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Review

Surgery and radiation therapy of triple-negative breast cancers: From biology to clinics

Jacques Bernier [a, *], Philip M.P. Poortmans [b]

[a] Department of Radiation Oncology, Swiss Medical Network, Genolier, Geneva, Switzerland
[b] Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands

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ABSTRACT

Triple negative breast cancer refers to tumours lacking the expression of the three most used tumour markers, namely oestrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2). These cancers are known to carry a more dismal prognosis than the other molecular subtypes. Whether a more aggressive local-regional treatment is warranted or not in patients with triple-negative breast cancer is still a matter of debate. Indeed there remain a number of grey zones with respect to the optimization of the extent and the timing of surgery and radiation therapy (RT) in this patient population, also in consideration of the significant heterogeneity in biological behaviour and response to treatment identified for these tumours. The objective of this review is to provide an insight into the biological and clinical behaviour of triple-negative breast cancers and revisit the most recent advances in their management, focussing on local-regional treatments.

Introduction

Molecular profiling is nowadays one of the driving forces in translational and clinical research on heterogeneity of breast cancer. The identification of well-defined distinct subgroups of breast cancers, by categorizing them as luminal A, luminal B, HER2 and basal-like, gave a first clinically useful tool, even being demonstrated later to be an oversimplification of the true heterogeneity of breast cancer [1,2]. Based on this clinically oriented definition, the terminology of triple-negative breast cancer (TNBC) refers to tumours lacking the expression of three common tumour markers, namely oestrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2).

TNBC appears to be more aggressive than the other breast cancer subtypes. It is generally associated with high tumour grade, basal cytokeratins 5/6, p53 overexpression, and BRCA1 mutations [3–8]. TNBC is also often characterized by younger age, a higher probability of "interval" breast cancer (detected in between 2 screenings), and unfavourable traits as cell necrosis and high mitotic indices [9–12]. In terms of treatment outcome, the presence of a triple-negative phenotype is known to affect negatively local-regional recurrence (LRR) rates during the first 3 years following the treatment [4,8,13–18]. In addition, TNBC is also more often associated with distant metastases [3,4,20]. This results in an elevated 5-year death rate compared to other breast cancer subtypes.

With respect to systemic treatment, classifying breast cancer by molecular subtypes is currently considered being the paradigm driving our decision-making processes to select the most appropriate systemic treatment. As for local-regional treatment, the behavioural heterogeneities of TNBC and, over the last decade, the introduction of more effective systemic treatment approaches, also influencing local-regional disease control, undoubtedly accounted for the conflicting results observed after local regional treatment in this patient population.

This review article used search strings on studies addressing the issue of triple negative breast cancer biology, prognosis and treatment (used search terms: breast cancer subtypes; triple-negative breast cancer; breast conserving therapy; mastectomy; surgery; radiotherapy; radiosensitization). It is based on full articles published since 2000 and retrieved from the Pubmed search engine (http://www.ncbi.nlm.nih.gov/pubmed). It will revisit those aspects of the biologic background linked to potential implications on treatment outcome following surgery and RT. A critical appraisal of

* Corresponding author.
E-mail address: jbernier@genolier.net (J. Bernier).

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the results recently published for TNBC will be used to propose guidelines for local-regional treatment.

Results

We reviewed the recent literature data from 4 angles: biological background; treatment outcome in TNBC and non-TNBC patients; treatment outcome in TNBC patients vs. type of surgery; and impact of radiation delivery on treatment outcome in TNBC patients.

a) Biological background

Often used as equally in the oncology community, the basal-like molecular subtype, an entity defined using gene expression analysis, is frequently defined by the absence of ER, PR, and HER2 expression, while it highly expresses HER1, c-Kit, and myoepithelial cytokeratins 5/6, and 17 [21–23].

Around 75% of molecularly defined basal-like breast cancers are triple negative. The other way around, TNBC most frequently represents basal-like tumours, but they also have been shown to characterize "claudin-low" tumours, both having low levels of claudin genes and often an epithelial-mesenchymal transition-like signature [24]. Though assimilated to TNBC, this "claudin-low" subtype is distinct from basal-like cancers [25]. In this review article, TNBC will denote the subtype defined, for clinical purposes, as lack of ER and PR, and the absence of HER2 amplification.

Overall, TNBC accounts for approximately 80% of mammary gland cancers diagnosed in women carrying a BRCA1 germline mutation, whilst about 11–16% of all TNBCs harbour BRCA1 or BRCA2 germline mutations [7]. As for sporadic TNBC, they share with BRCA1 similar defects in biological pathways, such as homologous repair deficiency [2,7,9].

