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Preoperative radiotherapy: A paradigm shift in the treatment of breast cancer? A review of literature

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ABSTRACT

The standard of care for early-stage breast cancer (BC) consists of breast-conserving surgery followed by postoperative irradiation. Recently, the concept of changing the usual sequence of treatment components in BC RT has been investigated. Potential advantages of preoperative RT in BC include a possible tumor downstaging with improved surgical cosmetic outcomes, accurate tumor site identification and better target volume delineation. Furthermore, preoperative RT could serve as a tool for treatment stratification for de-escalation of treatments in the event of pathological complete response. The present literature review analyzed the available clinical data regarding the potential impact of preoperative RT. Overall, available clinical evidence of preoperative RT in BC remains limited, deriving mostly from retrospective case series. Nevertheless, the experiences prove the feasibility of the preoperative RT approach and confirm the efficacy in almost all analyzed studies, including experiences using higher prescription RT doses or RT in combination with systemic therapy.

1. Introduction

The standard of care for early-stage breast cancer (BC) consists of breast conserving surgery followed by postoperative whole breast irradiation. Radiotherapy (RT) significantly reduces ipsilateral breast recurrences and BC-specific mortality in this setting (Darby et al., 2011; Corradini et al., 2014). An example is shown in Fig. 1. Recently, the concept of changing the usual sequence of treatment components in BC has been successfully applied: neoadjuvant chemotherapy has for example been proposed in cases of locally advanced BC, with the aim to achieve higher rates of pathological response, resulting in increased rates of breast preservation or to predict chemosensitivity of BC (Mauri et al., 2005). More recently, the hypothesis to anticipate RT before surgery, has been considered intriguing and of increasing interest. However, the concept of preoperative RT itself is not really new, as it has already been used in inflammatory breast cancer since the 1980s (Bristol et al., 2008). Potential advantages of preoperative RT in BC include accurate tumor site identification and better target volume delineation, as well as a possible tumor down-staging with increased rates of breast-conserving surgery (BCS). In addition, improved surgical cosmetic outcomes or reduced reconstruction complications are expected in patients who require breast reconstruction after mastectomy, by avoiding the irradiation of the tissue expander, implants or autologous tissue flaps (Pazos et al., 2017). Moreover, a preoperative RT strategy could overcome the possible technical treatment planning challenges after reconstructive surgery (Kaidar-Person et al., 2019, 2017; Ho et al., 2014). Preoperative RT might also increase the rates of total pathological complete response (pCR, nodal and primary), which could possibly represent a further step towards precision medicine, giving the opportunity to tailor BC RT to each patient and risk-stratify

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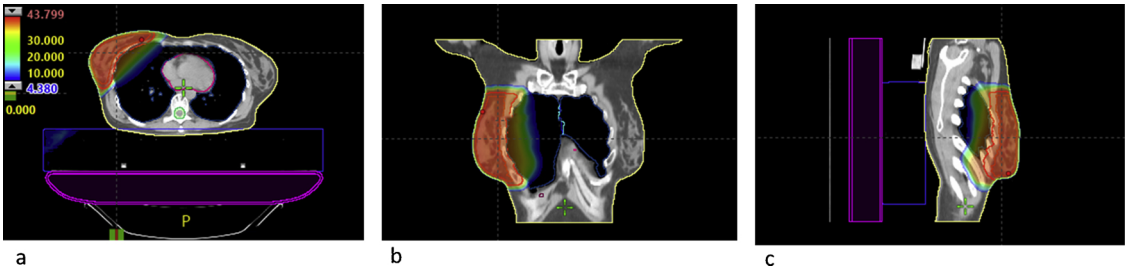

Fig. 1. a, b, c : Example for breast irradiation using a hypofractionated schedule (40.5 Gy/15 fractions) in early breast cancer. A: axial, b: coronal c: sagittal views.

for receipt of adjuvant therapies. If RT would be applied prior to surgery, RT could serve as a tool for treatment stratification, which could even be used as a predictive factor for de-escalation of treatments in the event of pathological complete response (Poleszczuk et al., 2017; Lightowlers et al., 2017; Palta et al., 2012). Increased utilization of hypofractionation and accelerated partial breast irradiation (APBI) has ushered in a new era of breast RT (Pazos et al., 2018), potentially alleviating issues, such as delay to planned chemotherapy with prolonged courses of preoperative RT.

The present review aimed to provide an overview on the topic of preoperative RT and to highlight the potential advantages and drawbacks of preoperative RT to evaluate its potential role for a future paradigm shift in the treatment of BC.

2. Methods

We searched MEDLINE/PubMed for articles published in English language. Search terms included (breast cancer[MeSH Terms] OR breast cancer) AND (radiotherapy[MeSH Terms] OR radiotherapy OR radiation OR irradiation) AND (neoadjuvant[MeSH Terms] OR neoadjuvant OR preoperative). We identified potential studies and exported them to an electronic reference management software program (Mendeley Desktop, version 1.19.3) to assess eligibility by first reviewing the title and abstract, and then the full article. A study was included if it reported on cancer-related RT for BC in a preoperative setting. All studies were analyzed for study design, follow-up time, number of patients, inclusion criteria, technique, dose and fractionation of RT, time interval to surgery, pathological complete response (pCR) rates, oncologic outcome and late toxicity. Pathological CR rates were reported whether they refer to lymph nodes, the primary tumor, or both, if this information was available. If this information was missing, it was referred to as “not specified, NS”.

