

RESEARCH

Open Access



Stereotactic body radiotherapy extends the clinical benefit of PD-1 inhibitors in refractory recurrent/metastatic nasopharyngeal carcinoma

Jing Lin^{1,2†}, Qiaojuan Guo^{2,3,4†}, Zengqing Guo^{1,2,4†}, Tianzhu Lu³, Gang Chen^{2,5}, Shaojun Lin³, Mei Chen³, Chuanben Chen^{2,3}, Jianping Lu⁵, Jingfeng Zong^{2,3}, Lina Tang⁶, Yu Chen^{1,2,4,7*} and Jianji Pan^{2,3*}

Abstract

Purpose: Emerging evidence shows that immune checkpoint inhibitors lead to durable responses in a variety of cancers, including nasopharyngeal carcinoma (NPC), however, combination approaches (i.e., stereotactic body radiation therapy, SBRT) are required to extend this benefit beyond a subset of patients. This study retrospectively evaluated eight recurrent/metastatic NPC patients, to investigate how radiation could potentiate PD-1 checkpoint inhibition therapy.

Methods: Between September 2016 and July 2017, eight consecutive cases with histologically confirmed PDL1-positive status, for which prior standard therapy had been ineffective (five patients), were treated at our institution and Macao Clinics and two patients had disease progression within 6 months of completion of definitive chemoradiation, or one patient refused to receive chemoradiotherapy. All received PD-1 inhibitors first, seven of them accepted SBRT with an unmodified PD-1 inhibitors regimen after first evaluation as they were unresponsive to PD-1 inhibitors alone. Treatment was discontinued as long as patients were experiencing a clinical benefit in the opinion of the physicians and at least five cycles were given before stoppage.

Results: Median follow-up time was 56.7 months. The confirmed objective response rate based on RECIST-v1.1 at first evaluation was 12.5% (1/8). For the seven cases who received SBRT, six of them experience an objective response (6/7, 85.7%) after SBRT. Only one patient showed rapid progress and die within 95 days after the initiation of SBRT intervention. Three patients who did not have all lesions exposed to irradiation were available to evaluate the incidence of an abscopal effect, however, it did not occur as expected. Median PFS and OS for the seven patients were 8.0 and 30.8 months after SBRT intervention, respectively. Two-year OS as indicated was 71.0%.

[†]Jing Lin, Qiaojuan Guo and Zengqing Guo contributed equally to this study

*Correspondence: 13859089836@139.com; panjianji@126.com

¹ Department of Medical Oncology, Fujian Medical University Cancer Hospital and Fujian Cancer Hospital, Fuzhou 350014, Fujian Province, China

² Cancer Bio-Immunotherapy Center, Fujian Medical University Cancer Hospital & Fujian Cancer Hospital, No. 420 Fuma Road, Fuzhou 350014, Fujian Province, China

Full list of author information is available at the end of the article



Conclusions: PD-1 inhibitors combined with SBRT demonstrated promising antitumor activity in patients with PD-L1 positive RM-NPC. Patients may benefit from continue immunotherapy beyond disease progression when SBRT was introduced.

Keywords: Stereotactic body radiotherapy, PD-1, Immunotherapy, Nasopharyngeal carcinoma

Background

Recurrent/metastatic nasopharyngeal carcinoma (RM-NPC) remains a disease associated with few therapeutic options, for which standard-of-care is platinum-containing combination therapy [1]. Although the response rates to this treatment modality has been reported to be higher than 50%, the duration of the response and survival time are limited [2]. This is especially true for patients who relapse with distant metastasis, with reported median survival times ranging from only 5 to 11 months [3–6]. For patients who have progressed beyond a first-line setting with platinum-refractory RM-NPC, there are no standard treatment options. Salvage second-line chemotherapy and targeted drugs only produce moderate anti-tumor activity as second-line or later treatment in this setting [6–9]. Given these outcomes, the need for a more effective therapy for patients with incurable NPC is clear.

