at identifying key clinical questions in current clinical practice and "grey" areas requiring research to improve management and outcomes, mainly related to radiation therapy (RT), including health-related quality of life (HRQoL). It expects to encourage research in the field and international collaboration.The ATTM working groups adopt systematic methods for their pre-ATTM work, surveys and presentations, with all content being evidence-based.

This white paper summarises the methodology, outcome of discussions, conclusions and study proposals of the 3rd ATTM which was held on 14th - 16th February 2020.

2. Methods

The ATTM design was described in previous white papers (Aristei et al., 2016; Arenas et al., 2020; Valentini et al., 2020). Briefly, in the months before the ATTM, controversial issues were identified through a review of the literature and clinical practice was investigated by means of an online questionnaire. Under 70% agreement on a treatment option indicated uncertainty i.e. an area of contention. Working groups reviewed data, on-going studies and the clinical challenges which were then discussed in-depth and subjected to intense brainstorming during the 3-day meeting.

For the 2020 ATTM there was consensus that the role of RT needed to be optimized and that clinical research should be conducted in each of the following topics:

1) Managing patients with frailty due to either age and/or multi-morbidity;

2) Stereotactic radiation therapy and systemic therapy in the management of oligometastatic disease;

3) Contralateral breast tumour prevention in BCRA-mutated patients.

3. Results

3.1. Topic 1. Managing patients with frailty due to either age and/or multi-morbidity

3.1.1. Current evidence and areas of contention

Today at diagnosis of breast cancer the approximate mean age is 60 years as it has been rising as populations have aged (Johnson et al., 2019). Rates of incidence vary with breast cancer subtypes: luminal A tumours account for 60%-70%, luminal B HER2-negative for 10%-20%, luminal B HER2-positive together with HER2-enriched non luminal for 13%-15%, and triple-negative for 10%-15% (Harbeck et al., 2019).

Current practice derives from guidelines and well-structured randomized trials. Since many trials excluded frail and older adult patients with or without comorbidities, it is unclear how results can be applied to them (Telli et al., 2019; Biganzoli et al., 2012; Martin et al., 2011), especially as "frail" and "older adult" are not clearly defined terms. Furthermore, the definition of "older adult" has shifted over the years and now many authors would consider it as referring to people aged 70 years or more (Wildiers et al., 2007).

Oncological management should not be determined by age alone but rather by a holistic assessment of frailty and multi-morbidity, both of which tend to be more frequent in the older age-groups (Biganzoli et al., 2012). At present, "frailty" is defined by the "phenotype" and "cumulative deficit" conceptual models. The former views "frailty" as a biological syndrome and a "cycle associated with declining energetics and reserves" (Fried et al., 2001) while the latter considers it as an accumulation of deficits across a number of domains (Mitnitski et al., 2001).

Despite these uncertainties, decision-making in breast cancer needs to take into account life expectancy, patient's health, autonomy and functional status, comorbidity-related risks of mortality, prognosis and risk of local recurrence, treatment benefit and toxicity in addition to patient preferences, priorities, and eventual social and financial issues (Biganzoli et al., 2012; Wildiers et al., 2007).

Controversial issues in managing patients with frailty due to either age or multi-morbidity which emerged at the ATTM are:

1) Deciding when a geriatric evaluation is indicated in frail patients;
2) Role of postoperative RT in pN0 patients receiving endocrine therapy (ET) after breast conserving surgery (BCS);
3) Selection of RT target volumes after BCS in pN1 patients: whole breast irradiation (WBI) *vs* WBI and regional nodes;
4) Indication for postoperative RT after mastectomy in pN1 patients;
5) Safety of hypo-fractionation for nodal irradiation;
6) Primary RT for inoperable patients.

3.1.1.1. Deciding when a geriatric evaluation is indicated in frail patients. The benefits and risks of RT seem different in a frail population and therapy de-escalation may be indicated. Consequently, patients at high risk of falls, dementia, hospitalization and death, need to be identified.

Subjective evaluation tests (Biganzoli et al., 2012; Wildiers et al., 2007) include the Comprehensive Geriatric Assessment (CGA) which determines a frail person's medical, psychological and functional capability to withstand a coordinated, integrated treatment plan and long-term follow-up (Parker et al., 2018; Overcash et al., 2019). Although recommended by the International Society of Geriatric Oncology (SIOG) (Wildiers et al., 2007), the CGA is too long and detailed for routine use in busy clinics. On the other hand, the Geriatric 8 (G8) Health Status Screening Tool consists of 8 questions that can be applied in approximately 10 minutes (Martinez-Tapia et al., 2017); the total score ranges from 17 (not at all impaired) to 0 (heavily impaired). For scores $\leq$14, full geriatric evaluation with the CGA test is recommended (Overcash et al., 2019). A shorter version of the G8 with weight loss, cognition/mood, performance status, self-rated health status, polypharmacy and history of heart failure/coronary heart disease as

independent predictors was established as a more useful diagnostic tool (Martinez-Tapia et al., 2017; Soubeyran et al., 2014).The ATTM experts agreed the G8 questionnaire or its modified version should be used to assist in deciding whether RT is appropriate in frail, elderly patients.

3.1.1.2. Role of postoperative RT in pN0 patients receiving ET after BCS. In older adult and/or frail patients, RT omission should be included as an option. Indeed, in older adults with a low risk of recurrence (e.g., small tumours, clear resection margins, negative axillary nodes, positive hormone-receptors, negative human epidermal growth factor receptor 2 -HER2-) RT omission is being extensively investigated, especially in the presence of ET (Hughes et al., 2013; Kim et al., 2019a; Fyles et al., 2004; Kunkler et al., 2015; Blamey et al., 2013). These studies, which were summarized in the 2018 ATTM report (Arenas et al., 2020), showed RT can be safely omitted in a selected low-risk sub-group who receive ET (Biganzoli et al., 2021; Burstein et al., 2021; Palumbo et al., 2021a). Ongoing studies, which are based on biomarkers and genomic profiling (Arenas et al., 2018, 2020; Franco et al., 2020), will better identify which patients are best candidates for RT omission after BCS.

As the alternative to RT is ET, its tolerance becomes crucial, since outside of clinical trials ET was often discontinued due to refusal and/or poor compliance or side-effects (Cortina et al., 2018). RT and ET are both suitable, as each was associated with an average annual 0.8% local recurrence rate in patients with T1N0 tumours, G1 or with good prognosis histology and no lympho-vascular invasion (Blamey et al., 2013). Consequently, post-operative RT alone might be considered for these patients.

The practice changing results of trials which explored hypo-fractionated schedules were discussed in depth in the 2018 ATTM report (Arenas et al., 2020). In 2020, ultra-hypo-fractionation was debated as an option for RT de-escalation in older adult/frail patients. The FAST Forward trial enrolled 4,096 patients with invasive breast carcinoma (pT1-3, pN0-1, M0) who were randomized to either 40 Gy (15 fractions), 27 Gy (5 fractions/1 week) or 26 Gy (5 fractions /1 week). The 5-year results showed the 5-fraction schedules were not inferior to the standard 15 fractions in terms of ipsilateral breast tumour relapse. Moderate or marked clinician-assessed side effects were reported as 9.9% with 40 Gy, 15.4% with 27 Gy and 11.9% with 26 Gy (Brunt et al., 2020a). Consequently, the authors recommended using the 26 Gy schedule which is now a standard of care option in the UK (Lewis et al., 2021). As it is particularly helpful for older adult/frail patients, it is likely to become the future standard in other countries. Alternatively, for frail patients a valid option is 28.5 Gy in 1 weekly fraction for 5 weeks (Brunt et al., 2020b).

Finally, RT may be de-escalated by reducing the irradiated volume. Level 1 evidence showed that PBI, as administered in hypo-fractionated or accelerated hypo-fractionated schedules, was not inferior to conventionally or hypo-fractionated WBI and was associated with a good toxicity profile (Polgar et al., 2013; Strnad et al., 2016; Schafer et al., 2018; Livi et al., 2015; Coles et al., 2017). PBI is delivered by means of multi-catheter interstitial brachytherapy, intra-cavitary brachytherapy, external beam RT (3D conformal or intensity-modulated) or intraoperative RT. Results depend on patient selection, dose distribution to the target, sparing of tissues at risk of toxicity and fractionation (Kaidar-Person et al., 2020). This topic was extensively analysed in the 2018 ATTM (Arenas et al., 2020). Since then, 26 Gy in 5 daily fractions for PBI has been strongly supported by the Royal College of Radiologists (RCR) Breast Radiotherapy Consensus update 2020 (Lewis et al., 2021) and is expected to be extended to other countries soon.

