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Radiation therapy for young women with early breast cancer: Current state of the art

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ABSTRACT

A diagnosis of breast cancer at a young age, defined per guidelines as ≤ 40 years, represents a challenging situation requiring additional attention by the treating physicians including radiation oncologists and surgeons involved in the local treatment of these tumors. The present review aims at providing updated evidence on the state of the art about the available techniques and indications for radiation therapy in patients with early breast cancer, specifically focusing on young women. In addition, future perspectives including the ongoing trials and the potential impact of combined approaches with systemic therapies (such as immunotherapy) are reviewed. Major conclusions from this overview are that young women affected by invasive breast cancer seem to receive the greatest benefit from the boost on the tumor bed. Most young patients affected by ductal carcinoma in situ should receive postoperative whole breast irradiation (WBI). When regional node irradiation is considered, young age should be considered as a high-risk factor. Partial breast irradiation is not suitable for young patients and should be recommended within the context of a clinical trial. Importantly, robust data have already supported the efficacy and safety of hypofractionated-WBI schedules that should now replace standard fractionated-WBI as gold standard for all patients irrespective of their age. Finally, organs-at-risk sparing systems as strategy for prevention of radiation-related long-term toxicities should be strongly considered for these patients. Considering the lack of inclusion of young patients in several published trials as well as in some of the ongoing ones, robust evidence to counsel young breast cancer patients on the optimal radiation therapy approach is still lacking. Further studies and *ad hoc* subgroup analyses in this specific patient population are strongly warranted.

1. Introduction

Breast cancer arising at a young age (defined per guidelines as ≤40 years (Cardoso et al., 2012; Paluch-Shimon et al., 2017)), is the most common malignancy diagnosed in women of reproductive age (Fidler et al., 2017). A diagnosis of breast cancer in a young woman represents a challenging situation requiring additional attention by the treating physicians (Rosenberg et al., 2015). Specifically, for radiation oncologists and surgeons, several age-related considerations with potential impact on the local management of tumors diagnosed in young breast cancer patients should be made.

These women have a worse prognosis than older patients (Partridge et al., 2016), being characterized by a higher risk of disease recurrence both distant and locoregional relapses (Aalders et al., 2016). Younger women tend to be diagnosed at a more advanced disease stage with a higher incidence of aggressive subtypes as compared to older patients (Lambertini et al., 2016). These have also been confirmed at the transcriptomic and genomic level (Azim and Partridge, 2014; Kan et al., 2018). Moreover, hereditary predisposition is more common in young breast cancer patients so that genetic testing is currently recommended in all women diagnosed at ≤40 years (Paluch-Shimon et al., 2017). The diagnosis of breast cancer secondary to a hereditary predisposition syndrome adds additional challenges also in terms of local management including the indication for risk-reducing surgeries (Paluch-Shimon et al., 2016). Finally, it has been shown that young breast cancer patients are at increased risk of psychological distress not only at

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diagnosis but also at long-term follow-up making survivorship issues a topic of great importance in this setting (Howard-Anderson et al., 2012). Among them, sexual dysfunction is a major concern being associated with a significant negative influence on their quality of life (Dizon et al., 2014; Condorelli et al., 2019). Local treatment can have an important impact on body image and self-esteem that contribute to sexual health (Dizon et al., 2014). Lower perception of sexual attractiveness was shown to be associated with greater sexual problems (Burwell et al., 2006). Further concerns on this regard are faced by women wishing to conceive following the completion of anticancer treatments and breastfeed their babies (Azim et al., 2010; Lambertini et al., 2018).

All these age-related issues should be considered when counseling young women about the optimal local management of their newly diagnosed breast cancer. Nevertheless, it should be highlighted that young patients are often under-represented in clinical trials also in those investigating local treatments. Therefore, there is a subsequent risk of over-treating these women based only on age considerations (Paluch-Shimon et al., 2017).

In terms of indications for radiation therapy in early breast cancer, current guidelines state that similar recommendations as for older patients should be followed (Paluch-Shimon et al., 2017; Polgár et al., 2010; Postoperative radiotherapy for breast cancer: UK consensus statements, 2016; Krug et al., 2017; Correa et al., 2017; Smith et al., 2018). Only exception specific to young women is a stronger contraindication to partial breast irradiation (PBI).

The present review of the literature aims at providing updated evidence of the available techniques and indications for radiation therapy in patients with early breast cancer, specifically focusing on young women. Different radiation therapy techniques and issues on dose, volumes and fractionation are reviewed including conventional versus hypofractionated radiation therapy, PBI with external beam, brachytherapy, and intraoperative radiotherapy (IORT), tumor bed boost, and indications for regional node irradiation (RNI). Furthermore, additional special issues in the field are addressed such as the radiation therapy management of ductal carcinoma in situ (DCIS), potential prevention strategies towards radiation-related toxicities (focusing on secondary cancers and heart/lung side effects) and the use of preoperative radiotherapy. Finally, future perspectives including the ongoing trials and the potential impact of combined approaches with systemic therapies (such as immunotherapy) are also reviewed.

2. Mastectomy versus breast-conserving surgery

The rates of mastectomy for early breast cancer declined after the 1990′s and started to raise again in 2005 (Tuttle et al., 2007; Albornoz et al., 2015). Several recent population-based studies reported that up to more than a third of the patients with early breast cancer opt for mastectomy as their primary surgical procedure (Tuttle et al., 2007; Albornoz et al., 2015; Kummerow et al., 2015; Agarwal et al., 2015). Furthermore, the rates of bilateral mastectomies for women diagnosed with unilateral breast cancer increased from 5.4% in 1998 to 29.7% in 2011; a similar increase in reconstructive procedures was also observed during the same years (from 36.9% to 57.2%) (Albornoz et al., 2015; Kummerow et al., 2015). The rates of bilateral mastectomies for unilateral breast cancer also increased in cases of ductal carcinoma in situ (Tuttle et al., 2009). The rates of immediate reconstruction after unilateral mastectomy increased from 10% in 1998 to 27% in 2011, while reconstruction after contra-lateral prophylactic mastectomy increased from 37% to 57% (Tuttle et al., 2007).

In the American Plastic Surgery Website, the number of breast augmentation procedures in healthy women increased by 41% from 2000 to 2017, suggesting the larger popularity of these procedures in recent years (Cosmetic Plastic Surgery Statistics, 2017). Notably, in the US, payment coverage for oncoplastic surgery and reconstruction procedures in breast cancer patients is mandated through federal and state legislation (Albornoz et al., 2015). Advances in both mastectomy (e.g. skin sparing and nipple sparing) and reconstructive techniques (increased use of implants rather than autologous flap) make these procedures more attractive to patients (Agarwal et al., 2015). The “Angelina Jolie story effect” in 2013 was also reported as a cause for the increasing number of bilateral mastectomies for unilateral breast cancer worldwide (Evans et al., 2019).

Taken together, these studies indicate that the rates of mastectomies and immediate breast reconstruction (mostly implants) have increased in the past decade; this attitude appears to be even more important in young breast cancer patients.

3. Different radiation therapy approaches

3.1. Conventional versus hypofractionated radiation therapy

Seminal trials demonstrated that breast-conserving surgery followed by adjuvant whole breast irradiation (WBI) with a schedule of 50 Gy/25 fractions in 5 weeks (standard fractionated whole breast irradiation, SF-WBI) was equivalent to mastectomy in terms of efficacy (Veronesi et al., 1981; Fisher et al., 1985). SF-WBI in the adjuvant treatment after breast-conserving surgery has been the standard for several decades, based on the assumption that larger radiotherapy fractions would yield higher toxicity to normal tissues (Fisher and Rabinovitch, 2014). However, the possibility to improve patient convenience and lower healthcare costs, without reducing the efficacy of SF-WBI, has been explored in the last two decades by adopting shorter radiation therapy schedules.

