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PERSPECTIVE

LATTICE RADIATION THERAPY: A PROMISING OPTION IN METASTATIC COLD TUMORS, WITH A LARGE PRIMARY LESION

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ABSTRACT: Metastatic cold tumors with a large primary site (*i.e.*, >5 cm) represent an open issue as surgery is often excluded and immunotherapy (IT) have reported limited response, because of the immunosuppression present in their microenvironments (cold TME). Due to their dimensions and hypoxia, large tumors are especially radioresistant, requiring to be irradiated with higher doses, not deliverable by conventional radiotherapy (RT) without an increased toxicity to the surrounding tissues. Even stereotactic body radiation therapy (SBRT) is excluded, as it is usually limited to targets with a diameter below 5 cm. Lattice Radiation Therapy (LRT) is a novel RT technique, based on an inhomogeneous dose delivery, that allows to safely achieve an outstanding cytoreduction of large lesions by concurrently administering ablative high doses inside the tumor and controlled doses near the adjacent organs at risk (OARs). In addition, preliminary data suggest that LRT might reengineer tumor microenvironment (TME), making it more immunogenic, and it could boost the host immune system response against irradiated and not irradiated lesions. Hence, LRT could represent an interesting strategy to deal with localized and widespread diseases in metastatic cold tumors with a large primary lesion.

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Impact statement: Lattice radiation therapy (LRT) is an innovative type of spatially fractionated radiation therapy. In addition to an outstanding cytoreduction, LRT is hypothesized to prime a vigorous immune reaction that could be exploited in cold tumors to rejecet metastatic cancer cells.

Key words: *lattice radiation therapy; cold tumors; radiotherapy; immune system; spatially fractionated radiation therapy.*

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INTRODUCTION

The advent of immunotherapy (IT) has revolutionized oncologic patients' managment, especially in the metastatic setting (1). However, metastatic patients with the so-called "cold tumors" and a large primary lesion (T) continue to represent an open issue, since they have a poor response to IT as well as to other systemic therapies (2).

According to the National Cancer Institute, several tumors of pancreas, prostate, ovary, brain, and breast can be considered as cold tumors. They are characterized by an immunosuppressive tumor microenvironment (cold TME), that prevents the creation of an adequate immune response and impairs IT effectiveness. Cold TMEs are a comfortable "ecological niche" for the carcinogenesis process, as they protects neoplastic cells from the host immune system. By evading the host immune-surveillance, cold tumors tend to grow and spread, reaching voluminous T dimension and causing invalidating symptoms. A large T usually present an atypical lympho-vascular matrix with many hypoxic and necrotic areas that prevent an effective drug concentration (3). In addition, when a large cold tumor becomes metastatic, the widespread lesions favour cancer cells polyclonal evolution and, consequently, drugs resistance.

The cytoreductive action of radiotherapy (RT), and in particular of stereotactic body radiotherapy (SBRT), could represent an appealing option to manage a large T. SBRT is traditionally considered

