Commentary

Radiosensitivity in the breast cancer management scenario: another step forward?

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We have recently read with interest the paper by Torres-Roca and colleagues (1); some relevant issues related to treatment tailoring on the basis of molecular signatures may raise considering showed results.

Briefly, a molecular signature estimating radiosensitivity (RSI), previously validated in a clinical context (2), was evaluated on 343 patients who underwent breast conservative therapy (BCT) and whole-breast radiotherapy (RT). Authors integrated RSI with tumor molecular subtypes, defined as luminal A (LUMA), luminal B (LUMB), luminal HER (LUMHER), Triple-negative (TN) and Human Epidermal Growth Receptor Factor 2 (HER2) positive, according to the expression level of genes ESR1, PR, ERBB2 and AURKA. The purpose of this analysis was refining classification of local recurrence (LR) risk in the study population.

Results showed that TN patients with RSI radioresistant score (RSI-R) patients had an increased risk of LR (HR =0.37; P=0.02), while TN RSI sensitive/intermediate (RSI-S/I) had a LR rate similar as LUMA and LUMB patients (HR =0.86; P=0.63). Age (P=0.001) and combined RSI-molecular subtype (P=0.004) were the most significant predictors of LR at multivariate analysis. Furthermore, RSI-R status was also a predictor of LR rate in estrogen receptor (ER) negative patients (HR =0.33; P=0.02), while no difference were found by RSI status in ER positive patients.

Currently, tumor stage, nodal status and histopathology guide breast cancer (BC) patient management, but a deeper knowledge of tumor cell biology, integrating both the information about risk of recurrence and response to RT, could change this paradigm.

Classifying BC on the basis of RSI may allow different treatment strategies for RSI-R and RSI-S/I tumors, including a de-escalation of adjuvant systemic treatment in selected patients.

Data from EBTCG meta-analysis showed that the risk of any recurrence at 10 years in a 50–60-year old, T2 N0, ER negative patient is 34% after BCT (3); according to results of Torres-Roca *et al.* (1), a similar patient with an RSI-S/I molecular arrangement could have a significantly lower recurrence risk, influencing treating physician in the choice of the adequate systemic management after radiation.

Speculation about showed results could also influence RT target volumes, because issues about RSI of tumor cells may concern tumor cells hosted in regional lymph nodes. Indeed, several recent studies demonstrated the benefit of adjuvant regional nodal irradiation (RNI), suggesting that eradication of subclinical nodal disease could reduce both local and distant failures (4,5).

In this context, data about the value of RSI status as a LR predictor in ER negative patients, could help to identify a BC subgroup in which the intrinsic radioresistance of tumor cells may overcome clinical gain of RNI, requiring a systemic approach rather than an aggressive local therapy. Given the potential side effects of RNI (potential increased symptomatic pneumonitis, arm edema, transient brachial plexus neuropathy, and ischemic heart disease), tailoring treatment strategy on molecular basis could allow to spare unnecessary toxicity, when RSI status may predict a lower benefit after RNI (6,7).

Furthermore, the results of ACOSOG Z0011 and IBSCG 23-01 trials (8,9) showed that selected patients with clinically negative axillae and 1–2 positive sentinel nodes

can safely omit axillary nodal dissection (ALND). However, information to determine when to include regional fields in treatment volume may be reduced is still limited, but a molecular signature predictive of RSI could help to choose the correct management in patients who omitted ALND.

In their analysis (1), the authors underlined that LUMA-B patients with RSI-R score had a lower LR rate if treated with dose >66 Gy; this result is of particular interest, considering that patients in 66 Gy group had a significantly higher rate of positive surgical margins and lymph node positive disease. Indeed, these patients are more likely to benefit from a dose escalation protocol, but more data on homogeneous population are needed in order to confirm this trend. Of course, as underlined by authors, dose-effect considerations about this study cohort are limited by the fact that patients were treated since 1984, comprehending non-computed tomography (CT)-based techniques and without the opportunity to assess the actual dose distribution of treatment plans.