In summary, not only the number of fractions, but also treatment volumes are currently being reduced in selected sub-groups of patients. Innovative ultra-hypo-fractionated schedules appear safe and effective in the mid-term, providing satisfactory oncological outcomes. In older adult/frail patients all these options may serve to increase compliance and reduce their hospital attendances for RT. Indeed, the need to minimize footfall within RT centres because of the COVID-19 pandemic has promoted the use of ultra-hypo-fractionation in some countries.

3.1.1.3. Selection of RT target volumes after BCS in pN1 patients: WBI vs WBI and regional nodes. Regional node irradiation (RNI) should be considered for patients with 1-3 positive lymph nodes and adverse prognostic factors: extensive lympho-vascular invasion, a large, high-grade primary tumour with an unfavourable molecular profile (Recht et al., 2016). Its potential outcome in older adult/frail patients should be assessed in terms of reduced loco-regional recurrence (LRR), better overall survival (OS) *vs* RT-related risk of toxicity, life expectancy because of cancer and multi-morbidity and the chances of withstanding appropriate systemic therapy. For pN1 cases in the older adult, frail population, the clinical advantages of adding RNI to WBI may appear insufficient for routine use, especially when side effects are likely to be greater.

In attempts to satisfy patients' needs and reduce the discomfort that is linked to hospital attendances, hypo-fractionated RNI appears to be a feasible option (see below, issue 5).

3.1.1.4. Indication for postoperative RT after mastectomy in pN1 patients. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) metanalysis showed that although post-mastectomy RT (PMRT) was associated with a proportional benefit, the absolute benefit changed in accordance with the absolute risk (EBCTCG, 2014). For example, a fit 65-year-old should be given PMRT since she has a good chance of living for another 10-20 years but PMRT may not be indicated if frailty and multi-morbidity change the risk benefit. Consequently, the indication to PMRT must be assessed individually by means of geriatric evaluation tests, considering tumour recurrence risk, life expectancy and comorbidities.

Few reports focused specifically on PMRT indications for intermediate-risk disease (i.e. pT1-T2N1) in older adults (Smith et al., 2006; Tseng et al., 2020; Shirvani et al., 2011; Smith et al., 2008). When patients were grouped as low-risk (pT1/T2 N0), intermediate-risk (pT1/T2 N1), or high-risk (pT3/T4 and/or N2/N3), SEER data analyses showed that, after a median follow-up of 6.2 years, PMRT was associated with a survival gain only for high-risk patients (Smith et al., 2006). These data are, however, flawed by the intrinsic bias of non-randomization and should be viewed with caution. For high-risk hormone receptor positive, HER2 negative patients, the phase III monarchE trial showed that adding abemaciclib to ET in the adjuvant setting reduced the risk of an invasive disease–free survival event by 30% and of distant relapse by 31%, at 3 years (Harbeck et al., 2021). The abemaciclib safety profile indicated about 5% higher incidence of grade >3 adverse events (mainly diarrhea and fatigue) in patients over 65 years compared with the younger age-group. Other, mainly low grade, events reported more frequently in the over 65 s included nausea, anemia, thrombocytopenia, and decreased appetite (Rugo et al., 2022). Studies are needed to evaluate the role of post-operative RT in patients who receive adjuvant abemaciclib-ET. Furthermore, the tumor biology responding best to adjuvant abemaciclib will be elucidated by the results of translational research investigating tissue and plasma samples from patients in the monarchE study (Johnston et al., 2020).

A hypo-fractionated schedule emerged as an option even though it was not specifically designed for delivering PMRT to older adult patients. Results of a phase 3 randomized trial reporting it was non-inferior to conventional fractionation and had a similar toxicity profile (Wang et al., 2019) were confirmed by a recent metanalysis (Liu et al., 2020). Although large randomized clinical trials are advocated to confirm the efficacy and safety of hypo-fractionated PMRT in intermediate-risk older adults, the ATTM panel were of the view that current evidence showed it was safe for all age-groups (Yarnold, 2019).

Finally, the innovative ultra-hypo-fractionated schedules (27 Gy or

26 Gy in 5 fractions) were used for post-mastectomy chest wall RT in the randomized FAST-Forward trial (see above). Given the results, 26 Gy in 5 fractions over 1 week were very strongly supported by the RCR Breast Radiotherapy Consensus (Lewis et al., 2021).

3.1.1.5. Safety of hypo-fractionation for nodal irradiation. After a long debate about the risk of hypo-fractionated RNI-related toxicity in normal tissue (Liu et al., 2020; Haviland et al., 2018), 40 Gy delivered in 15 fractions has become standard of care in many countries. A retrospective analysis was conducted on 864 (14.7%) patients who were selected from a cohort of 5,861 in 3 prospective randomized UK Standardisation of Breast Radiotherapy (START) trials (Haviland et al., 2018). Patients had been treated with BCS (662) or mastectomy (202) and nodal volumes were different across the trials. At a median follow-up of 10 years, RT-related adverse side effects on arm and shoulder were assessed by physicians, patient responses to the EORTC QLQ-BR23 questionnaire and protocol-specific questions. No differences emerged in the hypo-fractionated and conventional schedules, suggesting hypo-fractionation to the regional nodes was safe. Since more adverse effects occurred after 13 fractions of 3.3 Gy, guidelines do not recommend this schedule. At the 2022 ESTRO Meeting the results of two phase III prospective randomized trials confirmed 40 Gy in 15 fractions was safe. Indeed, similar rates were observed of acute toxicity, lymphedema, shoulder motion and breast induration (Milo et al., 2022; Offersen et al., 2022). Similarly, the FAST Forward trial suggested in its interim analysis at 2-3 years' follow-up, that there were no differences in arm or shoulder adverse effects after 26 Gy in 5 fractions and the standard regimen (40 Gy in 15 fractions). Definitive assessment of non-inferiority will, however, be available only at the 5 year the analysis (Wheatley et al., 2022). The results of the trials in Table 4 are awaited.

3.1.1.6. Primary RT for inoperable patients. Frailty might be a contraindication to surgery, the gold standard of breast cancer treatment. In the Netherlands, the 98.7% rate of primary surgical treatment for patients aged 75 years and under dropped to 48.9% in patients aged 90 years and older. Additionally, 32% of patients over 75 years old refused surgery (Hamaker et al., 2013). In 446 patients over the age of 80, Helsinki University found that 3% had undergone surgery under local anesthesia, 10% did not have surgery and 75% in the non-surgical group received ET (Ojala et al., 2019). In fact, 40% of UK patients over 70 years old received ET as an alternative to surgery (Ward et al., 2018). In a series of 29 patients with diverse co-morbidities, who were inoperable or had refused surgery and/or had transport difficulties, the Institute Curie reported that, instead of surgery, they were given 32.5 Gy/5 fractions/5 weeks, followed by 13 Gy boost (two fractions of 6.5 Gy). Positive axillary lymph nodes, but not internal mammary or supraclavicular nodes, were also irradiated in five weekly fractions of 5.5 Gy. After a median follow-up of 93 months, the 95.8% loco-regional control rate was excellent (Chargari et al., 2010). A single-centre series reported that, in combination with ET, 115 patients (median age 83 years) were treated once weekly with hypo-fractionated RT (32.5 Gy in 5 fractions/5 weeks), followed by 1-3 fractions of 6.5 Gy to the tumour bed. The 5-year local progression-free rate was a good 78% (Courdi et al., 2006). Consequently, primary RT, with or without ET, emerged as a feasible alternative strategy for patients who are not candidates for surgery due to age, comorbidity, or refusal.

3.1.2. Current research studies

Although many on-going trials are evaluating RT in breast cancer patients with no upper age limit, very few enroll patients with WHO/ECOG performance status > 2 and even fewer focus specifically on the older adult and/or frail patients, anticipating eventually a subgroup analysis for this population.