Progress made in the field of immunotherapy (i.e. PD-1/PDL1 checkpoint inhibition) has led to promising breakthroughs in treating various solid malignancies [10–12]. Exploration of immunotherapy with PD-1/PDL1 checkpoint blockade in RM-NPC patients beyond first-line treatment has been reported in clinical trials with relatively small samples [13–15], with all patients having received monotherapy with pembrolizumab, nivolumab, or camrelizumab. Although encouraging response rates of 19%~34% were reported in this subgroup of patients, there still remain a substantial number of patients that do not respond and fail to have a long-lasting clinical benefit. Apart from identification of biomarkers to select the patients who are likely to respond to PD-1 blockade beforehand, another potential method for improving the response rate is combining with traditional oncological interventions, one of which is radiotherapy [16–20].

Published data has revealed that the combination of radiotherapy with anti-PD1 treatment can lead to a synergistic effect, thereby enhancing response rates [17, 21–27]. Radiation-induced immune responses might be dose-dependent, using radiation doses in the ‘ablative’ range can not only effectively destroy tumor cells directly, but might also encourage these SABR-killed cells to function as a vaccine in situ [17, 28–31]. In addition, radiation can re-program the tumor stromal microenvironment against the immune evasion mechanisms of cancer [32]. There is a report from Desideri et al. that there are different responses to combined therapy with nivolumab

when using ablative vs. palliative RT [33]. Thus, there was the concept of “ISABR” (immunotherapy and stereotactic ablative radiotherapy) proposed by Prof. Chang [17]. This concept has been clinically reported for multiple diseases, including case reports of lung cancer and melanoma [34, 35]. However, this combination has not been reported in RM-NPC patients.

To further evaluate the efficacy of PD-1 inhibitors and its combination with SBRT in recurrent/metastatic NPC patients, we report our experience in eight RM-NPC patients who were treated in Macao Clinics and our institution. Our results will shed light on the toxicity and potential anti-tumor activity of this combination.

Methods

Patients and pretreatment evaluation

This retrospective study was approved by the Research Ethics Committee of our institution. Eight NPC patients treated with PD-1 inhibitors, with or without radiotherapy, between October 2016 and August 2017 were included. They were all histologically confirmed with RM-NPC, for which prior standard therapy was ineffective (five patients), had disease progression within 6 months of completion of definitive chemo-radiotherapy (two patients), or refused to receive chemoradiotherapy (one patient). All of them were classified as WHO type II/III and has an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0~2, and adequate organ function as determined by laboratory testing. As the PD-1 inhibitors were not yet available in Mainland China at that time, the PD-1 inhibitors were given at Macao Clinics, with regular follow-up, efficacy evaluation, and radiotherapy performed at our institution. None of them had received previous treatments that specifically targeted T-cell co-stimulation or checkpoint pathways.

PD-1 inhibitors administration

Treatment programs were developed after full discussion in multidisciplinary panels including medical oncologists, immunologists, and radiation oncologists. Nivolumab (Opdivo, Bristol-Myers Squibb) and pembrolizumab (Keytruda, Merck & Co) were given at 3 mg/kg and 2 mg/kg intravenously once every 2 and 3 weeks, respectively. The selection of these two drugs was not protocolized and was used according to the required dosage and drug

specifications, among which economic factors were fully taken into consideration. Due to financial limitations, most patients could not receive long-term PD-1 inhibitors administration. Treatment was discontinued as long as patients were experiencing clinical benefit in the opinion of the physicians and at least five cycles were given.

Radiotherapy

The timing of SBRT intervention depends on the expression of PD-L1 and CD8 + tumor infiltrating lymphocytes (TIL), and the response to PD-1 inhibitors. Since all eight patients presented with PD-L1 expression and CD8 + TIL (adaptive resistance) [36], they were first treated by PD-1 inhibitors alone and SBRT was introduced only when patients did not response to PD-1 inhibitors.

SBRT was used to irradiate all the visible lesions or the main recurrent and/or metastatic lesions or progressive lesions, with a radiation dose of 25-36 Gy (5~6 Gy/5~6Fx). The setting of the tumor target area and radiation dose and the formulation of the radiotherapy plan were all conducted under the guidance of the chief radiotherapy oncologist (JJ Pan) in our hospital. The dose fractionation scheme was individualized based upon the specific condition of each case and the history of past treatment was taken into consideration as well.

The Gross Target Volume (GTV) was defined as visible tumors by combining iconographic and metabolic information for all or part of the lesions. No additional margins were added for microscopic spread of disease. The GTV was expanded with 2–5 mm to the Planning Target Volume (PTV) to account for organ motion and setup error according to localization of the metastasis. More details of radiotherapy are indicated in Table 1.

