CASE REPORT

Coeliac lymph nodes SBRT Combined with Immunotherapy Rechallenge Induce Abscopal Effect in Metastatic Non-Small-Cell Lung Cancer: A Case Report and Literature Review

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Abstract

Stereotactic body radiotherapy (SBRT) may enhance synergistic effects of immunotherapies and radiotherapy (iRT), with the potential to induce abscopal effect in irradiated and non-irradiated sites. The case of a metastatic non-small-cell lung cancer (NSCLC) male patient with acquired immune checkpoint inhibitor (ICI) resistance (third-line setting) is reported. He received coeliac lymph node SBRT plus ICI re-challenge. This regimen induced abscopal effect on the patient's metastatic liver lesions. Despite negative PD-L1 expression and low tumour mutation burden (TMB) in liver biopsies, the patient achieved a progression-free survival (PFS) exceeding 12 months post-rechallenge, with 29 months of overall survival (OS) from initial ICI treatment (the follow-up ended in October 2021 due to the patient's death). Reports on draining lymph node (DLN) SBRT combined with ICI re-challenge in immunotherapy-resistant metastatic NSCLC remain scarce, especially when targetting coeliac lymph nodes. This case suggests that DLN SBRT plus ICIs could be a reasonable option for such immunotherapy-resistant patients.

Keywords: Non-small-cell lung cancer; Immune checkpoint inhibitor; Stereotactic Body Radiotherapy; Abscopal effect; Draining lymph node; Rechallenge.

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Introduction

Lung cancer remains the leading cause of cancer deaths worldwide (2022 global estimates).[1] Immunotherapies such as programmed cell death protein 1 (PD-1)/ programmed death ligand 1 (PD-L1)/cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors effectively treat a subset of non-small-cell lung cancer (NSCLC) patients.[2] However, only a small proportion benefit from it, and 30%-50% of patients develop primary or acquired resistance.[2] Combination treatments are being explored, with immunoradiotherapy (iRT) emerging as a promising approach.

Stereotactic body radiotherapy (SBRT) delivers higher doses per fraction than conventional radiotherapy; preclinical studies confirm that it releases more tumour-associated antigens (TAAs) and cytokines, triggering systemic immune responses.[3] Clinically, the phase 2 SWORD trial (advanced NSCLC) combined SBRT with Sintilimab and Granulocyte-macrophage colony-stimulating factor (GM-CSF), reported a 36.7% overall response rate (ORR).[4] Thus, the combination of SBRT and immunotherapy represents a potentially viable therapeutic strategy.

The abscopal effect—tumour regression in non-irradiated distant sites induced by local radiotherapy—relies on systemic anti-tumour immune responses.[5] Historically, this effect has been primarily reported in tumours with high immunogenicity, such as renal cell carcinoma, NSCLC, and melanoma, with an overall low clinical incidence.[5] While iRT has been explored in broader oncology contexts, reports of draining lymph node (DLN) SBRT plus immune checkpoint inhibitor (ICI) rechallenge inducing abscopal effect in immunotherapy-resistant metastatic NSCLC remain scarce. Herein, we present an immunotherapy-resistant metastatic NSCLC case that achieved local tumour control and abscopal effect with iRT, yielding meaningful clinical benefit. This case report aims to provide preliminary clinical evidence for this strategy.

Case Report

In June 2014, a 39-year-old male at the 904 Hospital of the Joint Logistic Support Force of the Chinese People's Liberation Army, Wuxi, Jiangsu Province, China, was diagnosed with stage IV-A large-cell lung cancer (LCLC) via left pneumonectomy (no EGFR/ALK alterations). He received four cycles of Pemetrexed plus Carboplatin. In October 2016, PET-CT revealed metastases in the left pleura, clavicular, and mediastinal lymph nodes (Figure 1A)—all of which are within the regional drainage and spread territory of the original left lung primary tumour.