3. Rationale for preoperative radiotherapy in breast cancer

Postoperative RT may lead to unfavorable outcomes concerning late-side effects and cosmesis. To overcome this issue, some clinical studies were conducted in order to investigate the benefits of RT in the preoperative setting (Horton et al., 2015; Nestle-Krämling et al., 2016). In comparison, the advantages of neoadjuvant chemotherapy for BC have already been demonstrated in large randomized trials (van Mackelenbergh et al., 2017; Hurvitz et al., 2018; Chen et al., 2018; Gillon et al., 2017; Charfare et al., 2005; Asselain et al., 2018). Preoperative RT may be applicable not only for patients with large or inoperable breast cancer, but also in the setting of early-stage BC (Oelssner, 1952; Fukutomi et al., 1992).

In a retrospective study from University of Düsseldorf, neoadjuvant radiochemotherapy achieved a total pCR rate (both in breast and axilla, ypT0 ypN0) of 29.2% and a significantly better 10-year relapse free survival and overall survival compared to adjuvant radiochemotherapy in patients with cT2 tumors (Roth et al., 2010). Furthermore, preoperative irradiation was associated with low grades of fibrosis and a good to excellent long-term cosmetic outcome. Also the overall quality of life (QLQ-C30) was rated “excellent” or “good” in 82% of patients with preoperative RT (Nestle-Krämling et al., 2016). Encouraged by these promising results, the study group is now planning a multicenter prospective trial. To date, prospective multi-center trials about the optimal timing and sequencing of RT and breast surgery are still pending. It is well known, that RT and surgery can both influence the contour, shape and quality of the skin and subcutaneous tissue of the breast, and significantly affect the cosmetic result (Cocquyt et al., 2003; Berbers et al., 2014). Furthermore, it is known from many other tumor entities, like rectal or esophageal cancer, that the most appropriate time interval after RT seems to be 4–6 weeks prior to surgery (Rodel et al., 2012, 2000; Sauer et al., 2004). Early surgery, as well as a time interval longer than 3 months would make surgeons wary of increased post-surgical complications and impaired wound healing (Lefevre et al., 2016). There are concerns about the safety of delaying surgery after RT, because of the potential development of fibrosis, which could increase technical difficulties and surgical complication. Moreover, there are concerns about lengthening the RT-surgery interval, as it would delay the administration of adjuvant systemic therapy and potentially increase the risk of metastasis (Garcia-aguilar et al., 2016).

Although for a different tumor site, the best data for no increased rates of complication rates after delayed surgery following chemoradiotherapy, is the TIMING trial for rectal carcinoma (Garcia-aguilar et al., 2016). This trial looked at concomitant chemoradiotherapy for a total dose of 50.4 Gy / 28 fractions, followed by 0 versus 2 versus 4 versus 6 cycles of additional chemotherapy (mFOLFOX) as bridging prior to surgery. The rationale for bridging the time between RT and surgery with chemotherapy was to prolong the time interval to achieve higher proportions of pCR rates. In this context, it is assumed that chemotherapy will impede wound healing and fibrosis formation, therefore making operative complications less likely if extending the gap to surgery by bridging with chemotherapy. In the TIMING trial, surgery was performed after a time interval of 6–8 weeks after completion of chemoradiation or 3–5 weeks following the additional chemotherapy cycles. Overall, no significant differences in severe complications, or postoperative complications were noted, even if surgery was performed up to 6 months after preoperative RT (Group 4). pCR rates were nearly two times higher than reported in other rectal cancer studies (Garcia-aguilar et al., 2016).

For BC, a similar trial should be conducted to better evaluate the optimal sequencing and timing of preoperative RT, chemotherapy and surgery. It is possible to hypothesize different multimodal treatment scenarios in the preoperative setting:

1) preoperative RT → followed by surgery within 6–8 weeks;

2) preoperative RT → neoadjuvant chemotherapy as bridging → surgery;

3) Neoadjuvant chemotherapy → preoperative RT → surgery;

4) Neoadjuvant chemotherapy → preoperative (chemo)RT → neoadjuvant chemotherapy → surgery

Unfortunately, the misleading term “preoperative radiotherapy” has been used in many studies regarding BC, even if the time interval between RT and breast surgery ranged from 6 months to sometimes several years. In contrast, preoperative RT or chemo-RT followed by

Table 1
Summary of the main advantages/disadvantages regarding preoperative radiotherapy for breast cancer.