Due to the increasing complexity of techniques, factors such as dose per fraction, dose homogeneity, and dose rate have to be considered in order to relate biological effects of prescribed dose to intrinsic RSI of tumor cells population.

In our opinion is crucial to point out that uniform treatment technique and thorough quality assurance assessment should be encouraged, in particular when radiobiological issues are in play, because differences in technique, dose prescription, reporting, and delivery could heavily affect study results.

Anyway, results from this study showed a differentiated impact in molecular subtypes by RSI status, suggesting distinct patterns of radioresistance in different subgroups. Thus, impact of radiation exposure may have a different biological effect on different BC molecular subtypes, and this could reasonably influence the clinical outcome of treatment. Trying to identify RSI patterns could be interesting, since many biomarker of radioresistance have been identified, with molecular targets potentially able to increase effects of radiation exposure of specific BC cell populations.

For example, EGFR family proteins showed to be overexpressed after repeated radiation exposures of 2 Gy, and these effects are confirmed for HER2, suggesting that response to radiation may be biologically related to ERBB2 expression (10). *In vitro* and *in vivo* experiences confirmed that HER2 silenced BC cell lines had increased RSI, and that HER2 xenograft tumors had enhanced radioresistance if compared to corresponding controls. These effects on RSI seemed to be related to HER2 mediated up-regulation of phosphorylation of focal adhesion kinase (FAK); as a counterproof, RSI was restored using a FAK inhibitor (11).

Interestingly, Torres-Roca *et al.* (1) reported that RT dose did not affect LR in LUM-HER RSI-R group, while dose response effect was significant in LUMA-B RSI-R patients (RT dose 66 Gy; HR =0.13; 95% CI: 0.02–1.01). Thus, clinical evidence supports the HER2 effect on RSI of BC tumors, indicating that HER2 patients are not likely to benefit from dose escalation protocols.

On the other hand, TN BC are considered to be radioresistant if compared to others subtypes (12), but TN RSI-S/I and LUMA-B patients were found to have a similar LR rate in the mentioned paper, suggesting that TN tumors could have a wide range of RSI.

Some molecular targets showed to be overexpressed in TN BC, such as the maternal embryonic leucine zipper kinase (MELK), a serine/threonine kinase involved in cell survival to exogenous stress (13). MELK showed to be related to radiation induced DNA double strand damage repair and stem cell self-renewal (14), and knockdown cell lines and *in vivo* models showed increased RSI and delayed tumor growth (15).

In the present paper, RSI-S/I status was related to lower LR in TN molecular subtypes and ER negative patients, and we may argue that in this population, MELK expression could be a crucial step in influencing RSI. Therefore to relate the RSI score to the abovementioned biomarkers may be a further step in order to reach a better knowledge on how different cancer cell line can overcome radiation damage.

Finally another issue to consider is the impact of biological therapy on such a complex scenario. Both concomitant and sequential use of targeted systemic agents is current standard in adjuvant treatment of BC; this could directly impact on response to radiation exposure, but also influence biological behavior of cells surviving to RT.

For example, HER2 positive cells are more likely to be resistant to radiation damage, regardless of RSI score status, but sensitive to anti-HER2 treatment administration. Due to the heterogeneity of HER2 expression within the tumor, RT could eradicate HER2 negative and select HER2 positive clones. Thus, we can assume that, in HER2 positive patients, RT and trastuzumab could have a synergistic effect. Such hypothesis, although attractive, are only speculative, but enhance once more the complexity of implementing a RSI score in clinical practice.

Nowadays intensity of adjuvant treatment and tailoring of therapies on the basis of biology do represent critical issues for the clinical oncologist (16,17).

Understanding the clinical meaning of these considerations is challenging, but integration between clinical, molecular, radiobiological and technical aspects is necessary, in order to develop an effective tailored approach to the patient.

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Footnote

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