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Left clavicular lymph node biopsy confirmed metastatic poorly differentiated squamous cell carcinoma (PDSCC); tissue tests showed negative PD-L1 expression and low tumour mutation burden (TMB). To resolve the histological discrepancy between the primary LCLC and metastatic PDSCC, both the 2014 pneumonectomy specimen and 2016 lymph node biopsy specimen were reviewed by two senior pathologists. The pathological consensus, combined with imaging findings, confirmed that the metastatic lesions represent subclonal progression of the original LCLC, driven by intratumoural heterogeneity. Notably, no evidence of a second primary lung cancer was identified on PET-CT/chest CT imaging; there were no new, discrete pulmonary nodules or hypermetabolic foci outside the distribution of the drainage region of the original left lung tumour, and all metastatic lesions were contiguous with the original tumour's metastatic pathway. The patient was evaluated as partial remission (PR) (All tumour response assessments were performed according to RECIST version 1.1 criteria)[6] through four cycles of Etoposide and Carboplatin (Figure 1B). In September 2017, follow-up PET-CT identified a new right parietal lobe lesion (Figure 1C), confirmed by MRI of the brain. The patient received local SBRT for the brain metastasis and four cycles of Pemetrexed plus Cisplatin, with stable lesions over 18 months of follow-up.

In April 2019, CT scan of the abdomen showed new liver metastases (Figure 1D). Liver biopsy confirmed metastatic PDSCC (negative PD-L1, low TMB; no specific mutations). The patient received five cycles of Pembrolizumab (200 mg, day 1, every three weeks) combined with Albumin-bound Paclitaxel (300 mg, day 1, every three weeks), achieving PR (Figure 1E), followed by five cycles of Pembrolizumab maintenance.

In March 2020, CT of the abdomen showed liver and abdominal lymph node progression at the Wuxi branch of Ruijin Hospital Shanghai Jiao Tong University School of Medicine, Wuxi, Jiangsu Province, China (Figure 1F). Since May 2020, the patient received the iRT regimen: SBRT to coeliac lymph nodes (CyberKnife: 3600 cGy in six fractions, prescribed to the 68% Isodose line) plus Pembrolizumab (200 mg, day 1, every three weeks). Follow-up CT in June 2020 showed persistent PR in irradiated DLNs and non-irradiated liver metastases (Figure 1G). PET-CT further confirmed reduced hyper-metabolic areas without new lesions (Figures 1HI). Peripheral blood lymphocyte subset analysis showed a brief decrease in CD3+ and CD8+ T lymphocytes after radiotherapy, with obvious increases in July 2020 and January 2021 (Figure 2D). Disease progression occurred in May 2021, and the patient died of the disease in October 2021.

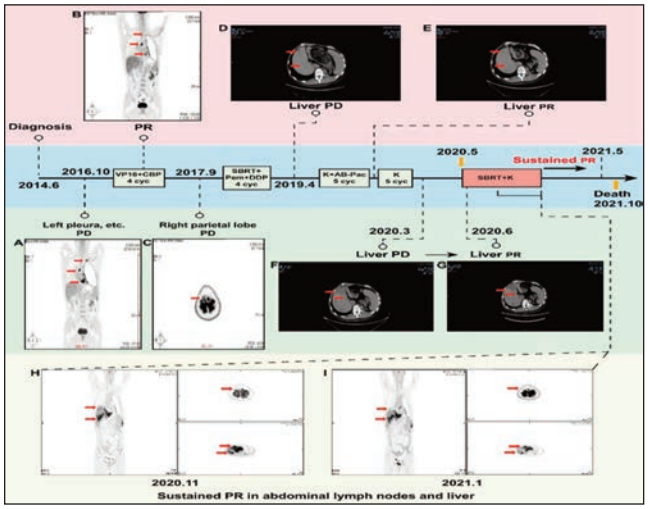

Figure-1: Comprehensive overview of the patient's diagnostic and treatment progression