Using key words "Older adult (65+)", "Interventional (Clinical Trial)", "Breast Cancer", "Elderly" and "Radiotherapy" a search was made for studies which were active or not yet open ("recruiting and not yet recruiting") and registered on "ClinicalTrial.gov". A total of 307 studies focused mainly on PBI or hypo-fractionated/accelerated WBI $\pm$ RNI, RT omission or replacement with ET. In the post-operative, intra-operative and pre-operative settings PBI has been, and is being,

Table 1
Studies on hypofractionation for whole breast/chest wall and regional node irradiation.

Trial	PI City, Country Accrual time	Population & study summary	Number of patients required	Primary endpoint
HYPOG-01 NCT03127995	Sofia Rivera, París, France. April 2017 – May 2021	Randomized. 40 Gy/ 15 fr/ 3 weeks (sequential boost 16 Gy/ 8 fr or SIB 42.3 Gy on CTV breast and 52.2 Gy on CTV boost in 18 fr) vs 50 Gy/ 25 fr/ 5 weeks (sequential boost 16 Gy/ 8 fr or SIB 51.52 Gy on CTV breast and 63 Gy on CTV boost in 28 fr) in BC with an indication for RNI	1265	Arm lymphedema at 5 and 10 years
Hypofractionated RT for Node-Positive BC NCT02700386	Christine Fisher, Colorado, USA. March 2016 - April 2021	Phase 2. 40.05 Gy/ 15 fr/ 3 weeks in BC with an indication for RNI, boost 10.68 Gy (2.67 Gy/ 4 fr)	112	Treatment-related adverse events as assessed by CTCAE version 4.03 up to 5 years
Hypofractionated RT for Patients With BC Receiving RNI NCT02958774	Shane Stecklein, Kansas, USA. Nov 2016 – April 2021	40.05 Gy/ 15 fr/ 3 weeks in BC with an indication for RNI, boost 10 Gy (2 Gy/ 5 fr)	389	Lymphedema rate at 1 year
The Skagen Trial 1 NCT02384733	Birgitte Offersen, Aarhus, Denmark. March 2015 – Feb 2020	Randomized. 40 Gy/ 15 fr/ 3 weeks vs 50 Gy/ 25 fr/ 5 weeks in BC with an indication for RNI, boost 2 dose levels, sequential: 16 Gy/8 fr and 10 Gy/5 fr, or SIB 63 Gy / 51.52 Gy / 28 fr, 57 Gy / 50 Gy / 25 fr, 52.2 Gy / 42.3 Gy / 18 fr, and 45.75 Gy / 40 Gy / 15 fr	2000	Arm lymphedema at 3 years
Conventional Versus Hypofractionated Adjuvant RT for Node Positive BC NCT02690636	Mahmoud Ellithy. Cairo, Egypt June 2016 – April2021	Randomized. 42.56 Gy (2.66 Gy/day)/ 16 fr/ 5 fr per week (sequential boost 2.66 Gy x 4 fr) vs 50 Gy/ 25 fr/ 5 weeks (sequential boost 2 Gy x 5 fr) in BC with an indication for RNI	500	Locoregional recurrence at 5 years

PI: Principal Investigator; RT: Radiotherapy; BC: Breast Cancer; RNI: Regional Nodal Irradiation; fr: fraction; SIB: Simultaneous Integrated Boost; CTV: Clinical Tumor Volume.

Table 2
Open phase III trials (recruiting and not yet recruiting) on whole breast irradiation for elderly patients.

Trial	PI City, Country Accrual time	Population & study summary	Number of patients required	Primary endpoint
NeoRad NCT04261244	Christiane Matuschek, Duesseldorf, Germany. Jul 2020 - Dec 2030	Neoadjuvant Chemotherapy Followed by Preoperative vs postoperative RT in High-risk BC patients	1826	DFS at 6 to 10 years
PMRT-NNBC NCT02992574	Tabassum Wadasadawala. Delhi, India. May 2016 – Dec 2028	Post-mastectomy RT (40 Gy in 15 fr to the chest wall + supra clavicular fossa) vs no RT in high risk, node negative early BC patients	1022	DFS at 5 years
PRART NCT04175210	Silvia Formenti, New York, USA. Nov 2019 – Dec 2025	WBI (40 Gy) with a concomitant boost (48 Gy) to the tumor bed over 15 fr / 3 weeks vs 34/42 Gy in10 fr/ 2 weeks in stage 0 ductal carcinoma in situ (Tis (DCIS), stage T1-T2, lymph node negative (N0) BC patients	400	Rate of grade 3 or higher changes in breast cosmesis up to 5 years
Hypofractionated Post Mastectomy Radiation With Breast Reconstruction NCT03414970	Matthew Poppe, Salt Lake City, USA. Feb 2018 – Aug 2035	Hypofractionated vs normofractionated RT in patients with stage IIa-IIIa cancer who have undergone mastectomy.	880	Reconstruction complication rate at 2 years
HYPOSIB NCT02474641	Juergen Dunst, Kiel, Germany. Jun 2015 – Jun 2023	Hypofractionated RT with SIB vs normofractionated RT with SIB or sequential boost in patients with early BC	2324	PFS at 3 to 6 years

PI: Principal Investigator; RT: Radiotherapy; BC: Breast Cancer; DFS: Disease free survival; BCS: Breast Conserving Surgery; WBI: Whole Breast Irradiation; fr: fraction; PFS: Progression free survival; SIB: Simultaneous Integrated Boost.

Table 3
Open phase III trials (recruiting and not yet recruiting) on regional node irradiation for elderly patients.

Trial	PI Country Accrual time	Population & study summary	Number of patients required	Primary endpoint
RHEAL NCT04228991	Timothy Whelan, Ontario, Canada. Nov 2020 – Dec 2027	40 Gy/ 15 fr/ 3 weeks vs 26 Gy/ 5 fr/ 1 week to the breast and RN after BCS, or to the chest wall and RN following mastectomy in patients with node positive BC	588	Lymphedema at 3 years post randomization
HARVEST NCT03829553	Jiayi Chen, Shangai, China. Feb 2019 – Dec 2028	Hypofractionated RT of (3 -4 weeks) vs conventional RT (5-6 weeks) using IMRT in BC patients with an indication for RNI following mastectomy or BCS	801	DMFS at 5 years
NCT01901094	Judy Boughey, Rochester, USA. Febr 2014 - Jan 2024	ALND and RT vs RT alone in patients with BC previously treated with chemotherapy and surgery	1660	Invasive BC recurrence-free interval up to 5 years

PI: Principal Investigator; RN: Regional Nodes (supraclavicular, axillary and internal mammary); RNI: Regional Nodes Irradiation; BC: Breast Cancer; TLNB: targeted lymph node biopsy; SNB: sentinel node biopsy; TAD: both TLDB+SNB; PST: primary systemic treatment; iDFS: Invasive disease-free survival; DMFS: Distant metastasis free survival; IMRT: intensity-modulated radiation therapy; BCS: Breast Conserving Surgery; ALND: Axillary Lymph Node Dissection.

extensively investigated in 43 mainly phase I or II trials. PBI is delivered by means of kV/MV photons, protons, electrons and 3D-conformal RT, IMRT or MR-LINAC. Treatment schedules vary in dosage, fractionation and overall times (1-10 fractions, 1-5 treatment days). Only 2/43 studies were identified when the search was narrowed down to phase III trials: the ongoing 2009-APBI trial (NCT01185132) and the EUROPA trial (NCT04134598) which was proposed at the 2018 ATTM (Arenas et al., 2020). Tables 1–3 summarize the trials which emerged after excluding PBI, supportive care, imaging, drug-testing, metastases or patients under 70 years old.

