Locoregional treatments for triple-negative breast cancer

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The absence of drug-targetable receptors in triple-negative breast cancer (TNBC) makes the use of targeted systemic therapy inappropriate for this breast cancer subgroup. Although patients with TNBC show sensitivity to some chemotherapy regimens, in early-stage disease greater emphasis is placed on locoregional treatments, based on surgery and radiation therapy (RT). Ongoing improvements in both screening and surgical techniques have reduced the need for radical surgical intervention in all breast cancers, and breast-conserving surgery (BCS) followed by RT is now increasingly common for all tumour types. However, while evidence has clearly established the importance of post-surgical RT for favourable long-term outcomes in breast cancer, it is less well-established as to where and under which conditions more radical surgeries than BCS, such as modified radical mastectomy (MRM), may be indicated for TNBC.

A high proportion of TNBC tumours are BRCA1-mutated and therefore patients with this type of tumour are at a potentially elevated risk of ipsilateral or contralateral recurrence. In addition, while some studies indicate that post-BCS locoregional TNBC relapse rates generally appear similar to other tumour types, some evidence suggests that distant relapse rates may be higher. There is evidence that some subtypes of TNBC may require MRM rather than BCS for optimal long-term outcomes. More research is needed to establish whether TNBC-specific approaches to locoregional treatment may be required.

Key words: locoregional, radiation, surgery, treatment, triple-negative breast cancer

introduction

Locoregional treatments of breast cancer encompass surgical excision of the breast tumour mass by mastectomy or breast-conserving surgery (BCS) and radiation therapy (RT). This article focuses on the utility of locoregional treatments in triple-negative breast cancer (TNBC), a subtype defined by immunohistochemistry (IHC) that lacks expression of estrogen receptors (ERs), progesterone receptors (PRs) and overexpression of human epidermal growth factor-2 (HER2) [1]. Due to the lack of surface markers, there are currently no molecularly targeted therapies approved for TNBC.

incidence of locoregional recurrence in TNBC and related molecular subtypes

TNBC tumour characteristics show considerable, but not complete, overlap with those of basal-like breast cancer; 71%–91% of TNBC tumours have a basal-like phenotype, and 77% of basal-like breast cancers are TNBC [2]. Basal-like breast cancer tumours are one of the five intrinsic breast cancer subtypes defined using DNA microarrays and patterns of gene expression [3]. Voduc et al. [4] used an enhanced immunohistochemical profile in order to relate subtypes defined by IHC and DNA microarray analysis. Their study (N = 2985) described TNBC tumours that were additionally negative for cytokeratin (CK) 5/6 and epidermal growth factor receptor (EGFR) as triple-negative phenotype (TNP)-non-basal. In addition, basal-like tumours were defined by this IHC panel as negative for ERs, PRs, not overexpressing HER2 and CK5/6 or EGFR-positive. This study allowed identification of patients at increased risk of locoregional recurrence, which was most evident for patients following mastectomy. When compared with luminal A tumours, all other subtypes showed a higher locoregional recurrence rate (13%–20% increase; statistically significant in all groups with the exception of TNP-non-basal).

In a study of 1601 patients with breast cancer, Dent et al. [5] compared the clinical features, natural history and outcome for women with TNBC against other breast cancer subtypes. They found that although similar rates of local recurrence were seen for patients with TNBC and those with other subtypes (13% versus 12%, respectively; P = 0.77), patients with TNBC showed a defined pattern of locoregional recurrence. Patients with TNBC were less likely to develop a locoregional recurrence before a distal recurrence, (25% of TNBC patients compared with 44% of women with other breast cancer subtypes; P = 0.02). In addition, a pattern of locoregional recurrence in
patients with TNBC was characterised by a rapidly rising rate in the first 2 years following diagnosis, a peak at 2 to 3 years followed by a decline in recurrence risk over the next 5 years, with a very low risk of recurrence thereafter. Unlike women with other types of breast cancer, the great majority of women with TNBC who had no evidence of progression after 8 years did not have any recurrence thereafter. These findings are confirmed in a study by Wang et al. [6], who conducted a retrospective analysis of 835 node-positive breast cancer patients, including 141 patients with TNBC. After mastectomy, an increased likelihood of locoregional recurrence was seen within the first 3 years after treatment, but not in the following 3 years, when compared with other breast cancer subtypes.

**surgical options in TNBC**

Since the early 1900s, surgical excision of the breast tumour mass has been the core strategy in treating breast cancer, with the exception of advanced inoperable metastatic disease, and comprises simple or radical mastectomy, or BCS (lumpectomy or quadrantectomy) [7–10]. Recent technological advances have led to the introduction of improved screening with a greater likelihood of diagnosis at early stage, and less invasive biopsy procedures. These include the introduction of sentinel lymph node biopsy as an alternative to conventional axillary dissection [11]. In addition, the increase in the use of magnetic resonance imaging (MRI) has led to the development of image-guided biopsy and surgical techniques for lesions only detectable by MRI [12].

