Radiotherapy for oligoprogressive disease in non-small cell lung cancer treated with pembrolizumab in first-line setting: a retrospective study

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Original Article

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Background: Oligoprogression (OP) is common in patients with metastatic non-small cell lung cancer (mNSCLC) treated with immune checkpoint inhibitors (ICIs). This study aims to assess the benefit and the safety profile of ablative radiotherapy (RT) for OP in mNSCLC treated with pembrolizumab in first-line setting.

Methods: We retrospectively analyzed records of all consecutive mNSCLC patients who underwent treatment with pembrolizumab (+/– chemotherapy) in first-line setting and developed an OP treated with ablative RT while continuing pembrolizumab, in a French Hospital from 2019 to 2022. Primary endpoint was time to next systemic treatment (TTNT). Secondary endpoints included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and safety profile. Furthermore, we investigated features associated with clinical outcomes.

Results: Thirty-six patients were included and 47 OPs were reported (27 patients experienced one OP, 7 two OP, and 2 three OP). The median TTNT (mTTNT) after the first OP was 19.6 months [95% confidence interval (CI): 12.4–not reached (NR)]. The median PFS (mPFS) after the first OP was 12 months (95% CI: 6.1–NR) and 10.4 months (95% CI: 3.9–NR) after the second or third OP. The median OS (mOS) from the first OP and from pembrolizumab initiation were NR. In multivariable analysis, the presence of adrenal gland was associated with shorter TTNT and OS, while OP involving bone metastasis was associated with shorter PFS. The ORR of the lesions treated with RT was 70.2%. No RT-induced severe adverse event was reported. Three patients experienced severe pembrolizumab-induced adverse events.

Conclusions: In this study, RT alongside the maintenance of pembrolizumab for patients experiencing OP during first-line pembrolizumab-based therapy for mNSCLC demonstrated an acceptable safety profile and favorable outcomes. Data from phase 3 randomized trials are needed to clearly establish the benefits of this strategy in treating oligoprogressive mNSCLC.

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Keywords: Non-small cell lung cancer (NSCLC); oligoprogression (OP); radiotherapy (RT); immune checkpoint inhibitor (ICI); pembrolizumab

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Introduction

Lung cancer is the leading cause of cancer death worldwide (1). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers (2). A significant majority of NSCLC cases are diagnosed at an advanced stage, rendering curative local-regional treatment unfeasible (2). Immune checkpoint inhibitors (ICIs), such as programmed death 1 (PD1) inhibitors, restore T-cell-mediated immune responses against multiple cancer types (3). Their emergence has fundamentally transformed the treatment paradigm in oncology, becoming widely prescribed across various malignancies (4). In the context of NSCLC, ICI and especially PD1 blockade have significantly improved overall survival (OS). Initially established in metastatic stages (5-11), then in locally advanced stages (12), and finally in the perioperative setting for localized stages (13,14).

Since ICIs exhibit an original mechanism of action that is based on enhancing the anti-tumor immune response, physicians are facing various patterns of tumor response and progression (15). Among them, pseudo-progression, long-term near-complete to complete response, hyperprogression, and oligoprogression (OP) (15,16) have been described. OP occurs when, in the context of metastatic cancer, only a limited number of lesions progress while others remain stable or respond to treatment (17). There is no unanimous agreement on the maximum number of progressing tumor lesions defining OP; however, most authors establish the threshold at ≤3 or ≤5 lesions (18). OP stems from clonal heterogeneity and tumor evolution, where a limited number of advancing lesions are propelled by resistant clones. This phenomenon can manifest in patients with oligometastatic cancer as well as those with polymetastatic disease (18,19). Recently, local ablative therapy (LAT), including surgery, radiotherapy (RT), microwave ablation, or cryotherapy, has emerged as a promising treatment approach for oligoprogressive disease (20-25).

In the context of metastatic NSCLC (mNSCLC), employing LAT for OP disease has demonstrated the potential to enhance progression-free survival (PFS) and extend the time to next systemic treatment (TTNT), particularly in cases of oncogenic addiction such as epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK), treated with targeted therapies (26-28). A large retrospective study found that ablative RT, combined with continued systemic treatment, could significantly delay the TTNT (29). The median time before changing systemic therapy was 8.8 months for patients with mNSCLC, regardless of the presence of oncogenic driver mutations (29). A recent randomized phase 2 clinical trial demonstrated that OP in patients with mNSCLC, with

Highlight box

Key findings

- Oligoprogression (OP) in first-line pembrolizumab-treated metastatic non-small cell lung cancer (mNSCLC) is common. Radiotherapy (RT) with pembrolizumab maintenance in OP could significantly delay second-line.

What is known and what is new?

- Retrospective studies have indicated that focal RT, combined with ongoing nivolumab administration, is associated with favorable clinical outcomes in the treatment of oligoprogressive mNSCLC during second or subsequent lines of therapy. A recent retrospective study involving a cohort of 39 advanced NSCLC patients treated with first-line pembrolizumab found that treating OP with RT was associated with longer survival compared to switching systemic therapy. However, the clinical benefits and toxicity profile of this therapeutic strategy, as well as the characteristics of the patients who benefit most from it, are yet to be determined.
- The median time to next treatment (TTNT) after OP was 19.6 months. The presence of adrenal gland was associated with shorter TTNT and overall survival, and OP involving bone metastasis was associated with shorter progression-free survival.

What is the implication, and what should change now?

- This therapeutic strategy, which includes continuing pembrolizumab with focal RT for OP in first-line mNSCLC patients, may be worth considering. For cases involving adrenal metastasis or OP with bone lesions, other local treatment options could also be considered.

86% of the patients lacking identified driver mutations, could be effectively managed using ablative RT combined with standard of care (30). This approach led to an increase in PFS compared to standard of care alone and significantly delayed the TTNT. Stereotactic body RT (SBRT) is a highly precise RT technique that delivers concentrated doses of radiation to the tumor with remarkable accuracy (31). Its efficacy lies in effectively targeting and eradicating cancer cells, while the precision of SBRT minimizes damage to surrounding healthy tissues (32). Intensity-modulated RT (IMRT) is an RT technique that delivers highly targeted radiation doses. It utilizes computer-controlled linear accelerators to adjust the intensity of each radiation beam, allowing for customization of dose distribution, thus minimizing damage to surrounding healthy tissues (33).