Hypofractionation is a treatment regimen that delivers higher doses of radiation in fewer fractions as compared to conventional schedule. It has become of increasing interest with the recognition of a potential improvement in therapeutic ratio with treatment delivered in larger-sized fractions (Timmerman, 2008).

Specifically, the efficacy and safety of hypofractionated-whole breast irradiation (HF-WBI) was assessed in four randomized clinical trials (Table 1) (Owen et al., 2006; START Trialists' Group et al., 2008a, b; Whelan et al., 2010). After 10-year follow-up, it can be concluded that HF-WBI provides the same efficacy of SF-WBI but with decreased acute toxicity and does not seem to affect breast appearance, late toxicity or patient-reported quality of life measures (Hickey et al., 2016). Only 21%–30% of the patients in the key randomized trials of HF-WBI were younger than 50 years, while patients $\leq$40 years were less represented (Table 1). Young age did not yield any detrimental effect in terms of local control in patients treated with HF-WBI. Interestingly, at the 10-year follow-up analysis of the START trials, HF-WBI appeared to yield a better control in terms of local-regional relapse in younger patients, even if not statistically significant. Importantly, disease-free survival was significantly better in the HF-WBI group versus the SF-WBI group for analysis of all patients (Haviland et al., 2013).

Notably, despite SF-WBI does not provide an incremental benefit in both tumor control and side effects compared to HF-WBI, the latter is not widely adopted as standard radiation therapy schedules for young patients in many countries (Bekelman et al., 2014), even though these women were well represented in the major phase 3 trials.

Reflecting current evidence from clinical trials and large cohort studies, the new 2018 ASTRO WBI guidelines recommended HF-WBI for breast cancer patients regardless of age, tumor stage and whether they have received chemotherapy (Smith et al., 2018). The 2016 postoperative radiotherapy for breast cancer UK consensus statements states that there is no indication to use more than 15 fractions for the breast, chest wall or nodal areas for standard adjuvant treatment (Postoperative radiotherapy for breast cancer: UK consensus statements, 2016). Indeed, HF-WBI schedules should replace SF-WBI as gold standard for all ages and should be adopted worldwide.

Table 1
Main published phase 3 trials investigating hypofractionated whole breast irradiation.

Trial	Study Period	Study patients, overall (young)	Young patients, %	RT technique, Study design	OS rates	LR rates	Subgroup analysis in young women
RMH/GOC (Owen et al., 2006)	1986-1998	1410 (107)^	7.6% (< 40 years) 30.3% (< 50 years)	39-42.9 Gy/13 fr° HF-WBI vs SF-WBI	NR	At 10 years: 14.8% (39/13) vs 9.6% (42.6/13) vs 12.1% (SF-WBI); p = 0.027	No
START A (START Trialists' Group et al., 2008a)	1999-2002	2236 (128)^	6% (< 40 years) 23% (< 50 years)	39-41.6 Gy/13 fr° HF-WBI vs SF-WBI	At 10 years: 81.6% (HF-WBI) vs 79.7% (HF-WBI) vs 80.2% (SF-WBI); p = 0.6	At 10 years: 8.8% (39/13) vs 6.3% (41.6/13) vs 7.4% (SF-WBI); p = NS	No
START B (START Trialists' Group et al., 2008b)	1999-2002	2215 (17)^	5% (< 40 years) 21% (< 50 years)	40 Gy/15 fr° HF-WBI vs SF-WBI	At 10 years:84.1 % (HF-WBI) vs 80.8% (SF-WBI); p = 0.042	At 10 years: 4.3% (HF-WBI) vs 5.5% (SF-WBI); p = 0.2	No
CANADIAN (Whelan et al., 2010)	1993-1996	1234 (296)	25% (< 50 years)	42.5 Gy/16 fr° HF-WBI vs SF-WBI	At 10years: 84.8% (HF-WBI) vs 84.6 % (SF-WBI); p = NR	At 10 years: 6.2% (HF-WBI) vs 6.7% (SF-WBI); p = 0.79	No

RT, radiotherapy; OS overall survival; LR, local relapse; fr, fraction; HF-WBI, hypofractionated whole breast irradiation; SF-WBI, standard fractionated whole breast irradiation; NR, not reported; NS, not significant.
° HF-WBI arm.
^ < 40 years.

Table 2
Main published phase 3 trials investigating partial breast irradiation.

Trial	Study period	Study patients, overall (young)	Young patients, %	RT Technique, Study design	OS rates	LR rates	Subgroup analysis in young women
IMRT APBI Florence (Livi et al., 2015)	2005-2013	520 (86)^	16.5% (40-49 years)	Accelerated IMRT° APBI vs WBI	At 5-year: 99.4% (APBI) vs 96.6% (WBI); p = 0.057	At 5-year: 1.5% (APBI) vs 1.5% (WBI); p = 0.86	No
GEC-ESTRO (Strnad et al., 2016)	2004-2009	1184 (182)^	15.4% (40-49 years) 16.9% (premenopausal)	Brachytherapy° APBI vs WBI	At 5-year: 97.27% (APBI) vs 95.55% (WBI); p = 0.11	At 5-year: 1.44% (APBI) vs 0.92% (WBI); p = 0.42	No
IMPORT LOW (Coles et al., 2017)	2007-2010	2018 (0)	0	Normofractionated IMRT PBI vs WBI	At 5-year: 3.7% (PBI) vs 5% (WBI); p = 0.693	At 5-year: 0.5% (PBI) vs 1.1% (WBI); p = 0.420	No
TARGIT-A (Vaidya et al., 2014)	2000-2012	3451 (0)	0	IORT° IORT vs WBI	At 5-year: 96.1% (IORT) vs 94.7% (WBI); p = 0.099	At 5-year: 3.3% (IORT) vs 1.3% (WBI); p = 0.042	No
ELIOT (Veronesi et al., 2013)	2000-2007	1305 (0)	0	IORT° IORT vs WBI	At 5-year: 96.8% (IORT) vs 96.9% (WBI); p = 0.59	At 5-year: 4.4% (IORT) vs 0.4% (WBI); p < 0.0001	No

APBI, accelerated partial breast irradiation; PBI, partial breast irradiation; IMRT, intensity modulated radiotherapy; EBRT, external beam radiotherapy; IORT, intraoperative radiotherapy; WBI, whole breast irradiation.
° Experimental arm technique.
^ aged 40–49 years.

3.2. Partial breast irradiation

PBI has been introduced as an alternative treatment method for selected patients with early breast cancer. Potential advantages of accelerated PBI include shorter treatment time, improved cosmesis, and reduced cost as compared with standard WBI. A number of methods of PBI exist: at the time of surgery using photons or electrons (IORT); external beam radiotherapy (EBRT) with electrons, conventional beam approaches or intensity-modulated radiotherapy (IMRT) techniques; brachytherapy using low dose rate (LDR), pulsed dose rate (PDR), and high dose rate (HDR) isotopes delivered using single catheter or multiple catheter implants (Stewart et al., 2010).

The role of PBI has been investigated in large-scale prospective phase 3 clinical trials (Table 2) (Livi et al., 2015; Strnad et al., 2016; Coles et al., 2017; Vaidya et al., 2014; Veronesi et al., 2013). Notably, the pivotal trials exploring PBI did not include young (≤40 years) patients (five phase 3 trials, 8478 patients), since preliminary data on boost studies (*see paragraph 3.3*) showed that younger patients largely benefit from a higher total dose to the tumor bed (more difficult to achieve when using IORT in single fraction).

Main recommendations published by the European (ESTRO) (Polgár et al., 2010) and the American Society for Radiotherapy and Oncology (ASTRO) (Correa et al., 2017) apply a specific age cut-off for defining the patients who are suitable for PBI: specifically, PBI is recommended only in patients older than 50 years.