These advances have led to the use of less radical surgical procedures, including BCS [13]. BCS has been shown to improve the perception of body image and quality of life in younger patients [14, 15]. However, some patients who opt for BCS subsequently require more intensive counselling owing to an increased fear of disease recurrence [16].

The TNBC tumour type shows considerable overlap with BRCA1-mutated tumours; 75%–85% of women with BRCA1 germline mutation-associated breast cancer are also characterised as having the TNBC subtype [17]. This has implications for the selection of surgical procedures for these tumours. While risk-reduction mastectomy is strongly considered for patients with BRCA1 mutation [9], two recent publications have presented conflicting results when assessing the outcome of patients with TNBC who have both BRCA mutations [18, 19]. In one study, out of 77 patients with TNBC, those with BRCA mutations [n = 15 (19.5%); 15.6% BRCA1 and 3.9% BRCA2] had a significantly better recurrence-free survival (RFS) when compared with patients with a wild-type BRCA gene [hazard ratio (HR) 0.19, 95% confidence interval (CI) 0.045–0.79, P = 0.016] [19]. However, in a cohort of patients with high-risk TNBC (n = 227), 50% (n = 114) of whom tested positive for BRCA1/2 mutations, Bayraktar et al. [18] showed that the overall prognosis for patients with TNBC and BRCA1/2 mutations was not significantly different from patients with wild-type BRCA1/2 within the first 5 years after diagnosis (RFS rates: 74% and 81%, P = 0.21). Further study is needed in order to determine whether surgical practice should be adjusted for patients with TNBC.

**impact of treatment choice on locoregional recurrence in patients with TNBC**

In order to determine whether surgical choice and/or RT has an impact on locoregional recurrence in patients with TNBC, several studies have investigated outcomes following treatments in TNBC compared with the general breast cancer population. The aggressive nature of the TNBC subtype may appear to exclude such patients from treatment with breast-conservation therapy (BCT)—under the assumption that more extensive treatment would be better applied in this case. Parker et al. [20] addressed this by carrying out a retrospective analysis of patients with TNBC, comparing their outcomes based on the surgical approach (BCT versus mastectomy). In this study, out of a total of 220 patients with TNBC, 61 (30%) patients underwent BCT and 141 (70%) patients underwent mastectomy. To determine whether the type of operative therapy had an impact on the outcome for patients with TNBC, overall survival (OS) and disease-free survival (DFS) were compared. The 5-year DFS rates for the BCT and mastectomy groups were 68% and 57%, respectively (P = 0.14). The median DFS was not reached for BCT, and was 79 months for the mastectomy group. The 5-year OS was better for the BCT than for the mastectomy group (89% versus 69%; P = 0.018). The median OS time was not reached in either group. Parker et al. [20] concluded that selected patients with TNBC should be given the opportunity to benefit from the less aggressive BCT. These results corroborated results found in several studies where no significant differences were found in the local control rates between TNBC and the other subtypes when BCT was carried out [21–23]. For example, a comparison of the outcome for 753 breast cancer patients (98 with TNBC) showed that the isolated 5-year locoregional recurrence was not significantly different (ER- or PR-positive: 2.3%; ER- and PR-negative but HER2-positive: 4.6%; and triple-negative: 3.2%) between the three subtype groups [21]. In contrast, other studies have demonstrated that the locoregional recurrence rate after BCT was significantly greater for those patients lacking ER and PR expression compared with other subtypes [4,24–26]. Solin et al. [26] conducted a study of 519 women with breast cancer, 90 with TNBC. After BCT with radiation, women with TNBC showed a higher 8-year rate of any locoregional recurrence (8% versus 4%; P = 0.041) and a lower 8-year rate of freedom from distant metastases (81% versus 92%; P = 0.0066). Although women with TNBC had a higher rate of locoregional recurrence after breast reconstruction with RT, following multivariate analysis, this difference was not statistically significant.

Taken together, these studies highlight the current lack of prospective clinical trials that assess the effect of treatment choice on locoregional recurrence in patients with TNBC. A more accurate identification of the TNBC patients within these studies, with complete follow-up of their progression and...
comparison with patients with non-TNBC, will help optimise locoregional treatment decisions in the future.

**RT in TNBC**

The importance of using post-BCS RT for optimal long-term outcomes has been established for patients with breast cancer [27–29]. Dragan et al. [30] investigated the influence of post-BCS RT on the outcome in patients with TNBC [30]. In this study, 53 patients (69%) received RT, with a median follow-up of 23.2 months. Patients who received RT were significantly more likely to be of a higher American Joint Committee on Cancer (AJCC) stage than patients who did not receive RT ($P < 0.001$). Despite this, the 3-year locoregional RFS probability for patients who received RT was higher than that for those who did not receive RT (79.6% versus 57.9%, $P = 0.049$).

RT for breast cancer has undergone technology-driven advances in recent years. For example, success has been reported using 3-D conformal accelerated partial breast irradiation (3D-APBI) [31], although further studies and follow-up are needed before this and similar approaches are advised outside of clinical trials [7, 9].

