Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: April 30, 2023

Citation: Matiello J, Dalenogare M, et al., 2023. Radiotherapy in Lung Cancer: Ally or Foe of Immunotherapy, Medical Research Archives, [online] 11(4). https://doi.org/10.18103/mra.v11i4.3748

DOI
https://doi.org/10.18103/mra.v11i4.3748

ISSN: 2375-1924

RESEARCH ARTICLE

Radiotherapy in Lung Cancer: Ally or Foe of Immunotherapy?

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ABSTRACT

Radiotherapy is the most common local treatment for lung cancer. The spectrum of its use ranges from the treatment of early-stage tumors in patients who are not candidates for surgery to the treatment of advanced, unresectable tumors and, very frequently, of metastatic lesions. With great interest, radiotherapy has also been currently cited as a source of neoantigens, stimulating the immune system and enhancing the effect of immunomodulatory drugs. However, the side effects of irradiation on the lung parenchyma and on the immune system can turn it into a hidden foe, impairing patients' quality of life and survival. Pneumonitis and immunosuppression are two of the side effects of radiotherapy that best exemplify this hidden damage. Studies have shown decreased survival in patients who develop radiation pneumonitis or have a large volume of immune tissue irradiated. Irradiating less lung tissue will reduce damage to lung function and loss of immune cells. However, this alone is not sufficient for dose protection in lymphoid tissue, given the circulation of lymphoid cells in the great vessels and heart and their production in thoracic vertebral bone marrow. Identifying the optimal total dose and the most appropriate daily dose to reduce damage and boost the immune system is the target of our investigations. Although we still do not have an optimal algorithm for dose, fraction, and cost-effectiveness for radiation doses delivered to healthy tissues, we know which path to take.

Introduction

Worldwide, lung cancer is one of the most frequent and lethal cancers.[1] Most cases are diagnosed at an advanced stage. Data from developing countries, such as Brazil, show that only 8% of patients have stage I disease at diagnosis.[2] In the United States, this rate is above 25%.[3] Anyhow, globally the disease is often detected at advanced stages. In this scenario, radiotherapy assumes the role of the primary local treatment option for lung cancer.

The introduction of 3-dimensional (3D) conformal radiotherapy, compared with 2D radiotherapy, has shown a small overall survival gain of 3%, a 3-year survival of 19% to 22%, and a 5-year survival of 11% to 14% in patients with locally advanced tumors.[4,5] The use of intensity-modulated radiotherapy (IMRT), a sophistication of the 3D technique, has not been sufficient to improve survival compared with 3D treatment alone.[6] IMRT tends to be used to reduce high doses in organs at risk, but as a side effect, it can increase the spread of low-dose radiation to the lung, great vessels, and heart.[7]

For many decades, there has been little or no increase in survival of patients with locally advanced lung tumors. Increasing the radiation dose turned out to be deleterious when used in large volumes, as it is for locally advanced cancer.[8] In this context, we can understand that, in large volumes, a large part of our immune system becomes the target of radiation damage.[9] Lymphocytes, which can be destroyed with very low radiation doses due to their high radiosensitivity, take a long time to return to their baseline values.[10]

In recent years, immunotherapy has emerged as a promising treatment modality for this lethal disease. Mature data from the PACIFIC trial[11] show absolute benefits for local disease control and survival: 19.0% vs 33.1% for local disease control and 33.4% vs 42.9% for overall survival with the use of placebo and durvalumab, respectively.

In the current scenario, radiotherapy may have a synergistic effect on immunotherapy or a deleterious one. The article provides a brief review of the potential of radiotherapy, both beneficial and harmful, in combination with immunomodulatory drugs.