Overall, more robust data (all ages) as delivery techniques for PBI exist in favor of brachytherapy (Strnad et al., 2016), accelerated and normo-fractionated EBRT (Livi et al., 2015; Coles et al., 2017). Conversely, IORT data are more conflicting. The ELIOT trial showed a higher local recurrence risk (hazard ratio of 9.3) for IORT as compared to WBI at a median follow-up of 5.8 years, and the non-inferiority could not be demonstrated (Veronesi et al., 2013). Moreover, the TARGIT-A trial was flawed by several selection biases and was published at short follow-up time (less than 3 years) (Vaidya et al., 2014). These data on the different available techniques should be strongly considered by the physicians when the PBI technical approach is chosen, especially in the case of younger patients.

Indeed, the 2016 UK consensus statements on postoperative radiotherapy for breast cancer recommended to consider PBI for patients ≥50 years, low grade, ≤3 cm, estrogen receptor-positive, HER2-negative and node negative using either EBRT or multiple catheter brachytherapy (Postoperative radiotherapy for breast cancer: UK consensus statements, 2016). Therefore, PBI do not represent a choice for young patients and should be considered only in the context of prospective clinical trials.

3.3. Tumor bed boost

The rationale for a boost of radiation therapy to the tumor bed in patients undergoing breast-conserving surgery and WBI stems from the evidence that local recurrence occurs mostly at the site of the primary tumor. In fact, between 44% and 90% of local recurrences are located in or near the primary tumor bed (Bartelink et al., 2007; Vaidya et al., 2010).

Five studies randomized 8325 women in a time frame spanning of 10 years to receive or not tumor bed boost after WBI (Table 3) (Romestaing et al., 1997; Teissier et al., 1998; Polgár et al., 2002; Hau et al., 2012; Bartelink et al., 2015). Overall, data obtained from these five trials demonstrated that adding a boost after WBI provided a benefit in terms of reduction in local recurrences, without any significant impact on other oncological outcomes (Kindts et al., 2017). Patients younger than 40 years represented the category of patients who were likely to receive the largest benefit from the boost. On the other hand, the use of boost increased late adverse effects, especially fibrosis (Bartelink et al., 2015).

Two decades have passed since the completion of these studies, and

Table 3
Main published phase 3 trials investigating tumor bed boost after breast conserving surgery.

Trial	Study Period	Study patients, overall (young)	Young patients, %	RT technique, Study design	OS rates	LR rates	Subgroup analysis in young women
EORTC (Bartelink et al., 2015)	1989-1996	5318 (449)^	8.4% (≤40 years) 33% (≤50 years)	EBRT; LDR brachytherapy^ WBI vs WBI + boost	At 20 years: 61.1% (WBI) vs 59.7% (WBI + boost); p = 0.33	At 10 years: 13% (WBI) vs 9% (WBI + boost); p < 0.0001	Yes
Lyon (Romestaing et al., 1997)	1986-1992	1024 (127)	12.4% (≤40 years)	EBRT^ WBI vs WBI + boost	At 5 years: 90.4% (WBI) vs 92.9% (WBI + boost); p = 0.24	At 3.3 years: 4.5% (WBI) vs 3.6% (WBI + boost); p = 0.44	No
Nice (Teissier et al., 1998)	1987-1994	664 (NR)	NR	EBRT^ WBI vs WBI + boost	NR	At 6 years: 6.8% (WBI) vs 4.3% (WBI + boost); p = NR	No
Budapest (Polgár et al., 2002)	1995-1998	207 (NR)	NR	EBRT; HDR brachytherapy^ WBI vs WBI + boost	NR	At 5 years: 5.1% (WBI) vs 7.3% (WBI + boost); p = 0.049	No
SWG (Hau et al., 2012)	1996-NR	674 (NR)	NR	EBRT^ WBI vs WBI + boost	NR	At 8.5 years: 2% (WBI) vs 4.4% (WBI + boost); p = NR	No

RT, radiotherapy; OS, overall survival; LR, local relapse; WBI, whole breast irradiation; EBRT, external beam radiotherapy; fr, fraction; LDR, low-dose rate brachytherapy; HDR, high-dose rate brachytherapy; NR, not reported;
^ Tumor bed boost techniques.
^ aged less than 40 years.

overall recurrence rates have decreased over time. The effective impact but higher toxicity of the radiation boost on local recurrences should be evaluated together with the improvements in systemic therapies, diagnostic imaging, and surgical techniques (Canavan et al., 2014). As young age has been demonstrated to be a risk factor for local recurrence, a dose escalation trial named "Young boost trial" (NCT00212121) has been conducted to investigate the efficacy and safety of the radiation boost in patients < 51 years. The study has recently completed the accrual of more than 2400 patients randomized to receive a boost dose of 26 Gy vs 16 Gy; results are expected to become available in 2020.

3.4. Regional node irradiation

The routine application of full regional node irradiation (RNI) after axillary lymph node dissection is still not proven; in addition, internal mammary chain irradiation may potentially increase injury risks to the heart. However, two phase 3 trials show significant improvement in favor of RNI in terms of 10-year disease-free survival (Whelan et al., 2015; Poortmans et al., 2015), and one large prospective population-based study showed a significant benefit in terms of 8-year overall survival (Thorsen et al., 2016) (Table 4).

Concerning young patients, no subgroup analyses were available in the two phase 3 trials (Whelan et al., 2015; Poortmans et al., 2015). In the NCIC MA.20 study, no data about the number of patients aged less than 40–50 was given (Whelan et al., 2015); the median age was 53 years (range 26–84) in the control arm and 54 years (range 29–84) in the RNI arm. Overall, RNI treated patients experienced significantly higher rate of pneumonitis and lymphedema Grade 2 or greater.

In the EORTC 22922/10925 trial, median age was 54 years both for RNI (range 19–75 years) and control (range 22–75 years) arms (Poortmans et al., 2015). While no specific data in young patients was reported, treatment effect according to menopausal status was reported: among premenopausal patients, 236/817 disease-free survival events occurred in the RNI arm versus 255/823 in the control arm (HR 0.92, 95%CI 0.77–1.10); 140/817 deaths occurred in the RNI arm versus 155/823 in the control arm (HR 0.90, 95%CI 0.71–1.13).

Conversely, the national prospective Danish study reported subgroup analyses based on patients' age and menopausal status (Thorsen et al., 2016). Overall 77 patients were aged less than 35 years (2% in both the internal mammary nodes [IMN] and control arms), 854 were aged between 35 and 49 years (28% in the IMN arm vs. 27% in the control arm); globally, 1261 women were premenopausal (41% in both the IMN and control arms). In the 8-year analysis, patients aged less than 35 years in the IMN irradiation arm experienced better overall survival rates (75.7% vs. 72.3%; HR 0.70, 95% CI 0.31–1.61). Premenopausal patients in the IMN arm also showed improved survival rates (79.3% vs. 74.8%; HR 0.71, 95% CI 0.57-0.90). Age younger than 35 years (HR 1.94, 95% CI 1.27–2.99; p = 0.02) and premenopausal status (HR 1.30, 95% CI 1.03–1.64; p = 0.03) were associated with a high hazard of distance recurrence.

However, these trials did not have selected surgical clearance, adequate and homogenous radiotherapy quality assurance protocols (regional nodal irradiated volumes significantly differed among trials) (Whelan et al., 2015; Poortmans et al., 2015). Younger age undoubtedly seems to represent a patient-related high-risk feature but is not sufficient by itself to recommend RNI.

The above-mentioned results, combined with a progressively more limited axillary surgical clearance, should be judiciously integrated in the RNI delivery decision-making process for the selection of high-risk patients, including young breast cancer patients.

Table 4
Major prospective studies investigating RNI.