Among NSCLC patients undergoing ICI treatment, OP is a common occurrence (10–40%) (34,35). Some retrospective studies have evaluated the clinical benefits of focal RT in cases of OP, coupled with the ongoing administration of nivolumab, in the treatment of mNSCLC during the second or subsequent lines of treatment (36). These studies have reported an association with favorable clinical outcomes, including prolonged PFS (36). In a more recent retrospective study, remarkably positive clinical outcomes were observed among a cohort of 39 advanced NSCLC patients. These individuals were treated with pembrolizumab in the first-line setting and underwent focal RT for OP while concurrently continuing their pembrolizumab treatment (35). Nevertheless, the clinical benefit and the safety profile of such a strategy combining RT with the ongoing use of ICI in the setting of OP in mNSCLC patients treated in first-line setting remain uncertain.

We report herein our local experience of focal RT (SBRT or IMRT) as LAT for oligoprogressive mNSCLC treated with pembrolizumab. We aimed to assess the clinical benefit, and the safety profile of ablative RT in oligoprogressive mNSCLC treated with pembrolizumab in first-line setting. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-554/rc).

Methods

Study design and patients

Data were retrospectively collected from all consecutive patients with histologically confirmed NSCLC who received pembrolizumab, from August 2019 to July 2022 in the Medical and Thoracic Oncology Department of Gabriel Montpied Hospital, a University Hospital in Clermont-Ferrand, France. Every patient with mNSCLC and treated with pembrolizumab was identified using the local database and assessed for inclusion. Inclusion criteria included: age ≥18 years, histologically confirmed mNSCLC, treated with pembrolizumab alone or in combination with chemotherapy in the first-line setting, exhibiting an OP defined as tumor progression according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria (37) of ≤5 lesions (preexisting and/or new tumor lesion), OP treatment with ablative RT (SBRT or IMRT), and continuing pembrolizumab treatment beyond the occurrence of OP. Exclusion criteria included refusal to participate to the study, death before subsequent oncologic treatment, no tumor progression during follow-up time, tumor progression not meeting the OP criteria, OP not treated with ablative RT, and OP treated with ablative RT with change in the systemic treatment.

Study treatment

Pembrolizumab was administered intravenously according to the current recommendation: 200 mg every 3 weeks or 400 mg every 6 weeks. Patients could be treated with pembrolizumab alone, or in combination with chemotherapy [cisplatin 75 mg/m^2 or carboplatine area under the curve (AUC) 5 with pemetrexed 500 mg/m^2 every 3 weeks, or carboplatine AUC 5/6 paclitaxel 175/200 mg/m^2 every 3 weeks up to four cycles]. Treatment maintenance with pemetrexed following the four cycles of platinum pemetrexed was allowed. SBRT or IMRT planning technique was according to physician choice, provided that the American Association of Physicists in Medicine report and constraints were used (38).

Endpoints

The primary endpoint was the TTNT. TTNT was calculated as the duration between the date of first OP diagnosis and the date of commencement of the following systemic treatment, palliative care initiation, or death. Where patients did not have a subsequent treatment, the TTNT was censored to the date of the last follow-up/close-out. Secondary endpoints were the PFS, OS, safety profile of the ablative RT, and the objective response rate (ORR) of the ablative RT. PFS was defined as the duration

between the date of OP and the date of disease progression (RECIST or not-RECIST progressive disease) or death. OS was defined as the duration between the date of OP and the date of death. For the safety evaluation, adverse events were retrospectively collected and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Given the retrospective nature of the study, we limited our collection of adverse event data to only those events that were classified as serious (CTCAE grade >2) or resulted in a dose reduction or interruption of treatment. The ORR of the ablative RT was assessed using the RECIST 1.1 criteria. Furthermore, we investigated the clinical and tumor characteristics associated with TTNT, PFS, and OS duration through both univariable and multivariable analysis.

Statistical analysis

The study population is described in terms of frequencies for qualitative variables, or medians and interquartile range (IQR) for quantitative variables. TTNT, PFS, and OS were estimated from Kaplan-Meier survival curves. The association between clinical and tumor characteristics and the outcomes (TTNT, PFS, and OS) was quantified using hazard ratios (HRs) with a 95% confidence interval (CI) derived from a Cox proportional hazards model, in both univariable and multivariable analyses. The multivariable model was selected using a stepwise selection procedure. The variables in the Cox proportional hazards model with a univariate analysis P value of ≤0.2 were included in the multivariable stepwise model. Stepwise selection was conducted using both forward and backward approaches to ensure consistency in the final model. Statistical significance was assessed using log-rank test. Missing values were managed by introducing a separate "unknown" category within the multivariable analysis, whenever applicable. For survival estimates, patients were censored at the time of their last database update or at the point of loss to follow-up. Analysis was performed using R version 4.1.3.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All living patients received written information and provided their written consent for data collection. Patients' clinical records were retrospectively gathered from electronic files using a de-identified form. The study was approved by the local Ethics Committee, "CHU de Clermont Ferrand IRB #1" (IRB00013412), with the study approval number 2023-CF025, with compliance to the French policy of individual data protection.

Results

Patient characteristics

Between August 2019 and July 2022, a total of 346 patients with NSCLC treated with pembrolizumab in first-line setting were identified through the local database. Two hundred and nine patients were excluded due to no OP during follow-up time: no tumor progression during follow up (n=105), death before subsequent oncologic treatment (n=83), and tumor progression not meeting OP criteria (n=71). Eighty-seven patients experienced OP during their pembrolizumab courses. Among them 51 were excluded due to no RT for OP (n=32), lost to follow-up before RT for OP (n=17), and RT for OP with change in systemic treatment (n=2). Among the 32 patients with OP not treated with RT, the reasons for the absence of RT included: oligoprogressive tumor lesions considered non-accessible to RT (n=29) (technically untargetable n=15, previously treated with RT n=3, and non-specified n=11), and altered performance statues (n=3) (*Figure 1*). Thirty-six patients were included. Median follow-up from pembrolizumab initiation was 42.1 months (Figure S1). The median age was 67 years (range from 36 to 84 years), 26/36 (72.2%) patients were male, 30/36 (83.3%) presented an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and 18/36 (50.0%) had a Charlson Comorbidity Index at 0. Regarding the tumor characteristics, 25/36 (69.4%) had an adenocarcinoma and 11/36 (30.6%) had a squamous-cell carcinoma, tumor programmed cell death-ligand 1 (PD-L1) levels were 0% for 9/36 (25.0%), 1–49% for 8/36 (22.2%), and ≥50% for 19/36 (52.8%), 21/36 (58.3%) had less than 3 metastatic sites at diagnosis, and 19/36 (52.8%) underwent pembrolizumab monotherapy and 17/36 (47.2%) combined with chemotherapy. The patient characteristics are listed in *Table 1*.

