Critical Reviews in Oncology / Hematology 131 (2018) 96–101

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Radiotherapy in triple-negative breast cancer: Current situation and upcoming strategies

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ARTICLE INFO

Keywords:
Triple negative breast cancer
Radiation therapy
Molecular subtypes
Radiosensitization

ABSTRACT

Triple-negative breast cancer (TNBC) (estrogen receptor-negative, progesterone receptor-negative, and HER2-negative) is viewed as an aggressive subgroup of breast cancer. Treating patients with TNBC remains clinically challenging. It's now well established than radiation therapy is able to improve locoregional control in breast cancer patients both after breast conserving surgery or mastectomy, with positive impact in high-risk patients for long-term survival. Biologic characterization of breast tumor different subtypes, in particular the heterogeneous subtype of TNBC could permit to adapt the treatment plan. In the present review, summarizing the molecular types, we describe clinical features and postoperative radiotherapy current situation for TNBC, and we provide new strategies and directions through an adapted radiation therapy.

1. Introduction

Breast cancer is the most common malignancy among women. Triple negative breast cancer (TNBC) is characterized by an absence of the estrogen (ER) and progesterone (PR) receptors, as well as the human epidermal growth factor receptor 2 (HER2/HER neu) and accounts for about 20% of all breast cancer cases. The absence of the three receptors significantly reduces targeted treatment options for patients with TNBC and studies have shown that TNBC and HER-2 over-expression breast cancer have higher local recurrence and distant metastasis rates than other types (Carey et al., 2007; Nguyen et al., 2008). Patients with TNBC usually have worse outcome than those with other types of breast cancer, but are more sensitive to chemotherapy and face more limited treatment options, so in addition to early diagnosis, chemotherapy has become an important treatment (Di et al., 2015).

Despite great progress based on molecular subtyping in the chemotherapy, endocrine therapy and targeted therapy for breast cancer, the value of molecular subtyping in radiotherapy has not been integrated much in clinical practice. Up until today, radiotherapy plays an important role in the treatment of breast cancer (Fisher et al., 1995) (Bartelink et al., 2001). Its main values include: radiotherapy after breast conserving surgery; chest wall or regional lymph node prophylactic irradiation for high-risk patients after mastectomy; radiotherapy for advanced breast cancer patients without surgical indication; radiotherapy for locally recurrent patients; and palliative radiotherapy for distant metastases. It's now well established than radiation therapy is able to improve locoregional control in breast cancer patients with positive impact in high-risk patients for long-term survival. The knowledge that different subtypes of breast cancer can have distinct locoregional patterns of recurrence is consisted in the literature data suggests that the biologic characterization of breast tumor subtype could permit to adapt the treatment plan. In the present review, summarizing the molecular types, we describe clinical features and postoperative radiotherapy current situation for TNBC, and we provide new strategies and directions through an adapted radiation therapy.

2. Evolution of breast cancer molecular subtyping

With the development of genomics, the classification of breast cancer has no longer been limited only to the traditional molecular subtyping that is based on immunohistochemistry, which is now considered a heterogeneous disease containing several independent molecular types that differ significantly in tissue morphology, immune phenotype, biological behavior, treatment response and prognosis. In

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https://doi.org/10.1016/j.critrevonc.2018.09.004
Received 29 August 2017; Received in revised form 30 July 2018; Accepted 5 September 2018
1040-8428/

2000, Perou et al. (Perou et al., 2000) was the first to report the four molecular subtypes of breast cancer by analyzing complementary DNA (cDNA) chips containing 8102 genes, namely luminal subtype, basal-like subtype, HER2 over-expression subtype and normal breast-like subtype. Subsequent studies further divided the luminal subtype into luminal subtype A, luminal subtype B and luminal subtype C. Expression of estrogen receptor (ER) and other related genes is the highest in the luminal subtype A, while low to moderate in the luminal subtypes B and C. In addition, the luminal subtype C also expresses some genes with unknown functions that are coexpressed in basal-like subtype and HER2 over-expression subtype. The luminal C breast cancer, however, was failed to be confirmed in the subsequent studies. So far, five molecular subtypes of breast cancer (luminal subtype A, luminal subtype B, HER2 over-expression subtype, basal-like subtype and normal breast-like subtype) have been established and confirmed in a number of independent studies. It should be pointed out that the presence of normal breast-like subtype is controversial, and some researchers believe that it is an artificial erroneous indication, which may be caused by small tumor content and large normal breast tissue content in the sample studied. After strict control of normal breast tissue content in the sample, this molecular subtype disappears. The 2011 St. Gallen Breast Cancer Consensus'(Goldhirsch et al., 2011) rough correspondance to immunohistochemistry and various molecular subtypes: luminal subtype A [ER and/or PR(+), HER-2(-), Ki-67 low expression (< 14%)], luminal subtype B [classified into HER-2(+) and HER-2(-hHER-2(-):ER and/or PR)(+), HER-2(-), Ki-67 high expression (> 14%); HER-2(+):ER and/or PR(+), HER-2(+), Ki-67 any level), HER-2 over-expression subtype [ER(-), PR(-), HER-2(+)] and tri-negative type [ER(-), PR(-), HER-2(-)]. The prognosis varies markedly by subtype, which is the best for the luminal subtype A, and the worst for the basal-like subtype/tri-negative type.