Trial	Study Period	Study patients, overall (young)	Young patients, %	RT Technique, Study design	OS rates	DFS rates	Subgroup analysis in young women
NCI Clinical Trial Group MA.20 (Whelan et al., 2015)	2000-2007	1832 (NR)	NR	RNI vs control arm	At 10 years: 82.8% (RNI) vs 81.8% (control); p = 0.38	At 10 years: 82% (RNI) vs 77% (control); p = 0.01	No
EORTC 22922/10925 (Poortmans et al., 2015)	1996-2004	4004 (1640)*	41% (premenopausal)	RNI vs control arm	At 10 years: 82.3% (RNI) vs 80.7% (control); p = 0.06	At 10 years: 72.1% (RNI) vs 69.1% (control); p = 0.04	No
DBCG (Thorsen et al., 2016)	2003-2007	3089 (77)°	2.5% (< 35 years) 27.6% (35-49 years) 40.8% (premenopausal)	RNI vs control arm	At 8 years: 75.9% (IMNI) vs 72.2% (control); p = 0.005	At 8 years: 72.6% (RNI) vs 70.3% (control)^; p = 0.07	Yes

RT, radiotherapy; OS, overall survival; DFS; disease-free survival; NR, not reported; RNI, regional node irradiation.
° less than 35 years.
* premenopausal status.
^ distant metastases-free survival rates.

Table 5
Major prospective randomized trials including radiotherapy for DCIS patients.

Trial	Study Period	Study patients, overall (young)	Young patients, %	RT Technique, Study design	OS rates	LR rates	Subgroup analysis in young women
NSABP B-17 (Fisher et al., 1998)	1985-1990	790 (263)	33.3% (< 50 years)	EBRT 50 Gy (2 Gy/fr) BCS vs BCS + RT	At 5 years: 99.6% (BCS) vs 99.9% (BCS + RT); p = 0.2	At 5 years: 5.1% (BCS) vs 2.1% (BCS + RT) ; p < 0.001	No
NSABP B-24 (Fisher et al., 1999)	1991-1994	1798 (602)	33.5% (< 50 years)	EBRT 50 Gy (2 Gy/fr) BCS + RT vs BCS + RT + ET	At 5 years: 98.8% (BCS + RT) vs 98.9% (BCS + RT + ET); p = 0.94	At 5 years: 9.3% (BCS + RT) vs 6% (BCS + RT + ET) ; p = 0.04	Yes
EORTC10,853 (Breast Cancer Cooperative Group et al., 2006)	1986-1996	1010 (65)	6.4% (< 40 years)	EBRT 50 Gy (2 Gy/fr) BCS vs BCS + RT	At 10 years: 95% (BCS) vs 95% (BCS + RT); p = 0.53	At 10 years: 26% (BCS) vs 15% (BCS + RT); p < 0.0001	Yes
SweDCIS (Emdin et al., 2006)	1987-1999	1067 (252)	23.6% (< 50 years)	EBRT 48-54 Gy (2-2.4 Gy/fr) BCS vs BCS + RT	At 5 years: 98.3% (BCS) vs 98.3% (BCS + RT); p = 0.97	At 5 years: 22% (BCS) vs 7% (BCS + RT); p < 0.0001	Yes
UK/ANZ DCIS (Houghton et al., 2003)	1990-1998	1030 (7)	0.7% (< 40 years)	EBRT 50 Gy (2 Gy/fr) 2 × 2 design (BCS ± RT ± ET)	At 4 years: 98.2% (no RT arm) vs 96.2 (RT arms)	At 4 years: 14% (no RT arm) vs 6% (RT arms); p < 0.0001	No
RTOG 9804 (McCormick et al., 2015)	1999-2006	585 (115)	19.7% (< 50 years)	EBRT 50-50.4 (1.8-2 Gy/fr) or 42.5 Gy (2.7 Gy/fr) BCS vs BCS + RT	At 5 years: 97.5% (BCS) vs 96.7% (BCS + RT); p = 0.18	At 5 years: 3.5% (BCS) vs 0.4% (BCS + RT); p < 0.001	No

RT, radiotherapy; OS, overall survival; LR, local relapse; EBRT, external-beam radiotherapy; fr, fraction; BCS, breast conservative surgery; ET, endocrine therapy.

4. Special issues in radiation therapy

4.1. Ductal carcinoma in situ

Major prospective phase 3 trials investigating the benefit of adjuvant radiation therapy after breast-conserving surgery for DCIS are summarized in Table 5 (Fisher et al., 1998, 1999; Houghton et al., 2003; Breast Cancer Cooperative Group et al., 2006; Emdin et al., 2006; McCormick et al., 2015).

The combined analysis of the B17 and B24 National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized trials confirmed that radiation therapy reduced the rate of invasive local recurrences after breast-conserving surgery (Wapnir et al., 2011). At the 15-year update, the EORTC 10,853 trial showed that almost one out of three non-irradiated women developed a local recurrence after local excision (Breast Cancer Cooperative Group et al., 2006); radiation therapy reduced this risk by a factor of 2. Use of adjuvant radiation therapy was also supported by the 20-year follow-up update of the SweDCIS trial; however, the modest protection against invasive recurrences still call for the need to find the groups of patients for whom radiation therapy could be avoided (Wärnberg et al., 2014).

Subgroup analysis focused on the role of radiation therapy after breast-conserving surgery for DCIS in young patients were performed in three prospective trials (Fisher et al., 1999; Breast Cancer Cooperative Group et al., 2006; Wärnberg et al., 2014). The NSABP-B24 trial showed an improved outcome in terms of local relapse in favor of patients aged more than 50 years old (HR 0.43; 95% CI 0.31–0.59) (Fisher et al., 1999). In the EORTC 10,853 study, the rate of local recurrence at 10 years was 43% and 23% in young women who underwent breast-conserving surgery alone or followed by radiation therapy, respectively (Breast Cancer Cooperative Group et al., 2006). In the multivariate analysis, age ≤40 was significantly related to risk of local recurrences (10-year local relapse rate: 34%; p = 0.026) (Breast Cancer Cooperative Group et al., 2006). After a median follow-up of approximately 10 years, the SweDCIS trial demonstrated a benefit for the use of radiation therapy that was modest in patients < 50 years (absolute risk reduction of 6%) but substantial (absolute risk reduction of 18%) in older women (Holmberg et al., 2008). These findings suggest that younger women may have a low protective effect of conventional radiation therapy at sector resection.

Even if strongly debated (Postoperative radiotherapy for breast cancer: UK consensus statements, 2016; Smith et al., 2018), conventional fractionation (schedules using 1.8–2.2 Gy per fraction) is still the most adopted radiation therapy regimen for DCIS. The role of tumor bed boost and adjuvant endocrine therapy remains unclear and they are not considered standard of care in the postoperative setting.

The ongoing Trans-Tasman Radiation Oncology Group (TROG) 07.01 trial (NCT00470236) aims to evaluate time to local recurrence in all-age women with DCIS treated with breast conserving surgery followed by WBI alone versus WBI plus tumor bed boost (radiotherapy using the standard fractionation schedule versus the shorter schedule).

Careful multidisciplinary evaluation is recommended in case of the presence of multiple adverse prognostic factors including final surgical margins less than 2 mm as well as premenopausal status. Nevertheless, omission of postoperative radiotherapy should be avoided in young patients since a simple and reliable prognostic score is still lacking. Therefore, existing evidence support the use of postoperative radiation therapy after breast-conserving surgery for most of young patients affected by DCIS.

4.2. Radiation therapy-induced toxicity

A main priority of radiation therapy is to maintain coverage of the target tissues and reduce the radiation dose to adjacent organs-at-risk. Current constraints related to normal tissue dose and volume are based on conventional fractionation (1.8–2 Gy per fraction) and 3D planning,

which might not be appropriate when using altered fractionation and other radiation therapy techniques. Toxicity may develop in any organ at risk that was exposed to radiation. Two major concerns when treating young patients are discussed below.