OP features and RT

The OP features and RT are presented in *Table 2*. Twenty-seven patients (27/36, 75.0%) experienced only one OP, seven experienced two OP (7/36, 19.4%), and two experienced three OP (5.6%), all while maintaining

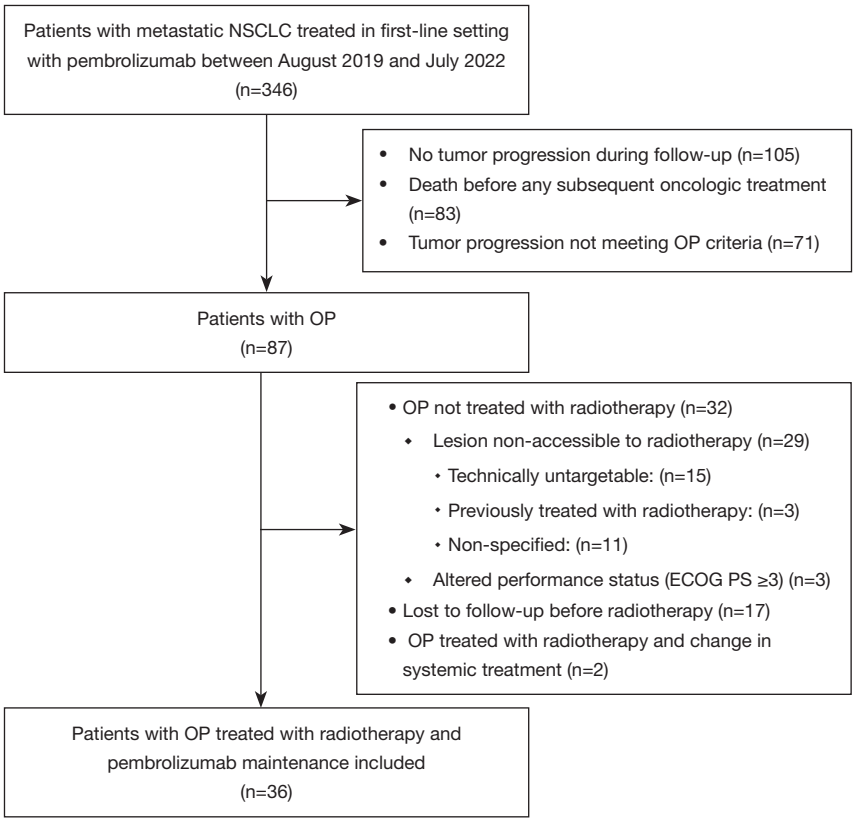

Figure 1 Flow chart. NSCLC, non-small cell lung cancer; OP, oligoprogression; ECOG PS, Eastern Cooperative Oncology Group performance status.

pembrolizumab treatment beyond the onset of OP. Thus, a total of 47 OP were reported. The median time between the initiation of pembrolizumab treatment and the occurrence of the first OP was 9.0 months (range, 1.6–48.4 months) (*Figure 2*). The majority of OP 43/47 (91.5%) involved only one lesion, 20/47 (42.6%) included new tumor lesion(s), and the main progressions sites were lung (17/47, 36.2%) and brain (13/47, 27.7%).

The RT treatment modalities were SBRT for 26/47 (55.3%), and IMRT for 21/47 (44.7%) of the OP. Four-dimensional RT (4DRT), also called respiratory gating was used for lung sites. Regarding lung OP, 13/18 (72.2%) were treated with IMRT, and 5/18 (27.8%) with SBRT. Regarding cerebral OP, 4/13 (30.8%) were treated with IMRT whole brain RT, and 9/13 (69.2%) with SBRT. Brain OP benefited with concomitant corticosteroids treatment to prevent brain oedema. Details of radiation treatment are listed in Table S1.

Efficacy

The median TTNT (mTTNT) was 19.6 months [95% CI: 12.4–not reached (NR)] (*Figure 3A*). In univariate analysis, the presence of adrenal gland metastasis at diagnosis (HR =3.19; 95% CI: 1.17–8.68; P=0.02), ECOG PS 2–4 (HR =3.4; 95% CI: 1.16–9.9; P=0.02) were associated with shorter TTNT (Table S2). In multivariable analysis, the presence of adrenal gland metastasis at diagnosis was associated with shorter TTNT (HR =3.95; 95% CI: 1.39–11.2; P=0.01). Notably, the presence of bone metastasis at diagnosis was associated with shorter TTNT, although this did not reach statistical significance (HR =2.86; 95% CI: 0.98–8.32; P=0.05) (Table S2).

The median OS (mOS) from the first OP (*Figure 3B*) and from pembrolizumab initiation were NR (95% CI: 24.0 months–NR and 36.5 months–NR, respectively). In univariate analysis, the presence of bone metastasis at

Table 1 Characteristics of the patients

Characteristics	Value (n=36)
Sex	
Female	10 (27.8)
Male	26 (72.2)
Age (years)	
<70	20 (55.6)
≥70	16 (44.4)
BMI (kg/m^2)	
<18.5	3 (8.3)
18.5–20	1 (2.8)
21–24	15 (41.7)
25–30	11 (30.6)
>30	6 (16.7)
Smoking status	
Currently smoking	20 (55.6)
Ex-smoker	13 (36.1)
Never smoked	2 (5.6)
Unknown	1 (2.8)
Smoking quantity (pack-year)	
<30	10 (27.8)
30–49	11 (30.6)
≥50	12 (33.3)
Charlson score (without lung cancer)	
0	18 (50.0)
1–2	12 (33.3)
3–6	6 (16.7)
ECOG category	
0–1	30 (83.3)
2–4	6 (16.7)
Stage at diagnosis	
I–III	8 (22.2)
IV	28 (77.8)
Metastasis sites at diagnosis	
Lung	14 (38.9)
Bone	9 (25.0)
Node	9 (25.0)
Brain	8 (22.2)
Adrenal gland	7 (19.4)
Pleural	3 (8.3)
Other	2 (5.6)
Liver	1 (2.8)
Number of metastasis site at diagnosis	
<3	21 (58.3)
3–5	12 (33.3)
>5	3 (8.3)
Tumor histology	
Adenocarcinoma	25 (69.4)
Squamous cell carcinoma	11 (30.6)
NGS	
Performed	23 (63.9)
TP53 mutated	11 (30.6)
KRAS mutated	8 (22.2)
BRAF mutated	3 (8.3)
MET mutated	2 (5.6)
STK11 mutated	2 (5.6)
HER2 mutated	1 (2.8)
PD-L1 (%) category	
0	9 (25.0)
1–49	8 (22.2)
50–100	19 (52.8)
First-line of treatment	
Pembrolizumab	19 (52.8)
Carboplatin pemetrexed pembrolizumab	13 (36.1)
Carboplatin paclitaxel pembrolizumab	3 (8.3)
Cisplatine pemetrexed pembrolizumab	1 (2.8)
Maintenance with pemetrexed	
No	23 (63.9)
Yes	13 (36.1)

Data are presented as n (%). BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; NGS, next generation sequencing; PD-L1, programmed cell death-ligand 1.

