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Precision medicine for early breast cancer radiotherapy: Opening up new horizons?

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ABSTRACT

So far most efforts put forth to test the value of predictive and prognostic tools in the field of breast radiotherapy remained globally disappointing, or at least below the convincing levels reached for systemic therapy. Nevertheless the addition of predictive tools to the clinical armament tends to prevail over the use of the sole prognostic factors, also in radiotherapy. A number of predictive assays, clinically validated or not, have recently elicited significant associations between molecular profiles and tumor biological aggressiveness and/or radiosensitivity levels. Will it take a long time for these radiation-specific assays to provide added value to the – already crowded – constellation of predictive tools in the breast cancer? On the one hand, optimizing radiotherapy through the integration of precision medicine into the breast cancer management still remains a challenging issue. On the other hand, recent advances in predictive assays aimed at distinguishing patients with a more radioresistant tumor that necessitates radiation dose escalation or a switch to therapeutic approaches other than radiotherapy, plea in favor of an increasing role, in a near future, for radiation-specific molecular signatures. Streamlining predictive assays platforms via concerted actions should imperatively be given high priority, also in terms of health economics.

1. Introduction

A pillar of local treatment after conservative surgery, adjuvant radiotherapy is delivered in most patients with invasive breast cancer patients, on the basis of clinical level 1 evidence. In terms of local regional control, treatment outcome has nevertheless been shown to vary among patients with early disease. On the one hand it has indeed been substantiated that, compared to luminal subtypes, HER2-positive and triple negative carcinomas carry a more dismal prognosis, even when postoperative radiotherapy (PORT) is delivered (Arvold et al., 2011; Gabos et al., 2010). On the other hand, identifying low-risk patients who can be spared PORT remains, for the clinician, a field full of ambushes.

One way to explore the whole spectrum of failure risks – and speaking of radiotherapy, also of radiosentivity levels – is to follow the example of the steps forward made in translational research for tumor molecular profiling and its capacity to tailor, on an individual basis, systemic therapies (Henry et al., 2016; Sorlie et al., 2003).

In consideration of the numerous efforts in that direction have been put forth by both the radiation biology and radio-oncology communities, it turns out we might be at a cross road along the development of radiation-specific assays. Although a lot of issues remain to be addressed in order to remove uncertainties revealed by testing their clinical relevance, recent advances paved the way for a broader use of molecular profiling in breast cancer radiotherapy.

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2. Chronology and inputs from the main contributions to radiation-specific assays

In the early 2000s, Torres-Roca et al. developed a classifier based on gene expression profiles able to predict the radiosensitivity of various tumor cell lines (Torres-Roca et al., 2005). Three genes (RbAp48, RGS19, and R5PIA) correlating with radiosensitivity were identified. After RbAp48 transfection into 3 cancer cell lines, the over-expression of this gene was shown to induce an up to 2-fold radiosensitization. HS-578T-RbAp48 also contained a higher number of cells in the radiosensitive G2-M phase (27% versus 5%).

In 2006, Nuyten et al., using various gene profiles known to predict survival indices, reported that it was only the 512 gene 'wound' signature which was able to distinguish low from high risks of loco-regional failure (LRF) after PORT (at 10 years, 5 vs. 29%, respectively) (Nuyten et al., 2006).

In 2012, Servant et al. reported on problems of clinical relevance yielded for a gene expression signature previously identified from a cohort of 165 Dutch breast cancer patients (Servant et al., 2012). Gene expression tumor profiles were obtained from 148 from these patients, and 195 French patients for independent validation. While the LRF signature was validated for the whole population of 343 cases, it was not contributive in the French cohort. Actually a differential expression of the signature between cases with or without LRF was observed only in triple-negative breast carcinomas (TNBC). The authors concluded that the LRF signature had not been validated on an independent data set.

In 2014, Tramm et al. showed that, while the microarray analysis they had performed for tumors from the Danish 82b/c patients identified 7 key genes associated with high LRF risk, this molecular signature was also able to identify a subgroup of patients with a very low risk of LRF. Indeed patients presenting with a luminal B subtype had not drawn any benefit from post-mastectomy radiotherapy (Tramm et al., 2014).

Ten years after their first publication on a radiation classifier in cancer cell lines, Torres-Roca et al. reported, in 2015, on a radiosensitivity index (RSI) and molecular subtypes in 343 patients treated with PORT (Torres-Roca et al., 2015). While RSI did not predict for LRF in the whole population, combining RSI and molecular subtypes allowed the identification of the TNBC/RSI-radioresistant group, as a subpopulation with an increased LRF risk (HR: 0.37; P = 0.02). In contrast, LRF rates in the TNBC/RSI-sensitive/intermediate group was similar to those of luminal subtypes (HR 0.86; P = 0.63). On multivariate analysis, combined RSI and molecular subtypes were significant predictors for LRF (P = 0.004).

