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LETTER TO THE EDITOR

Radiotherapy in nonmelanoma skin cancer: Radiosensitivity, radioresistance and radiocurability. In regard to Gracia-Cazaña et al.

Radioterapia en cáncer de piel no melanoma: Radio-sensibilidad,radio-resistencia y radio-curabilidad. En respuesta a Gracia-Cazaña et al.

Dear Editor,

We read with interest the article by Gracia-Cazaña et al. regarding resistance of nonmelanoma skin cancer to non-surgical treatments. Part II.[1] We would like to make some considerations about radiotherapy as local treatment in squamous carcinoma.

For radiation oncologists the concept of radiosensitivity has three possible meanings:

- The first one is related to cell cycle. Ionizing radiation (IR) produces a large number of lethal damage and the mitotic death is the most common form of cell death caused by IR. Response to IR varies widely depending on which phase of the cell cycle the cells are at the time of irradiation. The cells in M and G2 phases are nearly three times more sensitive to radiation than those who are in S phase.[2]
- The second meaning is related with the probability of DNA damage caused indirectly for IR through the action of free radicals. Oxygen reacts with these free radicals to make the DNA damage irreparable so more oxygenated cells are more sensitive to lethal damage by IR.
- Radiation damage to stem cells has serious repercussions while radiation induced damage to cells that are already on the path to differentiation is of little consequence. Thus, stem cells appear to be more radiosensitive than differentiated cells.[3]

Radiosensitivity is a measure of tumor-radiation response related to the degree and speed of regression during and immediately after radiotherapy. Unfortunately, this term has been frequently used as synonymous of radiocurability, which is referred to the eradication of the tumor. Tumors with a high rate of cell production and large cell loss factor are likely to regress quickly but recur early and regrow rapidly after unsuccessful radiotherapy, chemotherapy or surgery.[4] For many histologic types of cancer, higher radiation doses produce better tumor control. Moreover, depending on the location and extension of the tumor, treatment with high doses is sometimes not possible because of the risk of acute and late toxicity in normal tissue. Thereby, in a theoretically radiosensitive tumor, radiocurability may not be achievable.

Gracia-Cazaña et al. affirm that in some cases IR can promote cell division, probably they allude to the cell repopulation phenomena. This is a homeostatic tumor response caused by the cell loss after each fraction of radiation which induces compensatory cell regeneration due to the rise in the intra-tumoral oxygen levels but this is not strictly the same that ''promote the cell division''. Tumoral cell repopulation is the rationale for dose fractionation in radiotherapy.

Additionally, the authors also argued that IR may generate resistance. They cite two studies to support their asseveration but none of them address this question, actually both report the redox reactions secondary to the cellular response to IR insult.[5,6] For our best knowledge, IR do not confer radioresistance itself. However, as is noted by Gracia-Cazaña et al., certain molecular pathways that promote the cellular proliferation (i.e. EGFR and NF-$\kappa\beta$) have been linked to radiosensitization of tumoral tissue and nowadays its blockage is arising as a possible target in nonmelanoma skin cancer.

In synthesis, we would like to stress the important distinction between radiosensitivity and radiocurability. The former is related to biological effects in tumoral cell that may contribute to the tumor eradication. Radiosensitivity is the result of several phenomena in the tumoral environment more than an intrinsic feature of certain cancer histologies. Radiocurability is influenced by radiosensitivity but it also depends on the clinical parameters as tumor location, size and routes of spread. The influence of molecular factors is also appearing as a linked parameter.

Concerning to the results of radiotherapy, its clinical benefit has been widely reported although several treatments also have been used successfully and no direct comparisons between treatments have been made so far.[7] A better identification of high risk features (for recurrence and dissemination) in patients with nonmelanoma skin cancer is necessary to decide the best treatment modality.[8]

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