Review Article

Role of radiation therapy in triple negative breast cancer: current state and future directions—a narrative review

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Objective: This article is a narrative review of published data regarding locoregional radiotherapy in triple negative breast cancer (TNBC) patients.

Background: Patients with TNBC tend to recur earlier as compared to other subtypes. In addition, TNBC has been associated with distinct features such as young age, aggressive morphological features and worse outcomes that don't always correlate with traditional prognostic features. Moreover, regional and distant recurrences seem to occur more frequently than non-TNBC patients. Locoregional radiotherapy plays an important role in the management of these patients. Current challenges focus on the development of strategies combining locoregional management and systemic treatments. Furthermore manipulation of the immune system with a combination or radio-immunotherapy is being explored in trials to improve outcomes in this subtype which lacks expression of other molecular targets.

Methods: Using medical subject headings (MeSH) terms and text words related to 'breast cancer' 'radiotherapy' 'triple negative', PubMed and Medline (OVID) electronic databases were searched from 2009 till June 2020. Abstracts were reviewed and appropriate full-manuscripts retrieved. This search was complemented by the authors' personal and institutional expertise. We looked into the timing and pattern of recurrences, role of radiotherapy following neoadjuvant chemotherapy and possible immune-radiotherapy combination mechanisms to guide future strategies.

Conclusions: TNBC patients have a distinct recurrence pattern consisting in early recurrences, mainly regional nodal recurrences in the axilla and the supraclavicular region. Postmastectomy radiotherapy (PMRT) is of value in advanced disease, however it could be discussed in early stage disease in a patient presenting with multiple high risk factors of recurrence. Use of radiotherapy (RT) is strongly advocated after neoadjuvant treatments. Radio-immunotherapy should ideally be tested in the oligometastatic setting.

Keywords: Breast cancer; triple negative; radiation therapy; recurrence; outcomes

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Introduction

Triple-negative breast cancer (TNBC) represents 10–20% of all invasive breast cancers (1). It comprises multiple molecular subtypes with limited information currently existing on some of the subtypes. TNBC has been frequently associated with young age, *BRCA1* mutations, aggressive morphological features (tumor necrosis, high mitotic indices, high grade), and worse outcomes that do not always correlate with traditional prognostic features, such as stage, tumor size, or nodal involvement (2,3). Nevertheless, despite a lack of drug-targetable receptors and an overall poorer prognosis, there is an absence of

specific treatment strategies for this tumor subgroup, and hence TNBC is managed with conventional therapeutics, and recommendations for locoregional treatment of TNBC are overall similar to other invasive breast cancer subtypes. As such, this group of patients can pose a challenge in management, particularly because our understanding of this subtype is still in its infancy. Therefore, to improve therapeutic outcomes of TNBC there is a need to understand the underlying biology driving the aggressive behavior in order to adopt more personalized treatment strategies.

Herein, this narrative review focuses on the role of radiation therapy in advanced TNBC. First, the timing and patterns of recurrence in TNBC and how this can affect locoregional treatments will be summarized, followed by the role of radiotherapy according to surgical procedure and post neoadjuvant chemotherapy in this challenging subgroup of breast cancer and finally future directions and novel therapeutic strategies. Biological considerations and their implications on the response to radiation are discussed elsewhere and thus were not discussed in the present article (4). We present the article in accordance with the Narrative Review reporting checklist (available at: https://pcm.amegroups.com/article/view/10.21037/pcm-21-9/rc) (5).

Search strategy and data source

Using medical subject headings (MeSH) terms and text words related to 'breast cancer' 'radiotherapy' 'triple negative', PubMed and Medline (OVID) electronic databases were searched from 2009 till June 2020. Abstracts were reviewed and appropriate full-manuscripts retrieved. This search was complemented by the authors' personal and institutional expertise.

Timing and patterns of recurrence in TNBC

Timing and patterns of recurrences of breast cancer varies between subtypes.

Timing

Recurrences in TNBC occur early after diagnosis, with a median time-to-recurrence ranging between 1.6 to 3 years (1,6,7). The distinct pattern of relapse of TNBC was highlighted by Dent *et al.* in a study of 1601 breast cancer patients of whom 180 were triple negative TN (1). The study suggested that after a median follow-up of 8.1 years, TNBC patients had a higher risk of distant recurrence and death compared to non-TNBC patients with a HR of 2.6 (2.0–3.5) and 3.2 (2.3–4.5) respectively, within 5 years of diagnosis. The risk of distant recurrence peaked at 3 years for TNBC patients then declined rapidly while it was constant for non-TNBC patients. Mean time to local recurrence was shorter for TNBC (2.8 years) than for non-TNBC (4.2 years) however rates of local recurrence were similar in the two groups (13% versus 12%, respectively; P=0.77). Furthermore, Pogoda *et al.* reviewed a cohort of 2,534 patients of whom 228 had TNBC. After a median follow-up of 6 years, 35% of the patients experienced disease recurrence. The risk of developing loco-regional recurrences, brain and/or lung metastases was the highest at 2 years and significantly declined thereafter. The risk of bone and liver metastases peaked at 2–3 years but decreased only slightly, with bone events still seen after five years (8).