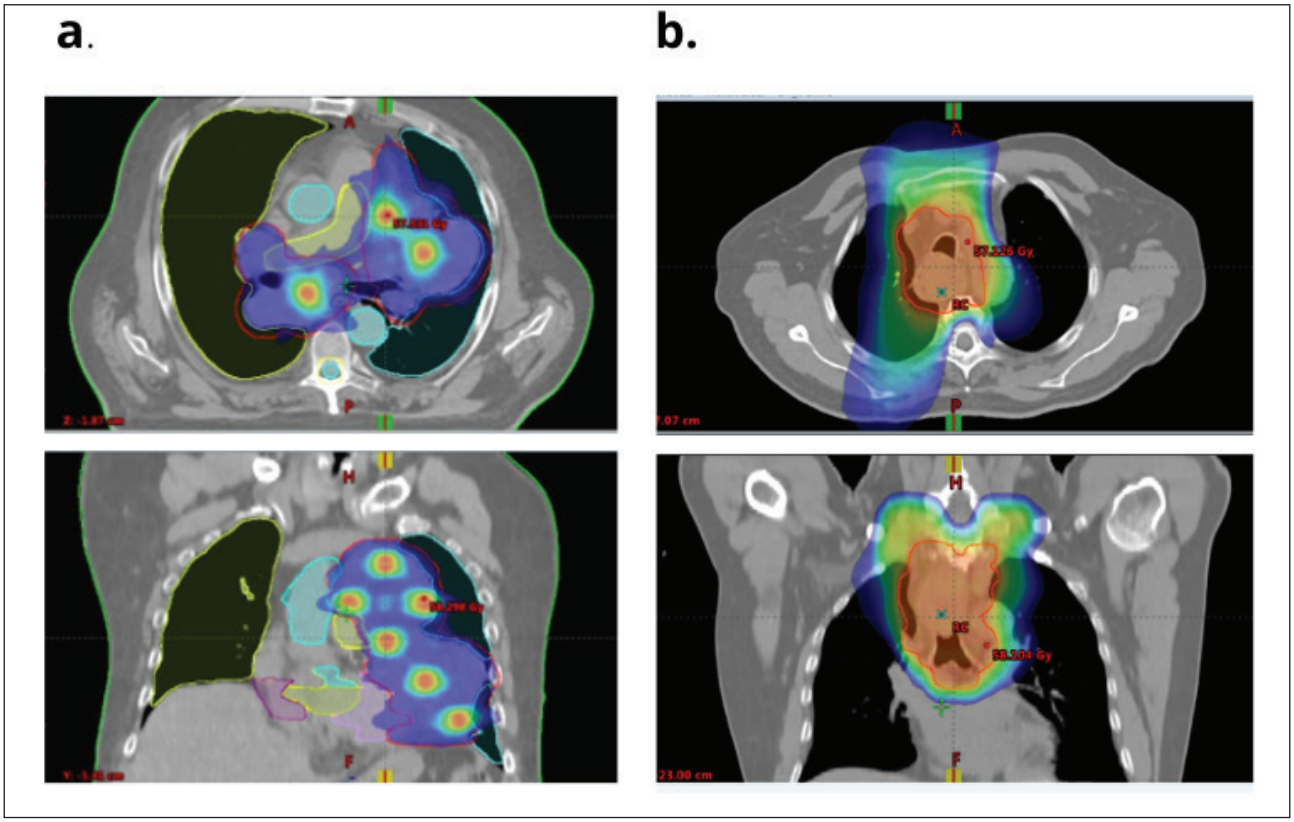
as an ablative treatment delivering daily fractions ≥5 Gy in a number of fractions from 1 to 5, to a lesion with a maximum diameter of 5 cm. There is a general agreement that the higher the delivered dose in a single fraction, the higher the tumor response. Thus, for eligible lesions, SBRT is preferred over conventional RT, however, for larger lesions, a SBRT treatment would entails an excessive extent of toxicity. Considering metastatic patients with a large T, this is particularly important, as these patients are often "fragile" due to the advanced disease stage and the burden of symptoms, and a viable therapeutic strategy should be as much tolerable as possible (4, 5).

In light of this, Lattice Radiation Therapy (LRT) could represent a promising option, as preliminary data show that it allows to safely deliver ablative doses to lesions above 5 cm, achieving a satisfactory response. In addition to the promising cytoreductive action, the literature data suggest that LRT can modulate cold TME. More precisely, LRT might reengineer the immunosuppressive TME making it more tumor-killing, priming host immune system and improving IT response. The aim of this article is to analyse, debate, and open up future research fields for LRT in the management of metastatic cold tumors with a voluminous T.

LATTICE RADIATION THERAPY

LRT is a spatially fractionated radiation therapy technique deriving from a 3D volumetric configuration of the 2D GRID therapy with a heterogeneous target irradiation. More precisely, LRT is based on the creation of an array inside the bulky lesion where the areas of high dose (namely, vertices or hotspots) and the areas of lower dose are interspersed as peaks and valleys (**figure 1**) (6).

This particular dose distribution allows to deliver ablative doses inside discrete sub volumes of the target and acceptable doses in the lesion periphery. The ablative dose increases the tumor control probability, allowing to reach outstanding responses of lesions not eligible for SBRT. Conversely, the area of lower dose limit the parasitic dose to closer OARs, reducing treatment toxicity (7).