3.1.3. Proposed research strategy

The ATTM identified an unmet need in the management of breast cancer patients who are not eligible for surgery due to frailty or who refuse it after receiving full information. Despite this niche status, the ATTM proposed a phase III trial for cT1-T4 N0-3 M0 (de novo or local/loco regional relapse) in patients with no upper age limit and WHO/ECOG performance status 0-3, who did not undergo surgery, independently of hormonal receptor and HER2 status. All candidates will be given standard treatment of choice (including best supportive care option) and will be randomized to ultra-hypo-fractionated RT (28.5 to 30 Gy/5 fractions/5weeks +/- boost or 26 Gy/5 fractions/1 week) or no RT, according to local guidelines. A cross-over is planned for local progression. The primary endpoint is QoL at 12 months. To identify predictive markers for RT response ancillary studies in collaboration with the Skagen group (a group of European physicians, who are investigating gains and risks from breast cancer RT), will focus on pre- and post- treatment biopsies and radiomics analysis. To encourage enrollment and facilitate data collection and analyses, the 2020 ATTM proposed an internal pilot study with 1-year recruitment and patient acceptance of randomization as go/no go criteria as well as a parallel "patient's preference cohort" for ineligible patients.

Table 4
Ongoing clinical trials on stereotactic cranial radiotherapy and systemic therapy in oligometastasic breast cancer. Recruiting trials.

Trial	PI Country Accrual time	Population & study summary	Number of patients required	Primary endpoint
SRT BRAIN M1 BC NCT04061408	Jin Meng, China. 2019-21	HER2 + BC with brain M1 (N: 1-10) → SRT (3-5 fx of 8 Gy) +/- anti-HER2 (allowed)	170 Phase 2	At 2 years: intracranial LC, distant M1, PFS, OS, adverse events
LOCAL THERAPY BRAIN M1 HER2+ BC (Local HER-O) NCT02898727	Claire Philips, Australia. 2017-20	HER2 + BC with brain M1 (N: 1-5) → neurosurgery and / or SRT (1fx 20 Gy to 3 fx (TD: 24 Gy)) + anti- HER2 (within 4 weeks of completion of brain M1 treatment	50 Phase 2	At 1 year: LC, distant M1, OS, adverse events, neurocognitive function
T-DM1 + TMZ + SRT BRAIN M1 HER2+ BC NCT03190967	Alexandra Zimmer, USA. 2018-22	HER2+ BC with brain M1→ SRT, resection or WBRT + T-DM1 (anti-HER2) + TMZ (dose escalation)	125 Phase 1-2	MTD of TMZ used with T-DM1, adverse event, time at progression, median survival
SRT + PEMBROLIZUMAB BRAIN M1 BC NCT03449238	Silvia Formenti, USA. 2018-24	BC with brain M1 (N: 2-10, 5 mm - 4 cm) → Pembro (anti-PD-1) + SRT	41 Phase1-2	Tumor response non-irradiated 8 weeks, abscopal response, OS
SRT + ATEZOLIZUMAB BRAIN M1 TNBC NCT03483012	Nancy U Lin, USA. 2018-21	TNBC with brain M1 (≤ 5) → Atezolizumab (anti-PD-L1) + SRT (inclusion: extracranial M1)	45 Phase 2	At 2 years: PFS, extracranial objective response, OS, toxicity, abscopal response
SRT + NIVOLUMAB BRAIN M1 BC NCT03807765	Kamran Ahmed, USA. 2019-22	BC with brain M1 (≤ 10, ≤4 cm) → Nivolumab (anti-PD-1) + SRT	12 Phase 1	DLT / Intracranial local / distant (3, 6, 12 months), PFS (1 year), OS (2 years)

PI: Principal Investigator; BC: breast cancer; fx: fraction; SRT: Stereotactic Radiation Therapy; M1: metastases; N: number; LC: local control; PFS: progression-free-survival; OS: overall survival; TMZ: temozolamide; WBRT: whole brain radiotherapy; TNBC: triple negative BC; MTD: Maximum Tolerated Dose; DLT: Dose Limiting Toxicities; TNBC: Triple Negative Breast Cancer.

3.2. Topic 2. Stereotactic radiation therapy and systemic therapy in the management of oligometastatic disease

3.2.1. Current evidence and areas of contention

Oligometastatic disease was originally described in 1995 as an intermediate state between localized cancer and widespread metastases (Hellman and Weichselbaum, 1995). As detected on imaging studies, oligometastasis is identified as low-volume metastatic disease with up to 5 small lesions which are not necessarily in the same organ and which are potentially amenable to local treatment for complete remission (Cardoso et al., 2020). The ESTRO and the European Organisation for Research and Treatment of Cancer (EORTC) recently reached a consensus on clinical presentations of oligometastasis, suggesting it should not be considered as a single entity. A history of polymetastatic disease before diagnosis was the criterion which differentiated induced from genuine oligometastatic disease. Whether oligometastasis was diagnosed during a treatment-free interval or during active systemic therapy and whether or not an oligometastatic lesion was progressing on current imaging led to the sub-classification of oligo-recurrence, oligo-progression and oligo-persistence, each with a different prognosis (Guckenberger et al., 2020) (Fig. 1).

Therapeutic approaches to these distinct clinical scenarios are based on a multi-disciplinary assessment and are usually multi-modal, including systemic therapies and local ablation. Lesion ablation, which can be achieved by means of stereotactic radiation therapy (SRT), is an excellent option for most patients as it is less invasive than surgery and can be used for several lesions at different sites (Cardoso et al., 2020; Corbin et al., 2013; Milano et al., 2008; Norihisa et al., 2008; Marazzi et al., 2020). Administered in hypo-fractionated schedules or in a single dose (radiosurgery, SRS), SRT is termed stereotactic body radiation therapy (SBRT) when delivered to extracranial lesions. Since advances in RT equipment and techniques allow most RT departments to adopt SRT safely, it is now commonly utilized for oligometastatic disease. As small volumes are irradiated with up to a maximum of 5 fractions, SRT

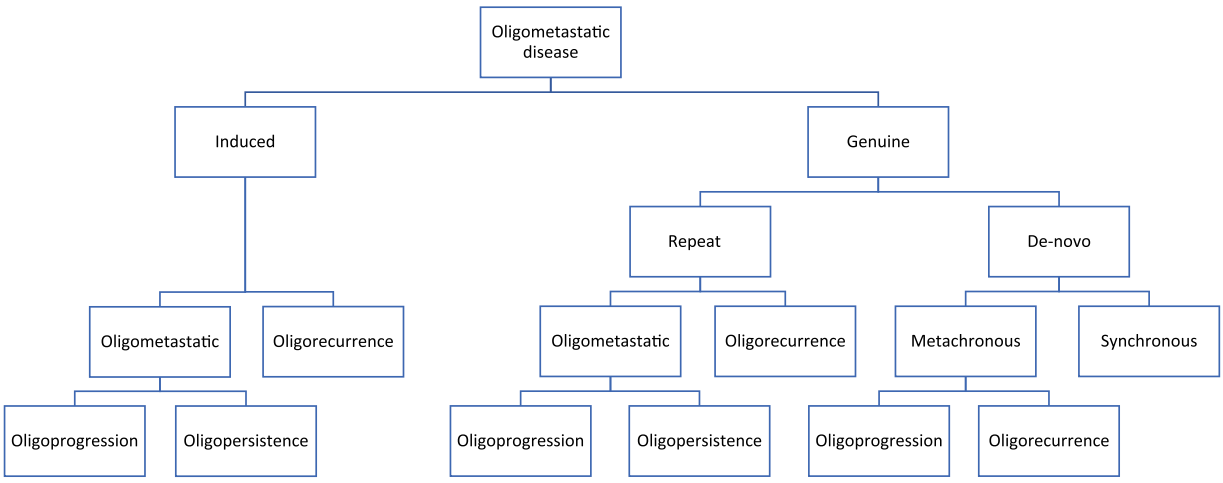

Fig. 1. Flowchart of classification of oligometastatic disease, modified from Guckenberger et al, Lancet Oncol 2020.

may interrupt systemic therapy briefly, or not at all, and may even be delivered concomitantly in some cases (Sharma et al., 2016).

Several phase II studies showed safety of SRT with favourable progression-free survival (PFS), and sometimes even OS rates (Gomez et al., 2019; Iyengar et al., 2018; Ost et al., 2018; Milano et al., 2019). After a median follow up of 25 months, the Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET) trial, which enrolled 99 patients with various cancers, each with up to 5 distant lesions, observed that the primary endpoint of OS significantly increased from 28 months to 41 months in the SBRT arm and PFS doubled from 6 months to 12 months; breast cancer cases were among the most represented ones (Palma et al., 2019).

