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CASE REPORT

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Durable complete response to PET-CT driven stereotactic radiation therapy plus pembrolizumab for pleomorphic Pancoast cancer: Case report and literature review

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Key Clinical Message

PET-driven SBRT plus pembrolizumab as first-line therapy against pleomorphic Pancoast cancer appears beneficial, probably due to high equivalent doses of SBRT on photopenic necrotic core and synergic immune system stimulation of immunoradiotherapy.

KEYWORDS

image-guided radiation therapy, immune checkpoint inhibitors, Pancoast tumor, pleomorphic lung cancer, radioimmunotherapy, stereotactic body radiotherapy

1 | INTRODUCTION

Pleomorphic carcinoma (PC) is a rare malignancy of the lung, with a more aggressive clinical course and a worse outcome than other non-small cell lung cancer (NSCLC). No consensus has been reached on therapy of this subtype of lung cancer. Surgery is the upfront treatment for the early stage of PC[1]; however, it may not always be a therapeutic option, due to the local extension and the location of the lesion, as for Pancoast tumor. In patients with an unresectable, non-metastatic Pancoast tumor who have good performance status, definitive concurrent chemotherapy, and radiotherapy are suggested[2] and there is no report in the literature about the use of high-dose RT with stereotactic technique.

However, conventional radiation therapy has had little effect on PC and this disease was found to be often refractory to chemotherapy regimens.[3] Therefore, the prognosis is poor and median survival time has been reported to be approximately 10 months.[4] Thus, other treatment strategies may be needed.

Immunoradiotherapy is a promising strategy: Accumulating evidence indicates that combining RT with anti-PD-1 treatment increases the anti-tumoral activity of both treatments and enhances outcomes, even for patients affected by lung cancer.[5–7]

With improvements in technology and precision of RT, stereotactic body radiation therapy (SBRT) and metabolic dose painting may become a key treatment option in modern cancer management, above all for high malignancy tumor.

We herein report the successful treatment of a patient affected by pleomorphic Pancoast cancer, which is the first in the literature to our knowledge consisting of combined PET-CT driven SBRT and pembrolizumab.

2 | CASE PRESENTATION AND TREATMENT

In April 2022, a 64-year-old man patient, smoker (three packs per day for 40 years), was visited in our radiation oncology unit. He complained of intense pain to the left arm (NRS 10), despite multi-drug oral pain therapy. On physical examination, he presented drooping eyelid and functional impotence of the left upper limb. He had a history of diabetes and hypertension, treated with oral hypoglycemic agent (metformin) and antihypertensive medicine (atenolol). His performance status was European Cooperative Oncology Group (ECOG) 0. In March 2022, a chest computed tomography (CT) scan revealed a huge mass in the left lung apex (maximum diameter 54 mm × 50 mm × 55 mm), infiltrating mediastinal pleura and the first two ribs with brachial plexus and contacting the subclavian artery. The PET-TC scan showed a high level of 18F-FDG uptake in the LUL mass (SUV max 16.1) and a hypermetabolic ipsilateral supraclavicular node (SUV max 6.2).

The histological examination after biopsy of the lung mass performed for diagnosis revealed frustules of non-small cell, poorly differentiated cancer, partially necrotic, histotype compatible with PC. The tumor did not exhibit EGFR or KRAS mutations, nor ALK or ROS-1 rearrangement. Immunohistochemistry also detected PD-L1 expression in >50% of tumor cells. The clinical stage was classified as stage III C (cT4 cN3 cM0).

Given histologically proven PC and the rapid worsening symptoms, curative radiation with SBRT to the LUL primary tumor was planned as patient was deemed not to be a surgical candidate. Pembrolizumab at a dose of 200 mg/kg every 3 weeks was prescribed until progression.

SBRT was started after a week from first immunotherapy infusion. The simulation four dimensional CT (4D CT) revealed no movement of the target; thus, lesion and positive nodes were identified as clinical target volume (CTV), and a 3-mm isotropic margin was added for planning target volume (PTV). PET-CT imaging fusion with CT simulation was used to contour photopenic necrotic core to boost. The dose prescription was 30 Gy in five fractions (6 Gy/fr) to PTV with a simultaneous integrated boost of 40 Gy in five fractions (8 Gy/fr) to photopenic necrotic core at 88% isodose. The treatment plan was realized in VMAT technique (Figure 1).