ADVANTAGES	DISADVANTAGES
1) Tumor is in situ 2) No delay to local therapy (e.g. due to wound healing after surgery) 3) Easier tumor site identification and better target volume delineation 4) Possible tumor down-staging with increased rates of BCS and improved surgical cosmetic outcomes 5) Increased rates of pCR, even in molecular subtypes that do not respond to NACT 6) Degree of pCR could be used to risk-stratify for receipt of adjuvant therapies 7) Potentially decreased reconstruction complications and technical RT challenges by avoiding tissue expander, implant or autologous flap irradiation 8) Surgery following preoperative RT removes irradiated tissue, allowing for potential re-irradiation in the salvage setting, especially if APBI was used 9) Possible predictive immunohistochemical, molecular and imaging biomarkers for response after preoperative RT	1) Possible delay of NACT if the sequencing "preoperative RT→NACT→surgery" is chosen (potential solutions: hypofractionation, APBI) 2) Possible delay of chemotherapy until after surgery, if the sequencing "preoperative RT→surgery→CT" is chosen 3) Increased risk of complications with delay of surgery after RT, if the sequencing: preoperative RT→NACT→surgery is used

Abbreviations: RT, radiotherapy; BCS; breast conservative surgery; CT, chemotherapy; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; APBI, accelerated partial breast irradiation.

surgery within a time interval of 4–16 weeks, univocally did not detect higher rates of surgical complications and showed a favorable cosmetic outcome with low complication rates (Roth et al., 2010; Mukai et al., 2013; Touboul et al., 1997).

In summary, retrospective and prospective trials emphasize the feasibility of preoperative RT in BC patients. Furthermore, preoperative RT could be related to decreased reconstruction complications by avoiding the tissue expander, implant and flap irradiation issues. Therefore, prospective multicenter verification of preoperative chemotherapy in the non-inflammatory setting is warranted, perhaps even more so in patients who are anticipated to require both, breast reconstruction and radiation therapy. Table 1 summarizes the main advantages and disadvantages regarding preoperative RT for BC.

4. Preoperative whole-breast irradiation

Data on whole-breast RT as the sole RT treatment modality in the neoadjuvant setting are sparse and mostly derive from historical case series. Neoadjuvant RT has been proposed preferably in patients not amenable to breast-conserving surgery. An overview is given in Table 2.

There is one large trial from Sweden, which randomized 960 patients with operable breast cancer to receive surgery consisting of modified radical mastectomy (MRM) alone versus MRM with pre- or postoperative RT. After a mean follow-up of 16 years, no significant difference between patients treated with adjuvant, compared to neoadjuvant RT were found in any of the analyzed endpoints. Unfortunately, no data on treatment response were available from this trial. Calitchi et al. reported on 75 patients with cT2-3 BCE not suitable for breast-conserving surgery treated from 1977 to 1992 (Calitchi et al., 2001). Patients received 45 Gy to the breast and regional lymph nodes. After RT, secondary tumorectomy was successfully performed in 96% of patients, followed by a brachytherapy boost. In 11% of patients a complete tumor regression was found. Only a minority of patients received adjuvant chemotherapy and/or endocrine therapy. After a median follow up of 10 years, the local and distant recurrence rates were 12% and 36%, respectively. Riet et al. treated 187 patients with cT2-4 or cN2 BC from 1970 to 1984 with 45–55 Gy in 18 fractions to the whole breast and regional lymph nodes (Riet et al., 2017). In 10% of patients a total pCR (ypT0 ypN0) was achieved. In contrast, among triple negative patients, the pCR-rate was 26%. In addition to these clinical trial and case series, there are several analyses from population-based databases comparing outcomes between patients treated with adjuvant and neoadjuvant RT (Poleszczuk et al., 2017; Fu et al., 2018). However, the results of these analyses remain contradictory and are severely hampered by the low number of patients treated with neoadjuvant RT, making them highly susceptible to bias.

5. Preoperative whole-breast irradiation combined with neoadjuvant chemotherapy

In most publications, whole-breast RT was used in patients with locally advanced BC in conjunction with neoadjuvant chemotherapy. The primary goal in most cases was to achieve a tumor downstaging and to make patients candidates for breast-conserving surgery. Semiglazov et al. conducted a randomized controlled trial from 1985 to 1990 comparing neoadjuvant chemo-RT to neoadjuvant RT in 271 patients with stage IIb-III BC (Semiglazov et al., 1994). Chemotherapy consisted of thiotepa, methotrexate and 5-FU; pCR (NS) was achieved in 29.1% of patients treated with chemo-RT, compared to 19.4% of patients treated with RT alone. There was a trend towards an improvement in disease-free and overall survival. There are several prospective phase II-trials of concurrent chemo-RT in patients with BC. The chemotherapy agents used for concurrent administration include infusional 5-FU (Skinner et al., 1997), docetaxel/paclitaxel (Brackstone et al., 2017; Chakravarthy et al., 2006; Formenti et al., 2003) and a combination of vinorelbine and 5-FU (Bollet et al., 2012). In summary, pCR-rates ranging from 16% to 34% have been reported using these combinations. Increased acute toxicity in terms of skin desquamation was common. Concurrent chemo-RT with docetaxel resulted in a grade 3 pneumonitis rate of 25%, including one grade 5-event (Brackstone et al., 2017). Adams et al. published a pooled analysis of 3 prospective phase II-trials with concurrent chemo-RT using paclitaxel 30 mg/m2 twice weekly. Overall, pCR (NS) was achieved in 34% of patients. In detail, patients with hormone receptor negative-tumors reached pCR in 54% and patients with hormone receptor-positive tumors in 18% (Adams et al., 2010). Several reports have shown that concurrent chemo-RT is a salvage option in patients with inoperable or progressive disease after neoadjuvant chemotherapy (Bourgier et al., 2012; Coelho et al., 2017; Gaui et al., 2007; Woodward et al., 2017).