Figures 1 ***a, b.*** *The figures illustrate the difference between dose prescription of:* ***a****. LRT and* ***b****. conventional RT in the axial and coronal planes (shown isodose: 20 Gy). The LRT plans show the hotspots where we delivered a dose of 66.70 Gy in the vertices and 20 Gy in the remaining volume (13.34 Gy and 4 Gy in 5 fractions, respectively). Conversely, the conventional RT plans depicts a mediastinal treatment with a dose prescription of 50 Gy in daily fractions of 2 Gy. The LRT allows to reach an ablative biological effective dose in the target and acceptable doses near OARs, to improve lesion response and minimize toxicity.*

In addition, it is hypothesized that the gradient generated in the treated volume could improve host immune system response against neoplastic cells both in irradiated and not irradiated sites (abscopal effect) (8). More precisely, the immunogenic cells death (ICD) in the hotspots should cause the release of many cancer antigens and damaged associated molecular patterns (DAMPs). These elements are recognized by the antigen presenting cells (APCs) on their major histocompatibility complex. This process should elicit an effective immune adaptive response, as the more preserved vascular system in the valleys improves the homing and the activation of the immune elements involved in the effector phase of the immune reaction (9). Hence, LRT could concurrently exploits both the ablative and the immune-modulating properties of RT.

COLD TME

The TME is a three-dimensional architecture of extracellular matrix that encompasses blood vessels, immune cells, local resident cells and neoplastic cells. According to the availability of cancer antigens (*i.e.*, the tumor mutational burden: TMB), the type of inflammation, and the presence of different immune elements or cytokines involved in the immune response, TMEs can be defined as hot (immunogenic) or cold (immunosuppressive). It is worth noting that the association between inflammation and TME is extremely complex and it can strongly influence tumor progression. The acute inflammatory response can contribute to an efficient anti-cancer immune response, while a chronic or smouldering inflammation can ease tumor progression (10). Acute inflammatory response is associated with an increase in INF-I production, APCs recruitment and cross presentation, and CD8 + lymphocyte priming. These immune elements are peculiar in a hot TME, where cancer cells rejection by the host immune system is more likely to occur (11).

Conversely, cold tumors are characterized by a cold TME with a low availability of targetable cancer antigens (*i.e.*, a low TMB). This leads to an enhanced expression of receptors and signalling molecules catalysed by cancer cells, which finally leads to the recruitment of cells normally involved in the de-escalation and in the ending of the immune reaction (anti-inflammatory wave). These immunosuppressive elements encompass the lymphocytes T regulatory, the macrophages M2, the myeloid derived suppressive cells, and the cancer-associated fibroblasts. The de-escalation is physiological to maintain the immune tolerance and to prevent the autoimmunity, however, in cold TME the anti-inflammatory wave is boosted, preventing an effective immune reaction and leading to a chronic inflammation (12).

As a result, the neoplastic cells can easily escape the immune surveillance, the carcinogenesis process can prosper, and every attempt to start a new immune system counterattack with IT administration is promptly neutralized (13, 14).

COLD TME RADIOMODULATION

TME is not a static element but it dynamically mutates, and it can be modulated by irradiation according to RT dose, schedule, and timing. Thus, RT can reengineer the TME from an immunosuppressive status (cold TME) to an immunogenic one (hot TME), which favours the host immune system action (13). More precisely, RT can cause the ICD with the release of DAMPs, moreover, it can increase the concentration of intra-cytosolic DNA that boosts INF-I production and CD8+ activities through the STING pathway.

Although the RT optimal schedule for converting cold TMEs are still under study, current data seem to support the delivery of 8 Gy daily fractions in 3 sessions (15, 16). Daily doses above 12 Gy are less effective as they provoke the activation of an exonuclease (TREX1) which degrades intra-cytosolic DNA, precluding STING pathway activation. Conversely, delivering daily doses below 8 Gy could not be sufficient to prime an effective immune response (16, 17). In addition, by creating a more favourable TME, RT can improve IT response. Hence the association of RT and IT could create an opportunity for the host immune system to reject neoplastic cells (**figure 2**).