A first question is as to how TNBC biology can impact on local-regional treatment outcome

As for RT, most pre-clinical studies which have investigated the response of TNBC cells to radiation suggest that, in vitro, these cells might be more radio-resistant than those from other subtypes. Chen al. recently reported that ERp29 expression in the triple negative MDA-MB-231 breast cancer cells significantly increased cell survival following ionizing radiation. This is by increasing promoter hypo-methylation of the DNA repair gene, O6-methylguanine DNA-methyl-transferase (MGMT), via a down-regulation of DNA methyl-transferase 1. Knockdown of MGMT in the ERp29-transfected cancer cells was shown to enhance radiosensitivity [26]. It has also been shown that the higher radioresistance experimentally observed for TNBC can derive from the overexpression of HER1 observed at the surface of these cells. As proof of principle, the in-vivo inhibition of the HER1 receptor by lapatinib, a HER1 and HER2 tyrosine kinase inhibitor, increases the response of basal-like cells to radiation [27]. Another study published in 2015 showed that a family of microRNA precursors, mir-27 a is significantly overexpressed in TNBC. A direct target of mir-27 a, DC-27 increases radioresistance of TNBC cells, through mechanisms of downregulation by this family of microRNA precursors [28].

Based on the fact that BRCA-deficient breast cancer and sporadic basal-like or TNBC share many clinical and pathological similarities [29], various pre-clinical studies have explored the mechanisms involved in the higher radioresistance levels previously demonstrated in the laboratory. In 2012, Ibrahim et al. showed that radioresistance levels observed in BRCA-proficient TNBC were reduced when BRCA1/2 expression was impaired by PI3K inhibition, a mechanism known to sensitize the cells to PARP inhibition [30]. In the same way, Yang et al. reported a similar reduction of radioresistance in BRCA-proficient TNBC cells exposed to olaparib, a PARP inhibitor, and to the PI3K inhibitor PI-103 [31].

Although these pre-clinical data suggest that TNBC might be more radioresistant than other sub-types, intrinsic radiosensitivity differences actually exist in the clinical setting for TNBC patients. Comparing transcriptome profiles of 12 locally recurrent TNBCs to 20 non-locally recurrent TNBCs treated with surgery, radiation and chemotherapy, Wushou et al. indeed observed that two gene signatures specifically identified a radiosensitive population that had an improved recurrence-free survival, with statistically significant differences between "radiosensitive" and "radioresistant" patients, both for a seven-gene radiosensitive gene signature (RSGS) (P: 0.024, Hazard Ratio – HR: 0.35) and for a three-gene RSGS (P: 0.035, HR: 0.38) [32].

A second question is as to whether or not treatment outcome after surgery might be influenced by the anatomo-pathological patterns specific to TNBC

After reviewing pathologic specimens from 369 women with invasive breast cancer treated with lumpectomy followed by re-excision, Sioshansi et al. reported that, overall, 32% of patients had invasive cancer in their re-excision specimens. As for patients with TNBC, residual invasive disease was found, on re-excision, in 51% of the cases, compared to about 30% for other sub-types. On multivariate analysis, TNBC subtype was associated with an elevated risk of residual invasive cancer, with an odds ratio of 3.28 (P: 0.002) [33]. By contrast, reviewing 2520 surgical procedures from a prospective database (2000–2012), Garvey et al. reported in 2015 that re-excision surgery was performed for 12% of breast conserving therapy procedures and 2% of mastectomies. In these series, triple-negative disease was not significantly associated with the presence of residual disease at re-excision, whatever the type of surgery [34]. Therefore, no clear evidence exists that TNBC patients express at higher need for re-excision after surgery, independent of the type of surgery.

b) Treatment outcome in TNBC and non-TNBC patients

In terms of local regional disease control, this review stratifies the published results in function of 3 types of datasets: breast conserving treatment (BCT); either BCT or mastectomy; and primary systemic therapy followed by surgery. Results are listed in chronological order.

b.1) Datasets on breast conserving therapy

Table 1 considers treatment outcome after breast conserving therapy, retrieved from 8 retrospective studies in TNBC and non-TNBC patients [13,14,19,35–39]. While 3 studies yielded significantly higher LRR rates in patients diagnosed with TNBC, [13,14,36] 5 reports were unable to elicit any differences between TNBC and non-TNBC patients for this endpoint [19,35,37–39].

b.2) Datasets on either breast conserving therapy or mastectomy

As for the 6 retrospective studies on either breast conserving therapy or mastectomy, in TNBC and non-TNBC patients [4,15,40–43], 3 studies yielded significantly higher local regional relapses in patients diagnosed with TNBC [41–43], while the other 3 reports were unable to elicit any difference for this endpoint between TNBC and non-TNBC patients (Table 2) [4,15,40].

In the meta-analysis performed by Chen et al., reviewing 15 retrospective studies involving 21,645 women, the highest risks for overall recurrence (HR: 3.19, 95% CI: 1.91–5.31) and local failure (HR: 3.31; 1.69–6.45) was observed in the TNBC population [44].