Immunohistochemical analysis for PD-L1, CD8, PD-1, CD3

Immunohistochemistry for CD3, CD8, PD-L1, and PD-1 were performed with CONFIRM anti-CD3 (2GV6) antibody (VENTANA, 790–4341), (790–4460) CONFIRM CD8 (SP57) antibody (VENTANA, 790–4460), PD-L1 (SP142) Assay (VENTANA, 740–4859), and anti-PD-1 antibody (MXB Biotechnologies, MAB-0743) using an automated slide stainer (BenchMark XT, VENTANA Medical Systems, Tucson, AZ, USA), the antibodies were directly added into the stainer without dilution.. The tissue sections were screened at low magnification (× 100) and measured at × 400 magnification.

Follow-up and statistical analysis

The overall evaluation of the treatment response was based on RECIST version 1.1. Follow-up evaluations for all patients were performed every 2–3 cycles of PD-1 inhibitor immunotherapy. Each follow-up included a complete history and physical examination, as well as basic serum chemistry, plasma EB-DNA, and imaging examination (CT and/or MRI and/or PET-CT) of the corresponding lesions. Toxicity during treatment was graded according to the CTCAE v.4.0.

The best objective response rate (ORR), overall survival (OS), and progression free survival (PFS) were evaluated as well. The OS was recorded from the day of treatment with PD-1 inhibitors to the date of death or last follow-up. The PFS was recorded from the day of SBRT intervention to disease progression or death. Kaplan–Meier survival analyses were used to estimate OS. Statistical analyses were performed using SPSS software, version 18.0 (SPSS, Inc., Chicago, IL, USA).

Table 1 Patient characteristics and treatment details

Patient No	Sex	Age	ECOG PS	Recurrent/metastasis status	oligometastasis	Number of previous lines of therapy
1	M	28	2	Liver and multiple bone metastasis (thoracic and lumbar vertebra, pelvis, sternum, bilateral femur, bilateral ribs, right humerus)	No	2
2	M	52	0	Multiple liver metastasis	Yes	2
3	F	53	1	Local recurrence, multiple sites in liver, hilar lymph node, left scapula	Yes	1 (refused to receive chemotherapy)
4	M	44	1	Metastasis in liver and in right axillary lymph nodes	Yes	2
5	M	41	0	Multiple metastasis in liver and bone (lumbar vertebra)		PD within 6 months
6	M	56	1	Multiple metastasis (right 6th rib, right axillary lymph nodes and multiple lung nodules)	Yes	4
7	M	48	1	Regional refractory in bilateral neck; liver and multiple bone metastasis (sternum, thoracic and lumbar vertebra)	No	PD within 3 months
8	M	39	2	Local and regional relapse in nasopharynx and bilateral neck	NA	2

F, female; M, male; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease

Results

Patient characteristics

Eight patients who were R/M NPC after the first treatment were included in this case series. The median follow-up time was 56.7 months (range: 6.1–61.1 months), and three patients were alive during the last follow-up. Baseline patient characteristics are presented in Table 1. The median age was 46 years (range: 28–56 years), with one female patient. Five patients (87.5%) received at least two lines of chemotherapy. Two patients progressed in 6 months after initial treatment. One patient (12.5%) with multiple metastatic NPC refused to receive chemoradiotherapy. Two patients (25%) had an ECOG performance status of 2, four (50%) were ECOG 1, and one (25%) was ECOG 0. According to the classification of PD-L1 and CD8 + TIL, all patients showed adaptive resistance (PD-L1 expression and CD8 + TIL).

Anti-tumor activity of PD-1 inhibitors alone

Since all the eight patients presented with a uniform immunophenotype of adaptive resistance, PD-1 inhibitors were given to the whole cohort at the beginning. After 2–3 cycles of PD-1 inhibitors, all patients were evaluated according to RECIST 1.1 and one patient had a CR, two had SD, and the remaining five had PD. The confirmed ORR and disease control rate (DCR) at 3

cycles of PD-1 inhibitors alone was 12.5% (1 in 8) and 37.5% (3 in 8), respectively (Fig. 1). Notably, patient 7#, who achieved a CR after just 3 cycles of PD-1 inhibitor, presented with new distant metastatic lesions 18 months later. After a panel discussion he received another 3 cycles of PD-1 inhibitor and again achieved a CR. What is worth mentioning is that this status continued up to August 27, 2020.