The risk of cardiovascular disease after radiation therapy for breast cancer is well reported and appears to result from direct exposure to radiations of heart and coronary vessels. Cardiac dose increases mainly in left-sided disease, mostly when the internal mammary nodes are targeted (Darby et al., 2010; Gagliardi et al., 2010; Boekel et al., 2016). The incidence of radiation-associated cardiovascular disease is relatively low (< 2%), ranging from 0.2% to 3.5% depending on whether the patient had prior cardiovascular risk factors (Darby et al., 2013). The risk of cardiac toxicity increases over time, therefore, this toxicity should be considered of particular concern in younger patients who have a life-long to develop cardiac disease (Darby et al., 2013, 2005). Various respiratory gated (breath-hold) radiation techniques were reported to reduce the cardiac dose by 26% to 80% compared to free-breathing in left-sided radiation for breast cancer (Latty et al., 2019). Hence, these methods should be preferred in young patients.

Breast cancer survivors have higher incidence of secondary non-breast cancer compared to the general population (23% increased risk for irradiated patients) (Grantzau and Overgaard, 2016). A systematic review investigating this issue reported that the risk in irradiated patients increases over time and the standardized incidence ratio (incidence of cancer in irradiated patients versus the incidence in the general population) at > 15 years after radiation therapy was 1.91 for lung cancer, 2.71 for esophagus cancer, 3.15 for thyroid cancer and 6.54 for secondary sarcomas (mainly angiosarcomas). Increased risk was seen in all age group, with the highest risk among women who are younger than 40 years at the time of treatment (Grantzau and Overgaard, 2016; Deutsch et al., 2003). Actions to reduce the risk of secondary cancers may include education for smoking cessation and actions to reduce the occurrence of lymphedema. Major efforts need to be taken when planning treatment in order to minimize toxicity and improve the therapeutic index.

Notably, most published data from pivotal trials did not take into account the fast development of radiation-related toxicity prevention strategies, such as deep inspiration breath hold, active breathing control systems, refined approaches (i.e. stereotactic body radiotherapy, volumetric modulated arc therapy, IMRT), and dedicated facilities (i.e. CyberKnife®, Tomotherapy®, GammaKnife®) able to deliver high-gradient dose radiation.

5. Future perspectives

Current research in breast radiotherapy is surprisingly diverse: tailored radiotherapy according to molecular breast cancer subtypes and gene signatures, hypofractionated radiotherapy, PBI, cardio-sparing treatments, quality of life and the use of proton beam treatments are some examples.

The potentially practice-changing research efforts currently ongoing are summarized in Table 6: the minimum age for inclusion is highlighted to draw attention to the trials in which young patients can be recruited.

One of the most important actual research directions is the investigation of pre-operative radiotherapy (Lightowlers et al., 2017). In parallel to the rise of neo-adjuvant chemotherapy, shifting radiation therapy to the pre-operative setting offers several advantages in comparison to its use in the adjuvant setting. The ability to evaluate the efficacy of breast radiation therapy directly on the tumor by measuring the residual cancer burden at the time of surgery is a unique method to test innovative radiotherapeutic approaches, such as extreme hypofractionation techniques or combinations with targeted therapy. As an example, the ABLATIVE trial (NCT02316561) is investigating the use of single fraction stereotactic body radiotherapy (SBRT) in low risk breast cancer (Charaghvandi et al., 2017). The primary endpoint of the trial is pathological complete response at the time of surgery that is planned more than 6 months after SBRT. However, it should be noted that inclusion criteria for this trial is limited to patients above 50 years of age, which is a consequence of the current lacking evidence on the use of PBI in young patients.

PARP-inhibitors and immunotherapy proved to be successful in the treatment of patients with advanced breast cancer and are now under development in the neo-adjuvant setting (Poggio et al., 2018; Wein et al., 2018). Publication of groundbreaking pre-clinical work on the impact of fractionation and radiation dose mechanisms with the combination of radiation therapy and immunotherapy paved the road to ongoing and future clinical trials investigating these promising combinations (Vanpouille-Box et al., 2017; Ye and Formenti, 2018). Enhancing the abscopal effect might not only be beneficial in the metastatic setting but possibly also in the early setting by eradicating micrometastases (Jatoi et al., 2018).

Lastly, pre-operative radiotherapy provides the opportunity to avoid irradiation of a reconstructed breast. As an example, the PRADA trial (NCT02771938) is evaluating the use of pre-operative radiotherapy followed by mastectomy and DIEP (deep inferior epigastric perforators) flap reconstruction. Other ongoing trials are investigating complication rate and cosmetic outcome of radiotherapy after reconstruction, an issue of great importance particularly for young patients.

6. Conclusions

The present overview on the current state of the art in radiation therapy for young women with early breast cancer highlights the lack of *ad hoc* subgroup analysis in most of the available trials to investigate the role of the different techniques in this specific patient population. Particularly, PBI has not been adequately studied in this setting, while most of the available data in young patients focused on RNI, DCIS, and tumor bed radiation boost

Based on this review, we developed an evidence-based algorithm with recommendations on radiation therapy for young patients with early breast cancer (Fig. 1). Young women affected by invasive breast cancer seem to receive the greatest benefit from the boost on the tumor bed. Most young patients affected by DCIS should receive postoperative WBI. When RNI is considered, young age should be accounted as high risk factor. PBI is not suitable for young patients and should be recommended within the context of a clinical trial. Importantly, robust data have already supported the efficacy and safety of HF-WBI schedules that should now replace SF-WBI as gold standard for all patients irrespectively of their age. Finally, organs-at-risk sparing systems as strategy for prevention of radiation-related long-term toxicities should be strongly considered for these patients.

An important final conclusion to be highlighted is the lack of inclusion of young patients in several published trials as well as in some of the ongoing ones. Therefore, robust evidence to counsel young breast cancer patients on the optimal radiation therapy approach is still lacking. Further studies and *ad hoc* subgroup analyses in this specific patient population are strongly warranted.

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Conflicts of interest

Matteo Lambertini served as a consultant for Teva and received honoraria from Theramex outside the submitted work. All remaining authors declare no conflicts of interest.

Table 6
A selection of ongoing trials in breast radiotherapy.

Trial identification	Trial name	Type of study	Study Hypothesis	Minimal age for inclusion	Number of treatment fractions of the experimental arm
Preoperative RT					
NCT02316561	ABLATIVE	Non-randomized	Investigate the feasibility of a preoperative, single dose, ablative APBI treatment in patients with early-stage BC	50	1
NCT02806258	NEOAPBI 01	Phase II, randomized	Primary chemotherapy versus primary chemotherapy and sequential APBI	18	8
NCT02913729	PAPBI-2	Phase III, randomized	Preoperative versus postoperative APBI	51	5
NCT02941835	PROBI	Phase I/II, non-randomized	Preoperative whole breast RT	18	21
NCT03520894	ROCK	Phase II	RT in preoperative setting with CyberKnife® for BC	50	1
Combination with targeted therapy (immunotherapy or PARP inhibitors)					
NCT03366844	/		Assessment of the safety and tolerability of pembrolizumab combined with a tumor RT boost before standard treatment (one or more of the following: breast-conserving surgery, RT to the entire breast/chest wall after surgery, and chemotherapy)	18	3 (boost only)
NCT03109080	RadioPARP	Phase I	Preoperative or postoperative RT with concurrent olaparib	18	25
Radiation and breast reconstruction					
NCT02927912	/	Phase II, single group	Investigation of the side effects of intraoperative electron beam RT as a boost in stage I-II BC patients who undergo reconstruction	18	1 (boost)
NCT03523078	/	Observational	Cosmetic outcome, patient-reported outcomes, and reconstruction-related complications in BC women treated with or without postmastectomy RT	20	unspecified
Planned	DBCG RT Recon Trial	Randomized	Immediate versus delayed breast reconstruction in early BC patients treated with mastectomy and adjuvant loco-regional RT	18	15
NCT03422003	FABREC	Randomized	Hypofractionated RT versus conventional RT in women who have undergone mastectomy and immediate breast reconstruction	18	16
NCT02771938	PRADA	Non-randomized	Preoperative radiation therapy: mastectomy and DIEP flap reconstruction 2-6 weeks following completion	18	15
Postoperative hypofractionated RT					
NCT02384733	SKAGEN		Investigate the difference in late RT morbidity between hypofractionated and normofractionated loco-regional breast RT	18	15
Proton beam radiation					
NCT02783690	/	Interventional, randomized	15 fraction vs. 25 fraction pencil beam scanning proton RT after mastectomy in patients requiring RNI	18	15

APBI, accelerated partial breast irradiation; BC, breast cancer; RNI, regional node irradiation; RT, radiotherapy; DIEP, deep inferior epigastric perforators.