A large cohort study on 315 patients with locally advanced, non-inflammatory BC treated with neoadjuvant chemo-RT has been published by a group from the University of Düsseldorf (Roth et al., 2010; Matuschek et al., 2012). Overall, 29.2% of patients were found to have a pCR (both in breast and axilla, ypT0 ypN0) which was however defined as total or near total therapeutic effect according to the classification by (Sataloff et al. (1995)). The incidence of pCR was correlated with a longer time interval between chemo-RT and surgery. Concurrent chemo-RT and pCR were independent predictors for improved overall survival on multivariate analysis (Matuschek et al., 2012). There is one phase II-trial on preoperative RT with concurrent endocrine therapy (Ishitobi et al., 2012). Anastrozole was administered for 24 weeks with RT starting after 12 weeks. 92% of patients had a clinical response; however, no pathologic complete response was observed.

Table 2
Main Studies of preoperative whole-breast irradiation

Author; Year of publication	Inclusion criteria	Number of patients	RT Technique/ total dose /single dose	Chemotherapy Yes/No	Time interval to Surgery	pCR	Outcome /local control/ Survival	Late toxicity
Adams et al. (2010)	Stage IIB-IIIC BC	105 (pooled from 3 trials including Chakravarthy and Formenti)	Breast, Axilla, SCV 45 Gy/1.8 Gy, boost 14 Gy to palpable tumor	Y (paclitaxel)	4 weeks	34% (NS)	5-year LRC 95.2% 5-year DFS 61.4% 5-year OS 71.6%	NR
Alvarado-Miranda et al. (2009)	Stage IIB-IIIB	112	Breast/regional LN 50 Gy/2 Gy, Boost 10 Gy electrons	Y (mitomycin/5-FU or cisplatin/gemcitabine after NACT)	6-8weeks	42% (in breast, ypT0) 58% (in axilla, ypN0) 29.5% (both, ypT0 ypN0)	5-year DFS 76.9% 5-year OS 84.2% Median FU 43 months	22.4% dermatitis grade 3
Bollet et al. (2012)	BC not amenable to BCS	59	Breast 50 Gy/2 Gy, IMN, SCV/ICV 46 Gy/2 Gy, boost optional	Y (vinorelbine + 5-FU)	minimal interval of 6 weeks	27% (in breast, ypT0)	5-year LRC 90% 5-year OS 88%	8% grade 3 (skin) 31% grade 2
Bourgier et al. (2012)	Chemotherapy refractory BC	14	Breast, axilla, SCV/ICV 50 Gy/ 2 Gy, optional boost to 60-70 Gy	Y (Capecitabine/5-FU +/- vinorelbine)	4-8 weeks	2/14 pCR (NS) of 10/ 14 patients undergoing surgery	5-year LRC 76% 5-year DFS 34% 5-year OS 74%	NR
Brackstone et al. (2017)	T3-4 or N2-3 BC	32	45 Gy/1.8 Gy, boost 5.4-9 Gy/ 1.8 Gy target volume not stated	Y (docetaxel)	NR	22.6% (NS)	3-year DFS 81% 3-year OS 89%	NR
Calitchi et al. (2001)	Unifocal BC T2-3	75	Breast, axilla, SCV, IMN 45 Gy/ 1.8 Gy, 20 Gy LDR-brachytherapy boost	N	11% NS	NR	NR	3% lymphedema, 3% fibrosis
Chakravarthy et al. (2006)	Stage IIA-IIIB BC	38	Regional LN 45 Gy/1.8 Gy Breast 46.8 Gy/1.8 Gy	Y (paclitaxel)	3-4 weeks, later amended to 5-7 weeks	34% (NS)	NR	NR
Coelho et al. (2017)	Inoperable BC after NACT	57	Breast, axilla, SCV 50 Gy/2 Gy	Y (8 patients, capecitabine, cisplatinum)	20 weeks (median)	0% of 75.4% of patients undergoing surgery	5-year DFS (surgery) 35.1% 5-year OS (surgery) 36.4%	NR
Colleoni et al. (1998)	T2-4, N0-2 BC	32	Breast, 50 Gy/2 Gy, Boost 10 Gy/ 2 Gy	Y (doxorubicin, cyclophosphamide)	NR	22% overall pathologic remission, 6% complete pCR	NR	CT related
Formenti et al. (2003)	Stage IIB-IIIB BC	44	Breast, Axilla, SCV 45-46 Gy/1.8-2 Gy	Y (paclitaxel)	minimum of 2 weeks after completion or 2 weeks after skin healing	16% pCR (NS)	DFS 75.6% OS 93.9% Median FU 32 months	NR
Gaui et al. (2007)	Stage IIb-III BC refractory to NACT	28	50 Gy/2 Gy, target volume not stated	Y (capecitabine)	6 weeks (median)	4.3% (NS) of 23 patients undergoing surgery	NR	NR
Ishitobi et al. (2012)	BC > 3 cm N0-2, ER + and/or PR +	25	Breast 50 Gy/2 Gy, SCV if clinically node positive	N (anastrozole)	7-8 weeks	0% of 92% objective reponse rate	NR	NR
Lerouge et al. (2004)	Stage IIIa-IIIc (isolated SCV only)	120	Breast/chest wall, SCV/ICV, IMN, axilla, 45 Gy/23 fx (Cobalt 60)	Y (doxorubicin, vincristine, cyclophosphamid, 5-FU)	4 weeks	6.5% complete pCR, 58% overall pathologic response	10-year OS 66.5% 10-year DFS 60%	Lymphedema arm 17% (with axillary LNE), Impaired shoulder movement 6% (BCS)

