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Tailoring radiotherapy according to cancer subtypes

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ABSTRACT

Radiotherapy 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. Recent advances in the precision of radiotherapy were based on the choice of the appropriate fractionation and technique. But the concept of adaptive radiotherapy is not only technical, and includes the biologic characterisation of the breast tumor. The knowledge that different subtypes of breast cancer can have distinct locoregional patterns of recurrence is consisted in the literature data. Luminal A tumor are at the lower risk of locoregional failure, and HER2 positive and triple negative at the higher risk. More evidence in the use of molecular markers for adjuvant radiotherapy can held in choosing the best treatment on individual. The combination of radiotherapy with molecular targeted therapies may enhance radiosensitivity, thus increasing the cytotoxic effects and improving treatment response. The appropriateness of an alternative fractionation, partial breast irradiation, intensification or de-intensification approaches, could be assessed better according the stratification of the risk categories.

1. Introduction

Adjuvant radiotherapy is an important part of the management of breast cancer, and is usually recommended in almost all patients treated by conservative surgery and in high-risk patients after mastectomy [1]. Traditionally, decisions in radiotherapy were mainly based on patient related factors, such as age or the presence of comorbidities, or on clinical and pathologic stage, such as positive margins, high tumor nuclear grade, presence of lympho-vascular invasion, and others, but now should be the time to make radiotherapy more adaptive to the biology of the tumor, individualizing the treatment according a wider spectrum of risk categories.

On the base of estrogen (ER), progesterone (PR), and human epidermal growth factor (HER2) receptor status, with immunohistochemistry surrogates for the main intrinsic biological subtypes, breast cancer can be classified in different molecular subtypes [2]. This classification includes luminal cancers, which express ER and PR positive receptors. Luminal cancers are divided into two subtypes, with luminal A cancers having low proliferation rate and HER2 negative receptor, and luminal B cancers having high proliferation rate or HER2 positive receptor. HER2 cancers are ER and PR negative and overexpress cErbB2 Her2 oncoprotein. Finally, Triple Negative (TN) cancers are hormone and HER2 negative, but can express some “basal-like” markers.

Although most studies of molecular subtypes reported differences in survival, with ER and PR positive cases at lower risk of mortality, HER2 positive at more aggressiveness than HER2 negative, and TN cases at higher risk of early spread of the disease, only few have examinated the differences in locoregional recurrence (LLR) rate [3].

This review addresses the current and the potentially available biologic tools for precision radiotherapy to tailor treatments according to a more accurate risk stratification according to the different molecular subtypes.

2. Molecular subtypes and locoregional control in radiotherapy setting

The LRR pattern according to the molecular subtypes was studied only on retrospective clinical trials, both for post mastectomy radiotherapy (PMRT) and whole breast irradiation (WBI).

A large retrospective analysis of the Danish Breast Cancer Cooperative Group (DBCG) 82b/c trials, in which high-risk patients were randomly assigned to PMRT or not, following systemic therapy, found that the best prognostic molecular subgroups for improved survival were the ER positive, PR positive and HER2

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negative tumors, while in the poorest prognostic subgroups (HER-2 positive and TN subtypes) no survival benefit was seen after PMRT. With respect to LLR, a reduced probability to develop it was found within the best as well the poorest prognostic subgroups, but with important differences, being both ER and PR negative less reduced than positive receptors cases [4]. A lower risk of LRR in Luminal A subgroup was also seen in a subset of PMRT patients, suggesting an underlying radiosensitivity. In this study there was an 8% of 10-year recurrence rate for Luminal A, compared with 14% for Luminal B, 17% for HER2 positive, and 19% for TN. A statistically significant difference in LRR rate at 5-years between TN subtype (11.8%) and other receptor combinations (3.9%) was also observed in another study, suggesting an underlying radioresistance [6]. In the era of HER-2 targeted therapy, tumors that were HER2 over expressing and treated with trastuzumab had a very low rate of LRR.

In patients received immediate breast reconstruction (IBR) following mastectomy a small but significant proportion of LRR was reported in the literature [7]. A series of consecutive 1742 patients who underwent total mastectomy, skin sparing mastectomy or nipple sparing mastectomy followed by IBR was reviewed according the subtype stratification [8]. The cumulative incidence of LLR rate was 5.5%. Luminal A subtype had the lowest LRR rate (2.5%). In contrast, luminal B, HER2 positive and TN tumors experienced the higher rates, at 5%, 9.8% and 10.9%, respectively. At the multivariate analysis, molecular subtype stratification confirmed the association with the risk of LRR, suggesting that also the assessment of breast cancer subtype should be considered in order to personalize the surgical approach.

TN subtype presented the highest risk of LRR rates also in breast conserving treatment, ranging between 7% and 14% [9,10]. These studies confirmed the lower rate of LRR in Luminal A (from 0.8% to 1.0%, respectively) and Luminal B disease (from 1.5% to 4.3%, respectively), and the higher rate in HER2 positive patients where trastuzumab was not used.