Provided patient safety was ensured, the ATTM panel agreed that, with the aim of achieving a measurable clinical advantage, SRT might be administered to selected cases with more than 5 lesions and/or lesions larger than the 5 cm which is the usual cut-off for SRT (Lievens et al., 2020).

Controversial issues in SRT for oligometastatic breast cancer which emerged at the ATTM were:

1. Optimal therapeutic window, SRT dose and technique;
2. Optimal standardized imaging;
3. Predictors of early distant metastases and tumour progression;
4. Combination of SRT and systemic therapies.

3.2.1.1. Optimal therapeutic window, dose and technique. As the biomolecular mechanisms underlying metastatic spread are not yet fully understood, uncertainties persist about the optimal therapeutic window for intercepting the trajectory of metastasis evolution. Success relies on early detection and eradication of one or a few progenitor lesions with the potential for a massive poly-metastatic cascade and RT timing may have a major impact on disease-free-survival (DFS), PFS and perhaps even OS. For example, in oligoprogression, which is assumed to derive from clones that are resistant to the systemic therapy (Correa et al., 2016), the rationale for the therapeutic window is managing drug-resistant lesions. Although SRT use has been increasing over time, an international survey revealed a moderate agreement for applying it in oligometastastic breast cancer, as opposed to lung and colorectal cancers (Dagan et al., 2016) as SRT could potentially delay the start of systemic therapy, especially in those cases of triple negative or HER2 enriched tumours (Donovan et al., 2019).

No specific indications are available for doses and technical modalities according to the primary tumour and metastases localization. General recommendations are to deliver high biologically effective doses (BED) using high-precision RT equipment. In oligometastatic breast cancer, radiobiological data showed BED should be $>$ 75 Gy (Kwapisz, 2019) as it correlated with higher OS (Hong et al., 2018) even though there are not enough pre-clinical or high-level clinical data to support one regimen over another (Wong et al., 2016). Furthermore, doses and fractionation schedules for brain and body SRT varied greatly across studies (Redmond et al., 2017).

3.2.1.2. Optimal standardized imaging. Although the imaging modality may influence the definition of oligo/polymetastatic disease, imaging workups for detecting oligometastases are not yet standardized, partly because guidelines provide no consensus. The general recommendation is to choose what best suits the disease site (e.g. magnetic resonance imaging for brain metastases). Additionally, lack of standardized interpretation may lead to bias, wrongful readings of imaging features, timing or response to treatment, as well as to poor estimates of tumour regression or progression etc., all of which may impact upon decisions about whether or not to administer or modify systemic therapy. Ultimately, the clinical outcome could be affected (deSouza et al., 2018).

These shortcomings may be overcome by collecting imaging data of oligometastatic patients in databases such as the EORTC-ESTRO Oligocare prospective registry trial (Guckenberger et al., 2020), so that future recommendations will be supported by clinical evidence. In this field, the use of large radiomic databases could be helpful.

3.2.1.3. Predictors of early distant metastases and tumour progression. In order to distinguish high-risk patients who will require personalized programs from those who are most likely to remain oligometastatic in the long-term (van de Vijver et al., 2002; Patel et al., 2019) predictors are needed to identify early distant metastasis occurrence and progression from oligometastases to polymetastases. It is unclear whether prognostic models stratifying patients into risk groups, on the basis of factors such as gender, performance status, DFS, can be applied to all tumour histologies or molecular subtypes (Van den Begin et al., 2019). In breast cancer better survival was associated with one metastatic lesion (*vs* 2-5), small tumour size, stable disease, disease regression before SRT and bone-only metastasis (Milano et al., 2019; Piroth et al., 2022). Indeed, the 5- and 10-year OS for patients with bone-only metastases was 83 and 75% *vs* 31 and 17%, respectively, for metastatic lesions at other sites. At the same time-points, patients with bone metastases had more freedom from widespread metastases (67% for both *vs* 30% and 15%, respectively). After 10 years local control of bone metastases was 100% *vs* 73% for other metastatic sites (Milano et al., 2019). The molecular subtype emerged as an independent prognostic predictor, with triple negative tumours being associated with worse survival (Possanzini and Greco, 2018).

With the aim of supplementing histological and clinical data, active investigations are focusing on tumour gene-expression profiling, single-cell sequencing, liquid biopsies, radiomic features (Cortinovis et al., 2021). In addition, microRNA expression was able to discriminate between post-SRT tendencies to remain oligometastatic or to progress to polymetastases (Lussier et al., 2011). In breast cancer research, "omic" technologies have not only enhanced the power of traditional models, but also revolutionized analysis of patient samples, making them an indispensable tool in translational studies. "Omic" studies have provided evidence that evolutionary processes in metastatic progression result in distinct biological entities that diverge greatly from the primary tumour (Winnard et al., 2020).

3.2.1.4. Combination of SRT and systemic therapies. In oligometastatic patients SRT can be concomitantly combined with various types of systemic therapy (i.e., chemotherapy, immune therapy, ET, targeted therapy) to optimize the therapeutic index of ionizing radiation; major concerns with the SRT/systemic therapy association are radiation-induced toxicity because of the potential synergic effect, combined toxicities and hypothetically an antagonist effect (Sharma et al., 2016; Rubino et al., 2022; Ingrosso et al., 2021; Palumbo et al., 2021b). For example, a drug may induce a cell cycle phase that is not responsive to RT (Cushman et al., 2018) and new targeted therapies may have unknown effects when combined with RT.

Very few safety and outcome data are available for concomitant SRT and systemic therapies in oligometastatic disease.

One study (Guénolé et al., 2020) recruited 95 oligometastatic patients with 188 lesions in different body sites (33 with breast cancer). SRT was administered concomitantly with diverse systemic therapies to 40% of patients without acute and late G3 toxicities.

Breast cancer is the leading cause of brain metastases, the risk of which is linked to the molecular subtype (Meattini et al., 2020). Some studies specifically analyzed outcomes in patients with HER-2 positive disease and brain metastases. In 84 patients with 487 brain metastases, 132 lesions (27%) were treated with SRS and concurrent lapatinib, and 355 (73%) with SRS alone. Concomitant SRS and lapatinib were associated with a significantly higher complete response rate (35% *vs* 11%, p=0.008), with no increase in the risk of grade 2+ radiation necrosis (1.0% with concurrent lapatinib *vs* 3.5% without, p= 0.27) (Kim et al.,

2019b). Confirming this finding, the incidence of symptomatic radionecrosis was low (3%) when SRS was associated with Trastuzumab Emtansine (T-DM1) (Mills et al., 2021). In another series of 126 patients with HER2-positive disease and 479 brain metastases, local failure was significantly less in 24 patients who received concomitant lapatinib and SRS (5.7% vs 15.1% ($p < 0.01$) at 12 months) (Parsai et al., 2020). Overall, these results suggest concomitant SRS and anti-HER2 therapy is safe and efficacious for local control.

Preclinical data demonstrated CDK4/6 inhibitors exerted radiosensitization effects by inhibiting DNA damage repair, enhancing apoptosis, blocking the cell cycle, inducing cellular senescence and promoting anti-tumor immunity (Yang et al., 2020). A retrospective study on 18 brain metastases reported that concurrent CDK4/6 inhibitors and SRT was well tolerated (Figura et al., 2019), and achieved 88% local control at 6 months follow-up which persisted at 12 months. In other reports palliative RT together with CDK4/6 inhibitors confirmed the safety and efficacy of the association (Kim et al., 2021; Ratosa et al., 2020). However, no conclusions can be drawn on the best combination due to the small cohorts and RT being delivered before, concurrently or after CDK4/6 inhibitors. Preclinical findings showed a greater antineoplastic effect when RT was delivered before CDK4/6 inhibitors compared with other treatment schedules. In order to confirm this result, the randomized CIMER (Combined IMmune Effects of therapies in metastatic ER-positice breast cancer) trial (NCT04563507) is recruiting women with newly diagnosed oligometastatic ER-positice breast cancer, who will be enrolled to receive either palbociclib/letrozole alone or preceded by SBRT to each metastatic lesion (Petroni et al., 2021).