(*continued on next page*)

Table 2 (*continued*)

Author; Year of publication	Inclusion criteria	Number of patients	RT Technique/ total dose /single dose	Chemotherapy Yes/No	Time interval to Surgery	pCR	Outcome /local control/ Survival	Late toxicity
Matuschek et al. (2012)	locally advanced non-inflammatory BC	315	Breast 50 Gy/2 Gy, 80% SCV, medial tumors including IMN. Boost via preoperative multi-catheter-brachytherapy and hyperthermia or electron boost	Y	NR	29.2% pCR, in both (ypT0 ypN0)	NR	NR
Monrigal et al. (2011)	BC with immediate breast reconstruction	210	50 Gy/2 Gy breast, 10 Gy/2 Gy boost	Y	6-8 weeks	35.2% (NS)	5-year DFS 71.6%/86.4%* 5-year OS 83.5%/91.8%*	26.2% (mainly implant-related)
Paillocher et al. (2016)	BC with immediate breast reconstruction	111	Breast, SCV (74.8%), IMN (35.2%) 50 Gy/2 Gy,	Y	Median 41 days	47.8% (NS)	5-year DFS 93.2% 5-year OS 98.3%	Secondary complications 43.2% (23.4% Shoulder capsulitis, 9% neurogenic pain)
Pazos et al. (2017)	BC with immediate breast reconstruction	22	Breast, SCV (68.2%), IMN (9.1%) 50.4 Gy/1.8 Gy	Y (81.8%)	Median 47 days	55% (NS)	2-year LRFS 95.2% 2-year DFS 79.8% 2-year OS 89.3%	Lymphedema 22.7%
Riet et al. (2017)	T2-4 or N2 BC	187	Breast, axilla, SCV, IMN 45-55 Gy/2.5 Gy	N	≥4 weeks (median 34 days)	10% pCR, in both (ypT0 ypN0)	30-year LRC 89% 30-year DFS 27% 30-year DFS 25%	NR
Roth et al.(2010)	Locally advanced noninflammatory breast cancers Stage IIA–IIIC (LABC)	315	Breast, SCV, IMN 50 Gy/2 Gy, 6- to 10-MV photons in large breasts (51%) versus 60Co in small breasts (49%)	Y (968%: EC, mitoxantrone, AC, CMF)	NR	36.8% in breast (ypT0); 56% in axilla (ypN0); in both (ypT0 ypN0) 29.2%.	10-year RFS 67.96% 10-year OS 68.59%	NR
Rutqvist et al. (1993)	Operable BC	960	Chest wall/breast, IMN, SCV, axilla 45 Gy/1.8 Gy	N	NR	NR	LRR 11% OS 53% Mean FU 16 years	NR
Semiglazov et al. (1994)	Stage IIB-III BC	271	Axilla, SCV/ICV 40 Gy/2 Gy, Breast 60 Gy/2 Gy Cobalt 60	Y (TMF)	3-4 weeks	29.1% (RCT) vs. 19.4% (RT) (NS)	5-year DFS 81% vs. 71.6% (p = n.s.)	NR
Shanta et al. (2008)	Stage IIB-IIIB BC	1117	Breast, regional LN for N2, 40 Gy/2 Gy, Cobalt 60	Y (cyclophosphamide, 5-FU, MTX)	3-6 weeks	45.1% (NS)	10-year OS 63.9% 10-year DFS 52.6%	Seroma 15% Wound infection 5.8%
Skinner et al. (1997)	Stage IIB-IV (N3, isolated SCV only) inoperable BC	30	50 Gy/2 Gy, target volume not stated	Y (5-FU)	4-6 weeks	20% pCR (in both) 26.7% in breast (ypT0)	NR	NR
Skinner et al. (2000)	Stage II B-III	29	Breast/regional LN, 45 Gy/1.8 Gy	Y (paclitaxel)	2 weeks	33% (NS)	NR	41% surgical complications

(*continued on next page*)

Table 2 (*continued*)

Author, Year of publication	Inclusion criteria	Number of patients	RT Technique/ total dose /single dose	Chemotherapy Yes/No	Time interval to Surgery	pCR	Outcome /local control/ Survival	Late toxicity
Touboul et al. (1997)	Stage IIIA-IV (M1 isolated SCV only)	97	Breast/chest wall, SCV/ICV, IMN, axilla, 45 Gy/23 fx, Cobalt 60	Y (doxorubicin, vincristine, cyclophosphamid, 5-FU)	4 weeks	42% (NS) of 64 patients undergoing surgery	5-year LRRR 16% 10-year OS 69% 10-year DFS 61% Median follow-up 93 months	Lymphedema 12.5%; shoulder movement limitation 3.5%
Woodward et al. (2017)	Progression after NACT, unresectable BC after NACT, unresectable recurrence, gross residual disease after surgery	32	50-57 Gy/1.8-2 Gy, boost optional (t0 60-72 Gy), target volume not stated	Y (capecitabine)	NA	NA	1-year LRRFS 65% 1-year OS 54%	NR
Zinzindohoué et al. (2016)	BC requiring mastectomy, RT and CT	84	50 Gy/2 Gy breast, axilla, SCV, IMN	Y	6-8 weeks	36% (NS)	NR	0% reconstruction failure

