Letter to the Editor

To answer Spałek's question: lattice radiotherapy is more hope than hype

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We appreciated Spałek's comments (1) regarding the case report published by Iori *et al.* (2). These authors reported a dramatic clinical response in a patient with advanced bulky sarcomatoid lung cancer to palliative lattice radiotherapy (LRT) treatment with no significant toxicity (2). Spałek was impressed by this result and others reported. However, he expressed some skepticism about the scientific evidence underpinning LRT, adducing the paucity of data supporting the effectiveness and safety profile of such a radiotherapy technique. Indeed, only case reports and small case series have been reported. Neither randomized controlled trials nor comparative observational studies have investigated the advantages of LRT over classic palliative radiotherapy treatments. Few case reports and a rather large case series consisting of different tumor histologies (3) have been published since our previous review, which collected limited clinical experiences with LRT (4). Arguably, the criticisms surrounding LRT stem from a lack of knowledge of its mechanisms and a fear of possible life-altering toxic events in patients already complaining of disabling cancer-related symptoms. As regards the first, we agree with Spałek and the most prevalent perspective on the topic, which attributes a determinant role to the reprogramming of the host immune cells against the tumor (1). This would be promoted by the high radiation doses within the vertices, as large doses per fraction proved to be able to provoke unexpected events, likely immune-mediated (5,6). The irreproducibility of these responses represents a major weakness of LRT. We assume that vertices act as immunomodulatory trigger points. Thus, one big question is about where delineating them within the tumor is more convenient. A geometric arrangement might be unsuitably rigid while a "metabolism-guided" one could be the most rational. Indeed, bulky tumors are made of subvolumes with different metabolism: a vertex in a necrotic core would be a bust, one in a well-oxygenated area may be unnecessarily overwhelming, whereas one in transition hypoxic zones could be the best solution (7). As previously explained in section 7 of reference (4), delivering high doses to hypoxic cancer cells rather than to a well-oxygenated counterpart may induce a greater release of antitumor factors. On the other hand, low radiation doses reverse tumor immune desertification by recruiting both innate and adaptive immune cells. Such immune cell engagement should be more effective in well-oxygenated tumor areas supplied by wide-open vessels. Therefore, the spatial fractionation of LRT alternating high-dose vertices in poorly perfused hypoxic subvolumes while lowering as much as possible the dose scattered to the well-oxygenated subvolumes may have a certain rationale (4). Moreover, specifically targeting the hypoxic subvolumes with a larger dose can also serve to overcome their intrinsic radioresistance, which is one of the possible reasons for treatment failure and tumor regrowth (8). Then, the detection of tumor oxygenation is crucial to implement the approach described in (7). Unfortunately, hypoxia-specific positron emission tomography (PET) tracers are

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not widely available in clinical practice (i.e., FMISO, FAZA, F-HX4), being mainly devoted to experimental applications. As well known, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET is inadequate to discriminate between well-oxygenated and hypoxic tumor subvolumes due to the Warburg and Pasteur effects reflecting opposing conditions of high glucose avidity (aerobiosis versus anaerobiosis). However, within a given tumor, different standard uptake values (SUVs) stand for different oxygenation patterns. Delineating vertices astride SUV-changing tumor areas should somehow involve targeting hypoxic cells with high radiation doses. This was the assumption that guided our practice in (3) and indeed, we reported impressive results. Although a "metabolism-guided" approach should produce no better results than a geometric one, it must be stressed that the former, with respect to the latter, is susceptible to some flexibility to reduce the integral dose to the peri-target tissues and organs at risk by ad hoc adjusting the number and positioning of vertices. In this regard, we would emphasize the amazing result obtained with only three vertices of 0.5 cc each duly placed far from any surrounding critical structures within a bulky gynecologic tumor of 5,428 cc (9). In this case, the positioning of the three vertices was guided by an apparent diffusion coefficient magnetic resonance imaging (ADC MRI) map starting from the assumption that tumor areas with the highest ADC values show a lower restriction to the movement of water molecules, likely due to the lesser concentration of membranes of actively proliferating cells. Considering that the number of the latter correlates with the oxygen supply, the ADC map might be used as a surrogate of tumor oxygenation in the absence of specific MR imaging [the blood oxygen level-dependent (BOLD) and tissue oxygen level-dependent (TOLD) sequences].

The above digression is intended to bring attention to some not yet adequately explored issues related to the possible capabilities of LRT. Regarding the best integration and timing of LRT with any conventional radiotherapy, we believe that a single fraction of LRT prior to a normofractionated course has a dual function: (I) administration of a single maximal dose of LRT is unaffected by any tumor re-oxygenation events that may occur after the use of fractionated doses, thus hampering an oxygen-guided approach in an ever-changing background; (II) a sequential scheme could be better than a simultaneous boost delivery by allowing a more effective recirculation of radiosensitive lymphocytes between the tumor microenvironment and draining lymph nodes. Then, a sequential scheme may prevent concerns about any "interfraction changes within the tumor". We share Spałek's doubts about the "contouring process" (1). We have used 1cm diameter spherical vertices but ignore which number, size, and shape are best. In our opinion, stereotactic equipment is the best choice for motion management (7).

Spałek's main concern is about the potential toxicity of LRT (1). In our experience, we reported no or minimal toxicity, no greater than that expected using classic palliative radiotherapy. In a recent comprehensive review, Iori *et al.* reported one case of death following tumor lysis syndrome after LRT delivery to a bulky endometrial cancer (10). However, this event is not specific to LRT as its occurrence has been reported for both chemotherapy and classic palliative radiotherapy.

How to optimally integrate systemic therapies, especially immunotherapy, with LRT is unknown.

We invite Spałek to discuss our findings and observations.

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