LATTICE RADIATION THERAPY FOR LARGE METASTATIC COLD TUMORS

In recent literature, monocentric studies reported positive feedbacks on LRT for large tumor (18, 19); however, no trials about LRT safety were conducted until the recent publication of the “LITE SABR M1 trial” (20). This study highlighted the safety of LRT cytoreduction and its promising results en-

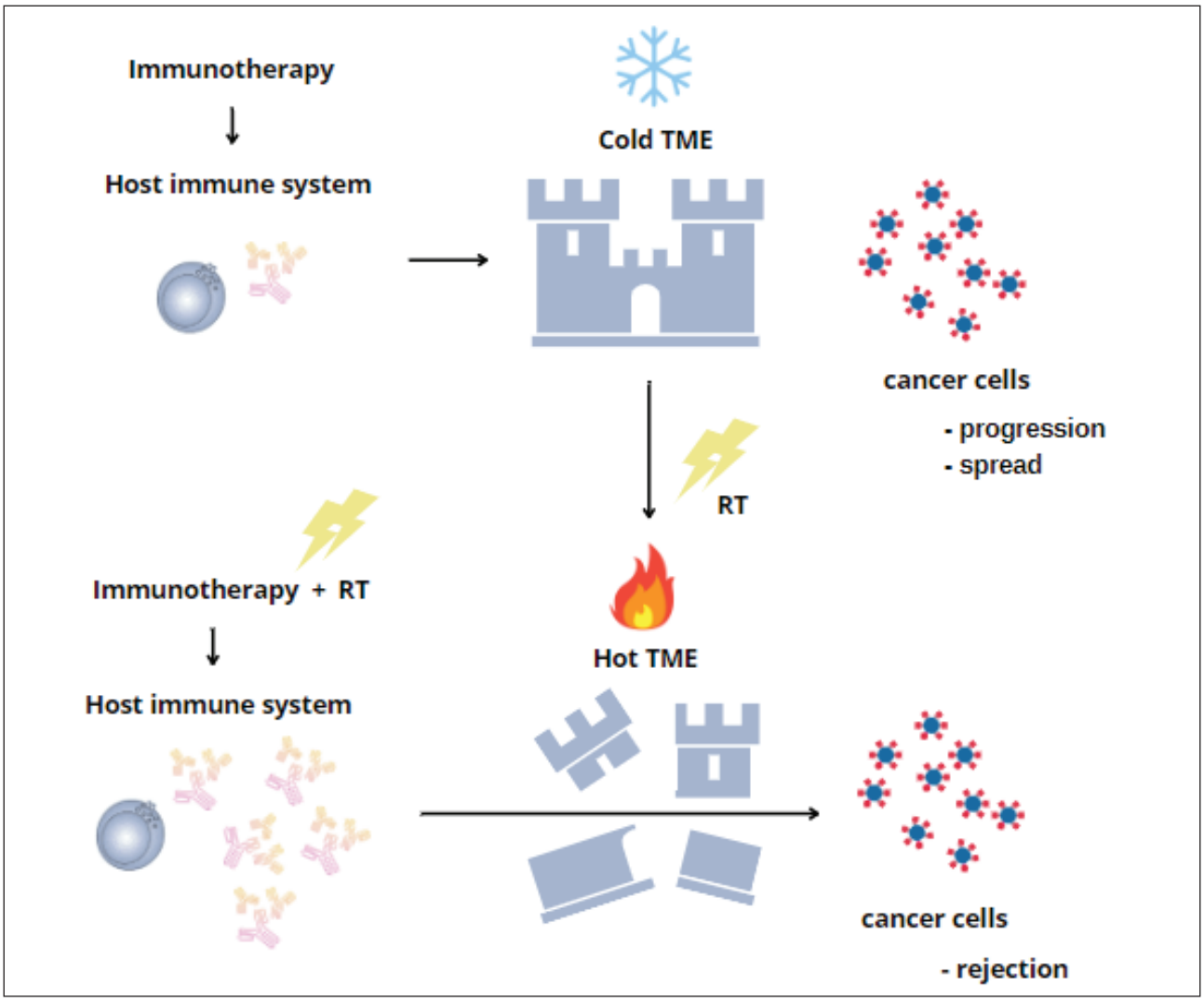


Figure 2. *A cold TME protects cancer cells from the host immune system response induced by IT administration. IT alone is unable to adequately counteract the cold TME immunosuppression and, consequently, the cancerogenesis process can progress and spread. The possibility to associate RT to IT strengthens the host immune system activation. In addition, RT is hypothesized to switch the TME from cold (i.e., immune-suppressive) to hot (i.e., tumor-killing), thereby depriving cancers cells of cold TME protection and favouring cancer cell rejection. As a result, cold TME irradiation associated with IT could produce an adequate host immune system counter-attack against cancer cells.*

couraged the authors to undertake a phase II clinical trial (*NCT 04553471*) to further investigate the LRT efficacy and its late toxicity.