Abbreviations: BC, breast cancer; LN, lymph node; RT, radiotherapy; RCT, chemoradiotherapy; BCS; breast conservative surgery; ER, oestrogen receptor; PR, progesterone receptor; CT, chemotherapy; NACT, neoadjuvant chemotherapy; IMN, internal mammary nodes; SCV, supraclavicular nodes; ICV, infraclavicular nodes NR, not reported; NA, not applicable; pCR, pathological complete response; LRR, local recurrence rate; OS, overall survival; DFS, disease-free survival; LRC, locoregional control; LRFS, local recurrence-free survival; LRRFS, locoregional recurrence-free survival; NS, not specified.

* patients with secondary mastectomy because of positive margins.

While nowadays, neoadjuvant chemotherapy is typically used to achieve downstaging and for in vivo-chemosensitivity testing for prognostic purposes, several groups have used preoperative instead of postoperative RT in patients planned for breast reconstruction. As mentioned above, reduced reconstruction complications are expected in patients who require breast reconstruction after mastectomy, by avoiding the irradiation of the tissue expander, implants or autologous tissue flaps. It is known from postmastectomy studies, that especially in patients with implant-based reconstruction, postoperative RT is still associated with a significantly increased rate of complications as compared to autologous reconstruction (Jagsi et al., 2017). Moreover, in patients receiving postoperative RT, the optimum timing in implant-based reconstruction remains unclear. Postoperative RT to the tissue expander is correlated to a significantly higher risk of reconstructive failure as compared to the permanent implant (Cordeiro et al., 2015). Nevertheless, the aesthetic results and capsular contracture rates are slightly better for tissue expander RT (Cordeiro et al., 2015). In addition, two-stage expander-implant exchange allows for capsulotomy prior to final implant placement (Peled et al., 2012). Taken together, there might also a potential role for tissue expanders after preoperative RT, to allow for capsulotomy at the time of implant placement. Zinzindohoué et al. conducted a prospective trial with 83 patients receiving neoadjuvant chemotherapy and radiotherapy followed by skin-sparing mastectomy with immediate breast reconstruction, consisting of latissimus dorsi-flap with or without placement of an implant (Zinzindohoué et al., 2016). Primary endpoint was the rate of skin necrosis, which occurred in 6% of patients but was healed within 6 months in all patients. There was one patient with infected hematoma but no case of reconstruction failure. Compared to adjuvant RT, this last tolerability profile is highly satisfactory.

Several other groups have reported on their experience with neoadjuvant chemoradiotherapy followed by breast reconstruction (Pazos et al., 2017; Monrigal et al., 2011; Paillocher et al., 2016). Overall, reconstruction-associated morbidity (rates of infections, permanent implant removal or replacement, cosmesis) seems comparable to patients having adjuvant RT (Ho et al., 2012; Jagsi et al., 2018; Manyam et al., 2018; Ho et al., 2017).

6. Preoperative partial breast irradiation, preoperative stereotactic body radiation therapy (SBRT) and radiosurgery (SRS)

Whole breast irradiation still represents the standard of care after breast conserving surgery for most patients affected by early BC (Darby et al., 2011). Recently, the interest in the development of treatment strategies with partial breast irradiation (PBI) or accelerated partial breast irradiation (APBI) has increased, especially in patients with low-risk tumors (Pazos et al., 2018; Krug et al., 2017; Shaitelman et al., 2012). The rationale for the partial breast approach is based on the fact that most in-breast recurrences are located in close proximity (within a 1–2 cm radius) to the initial tumor site, and that relapse rates outside this area seem to be the same as in the contralateral breast (Pazos et al., 2018). Overall, very different techniques (brachytherapy, intraoperative RT [IORT], external beam RT [EBRT], radiosurgery [SRS], stereotactic RT [SBRT] using various target volume definitions, dose and fractionation schedules) have been evaluated, resulting in conflicting results concerning toxicity and cosmetic outcome (Wenz et al., 2015).

At present, only few studies evaluated the efficacy and effectiveness of preoperative PBI. Among the benefits of preoperative PBI are improved visibility of the primary tumor, resulting in smaller target volumes, higher accuracy, and minimized risk of geographical error. In addition, surgery is performed after preoperative PBI and can therefore remove the area of the breast that received the highest RT dose, possibly leading to limited fibrosis and a good cosmetic result (van der Leij et al., 2015). Overall, the published series report experiences from a small number of cases and a short median follow-up time (range

Table 3
Main studies of preoperative partial breast irradiation and SBRT/SRS.