After RT, spontaneous tumour regression was documented at sites distant to the irradiated volume. This immune-mediated phenomenon is called the "abscopal" effect (Demaria et al., 2004; Formenti and Demaria, 2009). It was observed in metastatic non small cell lung cancer. Pembrolizumab + RT increased the rate of out- of-field (abscopal) response rate to 41.7% *vs* 19.7% pembrolizumab alone and achieved an abscopal control rate of 65.3% *vs* 43.4% (Theelen et al., 2020). In breast oligometastatic disease, concomitant immunotherapy and RT may have a potentially synergic effect, particularly in the triple negative setting. In19 patients with brain metastases SRT plus immunotherapy was compared with SRT alone. Concurrent immunotherapy was associated with better 1-year local control, OS, freedom from distant brain metastases but a significantly higher rate of radionecrosis (Guénolé et al., 2020). A phase II study assessed the efficacy and safety of pembrolizumab and SRT (30 Gy/ 5fr) on secondary lesions (Ho et al., 2020) in 17 patients. The overall response rate was 17.6% with 3 complete responders at 9 months follow-up and no G3 toxicity.

Predictive tumour (mutational burden, genomic mutation triggering radioresistance or radiosensitivity) and micro-environmental (T cell–inflamed gene expression profile) biomarkers are needed for predicting response to combined RT and immunotherapy. Markers of significant adverse immunoreactions are also needed (Muraro et al., 2017).

To reduce skeletal morbidity linked to both cancer and its treatments in breast cancer patients with bone metastases, whether symptomatic or not, guidelines recommend administering denosumab or zoledronate (Coleman et al., 2021) which reduced the risk of fracture, stimulated osteoclastic remodeling and increased immune response and radiosensitivity in preclinical and clinical studies. In a multicenter phase 1 study of 30 patients, (10% with breast cancer) 49 vertebral metastases received zoledronate combined with SRT (27 Gy in 3 fractions). Only one vertebral collapse was observed. Overall, the zoledronate-SRT combination was well tolerated, effectively relieved pain, and achieved good local tumor control with no late neurologic adverse effects (Pichon et al., 2016).

The ATTM panel concluded that more clinical, biomolecular and microenviromental data should be collected, pooled and analysed to provide definitive evidence of safety and outcomes after combined SRT and systemic therapy.

3.2.2. Ongoing clinical studies

Several ongoing clinical trials are exploring the roles of SRT (as delivered in a single fraction or with hypo-fractionated schedules to brain or extracranial metastases), and systemic therapy in the management of oligometastatic breast cancer with the most common primary endpoints being PFS, OS and toxicity (Cushman et al., 2018; Makhlin and Fox, 2020). Table 4 lists ongoing phase 1-2 clinical trials using brain SRT with systemic therapies. Inclusion criteria are up to 10 brain metastases, each of them up to 4 cm in diameter, and eventually extracranial metastases. Table 5 lists phase 1-2 and 3 ongoing trials of SBRT combined with systemic therapies in breast cancer patients with a maximum of five metastases, up to 10 cm in size. The multicenter STEREO-SEIN (NCT02089100), a key phase 3 trial, aims at assessing SRT effectiveness in de novo oligometastatic disease by evaluating PFS, local failure and OS rates. Inclusion criteria are up to 5 metastatic lesions (measurable or not). Measurable lesions have to be $\leq$ 10 cm in size ($\leq$ 7 cm for hepatic metastases). All lesions will be treated with SRT and compared with a systemic therapy arm delivering RT only for palliation. The "NRG BR002", a randomized phase II/III trial, will enroll newly oligometastatic breast cancer patients with $\leq$ 4 non-cranial lesions that did not progress after up to 12 months first line systemic therapy. Patients will be randomized to standard of care therapy with or without SRT and/or surgical resection of all metastatic sites. Similarly, STEREO-OS (NCT03143322), a phase 3 trial for breast, lung and prostate cancer patients with 1-3 bone metastases, will assess systemic therapy combined with SRT in different fractionations (9 Gy x 7 fractions or 7 Gy x 5 fractions) *vs* systemic therapy alone with palliative RT.

3.2.3. Proposed RT research strategy

The ATTM panel identified assessment of the SRT association with systemic therapy as a main unmet need in oligometastatic breast cancer.

Two main research areas emerged:

(A) To evaluate RT and new targeted therapies in the oligometastatic setting the ATTM proposed setting up a multi-centre study for retrospective and prospective analysis of breast cancer patients who received CDK 4/6 inhibitors ± sequential or concomitant RT, not necessarily SRT. Endpoints are local control, PFS, OS and treatment related toxicities.

(B) Sequential use of SRT and immunotherapy with atezolizumab to improve outcomes in triple negative, PDL1+ oligometastatic patients. The RATEO trial will be a prospective observational study on the effects and toxicity of SRT to all oligometastatic sites before ATEzOlizumab + nab-paclitaxel. The primary endpoint is toxicity; secondary end-points are PFS and OS.

3.3. Topic 3. Contralateral breast tumour prevention in BCRA-mutated patients

3.3.1. Current evidence and areas of contention

The main promoters of breast carcinogenesis are the tumour suppressor genes, BRCA1 and BRCA2 although low penetrance genes like PALB2, BARD1, RAD51C, RAD51D, ATM and CHEK2 were linked to breast cancer and correlated with it and its different sub-types in two large case control studies of women from the U.S., Europe and Asia ($author1$ et al., 2021; Hu et al., 2021).

Even though BRCA1 and BRCA2 confer cancer susceptibility with one germline defective chromosome copy, two defective alleles are needed for malignant transformation. BRCA1 and BRCA2 encode proteins that are involved in DNA repair via homologous recombination, cell cycle control via checkpoint modulation and maintenance of overall genomic stability (Brose et al., 2002; Lakhani et al., 1998; Paluch-Shimon and Evron, 2019; Pierce and Haffty, 2011; Venkitaraman, 2002). BRCA1 mutated breast cancers are typically high-grade tumours, with a high mitotic index, p53 over-expression and often have the triple-negative phenotype. BRCA2-mutated breast cancers are

Table 5
Ongoing clinical trials on stereotactic extracranial radiotherapy and systemic therapy in oligometastasic breast cancer. Recruiting trials.