Site of locoregional failure

The site of locoregional failure vary between TNBC and Non-TNBC patients. Nodal relapse as opposed to breast/chest wall relapse is more commonly reported in TNBC patients compared to non-TNBC patients (9-11). Wu *et al.* showed in a cohort of 1,088 patients of whom 146 had TNBC, that 80% and 20% of loco-regional recurrences in non-TNBC patients were in the breast/chest wall and regional nodes respectively, while 50% of locoregional recurrences in TNBC patients were nodal (9). Noh *et al.* reported a similar pattern in a cohort of 596 patients with 105 TNBC; breast and chest wall recurrences were more common in non-TNBC patients while nodal recurrences (particularly supraclavicular) were predominantly seen in TNBC (10). similarly, Haffty *et al.* showed that TNBC was associated with worse nodal relapse-free rate and cause-specific survival rate than non-TNBC in a cohort of 482 patients and 117 TNBC (11).

Distant failure incidence and failure sites vary also according to breast cancer subtype. TNBC tend to show distant recurrences more frequently than non-TNBC (1,9,11,12). Steward *et al.* showed in in a review of 414 TNBC patients that 26.6% of the patients experienced a recurrence of their disease after a median follow-up of 68.2 months. Isolated distant recurrence reached 16.9% and mixed distant and local recurrence was seen in another 5% of the cases (12). Dent *et al.* showed that a higher proportion of patients with TNBC experienced distant recurrence compared with patients with non-TNBC (33.9%

Table 1 Reported locoregional recurrence (LRR) and overall survival (OS) after breast conserving therapy (BCT) in triple negative breast cancer patients (TNBC) and non-TNBC

Study	Year	Patients (N)	TNBC patients (N)	Stage	Follow-up (months)	Locoregional recurrence* (%)		P value	Overall survival*		P value
						TNBC	Non-TNBC		TNBC	Non-TNBC	
Haffty *et al.* (11)	2006	482	117	I–III	95	17.0	17.0	NS	80%	89%	NS
Nguyen *et al.* (14)	2008	793	89	I–III	70	7.1	2.0	–	–	–	–
Solin *et al.* (15)	2009	519	90	I–III	47	8.0#	4.0	0.041	84%	88%	0.780
Freedman *et al.* (16)	2009	753	98	I–III	44	3.2	–	0.360	90%	–	0.150

*, values reported at 5 years; #, values reported at 8 years.

versus 20.4%, respectively; P<0.0001) (1). Haffty *et al.* showed also that TNBC patients had statistically lower distant metastasis-free rate (68%) than non-TNBC (11) and Wu *et al.* showed that distant metastasis was the highest in the TNBC patients (27.4%) (9).

Distant failure

The incidence and sites of distant failures in breast cancer also differ according to the phenotype. As compared to other subtypes, TNBC patients tend to have more visceral than bone metastases (6,9,13). Lin *et al.* reported 15.79%, 4.67% and 3.74% loco-regional, visceral and bone relapse respectively after a median follow-up of 3.15 years in 321 TNBC patients (7) Results from a subsequent study including 2,569 TNBC patients (out of 15,204) suggested that TNBC patients experienced more brain, lung and locoregional recurrences and less bone recurrences as first recurrences compared to non-TNBC, with a hazard ratio (HR) of 3.5 (2.1–5.85), 2.17 (1.47–3.21), 1.32 (1.01–1.74) and 0.26 (0.19–0.36) respectively (13). While brain and lung recurrence seem consistently reported in the literature some studies failed to show that bone and liver metastasis varied according to subtype. Noh *et al.* showed that brain recurrences were more frequent in TNBC patients (28.6%) however other metastatic sites were identical between subtypes (10). Wu *et al.* also showed that bone metastasis were comparable between subtypes (9).