3 | OUTCOMES AND FOLLOW-UP

At the first day of SBRT treatment, 1 week after simulation CT, the CTV was measured on CBCT and was found increased from 271.3 cc to 302.8 cc.

Radiological assessment after SBRT showed a progressive reduction in CTV: It measured 149.2 cc on follow-up CT after 45 days and 63.7 cc on 6-month follow-up PET-TC (Figure 2).

It also showed a reduction in the SUV max value of the lung lesion from 16.1 at staging PET-CT to 8.5 on 6-month follow-up PET-TC with a disappearance of lymphnode captation. Finally, PET-CT after 9-month follow-up showed post-radiation inflammatory signs without residual neoplastic lesion, therefore CTV was not measurable. Figure 3 shows progressive percentage reduction in tumor volume and metabolic activity during follow-up.

Clinically, a gradual improvement of symptoms was recorded during follow-up. The patient reported a pain reduction from 5 days after SBRT. At first follow-up visit, 2 months after SBRT, the patient complained slight deficiency of hand strength and ulnar paresthesia, with mild-intensity pain (NRS 5). At 6-month follow-up, the patient still reported episodic mild-intensity pain (NRS 5), taking halved oral pain therapy. At 9-month follow-up, the patient reported further reduction in pain intensity (NRS 3), despite the subsequent diminishing oral pain therapy.

Pembrolizumab was administered every 3 weeks, with an interruption due to the onset of drug-related acute renal failure. The patient also developed ICI-induced thyroiditis and diarrhea. At 18-month follow-up, a total body CT confirmed complete response and absence of recurrence.

4 | DISCUSSION

Immune checkpoint inhibitors (ICIs) were demonstrated to be beneficial for patients with NSCLC,[8] and a few cases with PC have been reported to show tumor shrinkage with immunotherapy.[9–12] Nonetheless, survival outcomes and response remain unsatisfactory, mostly because of the onset of primary or acquired resistance. Thus, ICIs cannot be considered adequate as monotherapy for PC treatment.

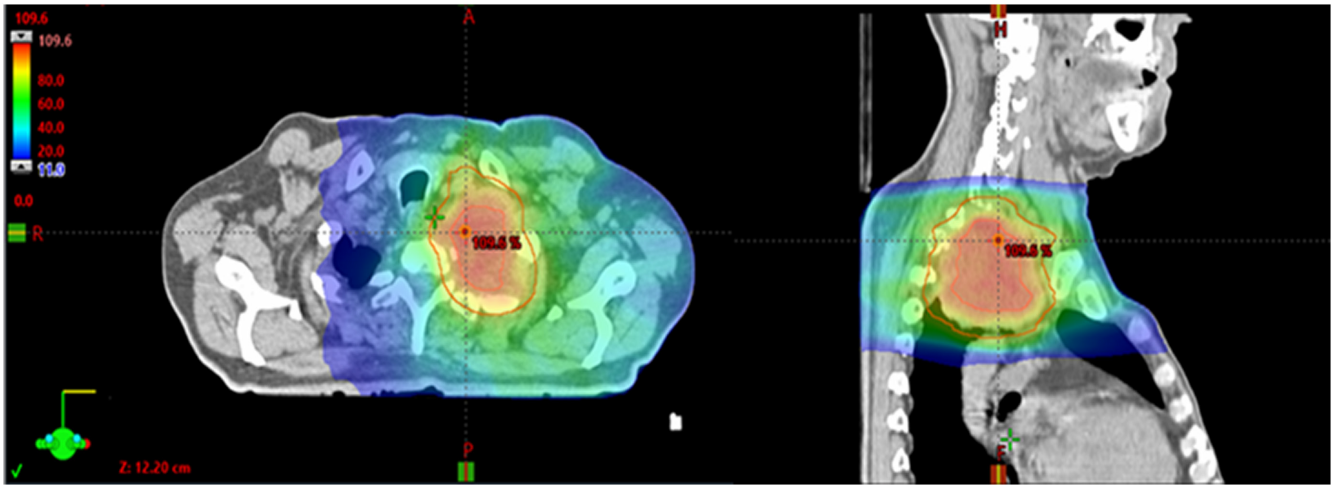

FIGURE 1 Radiation treatment planning. Transversal, sagittal, and coronal slices representative of SBRT isodose distribution (red area: 40 Gy, yellow area: 30 Gy).