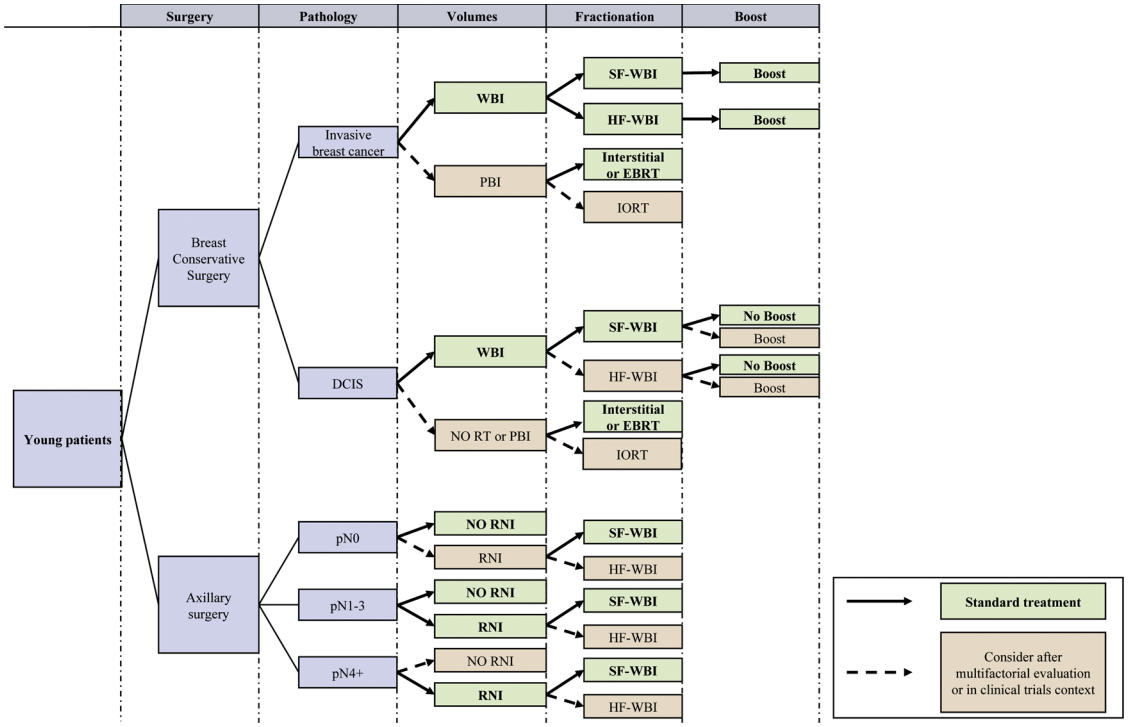

Fig. 1. Evidence-based algorithm with recommendations on radiation therapy for young patients with early breast cancer.
Abbreviations: WBIwhole breast irradiation; PBIpartial breast irradiation; SFstandard fractionated; HFhypofractionated; IORTintraoperative radiotherapy; EBRT; external beam radiotherapy; RTradiotherapy; RNIregional node irradiation regional node irradiation; DCISductal carcinoma in situ.

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References

Aalders, K.C., Postma, E.L., Strobbe, L.J., van der Heiden-van der Loo, M., Sonke, G.S., Boersma, L.J., et al., 2016. Contemporary locoregional recurrence rates in young patients with early-stage breast Cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 34 (June (18)), 2107–2114.

Agarwal, S., Kidwell, K.M., Farberg, A., Kozlow, J.H., Chung, K.C., Momoh, A.O., 2015. Immediate reconstruction of the radiated breast: recent trends contrary to traditional standards. Ann. Surg. Oncol. 22 (August (8)), 2551–2559.

Albornoz, C.R., Matros, E., Lee, C.N., Hudis, C.A., Pusic, A.L., Elkin, E., et al., 2015. Bilateral Mastectomy versus Breast-Conserving Surgery for Early-Stage Breast Cancer: The Role of Breast Reconstruction. Plast. Reconstr. Surg. 135 (June (6)), 1518–1526.

Azim, H.A., Partridge, A.H., 2014. Biology of breast cancer in young women. Breast Cancer Res. BCR 16 (4), 427.

Azim Jr, H.A., Bellettini, G., Liptrott, S.J., Armeni, M.E., Dell'Acqua, V., Torti, F., et al., 2010. Breastfeeding in breast cancer survivors: pattern, behaviour and effect on breast cancer outcome. Breast Edinb. Scotl. 19 (December (6)), 527–531.

Bartelink, H., Horiot, J.-C., Poortmans, P.M., Struikmans, H., Van den Bogaert, W., Fourquet, A., et al., 2007. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol Off J Am Soc Clin Oncol. 25 (August (22)), 3259–3265.

Bartelink, H., Maingon, P., Poortmans, P., Weltens, C., Fourquet, A., Jager, J., et al., 2015. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 16 (January (1)), 47–56.

Bekelman, J.E., Sylwestrzak, G., Barron, J., Liu, J., Epstein, A.J., Freedman, G., et al., 2014. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008-2013. JAMA 312 (December (23)), 2542–2550.

Boekel, N.B., Schaapveld, M., Gietema, J.A., Russell, N.S., Poortmans, P., Theuws, J.C.M., et al., 2016. Cardiovascular disease risk in a large, population-based cohort of breast Cancer survivors. Int. J. Radiat. Oncol. Biol. Phys. 94 (April (5)), 1061–1072.

Breast Cancer Cooperative Group, E.O.R.T.C., EORTC Radiotherapy Group, Bijker, N., Meijnen, P., Peterse, J.L., Bogaerts, J., et al., 2006. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853–a study by the EORTC Breast Cancer cooperative Group and EORTC Radiotherapy Group. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 24 (July (21)), 3381–3387.

Burwell, S.R., Case, L.D., Kaelin, C., Avis, N.E., 2006. Sexual problems in younger women after breast cancer surgery. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 24 (June (18)), 2815–2821.

Canavan, J., Truong, P.T., Smith, S.L., Lu, L., Lesperance, M., Olivotto, I.A., 2014. Local recurrence in women with stage I breast cancer: declining rates over time in a large, population-based cohort. Int. J. Radiat. Oncol. Biol. Phys. 88 (January (1)), 80–86.

Cardoso, F., Loibl, S., Pagani, O., Graziottin, A., Panizza, P., Martincich, L., et al., 2012. The European Society of Breast Cancer specialists recommendations for the management of young women with breast cancer. Eur. J. Cancer Oxf. Engl. 1990 48 (December (18)), 3355–3377.

Charaghvandi, R.K., van Asselen, B., Philippens, M.E.P., Verkooijen, H.M., van Gils, C.H., van Diest, P.J., et al., 2017. Redefining radiotherapy for early-stage breast cancer with single dose ablative treatment: a study protocol. BMC Cancer 17 (1), 181.