Author, Year of publication	Inclusion criteria	Number of patients	RT Technique/ dose /fractions	Chemotherapy Yes/ No	Time interval to Surgery	pCR	Outcome/local control/survival	Late toxicity	Follow-up (months)
Bondiau et al. (2013)	Unifocal BC not suitable for BCS, HER2 negative	26	Robotic SBRT/19,5-31.5 Gy/3 fx	Y	4-8 weeks after the last CT	36% (NS)	92% BCS rate 96% ORR	0	30
Horton et al. (2015)	Age $\geq$ 55 years, T1 BC or low-intermediate DCIS ≤ 2 cm, cN0, ER + and/or PR +, HER2-	32	IMRT/15-21 Gy/1 fx	N	within 10 days after RT	NR	Significant increase in MRI post-radiation vascular permeability and decreased cellular density	13 G2; 2 G3	23
Nichols et al. (2017)	Unifocal invasive BC < 3 cm at mammography or MRI, cN0	27	3D CRT /38.5 Gy/10 fx	N	> 21 days after RT	15% (NS)	ORR 88.9%; Ki-67 reduction after RT in 70.4%	PRCO fair and poor in 17% and 5% at 1 year, respectively	43.2
van der Leij et al. (2015)	Age > 60 years, invasive, unifocal BC ≤ 3 cm on MRI, non-lobular, negative SNB	70	3DCRT or IMRT or VMAT/40 Gy/10 fx	N	6 weeks after RT	NR	2 IBTR	70-11% mild-moderate induration at 12 months ; 46-2% mild-moderate fibrosis at 24 months	23
Yaremko et al. (2018)	Postmenopausal status, ductal BC, any grade, unifocal ≤3 cm, ER +, cN0	27	21 Gy/1 fx	N	1 week after RT	NR	all 27 patients are alive and free from recurrence	No significant differences in PRCO and HRQoL at 6 months compared to baseline	16.2

Abbreviations: RT, radiotherapy; BCS; breast conservative surgery; ER, oestrogen receptor; HER2, human epidermal growth receptor factor 2; SBRT, stereotactic body radiotherapy; IMRT, intensity modulated radiotherapy; 3DCRT, three dimensional conformal radiotherapy; VMAT, volumetric modulated arc therapy; CT, chemotherapy; ORR, overall response rate; pCR: pathological complete response; MRI, magnetic resonance imaging; SNB, sentinel bode biopsy; IBTR, ipsilateral breast tumor recurrence; PRCO, patient reported cosmetic outcome; HRQoL, health-related quality of life.

16.2–43.2 months) (Horton et al., 2015; van der Leij et al., 2015; Bondiau et al., 2013; Nichols et al., 2017; Yaremko et al., 2018). Main studies are summarized in Table 3.

Researchers from the Netherlands prospectively evaluated toxicity and cosmetic outcome of preoperative APBI in 70 low-risk patients (van der Leij et al., 2015). Included patients were aged > 60 years with an invasive, unifocal adenocarcinoma of the breast (< 3 cm) and a negative sentinel node. APBI consisted of 40 Gy in 10 daily fractions over 2 weeks. A wide local excision was performed six weeks after RT. After a median follow-up of 23 months (3–44 months), two patients developed a local recurrence. Overall, there were very low complication rates, with limited induration-fibrosis in a small volume and good to excellent cosmetic results (global cosmetic outcome was good to excellent in 77% at 6 months to 100% at 3 years).

Even though preoperative APBI appears to be a feasible and widely available technique with promising results for low risk breast cancer patients, uncertainties remain with regard to tumor delineation, adequate planning target margins, optimal fractionation and timing of surgery (Jagsi et al., 2015; Ohri and Haffty, 2018). Concerning the optimal treatment schedule for APBI, it is known from the long-term results of the UK FAST trial, that postoperative APBI with 28.5 Gy/5 fractions (1 fr/week) whole-breast RT appears to be equivalent to 50 Gy/25 fractions (5 fr/week) in terms of late cosmesis (Brunt et al., 2018; Dragun et al., 2017). Currently, the UK FAST-Forward Trial is testing a 1-week schedule (27 Gy/5 fr or 26 Gy/5 fr) with promising early results regarding toxicity (Brunt et al., 2016). Similarly, postoperative multi-catheter brachytherapy appears to have less late skin toxicity than 50 Gy/25 fractions whole-breast RT (Polgár et al., 2019). In contrast, 38.5 Gy/10 fractions (twice daily) external beam APBI resulted in higher late toxicity than conventional 50 Gy/25 fractions WBRT (Whelan et al., 2018; Vicini et al., 2018; Olivotto et al., 2019). It remains under investigation, which is the most suitable APBI treatment schedule in the preoperative setting.

Preoperative Stereotactic Body Radiation Therapy (SBRT) and radiosurgery (SRS) may represent a novel potential approach in the multimodal management of BC. SRS/SBRT allows a higher dose per fraction to be delivered in one or few fractions, which could improve patient compliance and consume fewer healthcare resources. Two phase I dose-finding SBRT trials were published (Horton et al., 2015; Bondiau et al., 2013). Bondiau et al. conducted a single institution phase I study with the aim of finding the maximum tolerable dose of preoperative SBRT delivered as a boost in locally advanced BC patients receiving neoadjuvant chemotherapy (Bondiau et al., 2013). Preoperative RT was delivered using a robotic SBRT system in 3 fractions on consecutive days to different dose escalation levels: 19.5 Gy (n = 3), 22.5 Gy (n = 3), 25.5 Gy (n = 6), 28.5 Gy (n = 7), and 31.5 Gy (n = 6). Surgery was performed 6–8 weeks after the last chemotherapy cycle followed by conventional postoperative RT (50 Gy/25 fr). Two patients experienced non-dose-limiting grade 2 toxicity, and one grade 3 dermatologic dose-limiting toxicity was reported at dose level 4. A complete pathologic response (pCR) was reported in 9 (36%) of the 25 patients. The pCR rate reached 67% at dose level 3, and 43% and 33% at dose level 4 and 5, respectively.