Radiotherapy generating neoantigens

The immunogenic potential of irradiation has been described and studied for more than 50 years, with the description of the abscopal effect as the starting point.[12-14] It is now known that both innate and adaptive immunity are stimulated by radiation damage. Radiation damage generates tumor-derived molecules that, like microbe molecules, act as a catalyst for the innate immune process, triggering an inflammatory cascade with monocytes as the main cellular component of this process. Adaptive immunity refers to specific immune responses to each antigen carried out by B and T lymphocytes, primarily by $CD4^+$ and $CD8^+$ T lymphocytes.[15]

Multiple types of cancer have very low mutational loads, with a reduced ability to respond to immune system stimulation.[16] Radiation, eliciting direct and indirect DNA damage in tumor cells, has been shown to induce mutations that can activate the immune system, facilitating immune checkpoint therapy.[17]

Radiotherapy inducing immunosuppression

Lymphocytes, critical to antitumor immunity, are extremely sensitive to radiation and can be lethally damaged with doses as low as 1 Gy.[18] Large irradiated volumes, irradiation of organs with high blood flow, such as the brain, heart, lung, and spleen, and irradiated bone marrow volume have been correlated with marked lymphocyte depletion.[19]

The estimated radiation dose to immune cells (EDIC) was then proposed in this setting, taking into account the radiation dose to the lung parenchyma and heart multiplied by the total dose and number of fractions. The model was validated using data from patients undergoing radiotherapy for lung cancer, demonstrating that the EDIC is able to predict lymphopenia in these patients.[20]

Clinical practice: Radiotherapy followed by immunotherapy

In metastatic tumors, radiotherapy prior to immunotherapy has been an ally in anticancer therapy. There is modern evidence of stereotactic body radiotherapy (SBRT) and hypofractionated radiotherapy obtaining local tumor control greater than or equal to that of conventional radiotherapy, with increased effectiveness in combination with immunotherapy.[21] In the KEYNOTE-0001 trial,[22] a post hoc analysis showed that patients with metastatic non-small-cell lung cancer (NSCLC) receiving immunotherapy and radiotherapy had a 73% 6-month overall survival compared with 43% in the non-irradiated group. However, in the presence of large irradiated volumes or multiple courses of radiotherapy, the benefit from combined therapy was lost and, in extreme situations, the effectiveness of immunotherapy was lost as well.[23]

The PACIFIC trial[11] gave new life to the treatment of advanced lung cancer. Improvements in overall survival and local disease control have been seen as promising results that might change the cure rates of locally advanced lung tumors.

Randomized patients from the PACIFIC trial[11] were later analyzed for the influence of immune population loss on overall and progression-free survival. The EDIC formula was used in this analysis to predict damage to immune cells.[24] Median overall survival was significantly shorter in patients with EDIC > 7.6 Gy than EDIC < 4.6 Gy (24.0 months vs not reached; $p < 0.001$), and recurrence-free survival was also shorter in patients with EDIC > 6 Gy than EDIC < 6 Gy (19.4 months vs not reached; $p < 0.001$).[24]

In early-stage lung cancer, SBRT promotes excellent local tumor control, but distant progression is an issue to be resolved.[25] Several ongoing trials aim to evaluate the benefits of SBRT followed by immunotherapy, including PACIFIC-4, SWOG 1914, and KEYNOTE-867.[26-28]

Concomitant immunotherapy and radiotherapy

Concurrent administration of immunotherapy and radiotherapy has been the subject of many current studies. After the PACIFIC trial demonstrated benefit with immunotherapy after combined treatment,[11] there has been a tendency to anticipate immunotherapy to be delivered concurrently with radiotherapy. Despite reports of safety and benefit with the concurrent immunotherapy combination,[29] one study reported absence of benefit from conventionally fractionated external beam radiotherapy combined with immunotherapy,[30] and one of the reasons may be a greater reduction in lymphocyte counts with protracted doses.

Immunotherapy before radiotherapy

Theoretically, receiving immunotherapy before radiotherapy would have the potential benefit of preventing lymphocyte depletion and actinic damage to the lung parenchyma that may lead to radiation pneumonitis (RP), interfering with the continuity of immunotherapy and the need for large-scale use of corticosteroids. However, radiation-induced neoantigen generation would be lost.[31] Definitive data are still lacking to resolve this issue. With a better evaluation of dose in immune tissues and lung parenchyma, with data included in the dose-volume histogram of radiotherapy treatment planning, irradiation could be aborted if the risk of immunosuppression or RP was high, delivering immunotherapy and then radiotherapy. It is an idea.