Coles, C.E., Griffin, C.L., Kirby, A.M., Titley, J., Agrawal, R.K., Alhasso, A., et al., 2017. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet Lond. Engl. 390 (September (10099)), 1048–1060.

Condorelli, M., Lambertini, M., Del Mastro, L., Boccardo, F., Demeestere, I., Bober, S.L., 2019. Fertility, sexuality and cancer in young adult women. Curr. Opin. Oncol. 31. https://doi.org/10.1097/CCO.0000000000000540. [Epub ahead of print].

Correa, C., Harris, E.E., Leonardi, M.C., Smith, B.D., Taghian, A.G., Thompson, A.M., et al., 2017. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. Pract. Radiat. Oncol. 7 (April (2)), 73–79.

Cosmetic Plastic Surgery Statistics, 2017. Cosmetic Plastic Surgery Statistics. Available at:. . https://www.plasticsurgery.org/documents/News/Statistics/2017/plastic-surgery-statistics-report-2017.pdf.

Darby, S.C., McGale, P., Taylor, C.W., Peto, R., 2005. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol. 6 (August (8)), 557–565.

Darby, S.C., Cutter, D.J., Boerma, M., Constine, L.S., Fajardo, L.F., Kodama, K., et al., 2010. Radiation-related heart disease: current knowledge and future prospects. Int. J. Radiat. Oncol. Biol. Phys. 76 (March (3)), 656–665.

Darby, S.C., Ewertz, M., McGale, P., Bennet, A.M., Blom-Goldman, U., Brønnum, D., et al., 2013. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N. Engl. J. Med. 368 (March (11)), 987–998.

Deutsch, M., Land, S.R., Begovic, M., Wieand, H.S., Wolmark, N., Fisher, B., 2003. The incidence of lung carcinoma after surgery for breast carcinoma with and without postoperative radiotherapy. Results of National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials B-04 and B-06. Cancer 98 (October (7)), 1362–1368.

Dizon, D.S., Suzin, D., McIlvenna, S., 2014. Sexual health as a survivorship issue for

female cancer survivors. Oncologist 19 (February (2)), 202–210.
Emdin, S.O., Granstrand, B., Ringberg, A., Sandelin, K., Arnesson, L.-G., Nordgren, H., et al., 2006. SweDCIS: radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncol. Stockh. Swed. 45 (5), 536–543.
Evans, D.G., Wisely, J., Clancy, T., Lalloo, F., Wilson, M., Johnson, R., et al., 2015. Longer term effects of the Angelina Jolie effect: increased risk-reducing mastectomy rates in BRCA carriers and other high-risk women. Breast Cancer Res. BCR 25 (November (17)), 143.
Fidler, M.M., Gupta, S., Soerjomataram, I., Ferlay, J., Steliarova-Foucher, E., Bray, F., 2017. Cancer incidence and mortality among young adults aged 20-39 years worldwide in 2012: a population-based study. Lancet Oncol. 18 (Dec (12)), 1579–1589.
Fisher, C.M., Rabinovitch, R., 2014. Frontiers in radiotherapy for early-stage invasive breast cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 32 (September (26)), 2894–2901.
Fisher, B., Bauer, M., Margolese, R., Poisson, R., Pilch, Y., Redmond, C., et al., 1985. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N. Engl. J. Med. 312 (March (11)), 665–673.
Fisher, B., Dignam, J., Wolmark, N., Mamounas, E., Costantino, J., Poller, W., et al., 1998. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 16 (February (2)), 441–452.
Fisher, B., Dignam, J., Wolmark, N., Wickerham, D.L., Fisher, E.R., Mamounas, E., et al., 1999. Tamoxifen in treatment of intraductal breast cancer: national Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet Lond. Engl. 353 (June (9169)), 1993–2000.
Gagliardi, G., Constine, L.S., Moiseenko, V., Correa, C., Pierce, L.J., Allen, A.M., et al., 2010. Radiation dose-volume effects in the heart. Int. J. Radiat. Oncol. Biol. Phys. 76 (March (3 Suppl.)), S77–85.
Grantzau, T., Overgaard, J., 2016. Risk of second non-breast cancer among patients treated with and without postoperative radiotherapy for primary breast cancer: a systematic review and meta-analysis of population-based studies including 522,739 patients. Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol. 121 (3), 402–413.
Hau, E., Browne, L.H., Khanna, S., Cail, S., Cert, G., Chin, Y., et al., 2012. Radiotherapy breast boost with reduced whole-breast dose is associated with improved cosmesis: the results of a comprehensive assessment from the St. George and Wollongong randomized breast boost trial. Int. J. Radiat. Oncol. Biol. Phys. 82 (February (2)), 682–689.
Haviland, J.S., Owen, J.R., Dewar, J.A., Agrawal, R.K., Barrett, J., Barrett-Lee, P.J., et al., 2013. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 14 (October (11)), 1086–1094.
Hickey, B.E., James, M.L., Lehman, M., Hider, P.N., Jeffery, M., Francis, D.P., et al., 2016. Fraction size in radiation therapy for breast conservation in early breast cancer. Cochrane Database Syst. Rev. 18 (July (7)), CD003860.
Holmberg, L., Garmo, H., Granstrand, B., Ringberg, A., Arnesson, L.-G., Sandelin, K., et al., 2008. Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 26 (March (8)), 1247–1252.
Houghton, J., George, W.D., Cuzick, J., Duggan, C., Fentiman, I.S., Spittle, M., et al., 2003. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet Lond. Engl. 362 (July (9378)), 95–102.
Howard-Anderson, J., Ganz, P.A., Bower, J.E., Stanton, A.L., 2012. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. J. Natl. Cancer Inst. 104 (March (5)), 386–405.
Jatoi, I., Benson, J.R., Kunkler, I., 2018. Hypothesis: can the abscopal effect explain the impact of adjuvant radiotherapy on breast cancer mortality? NPJ Breast Cancer 4, 8.
Kan, Z., Ding, Y., Kim, J., Jung, H.H., Chung, W., Lal, S., et al., 2018. Multi-omics profiling of younger Asian breast cancers reveals distinctive molecular signatures. Nat. Commun. 9 (April (1)), 1725.
Kindts, I., Laenen, A., Depuydt, T., Weltens, C., 2017. Tumour bed boost radiotherapy for women after breast-conserving surgery. Cochrane Database Syst. Rev. 11 (November) CD011987.
Krug, D., Baumann, R., Budach, W., Dunst, J., Feyer, P., Fietkau, R., et al., 2017. Current controversies in radiotherapy for breast cancer. Radiat. Oncol. Lond. Engl. 12 (January (1)), 25.
Kummerow, K.L., Du, L., Penson, D.F., Shyr, Y., Hooks, M.A., 2015. Nationwide trends in mastectomy for early-stage breast cancer. JAMA Surg. 150 (January (1)), 9–16.
Lambertini, M., Pinto, A.C., Ameye, L., Jongen, L., Del Mastro, L., Puglisi, F., et al., 2016. The prognostic performance of Adjuvant! Online and Nottingham Prognostic Index in young breast cancer patients. Br. J. Cancer 115 (December (12)), 1471–1478.
Lambertini, M., Kroman, N., Ameye, L., Cordoba, O., Pinto, A., Benedetti, G., et al., 2018. Long-term safety of pregnancy following breast cancer according to estrogen receptor status. J. Natl. Cancer Inst. 110 (April (4)), 426–429.
Latty, D., Stuart, K.E., Wang, W., Ahern, V., 2015. Review of deep inspiration breath-hold techniques for the treatment of breast cancer. J. Med. Radiat. Sci. 62 (March (1)), 74–81.
Lightowlers, S.V., Boersma, L.J., Fourquet, A., Kirova, Y.M., Offersen, B.V., Poortmans, P., et al., 2017. Preoperative breast radiation therapy: indications and perspectives. Eur. J. Cancer Oxf. Engl. 1990 82, 184–192.
Livi, L., Meattini, I., Marrazzo, L., Simontacchi, G., Pallotta, S., Saieva, C., et al., 2015. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur. J. Cancer Oxf. Engl. 1990 51 (March (4)), 451–463.
McCormick, B., Winter, K., Hudis, C., Kuerer, H.M., Rakovitch, E., Smith, B.L., et al., 2015. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 33 (March (7)), 709–715.
Owen, J.R., Ashton, A., Bliss, J.M., Homewood, J., Harper, C., Hanson, J., et al., 2006. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol. 7 (June (6)), 467–471.
Paluch-Shimon, S., Cardoso, F., Sessa, C., Balmana, J., Cardoso, M.J., Gilbert, F., et al., 2016. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 27 (September (Suppl. 5)), v103–10.
Paluch-Shimon, S., Pagani, O., Partridge, A.H., Abulkhair, O., Cardoso, M.-J., Dent, R.A., et al., 2017. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast Edinb. Scotl. 35 (October), 203–217.
Partridge, A.H., Hughes, M.E., Warner, E.T., Ottesen, R.A., Wong, Y.-N., Edge, S.B., et al., 2016. Subtype-dependent relationship between young age at diagnosis and breast Cancer survival. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 34 (September (27)), 3308–3314.
Poggio, F., Bruzzone, M., Ceppi, M., Conte, B., Martel, S., Maurer, C., et al., 2018. Single-agent PARP inhibitors for the treatment of patients with BRCA-mutated HER2-negative metastatic breast cancer: a systematic review and meta-analysis. ESMO Open 3 (4), e000361.
Polgár, C., Fodor, J., Orosz, Z., Major, T., Takácsi-Nagy, Z., Mangel, L.C., et al., 2002. Electron and high-dose-rate brachytherapy boost in the conservative treatment of stage I-II breast cancer first results of the randomized Budapest boost trial. Strahlenther. Onkol. Organ Dtsch. Rontgengesellschaft Al. 178 (November (11)), 615–623.
Polgár, C., Van Limbergen, E., Pötter, R., Kovács, G., Polo, A., Lyczek, J., et al., 2010. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol. 94 (March (3)), 264–273.
Poortmans, P.M., Collette, S., Kirkove, C., Van Limbergen, E., Budach, V., Struikmans, H., et al., 2015. Internal mammary and medial supraclavicular irradiation in breast Cancer. N. Engl. J. Med. 373 (July (4)), 317–327.
Postoperative radiotherapy for breast cancer: UK consensus statements, 2016. Postoperative Radiotherapy for Breast Cancer: UK Consensus Statements. Available at:. The Royal College of Radiologists, London. www.rcr.ac.uk/system/files/publication/field_publication_files/bfco2016_breast-consensus-guidelines.pdf.
Romestaing, P., Lehingue, Y., Carrie, C., Coquard, R., Montbarbon, X., Ardiet, J.M., et al., 1997. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 15 (March (3)), 963–968.
Rosenberg, S.M., Newman, L.A., Partridge, A.H., 2015. Breast Cancer in young women: rare disease or public health problem? JAMA Oncol. (October (7)), 877–878.
Smith, B.D., Bellon, J.R., Blitzblau, R., Freedman, G., Haffty, B., Hahn, C., et al., 2018. Radiation therapy for the whole breast: executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract. Radiat. Oncol. 8 (June (3)), 145–152.
START Trialists' Group, Bentzen, S.M., Agrawal, R.K., Aird, E.G.A., Barrett, J.M., Barrett-Lee, P.J., et al., 2008a. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 9 (April (4)), 331–341.
START Trialists' Group, Bentzen, S.M., Agrawal, R.K., Aird, E.G.A., Barrett, J.M., Barrett-Lee, P.J., et al., 2008b. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Lond. Engl. 371 (March (9618)), 1098–1107.
Stewart, A.J., Khan, A.J., Devlin, P.M., 2010. Partial breast irradiation: a review of techniques and indications. Br. J. Radiol. 83 (May (989)), 369–378.
Strnad, V., Ott, O.J., Hildebrandt, G., Kauer-Dorner, D., Knauerhase, H., Major, T., et al., 2016. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet Lond. Engl. 387 (January (10015)), 229–238.
Teissier, E., Héry, M., Ramaioli, A., Lagrange, A.J., Courdi, A., Bensadoun, R.J., Chauvel, P., 1998. Intérêt du complément d'irradiation du lit tumoral dans le traitement conservateur: résultats à 6 ans d'un essai randomisé. Cancer/Radiothérapie 2 (5), 484.
Thorsen, L.B.J., Offersen, B.V., Danø, H., Berg, M., Jensen, I., Pedersen, A.N., et al., 2016. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast Cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 34 (February (4)), 314–320.
Timmerman, R.D., 2008. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. Semin. Radiat. Oncol. 18 (October (4)), 215–222.
Tuttle, T.M., Habermann, E.B., Grund, E.H., Morris, T.J., Virnig, B.A., 2007. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 25 (November (33)), 5203–5209.
Tuttle, T.M., Jarosek, S., Habermann, E.B., Arrington, A., Abraham, A., Morris, T.J., et al., 2009. Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 27 (March (9)), 1362–1367.