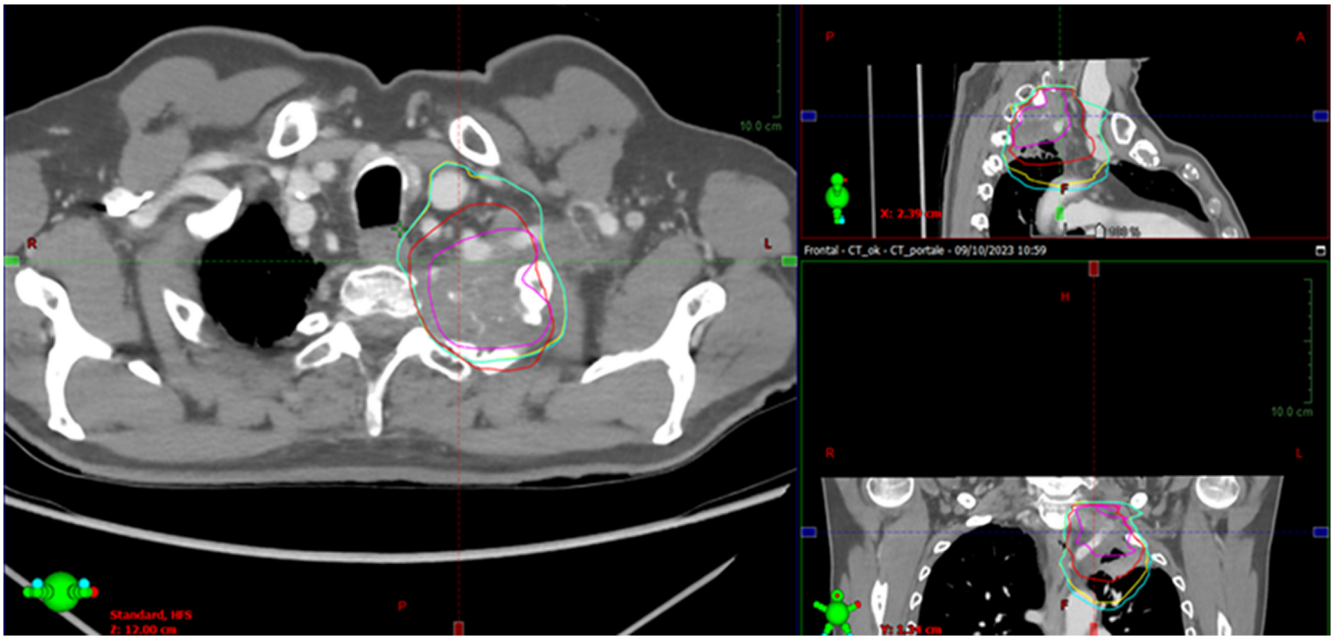

FIGURE 2 Progressive CTV reduction after SBRT. CTV contours on transversal, sagittal, and coronal slices of follow-up CT after 9 months: CTV on simulation CT in yellow line, on first CBCT in cyan line, on follow-up CT after 45 days in red line, on follow-up CT after 6 months in purple line.

Combining RT with immune checkpoint inhibition is a novel therapeutic strategy, supported by many preclinical and clinical evidence.[6] In particular, the randomized phase 2 PEMBRO-RT trial showed an augmenting effect of SBRT on the response to PD-1 blockade in patients with metastatic NSCLC, with a doubling overall response rate.[13]

Indeed, while SBRT directly damages malignant cells and promotes tumor antigen releasing, recognition and presentation, modulating tumor microenvironment, the enhanced expression of PD-L1 induced by SBRT can make patients more sensitive to subsequent PD-1/PD-L1 inhibitors.[14]

Optimal fraction and dose selection are still not clear; however, radiation-induced antitumor immunity might be dose-dependent and in several studies high-dose fraction RT combined with PD-1 antibody immunotherapy was find more effective in reversing the immunosuppressive microenvironment and controlling primary and distal metastatic tumors than conventionally fractionated radiotherapy.[15–17]