Table 2 Characteristics of OPs treated with ablative RT

Characteristics	OPs (n=47)
Number of OPs among the 36 patients	
1	27/36 (75.0)
2	7/36 (19.4)
3	2/36 (5.6)
Simultaneous oligoprogressive lesions	
1	43 (91.5)
2–3	3 (6.4)
>3	1 (2.1)
New lesion at OP	
No	27 (57.4)
Yes	20 (42.6)
OP sites	
Lung	17 (36.2)
Brain	13 (27.7)
Bone	6 (12.8)
Adrenal gland	4 (8.5)
Lymph node	3 (6.4)
Bone and pleural	2 (4.3)
Lung and lymph node	1 (2.1)
Pleural	1 (2.1)
RT method	
IMRT	21 (44.7)
SBRT	26 (55.3)
Concomitant corticoids	
Yes	13 (27.7)
No	34 (72.3)
Number of days of corticoids, mean	28

Data are presented as n/total or n (%), unless otherwise stated. OP, oligoprogression; RT, radiotherapy; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy.

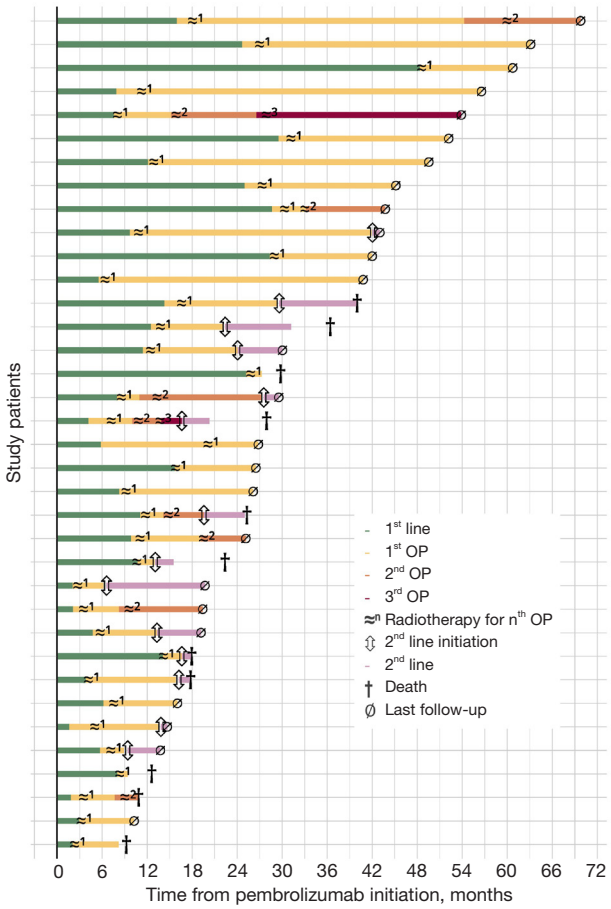

Figure 2 Swimmer plot for 36 patients within study. One patient could have several local ablative radiotherapies for several OPs. Twenty-one patients had first OP time (yellow line: from first OP to progression or death) superior to first-line (green line: from pembrolizumab initiation to first OP). OP, oligoprogression.

diagnosis (HR =3.83; 95% CI: 1.15–12.8; P=0.02), the presence of adrenal gland metastasis at diagnosis (HR =5.77; 95% CI: 1.4–23.74; P=0.006), and age >70 years (HR =3.66; 95% CI: 0.97–13.81; P=0.04) were associated with shorter OS (Table S3). In multivariable analysis, the presence of adrenal gland (HR =8.12; 95% CI: 1.73–38.1; P=0.008) and bone metastasis at diagnosis (HR =5.82; 95% CI: 1.48–22.9; P=0.01) were both associated with shorter OS (Table S3).

The median PFS (mPFS) after the first OP was 12 months (95% CI: 6.1–NR) and 10.4 months (95% CI: 3.9–NR) after the second or third OP. No significant difference of PFS was observed between the first OP compared to the second or third OP (HR =1.25; 95% CI: 0.53–2.97; P=0.61) (*Figure 4*). In univariate analysis, OP involving pleural (HR =5.09; 95% CI: 1.48–17.52; P=0.004) and bone (HR =3.21; 95% CI: 1.39–7.42; P=0.004) metastasis were associated with shorter PFS (Table S4). No significant difference in PFS was found between the two RT techniques, SBRT and IMRT (HR =0.69; 95% CI: 0.32–1.48; P=0.31) (Table S4 and Figure S2). In multivariable analysis, only OP involving bone metastasis was associated

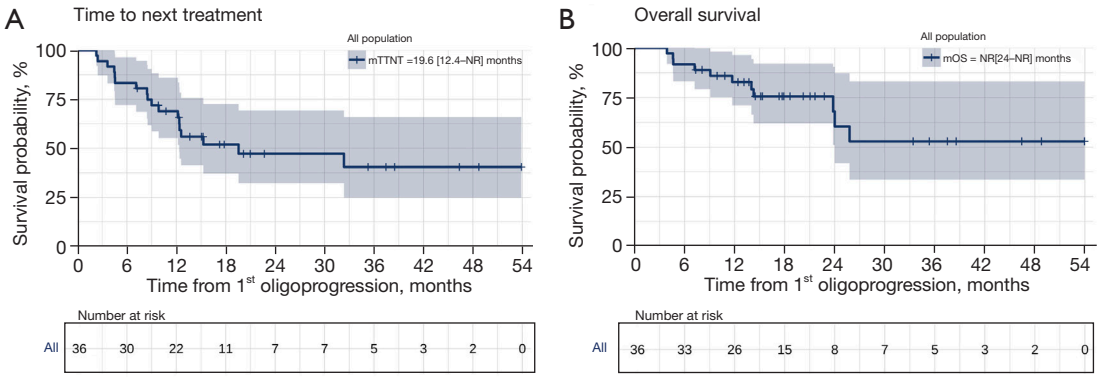

Figure 3 TTNT and OS from first OP. (A) Kaplan-Meier estimates of TTNT. TTNT was defined as the duration between the date of first OP to the date of next following systemic treatment line or death. Tick marks indicate censored data. (B) Kaplan-Meier estimates of OS. OS was defined as the duration between the first OP and the date of death. Tick marks indicate censored data. Data in square brackets represent 95% CI. mTTNT, median time to next systemic treatment; NR, not reached; mOS, median overall survival; TTNT, time to next systemic treatment; OS, overall survival; OP, oligoprogression; CI, confidence interval.