Trial	PI Country Accrual time	Population & study summary	Number of patients required	Primary endpoint
SBRT BC (STEREO-SEIN) NCT02089100	Celine Bourgier, France. 2014-23	HHRR+ BC ≤ 5 M1 lesions, ≤10 cm (for hepatic M1 ≤ 7 cm) → SBRT vs no therapy except for palliation. Beginning ST before 2 and 7 days after SBRT completion	280 Phase 3	At 3 years: LC, PFS and OS
SBRT FOR SPINAL M1 IN FAVORITE TUMORS NCT03392233	Ming Ye, China. 2017-27	BC, prostate, lung → SBRT spinal M1 (3 fx 24 Gy or 3 fx 30 Gy)	100 Phase 2	The rate of relieve pain (1 week after SBRT to 2 years later), toxicity
STANDARD OF CARE +/- SBRT +/- SURGERY M1 BC NCT02364557	Steven Chmura, USA. 2014-22	BC ≤ 4 M1 lesions, ≤ 5 cm → Standard of care (planned ST) vs SBRT (1-3-5 fx) or surgery + ST	402 Phase 2-3	PFS (3 years), OS (8 years), new M1, adverse effects, CTC blood, ctDNA plasma
STANDARD OF CARE +/- SBRT FOR M1 CANCER NCT03808337	Jonathan Yang, USA. 2019-22	BC, lung, 1-5 M1 → Standard of care (ST, targeted therapies, HT) +/- SBRT (For lung: 5 fx 50 Gy, 4 fx 48 Gy, 3 fx 54 Gy / Others: 3 fx 27-30 Gy, Bone: 1 fx 24 Gy)	142 Phase 2	Up to 2 years: PFS, OS
CORE STUDY NCT02759783	Vincent Khoo, UK. 2016-19	BC, prostate, NSCLC, ≤ 3 M1 → Standard of care +/- SBRT	245 Phase 2-3	At 3 years: PFS
SBRT vs STANDARD OF CARE BREAST AND LUNG M1 NCT03808662	C. Jillian Tsai, USA. 2019-22	BC, lung,1-5M1 → Standard of care vs SBRT (3 fx of 9-10 Gy, 5 fx of 10 Gy)	160 Phase 2	PFS, OS
SBRT LUNG LIVER M1 BC NCT02581670	Fiorenza De Rose, Italy. 2015-20	BC lung and liver M1 < 5 M1 < 5 cm → SBRT (VMAT)	40 Phase 2	Toxicity, LC (2 years), PFS, OS, QoL
INTERVENTION TO LIVER LUNG M1 BC (IMET) NCT02251353	Hasan Karalink, Turkey. 2014-22	BC lung and / or liver M1 → resection and / or radiofrequency ablation, Transcatheter arterial chemoembolization, CyberKnife SBRT vs no intervention	300 Cohort	At 3 years: OS, PFS, morbidity due to treatment modality (6 months)
STANDARD TREATMENT +/- SBRT SOLID TUMORS BONE M1 (STEREO-OS) NCT03143322	Sebastian Thureau, France. 2018-22	BC, prostate, lung, 1-3 bone M1→ Standard treatment + SBRT (7 fx of 9 Gy, 5 fx of 7 Gy) vs Standard treatment	196 Phase 3	At 1, 2 and 3 year: PFS, LC, OS, toxicities, QoL, cost utility
SBRT + ATEZOLIZUMAB TNBC M1 (AZTEC) NCT03464942	Sherene Loi, Australia. 2018-22	TNBC 1-4 M1 with at least 1 Untreated → SBRT (1 fx 20 Gy or 3 fx 24 Gy) + Atezolizumab	52 Phase 2	At 2 years: PFS, objective response, adverse events, OS
ANTI-VACCINATION WITH FIT3L, RT AND POLY-ICLC NCT03789097	Joshua Brody, USA. 2019-23	BC, NHL, HN → Pembro + FIt3L + SBRT + Poly-ICLC	56 Phase 1-2	DLT, overall response rate (6 months)
SBRT AND ONCOLYTIC VIRUS BEFORE PEMBROLIZUMAB FOR M1 TNBC AND NSCLC NCT03004183	Jenny Chamg, USA. 2017-22	BC, NSCLC → ADV/HSV-tk + Valacyclovir + SBRT + Pembro	57 Phase 1-2	At 30 days: overall response rate, duration of response, OS rate, PFS, adverse events, change in immunohistochemical expression

PI: Principal investigator; BC: breast cancer; SBRT: Stereotactic Body Radiotherapy; HHRR: hormonal receptors; M1: metastases; ST: systemic treatment; HT: hormonal treatment; LC: local control; PFS: progression-free-survival; OS: overall survival; QoL: quality of life; CTC: circulating tumor cells; ctDNA: circulating tumor DNA; TNBC: triple negative BC; DLT: Dose Limiting Toxicities; VMAT: Volumetric Modulated Arch Therapy; NHL: Non Hodgkin Lymphoma; HN: Head and Neck cancer; NSCLC: non-small cell lung cancer.

more likely to be estrogen and progesterone receptor positive (Lakhani et al., 1998). Furthermore, in the Prospective study of Outcomes in Sporadic versus Hereditary breast cancer (POSH), the BRCA mutation was more common in women with triple-negative disease (136/558 (24%) (Copson et al., 2018).

Germline mutations in BRCA1 or BRCA2 account for 3%-5% of breast cancers; prevalence is higher in patients < 50 years old, particularly BRCA1 carriers, who are at high risk of recurrent ipsilateral and contralateral breast cancer (Stjepanovic et al., 2020; Carbine et al., 2018), as well as ovarian cancer (Heemskerk-Gerritsen et al., 2019; Hartmann et al., 2001; Meijers-Heijboer et al., 2001), having an overall lifetime risk of up to 80% and 40%, respectively (Brose et al., 2002). BRCA1 is associated with a 53% lifetime risk (20-year risk 40%) for contralateral cancer development and BRCA2 with a 65% risk (20-year risk 26%) (Pierce and Haffty, 2011; Evron et al., 2014). The BRCA mutation was identified in 338/2,733 young women (12%) in the POSH cohort. At a median follow up of 8.2 years contralateral breast cancer was identified in 151 (6%) patients: 18% of BRCA1 carriers, 12% of BRCA2 carriers and 4% patients with no BRCA mutation. Median time to contralateral breast cancer diagnosis was 2.7-3 years (Copson et al., 2018). Although prognosis was reported to be worse in women with BRCA mutations than in patients with sporadic breast cancer, survival rates were similar in recent studies (Goodwin et al., 2012; Huzarski et al., 2013).

Controversial issues in managing BRCA1/2-mutated early breast cancer which emerged at the ATTM were:

1. Outcome after mastectomy and BCS ± RT (BCT);
2. BCT in BRCA1/2 carriers and non-carriers;
3. Risk-reducing contralateral mastectomy;

4. RT as prophylactic contralateral breast risk-reduction approach.

3.3.1.1. Outcome after mastectomy and BCT. In BRCA carriers with early breast cancer, mastectomy and axillary node assessment are often recommended even though no prospective randomised studies have compared mastectomy and BCS. In the POSH cohort of 3,024 breast cancer patients $\leq$ 40 years old, no differences emerged in distant disease-free survival or OS following mastectomy (1,464) or BCS (1,395) after adjusting for prognostic features (especially, T and N stage and hormone receptor status) (Maishman et al., 2017). A recent review by Vallard et al. noted that short-term local control, metastasis-free survival and OS were equivalent after mastectomy and BCT in BRCA carriers. Long-term local control remains a controversial issue as all long-term studies were retrospective, with few patients and infrequent use of the systemic therapies that are standard of care today (Vallard et al., 2019). Another metanalysis showed increased risk of locoregional recurrence after BCT while the risk of contralateral breast cancer, disease recurrence, disease-specific recurrence and death were equivalent after BCT and mastectomy (Davey et al., 2021). To manage hereditary breast cancer an expert panel from the American Societies of Clinical Oncology (ASCO), Radiation Oncology (ASTRO) and Surgical Oncology (SSO) suggested that "Germline BRCA status should not preclude a patient with newly diagnosed breast cancer otherwise eligible for breast conservation from receiving BCT" (Tung et al., 2020). In our view, concurring with others, BRCA mutation carriers should be appropriately counselled about both surgical options so as to achieve the best possible outcome.

3.3.1.2. BCT in BRCA1/2 carriers and non-carriers. After BCT, ipsilateral breast tumour recurrence (IBTR) appeared to be a new cancer rather than a true IBTR as its onset tended to be more than 5 years later, in another location to the primary tumour site with sometimes different histology (Morrow, 2022). In older series the incidence of IBTR was higher in BRCA1/2 carriers than in sporadic cases (Lakhani et al., 1998). Recent results suggested it was similar, especially if carriers had also undergone bilateral salpingo-oophorectomy (BSO) and received adjuvant systemic therapy (van den Broek et al., 2019; Bernier and Poortmans, 2015; Kirova et al., 2010, 2005; Pierce et al., 2006, 2010). Pierce et al. reported no significant difference in 10- and 15-year IBTR rates in BRCA1/2 carriers and sporadic cases and identified factors that reduced the risk of IBTR as older age, chemotherapy and BSO (Pierce et al., 2006). In a Dutch cohort of breast cancer patients, about half of whom underwent BCT, the 10-year cumulative risk of IBTR was 7.3% in BRCA1 carriers and 7.9% in non-carriers. The authors concluded that BCT may be offered to BRCA mutation carriers undergoing therapy for unilateral breast cancer (van den Broek et al., 2019). In a meta-analysis of 10 studies Valachis et al., reported that BCT did not increase the risk of IBRT in carriers and indicated that RT was equally effective in both groups. When analyses were restricted to studies with a follow-up of at least 7 years (five studies, with a total 1,634 patients), the local recurrence rate emerged as significantly worse in carriers (24% carriers *vs* 16% non-carriers; $p<0.003$) (Valachis et al., 2014). Clinical data suggested RT-related toxicity profiles were similar in BRCA1/2 mutated patients and sporadic cases (Shanley et al., 2006). A retrospective cohort study by Pierce et al. observed similar rates of acute or chronic toxicities in the skin, subcutaneous tissue, lung and bone, according to RTOG acute morbidity scoring criteria (Pierce et al., 2000).