Take home message

In summary, the available evidence shows that TNBC patients have a distinct recurrence pattern. They present early recurrences, mainly regional nodal recurrences in the axilla and the supraclavicular region. As a consequence, the use of locoregional irradiation in the treatment management of TNBC should be considered. Moreover, distant recurrences are also of concern compared to non-TNBC. They peak at 2–3 years mainly in the brain and the lung. Afterwards, that risk of recurrence fades while bone recurrence continues to occur even after 5 years. This information should be taken into account in the systemic treatment and follow-up timelines of TNBC patients.

Role of radiotherapy according to surgical procedure

Following the emergence of data regarding the aggressiveness of TNBC and its higher risks of local recurrence, proposing breast conservation for this subtype of patients raised some concerns. However multiple studies looked at the outcomes after breast conservation with adjuvant radiotherapy in TNBC and non-TNBC patients. These studies reported Locoregional recurrence (LRR) and survival outcomes according to subtype. *Table 1* summarizes the data of selected studies reporting only on breast cancer patients managed conservatively. They showed that LRR rates are quite low for this category of patients with the majority showing numbers lower than 10% at five years (14-16). Haffty *et al.* reported higher recurrences at 5 years in the order of 17% in both subtypes of patients (TNBC and Non-TNBC), however the time frame for the study inclusion was very large (11). While Haffty *et al.* and Freedman *et al.* showed no difference in LRR between subtypes, Nguyen *et al.* and Solin *et al.* did show that local recurrences for TNBC represent more than the double of those observed in non-TNBC patients, absolute numbers were however less than 10%. Luckily those results did not

translate into a survival difference. The majority of the studies showed identical overall survival (OS) at 5 years regardless of subtype. Other studies compared the outcomes of TNBC patients treated with either breast conservative treatment (BCT) or mastectomy. Abdulkarim *et al.* reported on 768 TNBC patients treated with BCT, mastectomy or mastectomy and PMRT. After a median follow-up (FU) of 86.4 months they found that LRR for BCT patients was 6% compared to 15% in mastectomy patients (P<0.001) and a HR of 3.44 (2.05–5.8). Overall survival was also in favor of BCT with a value of 87% *vs.* 82% (P<0.001). When looking at T1-2N0 patients only, they reported significantly lower LRR in the BCT group (4% *vs.* 10%, P=0.022), however no difference in OS was noted (17). Studies published by Lowery *et al.* and Zumsteg *et al.* showed identical outcomes for LRR in BCT *vs.* mastectomy while Adkins *et al.* showed significantly lower recurrences in BCT (18-20). In a meta-analysis published by O'Rorke *et al.* in 2016, studies comparing BCT *vs.* Mastectomy alone showed in 1,795 patients an advantage for BCT *vs.* Mastectomy alone with a HR of LRR of 0.61 (0.41–0.9) and an OS advantage for BCT with a HR of 0.56 (0.36–0.88) (21). When considering early stage disease alone (T1-2N0), HR for LRR was still significative with a HR of 0.55 (0.32–0.95), and no difference in OS with a HR of 0.74 (0.43–1.29). These data show that breast conservation with adjuvant radiotherapy is a perfectly acceptable options for TNBC because of the low number of local recurrences and the fact that survival is identical with other subtypes or with Mastectomy alone.

The next question that comes to mind is whether adjuvant radiotherapy could be skipped altogether for some patients. This has been studied for elderly patients notably hormone receptor positive patients. For this category, randomized trials have shown that omission of adjuvant radiotherapy doesn't compromise survival even if local recurrences are slightly higher (22,23). The data regarding this issue in TNBC patients is scarce. Two observational studies were reported; the first study is a SEER registry study published by Eaton *et al.* in 2016, this study analyzed 3,432 elderly patients with negative hormonal receptors and conservatively managed. Cumulative incidence of breast cancer specific death at 5 years for patients who received adjuvant radiotherapy was 10.8% compared to 24.1% for patients where adjuvant radiotherapy was omitted (P<0.0001). Local recurrences were not reported in the study however the need for mastectomy could be a good surrogate for recurrence. This outcome was reported and showed a statistically higher cumulative incidence of subsequent mastectomies at 5 years; 4.9% *vs.* 8.3% when omitting adjuvant radiation (24). The second study specifically looked at not only hormone receptor negative patients but particularly TNBC patients older than 70 years conservatively managed. It was a National Cancer Database review of 8,526 T1-2N0M0 TNBC patients. After a median FU of 38 months, it showed that 5y OS was higher in the group of patients who received adjuvant radiotherapy in the order of 77.2% compared to 55.3% in the surgery alone group (P<0.001). this effect persisted after stratifying for age, stage and chemotherapy use (25).