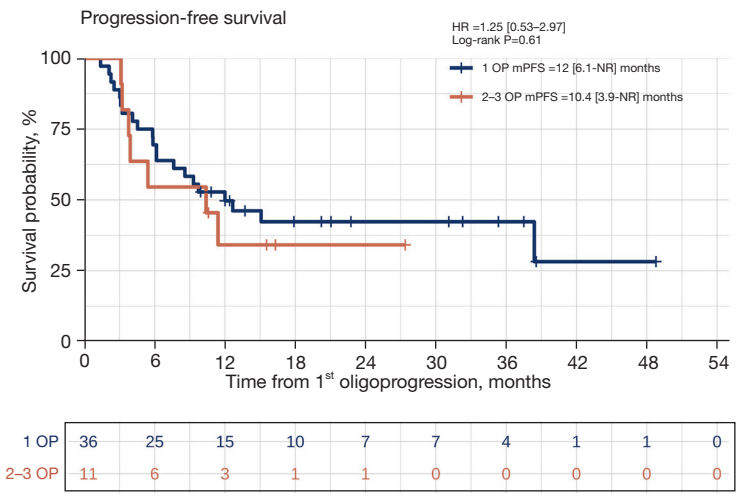

Figure 4 Kaplan-Meier estimates of PFS. PFS was defined as the duration between the date of the 1 OP or the 2–3 OP and the date of disease progression (RECIST or not-RECIST progressive disease) or death. Tick marks indicate censored data. Data in square brackets represent 95% CI. HR, hazard ratio; 1 OP, first OP; 2–3 OP, second or third OP; OP, oligoprogression; mPFS, median progression-free survival; NR, not reached; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; CI, confidence interval.

with shorter PFS (HR =3.21; 95% CI: 1.39–7.42; P=0.004) (Table S4).

Regarding the ORR of the tumor lesions treated with ablative RT in the context of OP, the ORR was 33/47 (70.2%) with 5/47 (10.6%) of complete response and 28/47 (59.6%) of partial response. Details of radiological responses with ablative RT are in Table S5.

The PFS from the first OP was superior to the PFS from pembrolizumab initiation for 67.7% of patients (21/31 patients with enough follow-up, five patients had not progressed). Encompassing all OP, all OP PFS (time of last treated progression after OP treatment) was superior to the PFS from pembrolizumab initiation in 74.2% (23/31) of patients (*Figure 2*).

Safety profile

No severe adverse events induced by RT (CTCAE grade >2) or adverse events leading to interruption of RT were reported. Three patients (3/36, 8.3%) experienced severe pembrolizumab-induced adverse events (CTCAE grade >2). One CTCAE grade 4 gastroduodenitis, one CTCAE grade 4 pneumonitis, and one CTCAE grade 4 leukopenia. These three immune-related adverse events (IRAEs) occurred after ablative RT for OP (respectively 1, 4, and 13 months after ablative RT).

Discussion

This retrospective study aimed to evaluate the efficacy and the safety profile of a treatment strategy that involves RT alongside the maintenance of pembrolizumab for patients experiencing OP during first-line pembrolizumab-based therapy for mNSCLC. In this cohort of thirty-six patients, this approach demonstrated an acceptable safety profile and, notably, yielded favorable outcomes, including prolonged TTNT, PFS, and OS.

The prevailing approach to manage metastatic cancer involves navigating through various systemic therapies, wherein local therapy is commonly reserved to alleviate symptoms. While ablative RT has demonstrated promise in addressing oligometastatic NSCLC (39), its efficacy in dealing with progressive or extensively spread metastatic disease remains uncertain. Systemic therapies continue to be the primary treatment approach; nevertheless, the development of resistance to these therapies occurs over time. The randomized phase 2 Consolidative Use of Radiotherapy to Block (CURB) oligoprogression clinical trial showed that OP in patients with mNSCLC could be effectively treated with SBRT plus standard of care, leading to more than a four-times increase in PFS compared with standard of care only (30). However, in this study, patients were treated with different systemic therapy lines at the onset of OP, which limits the applicability of these results to our setting. Some retrospective studies have highlighted a correlation with favorable outcomes when employing a strategy that combines local RT with the continuation of ICI treatment in instances of OP under ICI, spanning diverse tumor types (25,40). Another retrospective study reports an mPFS of 15 months using RT in case of OP under nivolumab in second for subsequent line setting mNSCLC (36). Moreover, a recent retrospective study reports remarkably favorable outcomes (mOS, 62.2 months) employing the same strategy in NSCLC patients treated with first-line pembrolizumab (35). However, in this study, a definitive distinction between "definitive" and "ablative" focal RT in the context of OP could not be established conclusively based on the available medical records. Also, the description of the safety profile of the approach is missing. Lastly, through multivariable analysis, the study concludes that RT in cases of OP is linked to improved OS. It is essential to note, however, that the study compared two groups with different characteristics.

In our cohort, the TTNT following the first occurrence of OP was significantly extended, with a median of 19.6 months (*Figure 3A*). It is noteworthy that the presence of adrenal gland metastasis at the time of diagnosis was associated with a shorter TTNT and OS (Tables S2,S3). This aligns with previous observations highlighting the adrenal gland as a sanctuary site for ICI in cancer patients. This phenomenon may be attributed to the presence of glucocorticoids in the adrenal gland microenvironment, leading to a substantial impairment of the antigen presentation pathway in adrenal gland metastases (41). We further investigated the influence of the site of OP on clinical outcomes. Significantly, OP involving bone metastases was found to be associated with a shorter PFS (Table S3). Another encouraging outcome from this study is the lack of severe adverse effects associated with RT. However, it's noteworthy that three patients experienced severe IRAEs following RT, albeit at significantly different time intervals (range, 1–13 months). It is challenging to attribute the occurrence of these IRAEs to the RT treatment.