In BRCA mutation carriers the 10-year cumulative risk of contralateral breast cancer was 23.9% when diagnosed before 41 years of age, dropping to 12.6% when diagnosed in the 41-49 age-group (van den Broek et al., 2016). Contralateral breast cancer risks were 25%-30% over 10 years and more than 40% over 15 years, compared with 3% and 7%, respectively, in non-carriers (Pierce et al., 2010; Metcalfe et al., 2004). Women with BRCA1 mutations had a significantly higher cumulative risk 20 years after breast cancer diagnosis than those with BRCA2 mutations (40% and 26%, respectively; $p = 0.001$) (Kuchenbaecker et al., 2017). The risk of contralateral breast cancer exceeded 40% in the entire series of 655 BRCA mutation carriers with early breast cancer who received BCS (302/655) or mastectomy (353/655). It was not significantly different whether postoperative RT was administered or not, suggesting no added risk from scatter RT at 10 and 15 years (Pierce et al., 2010). Likewise, no increase in radiation-related secondary malignancies, such as thyroid tumours, was observed in a large cohort of 230 BRCA mutation carriers with early breast cancer who were treated with breast and/or chest wall RT, with or without regional node irradiation (Schlosser et al., 2020). A high, long-term risk of developing contralateral primary breast cancer was initially reported in women <40 years of age who received a radiation dose >1.0 Gy to the contralateral breast (Stovall et al., 2008; Hooning et al., 2008). In the WECARE cohorts, however, analysis of BRCA-mutation carriers showed that the mutation itself, rather than the radiation dose, was associated with greater risk of contralateral breast cancer (RR 4.5) (Bernstein et al., 2013).

3.3.1.3. Risk-reducing mastectomy. Current recommendations for BRCA mutation carriers advocate an intensified screening programme, BSO (to reduce the risk of breast and ovarian cancer) (Elezaby et al., 2019) and consideration of bilateral risk-reducing mastectomy (Rebbeck et al., 2004). In a large Dutch prospective series with a median follow up of > 10 years, bilateral risk-reducing mastectomy was associated with lower mortality than surveillance only for BRCA1 mutation carriers and with similar BC-specific survival for BRCA2 mutation carriers. Most women in both mutational groups had opted for prophylactic BSO and more women who chose bilateral risk-reducing mastectomy rather than surveillance underwent BSO (Heemskerk-Gerritsen et al., 2019).

In BRCA1/2 carriers Rebbeck et al. found risk-reducing mastectomy decreased the risk of primary breast cancer by 90%; combining mastectomy with oophorectomy led to a 95% reduction (Rebbeck et al., 2004). Since risk-reducing mastectomy lowered the risk of contralateral breast cancer in BRCA mutation carriers, ASCO, ASTRO and SSO recommended offering it to all carriers who have been or are being treated with unilateral mastectomy (Tung et al., 2020). Despite this, evidence for improved survival was insufficient and a recent Cochrane analysis pointed out that risk-reducing mastectomy had not been evaluated in prospective randomized studies (Carbine et al., 2018). Furthermore, it could incur mutilation-related psychological costs as, fearing its effect on their body image, sexuality and sensation, many patients seek alternative preventive measures (Robson et al., 1998; Metcalfe et al., 2019). All these implications pose a difficult dilemma for many patients who may already be confused (Sacks and Morrow, 2020). Furthermore, the significantly high risk of ovarian cancer and its high mortality rate have to be kept in mind when decision making with women carrying BRCA mutations, particularly BRCA1.

Oophorectomy, chemotherapy and ET with tamoxifen all significantly decreased the risk of contralateral breast cancer after treatment of the primary tumour; increasing age was another factor linked with a lower risk (Valachis et al., 2014; Metcalfe et al., 2004). Overall, these findings support individualized counselling for patients with each BRCA mutation type.

3.3.1.4. RT as prophylactic contralateral breast risk-reduction approach. Israel has a relatively large cohort of BRCA mutation carriers, as around 20% of Israeli breast cancer patients are mutation carriers (Manchanda et al., 2019). From 2007 to 2017, 162 BRCA mutation carriers with unilateral breast cancer were enrolled in a phase II non-randomized trial (NCT00496288), offering standard loco-regional treatment of the primary breast cancer and the option of prophylactic contralateral breast irradiation instead of contralateral risk-reducing mastectomy. At a median follow-up of 5 years, contralateral breast irradiation significantly

reduced the risk of subsequent contralateral breast cancer (Evron et al., 2019). Compared with the diseased breast, early radiation-related toxicities were not increased and there were no major grade 3-4 acute events. Late toxicity rates were similar but one patient developed radiation-associated sarcoma in the prophylactically irradiated breast. Even though follow up will continue to assess late events (Poortmans and Kaidar-Person, 2019), present data justify further studies investigating the potential role of bilateral irradiation in BRCA carriers (Narod, 2019).

3.3.2. *Ongoing clinical studies*

To the best of our knowledge, only one ongoing clinical trial is evaluating contralateral risk-reducing RT in hereditary breast cancer patients (NCT00496288 from Assaf-Harofeh Medical Center). Five trials registered on Clinicaltrials.gov are focusing on psychological distress linked to risk-reducing mastectomy (NCT03061175; NCT02918474; NCT02263014; NCT00579007; NCT00555503).

3.3.3. *Research proposal*

The genetic risk of breast cancer has recently assumed a central role and recent findings justify growing interest in the issues of how BRCA mutated patients should be treated and whether RT protocols should be tailored to this genetic make-up. On the one hand, referring women for bilateral mastectomy is a major commitment for patients and health service organization and resources while on the other, prophylactic RT might be a valid alternative option for reducing the risk of contralateral cancer. The ATTM panel consequently propose an international, multicentre randomized phase III trial of prophylactic contralateral breast irradiation for BRCA mutation carriers who have declined contralateral risk-reducing mastectomy and are candidates for ipsilateral RT (breast or chest wall ± RNI) as part of their standard loco-regional treatment for early breast cancer.

Prophylactic contralateral breast irradiation (40 Gy/15 fr) in breast cancer patients bearing BRCA 1/2 mutations is expected to significantly reduce the risk of contralateral breast cancer within 10 years follow up. All eligible patients who are candidates for adjuvant RT will be given ipsilateral irradiation and will be randomized to receive or not contralateral breast irradiation. Ipsilateral and contralateral RT will be delivered concomitantly. The primary endpoint will be 10-year contralateral breast cancer free survival. Secondary endpoints will be toxicity and contralateral breast radiation–related complications, QoL, 10-year DFS and OS.

4. Conclusions

The ATTM, with its experts on breast cancer who brainstorm on RT-related hot topics, is attracting more and more attention worldwide in the scientific community. This 2020 ATTM white paper reports in-depth analysis of the state of the art, open questions (grey areas and controversies) in breast cancer RT and lively discussion on how to confront them when evidence-based data or expert opinions are insufficient to guide clinical decision-making. Furthermore, the ATTM assessment of the design and end-points of on-going studies is expected to lead to ideas for innovative investigations. All the authors of this white paper sincerely hope even more young radiation and clinical oncologists will attend future ATTMs so they are stimulated to become involved in research projects and improve their critical skills when faced with controversial clinical cases.

Role of the funding source

The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Legend to the Fig. 1: Flowchart of classification of oligometastatic disease, modified from Guckenberger et al., Lancet Oncol 2020

Conflict of interest

Dr Maria Cristina Leonardi received speaker fee from Accuray Inc. Prof. Icro Meattini reports occasional advisory boards supported by Eli Lilly, Novartis, Pfizer, and Roche, outside the submitted work. Prof. Philip Poortmans report a medical advisor role for Sordina IORT Technologies S.p.A. outside the submitted work. All other authors declare that they have no conflict of interest. All the Authors made substantial contribution to the conception and design of the study, data acquisition or analysis and interpretation, drafting the article or revising it critically. All have approved the final version which I am submitting. Our work has not been published previously and the manuscript has not been submitted elsewhere.

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