SBRT extends the clinical benefit of PD-1 inhibitors

As demonstrated above, only one patient obtained an objective response at first evaluation. The remaining seven patients were then given SBRT (25 ~ 36 Gy/5 ~ 6Fx, six fraction-regimen, typically 6 × 5 Gy, were preferred, detailed in Table 2) to irradiate all visible lesions or main lesions or only progressive lesions. The aim was to improve the treatment response to PD-1 inhibitors. It is noteworthy that radiotherapy did not interfere with the administration of PD-1 inhibitors. Second evaluation based on RECIST 1.1 was performed after SBRT. The ORR of these seven cases was 85.7% (6/7 cases), including two CR (28.6%, 2/7) and four PR (57.1%, 4/7). The remaining patient (patient #1) progressed during the treatment course and died within 95 days after the initiation of SBRT).

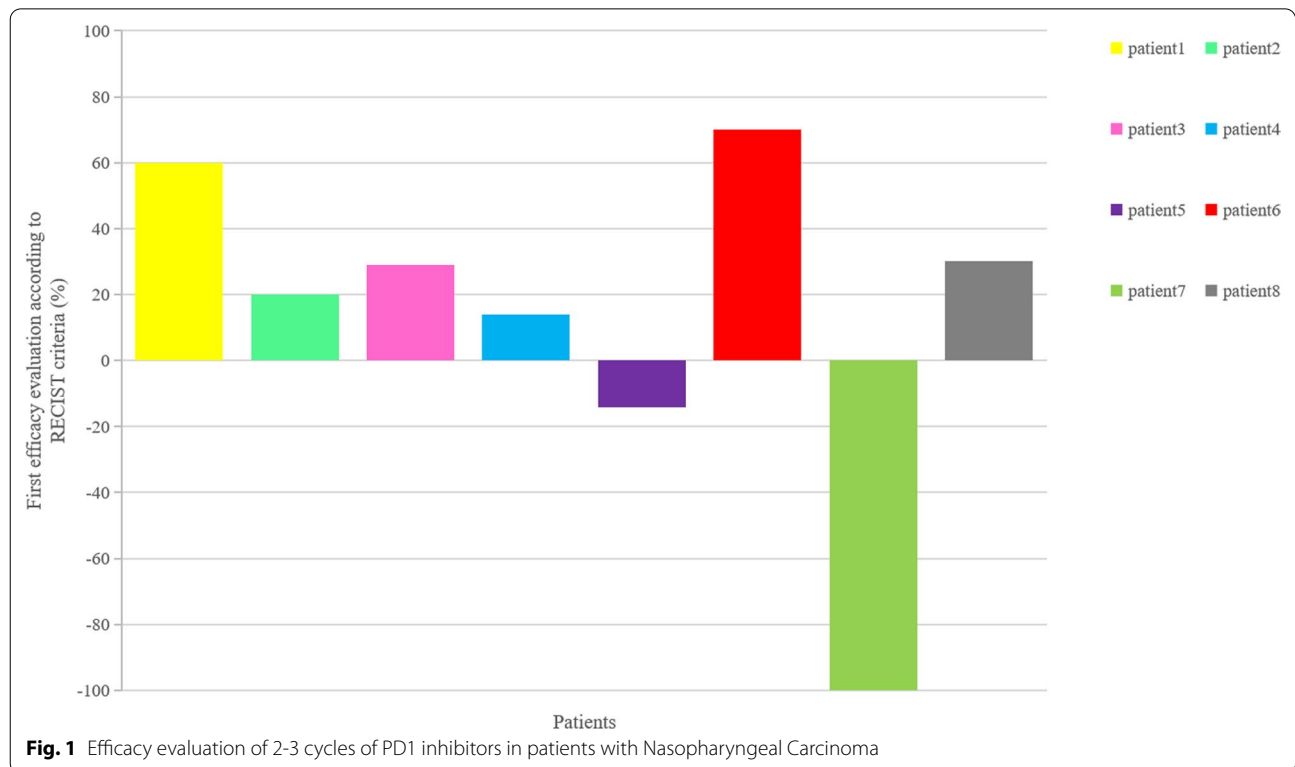


Table 2 The detail treatment and therapeutic evaluation of 8 patients

ID	PD 1 inhibitors	SBRT		Therapeutic evaluation		
		Dose	Radiation sites	PD-1inhibitor alone	Radiated lesions	Non-Radiated lesions
1	Nivolumab (5 cycles)	25 Gy/5Fx	Progressive lesions	PD	PR	PD
2	Pembroizumab (6 cycles)	30 Gy/6Fx	All visible lesions	PD	CR	NA
3	Nivolumab (5 cycles)	30 Gy/6Fx	Progressive lesions	PD	CR	Unevaluable
4	Nivolumab (14 cycles)	36 Gy/6Fx	Main lesions	SD	PR	SD
5	Nivolumab (11 cycles)	30 Gy/6Fx	Main lesions	SD	PR	SD
6	Nivolumab (6 cycles)	30 Gy/6Fx	All visible lesions	PD	CR	NA
7	Nivolumab (6 cycles)	No	NA	CR	NA	NA
8	Nivolumab (9 cycles)	30 Gy/6Fx	Progressive lesions	PD	PR	Unevaluable

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NA: not assessed

Evaluation of the abscopal effect of SBRT

To assess the abscopal effect of SBRT an objective response of irradiated and non-irradiated lesions was separately evaluated according to the criteria of RECIST 1.1. Of the seven patients who underwent SBRT, three and four patients eventually achieved a CR and PR of the irradiated lesions, respectively. Two of them received irradiation to all visible lesions, with no lesions being available to evaluate an abscopal effect. For the other five cases who underwent SBRT directed against progressive lesions or major lesions, only three patients were suitable for assessing the abscopal effect (patients #1, #4, and #5). None of the evaluable non-irradiation lesions showed an objective response, which meant that no abscopal effects was observed in our cohort. The dynamic imaging responses of all irradiated and non-irradiated lesions are shown in Fig. 2.

Survival analysis