Our study has several limitations, most of which relate to its retrospective and single-center nature. TTNT is a valuable surrogate endpoint for OS in advanced solid cancers (42). Using this endpoint, we also highlighted the time during which patients had chemo-free regimen, delaying cytotoxic associated adverse events that could have impaired their quality of life while controlling their disease. Only approximately half of the patients who experienced OP in our cohort received treatment with RT and pembrolizumab maintenance, underscoring the challenges associated with such a practice (*Figure 1*). Remarkably, our study cohort demonstrates notably favorable predictive factors for the efficacy of ICI, as highlighted in *Table 1*. Specifically, more than half of the participants exhibit a high PD-L1 level (43), the majority display favorable performance statuses (44), and a significant portion have a limited number of metastatic sites (45). Additionally, there is

heterogeneity among patients in terms of the first-line treatment setting, with some receiving pembrolizumab alone and others pembrolizumab combined with chemotherapy. The varying patient characteristics and utilization of different prior treatment regimens suggest that the study sample may not be fully representative of a typical mNSCLC patient. Furthermore, the RT regimens used in our study are not all equivalent, with some being more ablative than others. We emphasize the distinction between SBRT with ablative doses and IMRT with less ablative or palliative doses, typically used for symptom relief or local control. This increases the heterogeneity of the cohort and makes interpretations more challenging. Additionally, we recognize the inherent limitations of our statistical approach to the multivariable analysis, particularly due to the small number of events observed in our cohort. These limitations can introduce variability in HR estimates and potentially impact the stability of the model.

This study is one of the first to report the clinical outcomes and the safety profile of a treatment strategy that involves RT alongside the maintenance of pembrolizumab for patients experiencing OP during first-line pembrolizumab-based therapy for mNSCLC. Our analysis suggests that this approach might be effective in this setting with an acceptable safety profile. Nevertheless, this therapeutic approach should be tailored to specific patient profiles, as indicated by our analysis of factors linked to its efficacy. Our findings reveal correlations with unfavorable clinical outcomes and specific tumor characteristics (adrenal metastasis at the time of diagnosis, and oligoprogressive bone metastasis).

Given the success observed with RT in oligometastatic disease, the increasing understanding of tumor heterogeneity's role in therapy resistance, and the positive clinical outcomes documented in our retrospective study, we believe that RT, without altering the systemic treatment regimen in the event of OP in mNSCLC patients treated with pembrolizumab in the first-line setting, holds promise as a viable strategy. Nevertheless, further prospective and comparative studies are needed to evaluate the potential of this treatment approach.

Conclusions

In this retrospective study, RT alongside pembrolizumab maintenance for patients experiencing OP during first-line pembrolizumab-based therapy for mNSCLC demonstrated an acceptable safety profile and, notably, demonstrated a substantial time of delaying the introduction of second-line chemotherapy. Data from phase 3 randomized trials are needed to clearly establish the benefits of this strategy in treating oligoprogressive mNSCLC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-554/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-554/coif). P.G. reports consulting fees for BMS, academic grant from Sanofi and travel accommodation by Eisai. C.R.D. reports serving as a consultant/receiving honorarium/travel reimbursements from AstraZeneca, Sanofi, GSK, Menarini, and Asten for educational events (payment to her) and from Asten, Sanofi for attending ERS meeting. L.C. reports serving as a consultant/receiving honorarium/travel reimbursements from AAA, Amgen, Astellas, Bayer, BMS, Eisai, Ipsen, Janssen, MSD and Pfizer for educational events (payment to her); and Pfizer, Janssen, Bayer and Ipsen for attending ESMO, ASCO GU and ASCO. B.A. has received research grants from MSD Avenir and consultant or advisory role fees from Novartis, Astellas, Sanofi, AstraZeneca, BMS, and MSD. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All living patients received written information and provided their written consent for data collection. Patients' clinical records were retrospectively

gathered from electronic files using a de-identified form. The study was approved by the local Ethics Committee, "CHU de Clermont Ferrand IRB #1" (IRB00013412), with the study approval number 2023-CF025, with compliance to the French policy of individual data protection.

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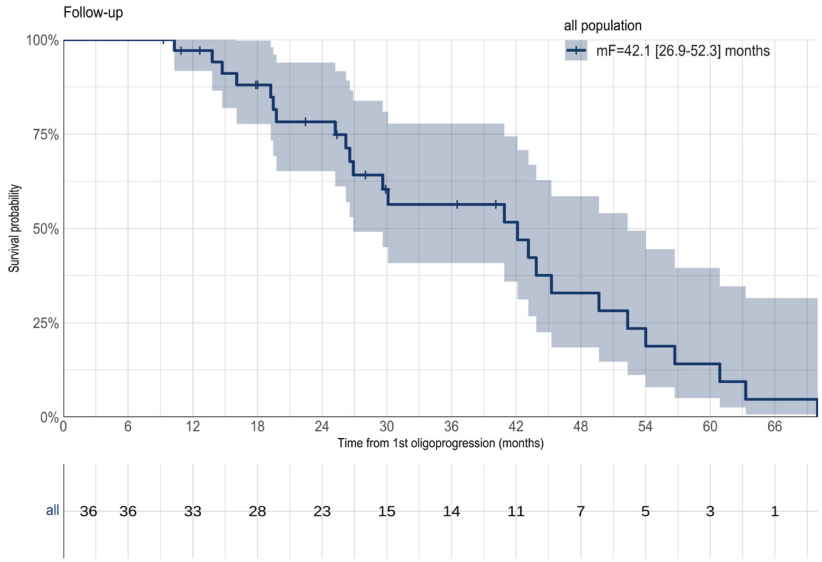

Figure S1 Follow-up from pembrolizumab initiation. Kaplan-Meier estimates of follow-up time using the reverse Kaplan-Meier method. Tick marks indicate censoring of data (patient death). Data in square brackets represent 95% CI. mF, median follow-up; CI, confidence interval.

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Table S1 Details of radiation treatment for OP

OP site	RT method	Number of fractions	Dose (gray)	Number of treated sites/total progressive sites
Adrenal gland	SBRT	5	30	2/4
		5	35	1/4
		5	45	1/4
Bone	SBRT	5	20	2/6
		5	30	1/6
		5	35	1/6
	IMRT	10	30	2/6
Bone and pleural	SBRT	5	30	1/2
	IMRT	10	30	1/2
Brain	SBRT	1	14	3/13
		5	33	1/13
		4	33	1/13
		3	33	2/13
		4	20	1/13
		2	11	1/13
	IMRT	10	30	2/13
		5	20	2/13
Lung	SBRT	5	50	1/17
		5	62,5	2/17
		3	56	1/17
		3	45	1/17
	IMRT	15	45	4/17
		17	51	6/17
		10	30	1/17
		33	66	1/17
Lung and lymph node	IMRT	10	30	1
Lymph node	SBRT	3	51	1/3
		3	33	1/3
		5	30	1/3
Pleural	IMRT	10	30	1

OP, oligoprogression; SBRT, stereotactic body radiotherapy; IMRT, intensity-modulated radiotherapy.