3. Molecular subtypes and characteristics of TNBC

It has been a broad consensus in recent years that different subtypes of TNBC are a molecular-genetically heterogeneous disease. The development of genetic engineering technology has provided a powerful tool for the molecular subtyping of breast cancer. Based on gene chip technology(Prat et al., 2013), TNBC is classified into: (1) basal-like breast cancer (BLBC), which accounts for about 50%～75% of TNBC; and (2) non-basal-like breast cancer, which includes Claudin-low breast cancer (30%), HER2-enriched breast cancer (9%), Luminal A breast cancer (5%), Luminal B breast cancer (6%) and Normal-like breast cancer (1%). Lehmann et al.(Lehmann et al., 2011) molecularly classified TNBC into six subtypes by gene expression profiling: two basal-like subtypes (BL1 and BL2), immunomodulatory subtype (IM), mesenchymal subtype (M), mesenchymal stem cell subtype (MSL) and luminal androgen receptor subtype (LAR). TNBC subtypes based on gene expression profiles are summarized Fig. 1. In addition, there are also researchers who studied the heterogeneity of TNBC, and classified TNBC into six subtypes: basal-like subtype, BRCA-related subtype, CK and EGFR over-expression subtype, Claudin-low subtype, other pathologic subtype and immune system subtype(Metzger-Filho et al., 2012). Therefore, high heterogeneity of TNBC is a consensus, but subtypes vary by classification method, and there is yet any established subtype classification method.

As can be seen from the above, "triple negativity" is merely the common representation of TNBC's complex heterogeneity, and the clinical, pathological features and prognosis vary by subtype. BL1 subtype highly expresses cell proliferation- and DNA damage-related genes; BL2 subtype highly expresses genes related to growth factors, glycolysis and gluconeogenesis pathways; and IM subtype highly expresses immune response-related genes. M subtype and MSL subtype both present epithelial-mesenchymal transition and stem cell characteristics, the difference between them is that the latter lowly expresses the proliferation- and cell junction-related genes. LAR subtype is ER-negative, but has apparently active hormone-regulated pathway, which highly expresses AR and its downstream targets and coactivators, suggesting that the pathogenesis of LAR breast cancer is associated with AR. Claudin-low, as a new subtype, lowly expresses HER2 gene and luminal epithelium-related genes similar to BLBC. But unlike BLBC, this subtype expresses immune- and mesenchymal-related genes, and lowly expresses cell junction- and proliferation-related genes. These features are similar to epithelial-mesenchymal transition and show stem cell characteristics.

The poor prognosis of TNBC is closely related to BLBC. Although BLBC and TNBC share many similarities in terms of clinical and biological characteristics, not all of the BLBC are TNBC. TNBC is differentiated with CKs and EGFR expressed by BLBC. The overlap ratio of BLBC and TNBC accounts for 56% in BL subtype, while in non-TNBC, this ratio is only 11.5%. Morphologically, the similarities between BLBC and TNBC are the high Ki67 index, significant nuclear polymorphism, higher grade, central necrotic zone and significant lymphocyte infiltration and more metaplastic components than other types of breast cancer. Their common clinical features are frequent occurrence in young, premenopausal women and African Americans, high clinical invasiveness, less spread to the axillary lymph nodes and bone, and easier hematogenous dissemination to the brain and lungs. Therefore, TNBC and BLBC are closely correlated although not exactly the same, both of which have poor clinical prognosis and still lack targeted systemic treatment. TNBC expressing basal phenotype is found to have obviously shorter disease-free survival than that without basal phenotype expression(Rakha et al., 2007). In addition, BRCA1 is an important breast cancer susceptible gene; more than 75% of BRCA1 mutant breast cancer is TNBC or BLBC, and 19.5% of TNBC carries the BRCA gene mutations(Anders and Carey, 2009). Compared to the non-BL TNBC, BLBC is more closely related to BRCA1 mutation, has a unique distant metastasis pattern, and is more sensitive to chemotherapy, but has poorer prognosis. BRCA1 gene is associated with the homologous recombination repair of double-strand DNA breaks, where the BRCA1 gene functional deficiency will lead to loss of double-strand DNA break repair function, thereby increasing the genomic instability. BLBC has many identical biological characteristics with BRCA1 mutant breast cancer. BLBC lacks the ability to repair stationary replicating forks, which is also one of BRCA1′s functions. Those carrying BRCA mutations present DNA repair defects, so this type of breast cancer should be sensitive rather than resistant to radiotherapy. Hence, identifying this defect in TNBC will give decisive significance to clinical decision-making. TNBC carrying BRCA1 mutations may be highly sensitive to cytotoxic chemotherapeutics and radiotherapy that disrupt DNA chemical structures, which provides a theoretical basis for exploring the individualized treatment regimen for TNBC that is based on molecular subtyping.

4. Association of TNBC with tumor size and lymph node metastasis

The size of primary tumor and the status of axillary lymph node metastasis are the important bases for determining the pTNM staging, adjuvant therapy and prognosis of breast cancer. Meanwhile, they are also associated with distant metastasis. With the increasing tumor volume, the probability of contact between tumor and lymphatic vessel increases, so the probability of lymphatic vessel invasion and lymph node metastasis increases as well. Silverstem et al. (Silverstein et al., 2001)claimed that tumor size is one of the independent factors in predicting the risk of axillary lymph node metastasis, and that the volume of primary tumor is positively correlated with both the number of metastatic lymph nodes and the metastasis rate. However, in the actual clinical work, tumor size and lymph node metastasis are influenced by many external factors aside from the close association with pathological type and characteristics of molecularly subtyped breast tumors, such as patients' degree of concern about the disease and their educational