Researchers from Duke University designed a phase I dose escalation trial of a single-dose preoperative radiation treatment for early stage unifocal BC patients (Horton et al., 2015). Patients were recruited in different dose escalation levels of 15 Gy (n = 8), 18 Gy (n = 8) or 21 Gy (n = 16). No acute dose-limiting grade 3 radiation-related toxicities or wound healing problems were observed. Furthermore, with a median follow-up of 23 months, no evidence of tumor progression was documented.

7. Conclusions and future perspectives

Over the last decades, several approaches have been changed in BC RT based on new established evidences. In terms of surgery, the most

significant step forward was the reduced use of mastectomy, due to the clinical implementation of the breast conservative approach, introducing RT as an essential element for maintaining high local effectiveness. Similarly, systemic therapies have been continuously adapted using new treatment schedules, new chemotherapy combinations, introducing new molecular and targeted therapies. Nevertheless, the real step forward in the treatment of advanced BC was to anticipate drug administration prior to surgery with the aim of tumor shrinkage and to early assess the tumor sensitivity to antineoplastic drugs. In this evolving scenario, the possibility to anticipate RT prior to surgery has been considered object of raised interest, as confirmed by several experiences here reported. In the current literature review the available clinical data regarding the potential impact of preoperative RT in the treatment of BC were analyzed. The hypothetical role of such a preoperative approach in the BC setting could be related to two main reasons: i) from a targeting perspective, in order to accurately identify the local tumor extension compared to the postsurgical bed and ii) to obtain higher rates of pathological complete response (pCR) following neoadjuvant therapies. Probably, this last therapeutic intent could justify the ambitions of clinicians to explore the role of preoperative RT in BC in terms of potentially higher pCR rates compared to standard neoadjuvant systemic treatment. It is well recognized that BC patients who obtain a pCR defined as ypTis ypN0 or ypT0 ypN0 have an improved overall survival. Notably, this association is strongest in aggressive tumor subtypes, such as HER-2 positive or triple-negative BC (TNBC) (Loibl and Gianni, 2017). In detail, in HER2positive/hormone receptor (HR) negative disease, the pCR rates are higher than in HER2 positive/HR positive BC, mostly after the recent adoption of the dual HER2 blockade. Although neoadjuvant therapies should be pursued in case of HER2 positive disease, as well as in high-risk or triple negative BC, this last tumor subtype remains challenging. In fact, pCR rates are generally lower for TNBC as compared to HR negative/HER2 positive disease and the outcome of patients with TNBC who don't achieve pCR is poor. Thus, in order to improve the oncologic outcome in these patients, several approaches to increase the efficacy of neoadjuvant therapies could be investigated, including a hypothetical addition of preoperative RT in selected BC cases (Harbeck and Gluz, 2017). An open question remains whether pCR after chemo-RT remains comparable to chemotherapy alone, with regard to further prognosis and consequences for escalated post-neoadjuvant chemotherapy. In the case of the Her2 positive and TNBC, current studies in patients without pCR after neoadjuvant chemotherapy tested a further escalation of adjuvant target therapy (T-DM1) or adjuvant chemotherapy (KATHERINE (Geyer et al., 2019) and CREATE-X Trial (Masuda et al., 2017)). This last study (Whelan et al., 2018) raises the question whether we can give capecitabine with preoperative RT, and then adjuvant chemotherapy after surgery. Another exciting question is whether neoadjuvant chemoradiation, especially in triple negative BC, with adjuvant immunotherapy (PD-1 / PD-L1 antibodies) could have a similar effect on PFS and OS improvement as in the PACIFIC (NSCLC) trial (Antonia et al., 2018).

Breast cancer RT has recently been in the midst of several changes, not only in regard to new technologies utilized for a safer and more accurate breast irradiation. The original concept of breast RT itself has been re-thought in terms of doses and volumes and resulted in the introduction of hypofractionation and (A)PBI. Analyzing the available literature, we tried to assess concrete results of preoperative RT to evaluate its translation into daily applicability outside of clinical trials. Obviously, there is a need to distinguish between early BC and locally advanced disease, as well as between different approaches that varied from whole breast irradiation to partial breast RT, and from standard fractionation to extreme hypofractionated schedules adopted for SBRT. To date, summarizing the available clinical experiences of preoperative RT in BC, the results remain limited and of low level of evidence, most of them consisting of case series including very few patients. Nevertheless, the presented evidence demonstrate the feasibility of the preoperative RT approach and confirm the efficacy in almost all analyzed studies, including experiences using higher prescription RT doses or RT in combination with several anticancer drugs.

To date, the potential advantages of using RT prior to surgery seem promising, leaving its real impact on BC under investigation. The ongoing studies (https://clinicaltrials.gov/ct2/results?cond=preoperative+radiotherapy+breast+cancer) are mainly focused on the possibility to adopt high doses of irradiation, towards a local ablation of the tumor using stereotactic modalities. In conclusion, results from ongoing trials are awaited to definitively assess the role of preoperative RT in the multidisciplinary treatment of breast cancer patients.

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