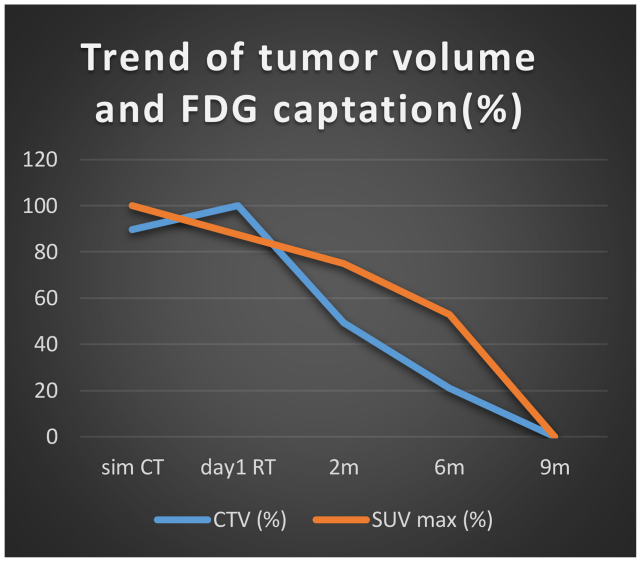

FIGURE 3 Trend of tumor volume and FDG captation. The graph shows the progressive percentage reduction in tumor volume (blue line) and metabolic activity (orange line) at radiological assessment during FUP.

In the literature, optimal radiation dose appears to be a window of 5–10 Gy per fraction regarding immunological response, which may be the trade-off between maximum tumor lysis and minimal vascular disruption.[18,19]

However, hypoxic and anoxic regions, especially within bulky tumor, require relatively higher doses per fraction of RT for comparable cell kill. The recent technology evolution of RT techniques allows optimization of delivering inhomogeneous differential doses to these varied areas by dose painting.[20] This technique can deliver controlled hot spots within the gross tumor volume to target the specific areas of resistant cell locations, which can be identified by fluorodeoxyglucose (FDG). The modern SBRT-targeted hypoxic segments already showed very inspiring results in other studies, suggesting a bulky tumor control rate of 95% (bystander effects) and non-irradiated metastases of 45% (abscopal effects).[21,22]

Therefore, a fractionated SBRT of 6 Gy/fr to the bulky lesion with a SIB of 8 Gy/fr on biological target subvolume defined by PET was chosen in the reported case.

In phase II trials and other review studies, SBRT with immunotherapy showed grade 3+ toxicity rates up to 30%.[23] However, PD-1 inhibitors as monotherapy, even well tolerated, shows thyroiditis, colitis, nephritis and a rate of pneumonitis around 7%, not deemed dose-related.[24–26] In a recent phase II study of pembrolizumab, drug-related grade 3 or 4 adverse events (AEs) occurred in 12% of patients, with 5% of patients having drug-related serious AEs s and 3% of patients discontinued treatment because of drug-related AEs.[25] Also in this case report, the patient presented ICI-related thyroiditis, diarrhea, and acute renal failure required treatment interruption, but no clinical nor radiological signs of pneumonitis were recorded.

High precision therapy using simultaneously integrated protector volumes and biological dose painting may allow to deliver high dose and to reach complete response, limiting the dose to the normal tissue and reducing the potential toxicities of combined treatment.

5 | CONCLUSION

To our knowledge, this is the first case report in the literature about the use of PET-driven SBRT plus pembrolizumab as first-line therapy against pleomorphic Pancoast cancer. This kind of association appears beneficial in symptomatic patients. It is an effective treatment, at least when PD-L1 expression is high, probably due to high equivalent doses of SBRT on photopenic necrotic core and synergic immune system stimulation of immunoradiotherapy. Further reports to compare effectiveness with different treatment methods are needed to establish the best effective treatment strategy for this type of cancer.

AUTHOR CONTRIBUTIONS

Alessandra Castelluccia: Conceptualization; methodology; writing – original draft; writing – review and editing. **Angela Sardaro:** Supervision; validation. **Artor Niccoli Asabella:** Supervision; validation. **Antonio Rosario Pisani:** Supervision; validation. **Dino Rubini:** Supervision; validation. **Maurizio Portaluri:** Supervision; validation. **Francesco Tramacere:** Data curation; supervision; validation.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests or other interests that might be perceived to influence the results and/or discussion reported in this paper.

DATA AVAILABILITY STATEMENT

All main data are reported in the manuscript.

CONSENT

Written informed consent was obtained from the patient before the study for the publication of this Case Report and any accompanying images.

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