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Table S2 Univariate and multivariable analysis of features associated with TTNT

Variables	Strata	Number	Median TTNT (95% CI) (months)	Univariate		Multivariate	
				HR (95% CI)	P value	HR (95% CI)	P value
Sex	Female	10	NA (12.2–NA)	Reference	0.41		
	Male	26	19.6 (9.9–NA)	1.59 (0.52–4.86)			
Smoking status	Currently smoking	20	15.3 (9.9–NA)	Reference	0.87		
	Ex–smoker	13	19.6 (12.2–NA)	0.77 (0.28–2.08)			
	Never smoked	2	4.5 (4.5–NA)	0.85 (0.28–2.08)			
Stage at diagnosis	I–III	8	32.4 (8.5–NA)	Reference	0.55		
	IV	28	15.3 (12.2–NA)	1.45 (0.42–5.03)			
Bone metastasis at diagnosis†	No	27	32.4 (12.6–NA)	Reference	0.12	Reference	0.05
	Yes	9	9.9 (7.1–NA)	2.2 (0.79–6.13)		2.86 (0.98–8.32)	
Adrenal gland metastasis at diagnosis†	No	29	32.4 (12.6–NA)	Reference	0.02	Reference	0.01
	Yes	7	8.4 (3.6–NA)	3.19 (1.17–8.68)		3.95 (1.39–11.2)	
Lung metastasis at diagnosis	No	22	16.1 (9.9–NA)	Reference	0.52		
	Yes	14	NA (12.2–NA)	0.72 (0.25–2.02)			
Node metastasis at diagnosis	No	27	32.4 (9.9–NA)	Reference	0.79		
	Yes	9	19.6 (12.4–NA)	0.87 (0.3–2.48)			
Brain metastasis at diagnosis	No	28	15.3 (12.4–NA)	Reference	0.95		
	Yes	8	19.6 (7.1–NA)	1.04 (0.34–3.2)			
Pleural metastasis at diagnosis	No	33	22.7 (15.3–NA)	Reference	0.43		
	Yes	3	19.1 (17.3–NA)	1.84 (0.4–8.56)			
Other meta sites at diagnosis	No	33	19.6 (12.4–NA)	Reference	0.83		
	Yes	3	NA (7.1–NA)	0.81 (0.11–6.13)			
Number of metastasis sites at first-line	0	5	32.4 (8.5–NA)	Reference	0.3		
	1–2	16	NA (12.4–NA)	0.56 (0.13–2.36)			
	≥3	15	12.6 (8.4–NA)	1.34 (0.13–2.36)			
Tumour histology	Adenocarcinoma	25	19.6 (12.4–NA)	Reference	0.8		
	Squamous cell carcinoma	11	15.3 (9.9–NA)	0.9 (0.32–2.54)			
ECOG category†	0–1	30	32.4 (12.4–NA)	Reference	0.02		
	2–4	6	8.5 (4.6–NA)	3.4 (1.16–9.9)			
Age (years)	<70	20	32.4 (12.2–NA)	Reference	0.4		
	≥70	16	12.6 (9–NA)	1.44 (0.56–3.68)			
PD-L1 (%)†	0–49	16	12.4 (4.6–NA)	Reference	0.14		
	50–100	20	NA (12.6–NA)	0.5 (0.2–1.27)			
Charlson index (without lung cancer)	0	18	15.3 (9.9–NA)	Reference	0.6		
	1–2	12	32.4 (19.6–NA)	0.77 (0.26–2.32)			
	3–6	6	12.3 (2.5–NA)	1.44 (0.26–2.32)			

†, variables with a univariate P value <0.2 were used in the stepwise model for multivariable analysis. TTNT, time to next systemic treatment; HR, hazard ratio; CI, confidence interval; NA, not achieved; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-ligand 1.

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Table S3 Univariate and multivariable analysis of features associated with OS

Variables	Strata	Number	Median OS (95% CI) (months)	Univariate		Multivariate	
				HR (95% CI)	P value	HR (95% CI)	P value
Sex	Female	10	NA (29.9–NA)	Reference	0.78		
	Male	26	NA (36.5–NA)	1.21 (0.32–4.6)			
Smoking status	Currently smoking	20	40.1 (29.9–NA)	Reference	0.43		
	Ex–smoker	13	NA (NA–NA)	0.45 (0.09–2.12)			
	Never smoked	2	12.7 (12.7–NA)	1.37 (0.09–2.12)			
Stage at diagnosis	I–III	8	NA (NA–NA)	Reference	0.32		
	IV	28	NA (36.5–NA)	3.36 (0.43–26.32)			
Pleural metastasis at diagnosis	No	33	NA (36.5–NA)	Reference	0.84		
	Yes	3	25.4 (25.4–NA)	1.64 (0.2–13.61)			
Bone metastasis at diagnosis[†]	No	27	NA (NA–NA)	Reference	0.02	Reference	0.01
	Yes	9	28 (12.7–NA)	3.83 (1.15–12.8)		5.82 (1.48–22.9)	
Adrenal gland metastasis at diagnosis[†]	No	29	NA (40.1–NA)	Reference	0.006	Reference	0.008
	Yes	7	25.4 (17.9–NA)	5.77 (1.4–23.74)		8.12 (1.73–38.1)	
Lung metastasis at diagnosis	No	22	NA (29.9–NA)	Reference	0.70		
	Yes	14	NA (40.1–NA)	0.68 (0.18–2.56)			
Node metastasis at diagnosis	No	27	NA (29.9–NA)	Reference	0.73		
	Yes	9	NA (22.5–NA)	0.97 (0.26–3.68)			
Brain metastasis at diagnosis	No	28	NA (36.5–NA)	Reference	0.65		
	Yes	8	NA (22.5–NA)	0.9 (0.19–4.18)			
Other meta sites at diagnosis	No	33	NA (24–NA)	Reference	0.52		
	Yes	3	NA (7.2 –NA)	1.62 (0.33–8.02)			
Number of metastasis sites at first-line	0	5	NA (29.9–NA)	Reference	0.62		
	1–2	16	NA (28–NA)	1.7 (0.19–15.27)			
	≥3	15	40.1 (36.5–NA)	3.07 (0.19–15.27)			
Tumour histology	Adenocarcinoma	25	NA (29.9–NA)	Reference	0.66		
	Squamous cell carcinoma	11	40.1 (36.5–NA)	1.34 (0.39–4.59)			
ECOG category[†]	0–1	30	NA (40.1–NA)	Reference	0.13	–	–
	2–4	6	29.9 (29.9–NA)	2.72 (0.7–10.6)			
Age (years)[†]	<70	20	NA (NA–NA)	Reference	0.04	–	–
	≥70	16	40.1 (25.4–NA)	3.66 (0.97–13.81)			
PD-L1 (%)	0–49	16	29.9 (28–NA)	Reference	0.69		
	50–100	20	NA (40.1–NA)	0.65 (0.19–2.17)			
Charlson index (without lung cancer)	0	18	NA (40.1–NA)	Reference	0.71		
	1–2	12	NA (29.9–NA)	1.13 (0.27–4.75)			
	3–6	6	28 (22.5–NA)	2.05 (0.27–4.75)			