Schaematic diagram of the treatment process and efficacy evaluation from initial treatment to the death of the patient. The PET-CT comparison of de novo multiple metastatic lesions in the left pleura, clavicle, and mediastinal lymph nodes after four cycles of etoposide and carboplatin therapy (A, B); The progression in the right parietal lobe during post-treatment follow-up (C). Abdominal CT shows liver metastasis detected during follow-up after brain SBRT combined with Pemetrexed and Cisplatin therapy (D); Abdominal CT demonstrates PR of liver metastases after treatment with Pembrolizumab combined with Nab-paclitaxel, followed by subsequent progression indicative of drug resistance (E, F); Abdominal CT shows synergistic effect of abdominal lymph node SBRT combined with Pembrolizumab leading to PR in liver lesions (G); PET-CT shows no new hypermetabolic lesions during follow-up, with persistent reduction of abnormal signals in the liver and abdominal lymph nodes (H, I). Abbreviations: PD, Progressive Disease; PR, Partial response; VP16, Etoposide; CBP, Carboplatin; SBRT, Stereotactic body radiotherapy; Pem, Pemetrexed; DDP, Cisplatin; K, Pembrolizumab; AB-Pac, Albumin-Bound Paclitaxel. Red arrows indicate the patient's Tumour lesions. Figure 1 depicts the patient's full clinical timeline from initial treatment to his death in October 2021, with no disease progression noted between May and October 2021. All diagnoses, treatments, and follow-up evaluations throughout the clinical course were performed at relevant medical institutions in Wuxi, with continuous management by the same treating physician to ensure the consistency and integrity of clinical data.

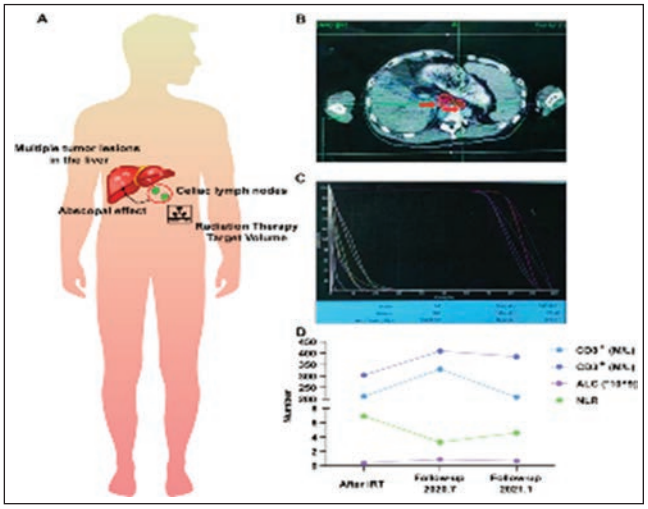

Figure-2: Radiation localisation images of SBRT to coeliac lymph nodes and Schematic diagram of the number of lymphocytes.

Schematic of abdominal lymph node radiation therapy target volume and abscopal effect on multiple liver lesions (A). Abdominal CT images of radiation localisation of SBRT to coeliac lymph nodes (B). Radiation dose specification for coeliac lymph node SBRT (CyberKnife): 3600 cGy delivered in 6 fractions, prescribed to the 68% isodose line (C). Changes in lymphocyte counts and proportions during SBRT combined with Pembrolizumab therapy (D). Red arrows represent metastatic coeliac lymph nodes accepted SBRT. Abbreviations: NLR, neutrophil/lymphocyte ratio; ALC, absolute number of lymphocytes; CD3+, CD3 positive T lymphocytes; CD8+, CD8 positive T lymphocytes; iRT, SBRT + Pembrolizumab.

In this context, DLN SBRT combined with ICI rechallenge in this metastatic NSCLC patient achieved a PFS exceeding 12 months after acquired ICI resistance (third-line setting), and 29 months of OS from the initiation of initial ICI treatment (April 2019 to October 2021).