Would using this approach only in patients at high risk of RP be an option?

Radiation pneumonitis

Worldwide, we use standardized dose limits in the lung parenchyma, such as 20 Gy and 5 Gy in the entire lung volume, for any patient, from patients with completely healthy lungs to those with severe chronic obstructive pulmonary disease (COPD). Even complying with the dose limits suggested in the literature, it is plausible that some patients will have severe radiation damage, whereas others will recover without any noteworthy complications, since the total lung volume does not reflect the total functional volume. Other variables such as age, presence of COPD, and interstitial fibrosis[32] have been shown to increase the risk of severe pneumonitis, but they end up not being considered in the dose limits for the lung parenchyma.

An interesting Japanese study conducted by Kashihara et al.[33] evaluated potential predictive factors of RP after concurrent chemoradiation therapy (CCRT) and adjuvant durvalumab in patients with locally advanced NSCLC. The analysis included the Brinkman index (number of cigarettes smoked per day x number of years of smoking), age, comorbidities, percentage of lung volume receiving a dose of ≥ 20 Gy (V20) and ≥ 5 Gy (V5), heart dose, and interstitial lung abnormality score (ILAS) rated from 0 to 2 (original ILASs: 0, none; 1, interstitial lung abnormality without honeycombing [ground-glass attenuation, fine reticular opacity, and microcysts]; and 2, honeycombing). The results showed that only ILAS was statistically relevant in predicting RP. Of 117 patients analyzed, 19 had an ILAS 1 and 9 had an ILAS 2. Of 19 patients with an ILAS 1, 8 (42%) required corticosteroid treatment for their RP. Of 9 patients with an ILAS 2, 6 (66%) required oxygen and 2 (22%) had grade 5 toxicity. Lung V5 and V20 lacked the statistical power to predict RP when included in the multivariate analysis with ILAS.[33]

Corticosteroids are the drug of choice for the treatment of RP. However, patients with NSCLC receiving a corticosteroid dose of ≥ 10 mg of prednisone equivalent at the start of immunotherapy had poorer tumor control outcomes.[34]

In patients receiving previous radiotherapy, the occurrence of pneumonitis during the course of immunotherapy can play a decisive role in discontinuing immunomodulatory drugs. However, the lung damage may have been caused by previous irradiation. In the PACIFIC trial,[11] comparing CCRT plus adjuvant durvalumab with CCRT alone, pneumonitis or RP of any grade occurred in 33.9% of patients treated with CCRT plus adjuvant durvalumab and in 24.8% of those treated with CCRT plus placebo.

Ultimately, lung density data may help us distinguish fibrotic and emphysematous lung from normal-density lung and provide us with a new lung tissue volume, inducing a new dose-volume histogram. However, will this alone be enough? We do not know yet, but our group is investigating these issues. Are entry fields in known non-functioning areas feasible possibilities? We are also investigating it. In any case, it is important to take an overall look at lung parenchymal toxicity. It is not uncommon for us in clinical practice to see patients with no evidence of tumor disease who have met the suggested dose limits but are oxygen dependent and experience a marked deterioration of functional status. Does irradiation always pay off? At which dose and fraction?

We need a more efficient way to assess how deleterious we will be to patients by irradiating their lung parenchyma (often already reduced due to COPD) and how much this will impact their immunotherapy and their risk of severe pneumonitis.

Conclusion

Given the benefits of irradiation in stimulating the innate and adaptive immune systems, its early use in patients who will receive immunotherapy is interesting and motivating. However, understanding the exact deleterious potential of irradiation with properly calculated damage to the immune system and lung parenchyma is crucial. Preclinical and clinical trials are underway and, probably, the use of the well-known old lung constraints will be modified soon.

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