Are We Ready for Histology-Driven Stereotactic Ablative Radiotherapy?

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Stereotactic ablative radiotherapy (SABR) is generally shared as a treatment option for early-stage NSCLC, especially in those unfit for radical surgery.[1] Cornerstones of SBRT in lung cancer are a biologically effective dose (BED) to the tumor (for an alpha/beta ratio of 10 [BED10]) of 100 Gy or more[2] and extreme hypofractionation (generally more than 10 Gy per fraction) with respect to mediastinal structures.[3]

In the present issue of *Journal of Thoracic Oncology*, Shiue et al.[4] have evaluated data on 508 patients with early-stage NSCLC and 561 lesions (442 and 482 with complete dosimetric information, respectively) treated between 2000 and 2016, underlining the role of tumor volume and histologic subtype on outcome. The data are interesting thanks to the propensity score–matched analysis performed to reduce selection bias, which is very common in any retrospective evaluation.

In particular, in-field control is independent from BED in adenocarcinomas (ADCs) (the same results are achieved with a BED10 of 105.6 Gy versus 151.2 Gy), whereas in squamous cell carcinoma (SCC), a lower BED translates to a worse outcome. To overcome this effect, the authors stated that 18 to 20 Gy in three fractions (BED10 >150 Gy) should be administered in cases of SCC.

We have other data about SABR and histologic subtype going in the same direction, with worse results in SCC[5,6] that are generally overcome by a BED10 higher than 150 Gy.[7] Thus, why should histologic subtype affect this result?

A possible answer could be found by considering histologic subtype as an expression of different tumor biology. First, some ADCs are EGFR positive, which means more rediosensitive disease proved both in vivo[8] and in vitro.[9] Moreover, different expression of the thymidylate synthase gene (*TS*) and thymidylate synthase (TS) protein is reported in SCC and ADC.[10] Therefore, the lower level of TS in ADC could reflect less ability to repair DNA damage and eventually higher tumor response to radiotherapy, as in rectal cancer.[11]

Finally, SCC appears to be more *immunosuppressive* because of its expression of program death ligand 1 (PD-L1). In a recent real-life Italian analysis (unpublished data on more than 400 SCC and 1500 nonsquamous cell tumors), 31.3% of SCCs have a level of PD-L1 expression of 50% or higher versus 23.1% for nonsquamous cell carcinomas.

When SABR is performed with dose per fraction of 15 Gy or higher, the antitumor effect is also mediated by vascular damage, with subsequent deterioration of the intratumor microenvironment.[12]

Moreover, SABR to parenchymal sites (lung and liver) induces in vivo systemic immune changes with possible increased homing and migration of immune cells to the irradiated tumor site.[13] This is consistent with the hypothesis that radiation contributes to generation of an in situ vaccine by its ability to induce immunogenic tumor cell death,[14] particularly when a lower dose per fraction is adopted.[15]

Therefore, SCC has a greater chance of a level of PD-L1 expression higher than 50% requiring a higher dose to kill the tumor and vascular cells reducing efficiency of the microenvironment, whereas ADC could be more radioresponsive for EGFR mutation or less TS expression, along with the likelihood of immune activation requiring an effective microenvironment that has not been damaged by high-dose SABR.

This fascinating scenario, which is highlighted by the article of Shiue et al,[4] deserves prospective and external validation to conform radiotherapy not only to disease shape, location, and volume but to its biology too.

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