In 2012, a meta-analysis conducted on 15 studies presented data for more than 12,500 patients, systematically appraised the influence of breast cancer subtype on LRR following breast conserving therapy or mastectomy [11]. The data demonstrated that TN have at least two times more risk than grouped Luminal A and B cancers to develop a LLR, and almost as poorly as HER2 overexpressing cancers in an era prior to the use of trastuzumab. No significant difference was observed in TN cancers treated with conserving surgery or mastectomy, and this observation could support the indication to conservative approach.

The effectiveness of trastuzumab in decreasing LRR rate in HER 2 positive tumors, with stage I to III, who underwent mastectomy (and in the 30% of the cases additional PMRT), was recently confirmed in a wide cohort of patients collected by the National Comprehensive Cancer Network (NCCN) Breast Cancer Database, suggesting a possible reassessment of the role of local therapy in these patients [12]. By contrast, TN tumors remain at high risk of LRR, and appeared less responsive to PMRT, highlighting the importance of further investigation into additional molecular markers in order to develop a target therapy for this subgroup of tumors.

More recently data confirmed that also in the setting of breast conserving treatment, when luminal A subtype is combined with other clinical or pathological factors, such as age older than 60 years, T1 stage, grade 1 or 2 histology the benefit of WBI may be small [13]. A recent large cohort of more than 2200 patients with early stage disease treated with breast conserving therapy between 1998 and 2007 tried to identify categories who might benefit from an intensification of treatment and others for whom a de-intensification could be appropriate [14]. Multivariate analysis demonstrated that non-Luminal A subtypes (Hazard Risk for Luminal B = 2.64, HER2 = 5.42, and TN = 4.32), younger age (Hazard Risk for age >50 years = 0.56), and nodal disease (Hazard Risk = 1.06 per each involved node) were associated with LRR. Based on these results two clinical trials have launched to further personalize the treatment and adapt to the individual patient. Patients beyond the first-age quartile with node negative and Luminal A cancer checked by PAM-50-based molecular profiling are candidate to omit the adjuvant WBI (Clinical Trials.gov NCT02653755). Conversely, a Phase I trial is ongoing to intensify the adjuvant treatment in TN patients, by adding concurrent cisplatin as a radiosensitizer to WBI (Clinical Trials.gov NCT01674842).

Some paper tried to assess the role of tumor size or axillary node status in different subsets of molecular profile. In a large cohort of patients with HER2 positive disease and negative lymph nodes, treated with lumpectomy plus WBI or mastectomy, a statically significant higher risk of LRR was observed in T1b stage, and particularly T1b with a tumor size of one cm, when compared to T1a stage tumors (P = 0.009), even with an absolute low rate in total [15]. This indicated the importance of careful attention to local treatment also in this category of early stage cancer. In addition, it appeared than the 1.0-cm T1b tumors carried the majority of the distant risk for the whole group. In another study, the record of 701 patients with pT1-2, N1 (1–3 positive nodes), and M0 breast cancer who did not undergo PMRT were analysed [16]. The HER2-enriched and basal-like subtypes were associated with an increased risk of LRR (p = 0.002 each). In the multivariate analysis, the results showed that also other characteristics were independent prognostic factors for LLR, as age ≤35 years, medial tumor location, pT2 stage and the presence of 2–3 positive nodes. Patients with at least three of the previous listed risk factors, including molecular subtypes, should be recommended for PMRT to the chest wall and supraclavicular area.

3. Molecular subtypes and different approaches of radiotherapy

The availability of novel approaches for local radiation treatments, which include different dose levels, various fractionation schedules, and changes in target volume to be treated, is expected to improve the capability to offer to breast cancer patients less or more intensified treatments, based not only on well established clinical and pathological risk factors, but also on the ability to predict good or bad responders taking into account the molecular profile of the patient.

3.1. Boost dose

The results of the trial “boost versus no boost” has clearly demonstrated that a higher dose increases local control in selected, age-correlated, subgroups of breast cancers, suggesting different levels of radiosensivity [17]. A multi-joint task force developed a highly radiotherapy-specific multigene expression model, the radiation sensitivity index (RSI), to estimate cellular radiation sensitivity [18]. In a selected subgroup of patients enrolled in the previously mentioned study, when combined with intrinsic subtypes and age, an increased dose of radiotherapy, at a cut-off of 66 Gy, resulted in lower LRR rate only in ER positive patients, and not in ER negative patients. In contrast, when accounted for RSI, the increased dose reduced LLR rate only in the RSI-Sensitive group, independently from Luminal A or Luminal B status. In addition, inside the TN subtype, the authors described a majority of these subpopulations with more frequent RSI-sensitive tumors, with a similar LRR risks to those of luminal tumors, suggesting a clinical utility of radiosensivity test in defining a biology-based decision in prescribing dose level.

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