**Locoregional post-mastectomy RT in patients with TNBC**

Gabos et al. [32] did not find an increased risk of locoregional recurrence associated with TNBC in patients receiving BCS, but an increased risk was seen in patients who received modified radical mastectomy (MRM) and who had TNBC (HR 4.72, 95% CI 1.53–14.52, $P = 0.0069$) [32]. This indicated a need for further study to determine the risk of locoregional recurrence in patients also receiving post-mastectomy RT (PMRT).

Abdulkarim et al. [33] compared the locoregional recurrence risk following MRM without adjuvant RT with BCS in a population of patients with TNBC and a subgroup of patients with T1-2N0 TNBC. At a median follow-up of 7.2 years, 10% of patients with TNBC developed locoregional recurrence, and MRM without RT represented the only independent prognostic factor associated with increased risk of locoregional recurrence in the T1-2N0 subgroup when compared with BCS (HR 2.53, 95% CI 1.12–5.75, $P = 0.0264$). Other studies have also suggested that some T1-2N0 patients may benefit from MRM plus adjuvant RT [34, 35], which is not recommended in the current guidelines [7–9].

In a study with a longer follow-up, Kyndi et al. [36] reported that for patients with TNBC, PMRT did not significantly impact OS when compared with those patients not receiving PMRT (39% and 32%, respectively, $P = 0.4$). However, this study did show a statistically significant reduction in the probability of locoregional recurrence when patients with TNBC were treated with PMRT compared with those who were not (15% probability of locoregional recurrence with RT compared with 32% without; $P = 0.001$). This study found a decreased effect of PMRT for patients with TNBC when compared with other breast cancer subtypes (ER-positive/PR-positive and the ER-positive/PR-positive/HER2-negative subtype). Taken together, the authors suggested relative radioresistance of the TNBC subtype as a consequence of the ER-negative receptor status. ER expression results in a decrease in cell-cycle duration, reducing the time available for the repair of DNA damage caused by radiation. It was suggested that ER-negative cells as found in TNBC and basal-like breast cancer would thus exhibit radioresistance, as DNA repair is allowed to progress during the slower cell cycle [24, 36].

The impact of locoregional recurrence on OS is of importance to patients with TNBC, and there have been conflicting reports in this area. In contrast to the Kyndi study on PMRT described above, a recent study by Montagna et al. [37] showed that locoregional recurrence was predictive of a higher risk of subsequent events and death, particularly in patients with TNBC. Overall, this conflicting evidence indicates a need for further validation from prospective clinical trials.

**Current guidelines for combined BCS and RT**

Current guidelines recommend the use of BCS + RT when the tumour size is <4 cm and where surgical margins are negative [7–9]. The recommended RT protocol depends upon the extent of surgery (BCS or mastectomy) and lymph node status. However, for patients with a BRCA1/2 mutation, prophylactic bilateral mastectomy may be considered for risk reduction [9], as this patient population may have an increased risk of ipsilateral breast recurrence or contralateral breast cancer following BCS + RT [9].

Neoadjuvant treatment with chemotherapy (described in detail by G. von Minckwitz and M. Martin in this supplement) is used to shrink tumour mass and thus allows patients to be eligible for BCS.

**Effect of systemic treatment on local therapy decisions and locoregional recurrence**

The TNBC subtype has been shown to be sensitive to some systemic therapy treatments [38], although Liedtke et al. [38] described a distinct pattern of early recurrence in patients with TNBC when compared with other breast cancer subtypes following neoadjuvant therapy. Adjuvant and neoadjuvant chemotherapy treatment regimens for TNBC are described by H. Joensuu and J. Gligorov (adjuvant treatment) and G. von Minckwitz and M. Martin (neoadjuvant treatment) in this supplement.

**Role of new molecularly targeted agents in TNBC**

Targeted agents currently being investigated include poly (ADP-ribose) polymerase inhibitors, EGFR inhibitors and anti-angiogenic (e.g. anti-vascular endothelial growth factor/receptor) compounds. The mammalian target of rapamycin (mTOR) is an effector of the phosphoinositide 3-kinase signalling pathway regulated by AKT and the tumour
suppressor phosphatase and tensin (PTEN) homologue. This pathway is aberrant in breast cancer, and loss of PTEN is common in TNBC [26]. Albert et al. [39] investigated the effects of radiation on this signalling pathway in breast cancer cell models. They showed that the mTOR inhibitor RAD001 (everolimus) enhanced the cytotoxic effects of radiation in these cell models by preventing radiation-induced pro-survival AKT/mTOR signalling. Further study is needed to determine how this promising method of radiosensitisation of breast cancer cells could impact the suggested insensitivity of TNBC tumours to RT.

**conclusion**

Despite the unfavourable prognosis associated with TNBC [40], current evidence supports BCS as a viable option for these patients, in line with the general breast cancer population [20, 23]. The surgical and RT treatments described here are supplemented by systemic chemotherapy in the neoadjuvant or adjuvant setting; these are reviewed in more detail in other articles within this supplement. With regard to surgical choices, current guidelines do not recommend treating TNBC patients differently from the general breast cancer population [7–9].

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**references**