The final point to discuss is the value of adding radiotherapy after mastectomy compared to mastectomy alone. Little evidence is published regarding this issue. Data from early Danish Trials was published by Kyndi *et al.* (26). They showed that PMRT significantly reduced LRR in TNBC patients (P<0.01), however it didn't improve OS. In fact in that study, PMRT was associated with improved OS in the hormone receptor positive groups only. Abdulkarim *et al.* showed a reduction of LRR with the addition of PMRT in TNBC (15% *vs.* 13%) (17). Wang *et al.* also showed a lower recurrence rate with the addition of PMRT (25.4% *vs.* 11.7%, P=0.02), OS was also in favor of PMRT with 78.7% in the mastectomy alone group *vs.* 90.4% in the PMRT group (P=0.03) (27). On the other hand, a recent analysis of the National Cancer Database published by Haque *et al.* showed that the addition of radiotherapy after mastectomy for TNBC patients with node negative disease (T1-4N0) was not associated with a significant improvement in OS in the whole group (HR of 0.88 and 95% CI: 0.75–1.03). Only T3N0 patients benefited significantly from PMRT in terms of OS (28). This study is limited by its observational nature and the low number of young patients (33% compared to 60% in the wang study), as younger patients may benefit more from PMRT. LRR data are not also available in national cancer database (NCDB) registries.

Take home message

In summary although PMRT could be of value for TNBC patients with advanced disease, no firm data could warrant *systematic* use of radiotherapy after mastectomy in even early stage T1-2N0 patients. This could be proposed to select patients with multiple high risk factors (such as young age or high grade). On the other hand, T3N0 patients may benefit from the addition of PMRT to standard chemotherapy.

Table 2 Locoregional recurrence (LRR) according to breast cancer subtype in the setting of neoadjuvant systemic therapy (NAT)

Author	Year	Patients (N)	TNBC patients (N)	Median follow-up (months)	Type of surgery		LRR (%)	Multivariable Analysis	
					BCT*	Mastectomy		Association of TNBC	Hazard ratio (95% CI)
Werutsky *et al.* (31)	2020	10,075	2,229	67	+	+	9.5	Yes	2.72 (2.23–3.31)
Cho *et al.* (32)	2019	189	54	78		+	8.1	No	–
Chen *et al.* (33)	2018	104	104	64		+	26.5	No	–
Jwa *et al.* (34)	2016	335	61	86	+		11.0	Yes	8.1 (2.5–26.6)
Yang *et al.* (35)	2015	233	57	62		+	8.0	Yes	4.4 NA (P=0.003)
Zhang *et al.* (36)	2015	160	36	28	+	+	8.0	Yes	3.33 (1.04–10.7)
Mamounas *et al.* (37)	2014	11,955	1,157	65	+	+	6.8	No	–
Wright *et al.* (38)	2013	464	149	46		+	5.8	Yes	8.5 (3.48–20.79)
Caudle *et al.* (39)	2012	595	193	64	+		6.2	Yes	5.7 (2.6–12.3)
Meyers *et al.* (40)	2011	149	49	55	+	+	7.0	No	–
Vargo *et al.* (41)	2011	331	76	43	+	+	2.2	No	–

*, breast conserving therapy.

Radiotherapy after neoadjuvant systemic therapy (NAT)

Indications of NAT in breast cancer have been expanding in the last few years. Initially used in larger tumors in order to downsize the tumor for optimal breast conservation, NAT was later used for patients with at least T2N0 breast cancer, Her2+ and TNBC patients with the idea of evaluating the response of the disease to the systemic treatment and optimize adjuvant therapies. This approach however opened discussions to the appropriate use of radiotherapy in these patients and its value. Current guidelines do not specifically address the indications of radiotherapy for specific breast cancer subtypes. In the scope of the current review, namely regarding the management of TNBC, we have reviewed the guidelines and the available data to try to see if the general guidelines apply to TNBC.

The American Society of Breast surgeons published in 2015 guidelines regarding breast cancer patients management after NAT (29). They recommended the systematic use of radiotherapy in the context of breast conservation. After mastectomy, they recommended the use of radiotherapy according to the initial clinico-pathologic stage regardless of the response to NAT. The American Society of Radiation Oncology also published recommendations for guidance on the use of radiotherapy after mastectomy in the setting of NAT. They endorsed the use of postmastectomy radiotherapy (PMRT) for patients who failed to achieve a complete nodal response. However for patients who responded well to NAT, no definite recommendation could be done about withholding PMRT due to the lack of consistent data (30). Further trials are needed to address this particular question.