Exploring available literature, it is possible to single out different LRT approaches. In some studies an initial LRT fraction is followed by a conventionally fractionated RT, while in others the whole treatment is delivered exclusively with LRT fractions (**table I**).

An interesting case series of Amendola et al. analyses the response of 10 patients affected by large NSCLC, to the combined approach of LRT and conventional RT (18). They administered a single LRT fraction (18 Gy on hotspots and 3 Gy on the remaining volume) followed by 25-33 RT conventional daily fractions (1.8-2 Gy per fraction), achieving a median volume reduction of around 42%, while not observing significant toxicities (18). In addition, they reported another case series of 10 patients affected by stage IIIB–IVA bulky cervical cancers, that received three upfront LRT fractions (24 Gy on the vertices and 9 Gy on the periphery in 3 fractions) followed by 39.60-45.00 Gy, in 1.8 Gy per fraction (21). Again, a mean tumor regression of around 54% was observed, with no grade ≥3 toxicity.

Regarding the other approach, Duriseti et al. and Iori et al. both administered exclusive LRT fractions, still without observing a grade ≥3 toxicity. Duriseti *et al.* delivered an exclusive LRT to a cohort of 20 patients with lesions >4.5 cm, with doses up to 66.70 Gy in the hotspots and 20 Gy in the periphery, in 5 daily fractions (20). Iori F *et al*. reported the case of a patient affected by a sarcomatoid lung

	N PATIENT	D VERTICES	D PERIPHERY	LRT FRACTIONS	FOLLOWED BY CONVENTIONAL RT
Amendola BE *et al.* (21)	10	9 Gy	3 Gy	3	Yes
Duriseti S *et al.* (20)	5	13.34 Gy	4 Gy	5	No
Iori F *et al.* (19)	1	11 Gy	4 Gy	5	No
Amendola BE *et al.* (18)	10	18 Gy	3 Gy	1	Yes

Table I. *Shows the available studies about different LRT approaches, reporting the number of LRT fraction delivered, whether the LRT was followed by a conventional RT, the LRT dose on the vertices and periphery per fraction.*

cancer with a T of 19 cm x 16 cm, who received 55 Gy on the hotspots and 20 Gy on the periphery in 5 consecutive fractions, reaching a 70% lesion reduction at 3 months (19). These preliminary data seem to suggest that both LRT approaches could be valid to safely reach a marked T response. As a result, both LTR approaches should be positively welcome and investigated for the time being.

There are interesting preclinical data on LRT modulation of cold TME and its possible association with IT, as LRT might influence the growth of metastatic sites through immune system and TME modulation. Kanagavelu *et al*. showed that the heterogeneous dose distribution (*i.e*., LRT) can be more efficient in activating the host immune system and in converting TME from cold into hot, compared with homogeneous tumor irradiation (*i.e*., conventional RT or SBRT) (22). Hence, in addition to large T control, the potent LRT immunomodulation properties could be strengthened with the IT administration to create an immune adaptive response that achieves a complete response in metastatic patients (23).

FUTURE PERSPECTIVE

Albeit the interesting perspectives on LRT cytoreductive and immunomodulatory actions, further research is mandatory. The combination of LRT with IT could become a key strategy for the management of cold tumors with a large T. Since LRT may allow a full exploitation of beneficial RT biological effects, it could be implemented as a key component of potential multimodal treatments with IT, and, considering its advantages, LRT could be used in the future with a curative intent. These preliminary data should encourage a multidisciplinary collaboration between radiation oncologists, medical oncologists, and immunologists to design and explore the LRT potentialities in clinical trials, and to spread its use into clinical practice.

ETHICS

Fundings

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Conflict of interests

The authors declare no conflict of interests.

Availability of data and materials

No new data were generated or analysed in this research.

Authors' contributions

FI, CI, SC contributed to the study conception and design. SC, CI, PC, FI performed material preparation. The first draft of the manuscript was written by FI, DF, VT, PC.

Ethical approval

N/A.

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