Discussion

ICI resistance remains a major challenge in advanced NSCLC, particularly in 'cold tumours'. SBRT activates immunity by releasing TAAs and cytokines, driving dendritic cell maturation and cytotoxic T lymphocytes activation—key steps for overcoming such tumours. Clinical evidence shows that compared with Pembrolizumab monotherapy, SBRT plus Pembrolizumab prolongs PFS in cold NSCLC.[7] The combination group exhibits enriched expression of gene sets for interferon-γ, interferon-α, and antigen processing/presentation, and increased newly expanded T cell receptor (TCR) clones in tumour tissues and peripheral blood.[7] The current case aligns with this: the patient had a 'cold' tumour phenotype (PD-L1 negative, low TMB), yet he responded to SBRT plus Pembrolizumab. This raises the speculative hypothesis that SBRT may bypass typical 'cold tumour' barriers by enhancing lymph node antigen presentation, though unconfirmed due to lack of correlative biomarker data from irradiated nodes or metastases, warranting further investigation.

However, lymph node SBRT's synergy with immunotherapy is controversial due to radiation-induced lymphopenia—low absolute lymphocyte count (ALC < 0.50×10^9/L) and high neutrophil/lymphocyte ratio (NLR > 4) correlate with poor survival in metastatic solid tumours.[8] The current patient mirrored this transient toxicity: within two weeks of finishing DLN SBRT (CyberKnife: 3600 cGy in six fractions, prescribed to the 68% Isodose line), his NLR spiked to 6.91 and ALC dropped to 0.37×10^9/L, with CD3+ and CD8+ T cell counts at 304 cells/μL and 212 cells/μL, respectively. Consistent with prior studies, this toxicity was transient—likely attributed to SBRT's hypofractionated delivery which better preserves lymphocytes than conventional fractionated radiotherapy.[9] Crucially, these markers recovered with continued Pembrolizumab; by July 2020, NLR fell to 3.30, ALC rose to 0.88×10^9/L, and CD3+/CD8+ T cells increased to 409/330 cells/μL. This recovery—paired with sustained PR (Figure 1E)—highlights that hypofractionated DLN SBRT may induce transient rather than permanent lymphotoxicity, making it safe to combine with ICIs even in patients with pre-existing lymphopenia.

The abscopal effect of iRT exhibits tumour-type and organ specificity, as supported by prior studies. Historically, this effect is more frequently reported in high-immunogenicity tumours, accounting for 60% of abscopal response cases; notably, 40% occur in low-immunogenicity tumours.[5] Metastatic sites with highest prevalence are lungs (41%), lymph nodes (31%), and liver (15.7%).[10,11] Notably, the current low-immunogenicity 'cold tumour' patient (PD-L1 negative, low TMB) benefited, suggesting immunogenicity is not a decisive iRT contraindication. When exploring the tumour-type preference of the abscopal effect, some prior studies often did not distinguish single radiotherapy from iRT,[5] which may explain this. Recent evidence confirms that iRT enhances abscopal effect prevalence,[10] with immunotherapy amplifying radiotherapy's immune effects in low-immunogenicity tumours.

Conclusion

Coeliac DLN SBRT plus ICI re-challenge induced meaningful abscopal effect and prolonged survival (≥12 months PFS; 29 months OS from initial ICI) in an ICI-resistant, 'cold tumour' (PD-L1 negative, low TMB) metastatic NSCLC patient. This hypothesis-generating observation requires prospective validation in larger cohorts, with limitations including single-case design and inherent iRT response heterogeneity.

Consent to publish: Written informed consent to publish the clinical details and images were obtained from the patient.

Statements & Declarations: All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. No artificial intelligence was applied during the preparation of this manuscript. The patient deceased in late 2021. We began to sort clinical data and write the manuscript right after, but the COVID-19 Omicron pandemic across Shanghai, Jiangsu and surrounding areas throughout 2022 severely affected our clinical and research work. We restarted the relevant work in early 2023. The manuscript was submitted to different journals and revised repeatedly in the next period, and we formally submitted it to this journal on May 2, 2025.

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was obtained from the patient. All methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

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Author Contribution:
JY: Design, writing, editing and final approval.
YG & WZ: Acquired clinical data, performed patient follow-ups and final approval.
XZ: Writing and final approval.
YY: Editing and final approval.
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