A paucity of studies have looked at the risk of locoregional recurrence (LRR) according to the breast cancer subtype in the setting of NAT and are summarized in *Table 2*. Reported results suggest that the subgroup of patients with triple negative breast cancer (TNBC) are at a higher risk of LRR that could reach 25% in some studies (33), while the overall LRR rate after NAT is relatively low (range of 2.2% to 11%) (31,32,34-41). The association of TNBC phenotype with LRR is not consistent across all reported studies; TNBC phenotype is reported as an independent predictor of LRR in the majority of available studies, with reported Relative Risks (RR) ranging between 2.72 and 8.5 (31,34-36,38-40). Nevertheless Cho *et al.* and Vargo *et al.* did not find any association between TNBC and LRR (32,41). Other high-risk factors traditionally associated with LRR should be considered in the setting of NAT. These include young age [RR 1.35 (1.16–1.57)] (31), advanced clinical stage cT3T4 [RR 5 (2.5–10.1)] (34), high grade disease [RR ranging between 1.33 and 6.93] (31,36), failure to achieve a pathologic complete remission (pCR) (31,39), clinically positive axillary nodes [RR 1.47 (1.29–1.71)] (31) and failure to achieve a

complete response in the axillary nodes (RR 9.8 for positive residual nodes regardless of their number and 2.9 for more than four residual nodes) (35,39). Chen *et al.*, suggest that residual axillary nodes after NAT is an independent predictor of LRR with a RR of 10.23 (3.19–32.78) for TNBC patients (33).

Take home message

In light of the available evidence, the use of radiotherapy for patients with TNBC in the setting of NAT is strongly advised after BCT and after Mastectomy for patients with residual positive nodes. In the advent of a negative pathological axilla, radiotherapy should be strongly considered especially if other high-risk features are present such as young age (<50 years), high stage or high grade.

Future directions and novel therapeutic strategies

Because of the lack of known therapeutic targets to date, the development of targeted therapies have been challenging in the setting of TNBC. Hence, manipulation of the immune system represents an attractive strategy, particularly given the hypothesis that TNBC is the most immunogenic among breast cancer subtypes (42). The presence of tumor infiltrating lymphocytes (TILs) within the tumors of patients with early invasive TNBC has been associated with improved prognosis (43). Immune checkpoint inhibitors have yielded promising results in both advanced and early-stage disease of TNBC patients and are expected to substantially improve the overall prognosis of TNBC (44). Of particular interest in the clinical management of TNBC would be the use of radiation to augment responses to immunotherapy. Radiation increases mutational load of tumors, optimizes antigen presentation, and may act to decrease immune suppressors in the tumor microenvironment, priming the tumor for immunotherapy (45). This enhances tumor immunogenicity and increases the presence of effector immune cells to the tumor site. The combination of local radiation to primary breast tumor with CTLA-4 blockade and PD-1/PD-L1 blockade has shown synergistic activity in preclinical murine models (46). Radiotherapy, has been characterized as "immunomodulatory" and considered as signaling "danger," through the induction of proinflammatory cytokines which are, capable of generating an *in vivo* vaccination effect (47). Another potential benefit of the association of RT and immunotherapy relates to the considerable evidence suggesting that RT can have inhibitory effects on tumor cells outside of the irradiation field (48).

An appropriate combination of a radiation regimen (dose, fractionation, volume) with an immunotherapy would therefore theoretically be locally and systemically highly effective. Preclinical data have shown maximum RT-immunotherapy interactions with SBRT fractions such as 6–8 Gy delivered in one to three fractions (49). A number of ongoing clinical studies combine RT and immunotherapy in the metastatic setting, in TNBC. All of the studies are early phase and test tolerance of the association, with several testing efficacy in terms of local and distant control, in search of an abscopal effect. The timing of the introduction of immunotherapy with or without immune-stimulatory RT seems to be important, since, the least the tumor burden, the more efficient these treatments are expected to be. Therefore, optimal RT-immunotherapy studies should ideally be designed in the early or oligometastatic setting.

On another hand, preoperative breast radiation therapy (RT) has been used in the past, but older studies failed to change practice. Retrospective studies have demonstrated that RT as a sole preoperative treatment is effective, especially in triple-negative breast cancer with pCR documented in 26% patients (50). More recently; there has been interest in revisiting pre-operative RT using modern techniques and novel RT-drug combinations (51). Multidisciplinary collaboration with medical oncology, surgery and basic and translational research is essential for the eventual success of this approach.

In conclusion, patients with TNBC should be encouraged to participate in clinical trials as many unanswered questions still remain surrounding the management of this aggressive subtype of breast cancer. Future research directions should focus on the combination of immunotherapy and radiation particularly in the setting of oligometastatic and oligoprogressive TNBC.

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