[†], variables with a univariate P value <0.2 were used in the stepwise model for multivariable analysis. OS, overall survival; HR, hazard ratio; CI, confidence interval; NA, not achieved; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-ligand 1.

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Table S4 Univariate and multivariable analysis of features associated with PFS

Variables	Strata	Number	Median PFS (95% CI) (months)	Univariate		Multivariate	
				HR (95% CI)	P value	HR (95% CI)	P value
Tumour histology	Adenocarcinoma	33	12.6 (5.8–NA)	Reference	0.49		
	Squamous cell carcinoma	14	9.5 (6.1–NA)	1.31 (0.6–2.85)			
Number of OP	1	36	11.9 (6.1–NA)	Reference	0.87		
	2	9	10.3 (3.8–NA)	1.28 (0.51–3.2)			
	3	2	3.1 (3.1–NA)	0.98 (0.51–3.2)			
New lesion at OP	No	27	12.6 (7.6–NA)	Reference	0.27		
	Yes	20	8.5 (3.8–NA)	1.52 (0.72–3.21)			
Adrenal gland OP	No	43	9.7 (5.8–NA)	Reference	0.17		
	Yes	4	NA (11.3–NA)	0.27 (0.04–1.98)			
Pleural OP[†]	No	44	11.9 (7.6–NA)	Reference	0.004	–	–
	Yes	3	2.5 (2–NA)	5.09 (1.48–17.52)			
Bone OP[†]	No	39	12.6 (9.2–NA)	Reference	0.004	Reference	0.004
	Yes	8	3.9 (3–NA)	3.21 (1.39–7.42)		3.21 (1.39–7.42)	
Lung OP[†]	No	29	8.5 (4–NA)	Reference	0.04	–	–
	Yes	18	NA (9.2–NA)	0.44 (0.19–0.99)			
Brain OP	No	34	11.9 (8.5–NA)	Reference	0.52		
	Yes	12	8.2 (3.2–NA)	1.34 (0.56–3.21)			
Lymph node OP	No	43	10.3 (6.1–NA)	Reference	0.73		
	Yes	4	12.6 (3–NA)	1.24 (0.37–4.11)			
RT method	Conformational	21	8.5 (5.8–NA)	Reference	0.31		
	Stereotaxy	26	12.6 (6.1–NA)	0.69 (0.32–1.48)			
Concomitant corticoids	No	34	10.3 (7.6–NA)	Reference	0.68		
	Yes	13	15 (3.2–NA)	1.19 (0.52–2.7)			

[†], variables with a univariate P value <0.2 were used in the stepwise model for multivariable analysis. PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OP, oligoprogression; NA, not achieved; RT, radiotherapy.

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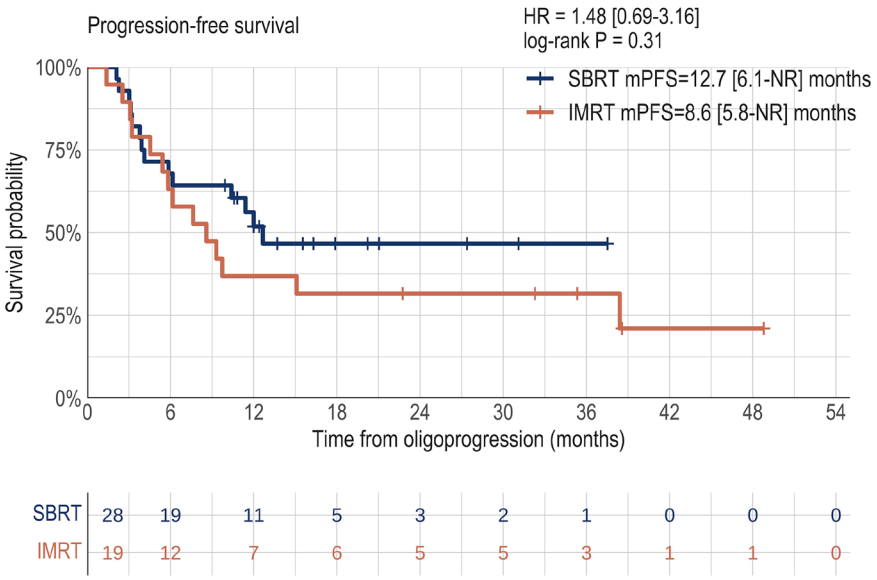

Figure S2 Kaplan-Meier estimates of PFS according to RT technique group. PFS was defined as the duration between the date of the first OP and the date of disease progression (RECIST or not-RECIST progressive disease) or death. Tick marks indicate censored data. Data in square brackets represent 95% CI. HR, hazard ratio; SBRT, stereotactic body radiotherapy; mPFS, median progression-free survival; NR, not reached; IMRT, intensity-modulated radiotherapy; PFS, progression-free survival; RT, radiotherapy; OP, oligoprogression; RECIST, Response Evaluation Criteria in Solid Tumors.

Table S5 Best radiological response of oligoprogressive lesions treated with RT according to RECIST 1.1 criteria

Response pattern	OPs (n=47)
Complete response	5 (10.6)
Partial response	28 (59.6)
Stable disease	10 (21.3)
Progressive disease	2 (4.3)
Not available	2 (4.3)

Data are presented as n (%). A total of 47 OPs among the 36 patients. RT, radiotherapy; RECIST, Response Evaluation Criteria in Solid Tumors; OP, oligoprogression.

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