In 2015, Speers et al., analyzing the surviving fraction after a 2-Gy irradiation (SF–2 Gy) in 16 breast cancer cell lines, identified large differences in radiosensitivity, with SF–2 Gy ranging from 17% to 77% (Speers et al., 2015). There was no significant correlation between these radiosensitivity values and the tumor subtypes. After eliciting a radiosensitivity signature (RSS) comprising 51 genes in a training cohort of patients treated with PORT, the authors validated it in an independent series of 228 cases. At 10 years, RSS predicted the risk of LRF with a sensitivity and negative predictive value of 84 and 89%, respectively. In this study, TACC1 and RND3 genes were linked to enhanced radioresistance. On multivariate analysis, RSS outperformed clinical factors in predicting LRF. In addition, the authors observed that it performed equally to prognostication tools as OncoType Dx to predict relapse (Goldstein et al., 2008).

In 2016, Scott et al., analyzing several cohorts of patients with various tumor types, used the gene-expression-based radiation-sensitivity index and the linear quadratic model to derive the genomic-adjusted radiation dose (GARD) (Scott et al., 2016). In one of the breast cancer patient cohorts (Erasmus Breast Cancer cohort; n: 263), GARD outperformed both gene-expression-based radiosensitivity index and $BED_{2.88}$, the biologically effective dose assuming a constant α/β ratio of 2:88 for breast cancer. In this, Scott et al. actually reported on the first framework to design genomically-stratified, radiotherapy-based trials.

Late toxicity, an important factor of the radiotherapy therapeutic index, has also been investigated in the framework of the association of molecular signatures and radiation-induced adverse events. Although the severity of late side-effects is known to be a function of treatment- and host-related factors, it has also been shown to be influenced by the ptient's genetic profile (Popanda et al., 2009): in a cohort of 409 patients with breast cancer, Chang-Claude J. et al., evaluating polymorphisms in genes involved in DNA repair and damage response (TP53, P21), found that TP53 variant was significantly associated with late skin toxicity (telangiectasia odd ratio = 1.97) (Chang-Claude et al., 2009).

3. Lessons from the past

As for systemic treatments of breast carcinomas, personalized medicine markedly improved with the integration of both predictive biomarkers and prognostication algorithms (Henry et al., 2016). Recently, genomic profiling helped identify biological subtypes characterized by significant differences in outcome (Sorlie et al., 2003), using retrospectively validated technologies (Goldstein et al., 2008; Buyse et al., 2006; Sparano et al., 2015; Cardoso et al., 2016). Nowadays, these assays are routinely integrated into decision making processes (Harris et al., 2016).

In terms of predictive assays for local regional outcome, the 21-gene OncotypeDX recurrence score (RS) was found to be, on multivariate analysis, an independent significant predictor of LRF. Even among the patients presenting with the low-risk luminal subtype, the molecular profile was able to identify a subgroup with a higher LRF risk, thereby justifying the radiotherapy delivery to these patients (Mamounas et al., 2010).

Through the past 5 years, 3 inspiring reports on radiosensitivity classifiers have been rekindling the interest for prediction tools with respect to radiotherapy indications and expected efficacy in breast cancer patients.

One of them focuses on radiosensitivity The Speer's study uses clonogenic survival assays and unsupervised hierarchical clustering to both yield radiosensitivity scores correlating with gene expression and formulate a breast cancer-specific molecular signature of response to radiation (Speers et al., 2015). The messages from this study are twofolds. Firstly, the functional analysis of RSS genes is now able to identify radioresistance-associated genes. Secondly, RSS turns out to be, on multivariate analysis, the most significant factor in predicting local recurrence, outperforming all traditional clinical factors. As claimed by the authors, RSS paves the way for medicine precision by identifying patients with tumors refractory to conventional radiotherapy doses. Yet the assay turns out to be unable to yield any significant correlation between tumor cell radiosensitivity levels and biological subtype. A number of caveats may actually affect some of the conclusions drawn from Speer's study, which included non-randomized cohorts of patients. As hypothesized by Ow and Lee (Ow and Lee, 2016), the presence of confounding factors, such as huge variations in both radiotherapy techniques and systemic treatments – especially as regards biases linked to the "pre- and post-trastuzumab" eras – may account for uncertainties in the interpretation of the results (Servant et al., 2012; van de Vijver et al., 2002). It remains that, in this study, the predictive value of biologic subtypes got lost as soon as RSS was integrated into the analysis. This observation suggests that radiation-specific assays can have strong potentialities to distinguish patients presenting with tumors sensitive or, oppositely, refractory to adjuvant radiotherapy.