Vaidya, J.S., Joseph, D.J., Tobias, J.S., Bulsara, M., Wenz, F., Saunders, C., et al., 2010. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet Lond. Engl. 376 (July (9735)), 91–102.

Vaidya, J.S., Wenz, F., Bulsara, M., Tobias, J.S., Joseph, D.J., Keshtgar, M., et al., 2014. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet Lond. Engl. 383 (February (9917)), 603–613.

Vanpouille-Box, C., Alard, A., Aryankalayil, M.J., Sarfraz, Y., Diamond, J.M., Schneider, R.J., et al., 2017. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat. Commun. 9 (June (8)), 15618.

Veronesi, U., Saccozzi, R., Del Vecchio, M., Banfi, A., Clemente, C., De Lena, M., et al., 1981. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N. Engl. J. Med. 305 (July (1)), 6–11.

Veronesi, U., Orecchia, R., Maisonneuve, P., Viale, G., Rotmensz, N., Sangalli, C., et al., 2013. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 14 (December (13)), 1269–1277.

Wapnir, I.L., Dignam, J.J., Fisher, B., Mamounas, E.P., Anderson, S.J., Julian, T.B., et al., 2011. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J. Natl. Cancer Inst. 103 (March (6)), 478–488.

Wärnberg, F., Garmo, H., Emdin, S., Hedberg, V., Adwall, L., Sandelin, K., et al., 2014. Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 years follow-up in the randomized SweDCIS Trial. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 32 (November (32)), 3613–3618.

Wein, L., Luen, S.J., Savas, P., Salgado, R., Loi, S., 2018. Checkpoint blockade in the treatment of breast cancer: current status and future directions. Br. J. Cancer 119 (July (1)), 4–11.

Whelan, T.J., Pignol, J.-P., Levine, M.N., Julian, J.A., MacKenzie, R., Parpia, S., et al., 2010. Long-term results of hypofractionated radiation therapy for breast cancer. N. Engl. J. Med. 362 (February (6)), 513–520.

Whelan, T.J., Olivotto, I.A., Parulekar, W.R., Ackerman, I., Chua, B.H., Nabid, A., et al., 2015. Regional Nodal Irradiation in Early-Stage Breast Cancer. N. Engl. J. Med. 373 (July (4)), 307–316.

Ye, J.C., Formenti, S.C., 2018. Integration of radiation and immunotherapy in breast cancer - treatment implications. Breast Edinb. Scotl. 38 (April), 66–74.