All included patients received 5–30 doses of PD-1 inhibitors (median: 14 cycles). Figures 3 and 4 show the duration of study treatment for all eight patients, in which evaluation time points and results are clearly detailed. Changes in tumor burden over time, and the specific time of radiotherapy are also shown. For the eight patients, the median OS was 30.9 months 95%CI (15.6, 46.1), and the 2-year OS was 75% (Fig. 5). The PFS of the seven patients who did not respond to PD-1 inhibitors was 10 months, with the 1-year PFS at 43.5%.

Toxicity of immune-radiotherapy

Seven out of eight patients (87.5%) experienced at least one adverse event. Adverse events that occurred in 15% or more of the patients were as follows; fatigue, asthenia, nausea, decreased appetite, diarrhea, dry mouth, vomiting, rash, pruritus, and anemia (Table 3). Grades 3–4

related toxicity occurred in three cases (37.5%), including one each of nausea, decreased appetite, and vomiting. There were no treatment related dose interruptions and no unexpected toxicities occurred.

Atypical case who achieved complete responses after combined SBRT with PD-1 inhibitors

Patient #6 was a 56-year-old man who had been heavily pretreated and received PD-1 inhibitor as 4th line systemic therapy for metastatic disease in the right 6th rib and right axillary lymph nodes, as showed in Fig. 6. A large number of CD8+T cells in the tumor region together with PD-L1 positive expression (17%: TC 15%, IC 2%) were observed in a pretreatment biopsy. After two doses of nivolumab, radiologic measurements indicated that lymph nodes in the right axillary were increased in number and size. A subsequent biopsy in this area excluded the possibility of pseudoprogression and showed a similar immune microenvironment to a pre-dose tissue sample. There was no evidence of an existing immune response and no necrosis was observed under the microscope. After discussion by the multidisciplinary treatment group it was decided to combine radiotherapy so as to convert the tumor cells into an in situ tumor vaccine, as indicated in a previous report [21]. He then underwent 3rd and 4th cycles of nivolumab followed by SBRT given in between at all detected metastatic sites (right 6th rib and axillary lymph nodes), 3000 cGy in six fractions were delivered. Five weeks after the SBRT a PET-CT scan showed a PR with smaller metastatic sites in the right 6th rib and axillary lymph nodes. Considering the effectiveness of the combined therapy, another two doses of nivolumab were given. Finally, as presented in Fig. 3, PET-CT imaging showed all metastatic lesions had disappeared, and a metabolic CR was declared.

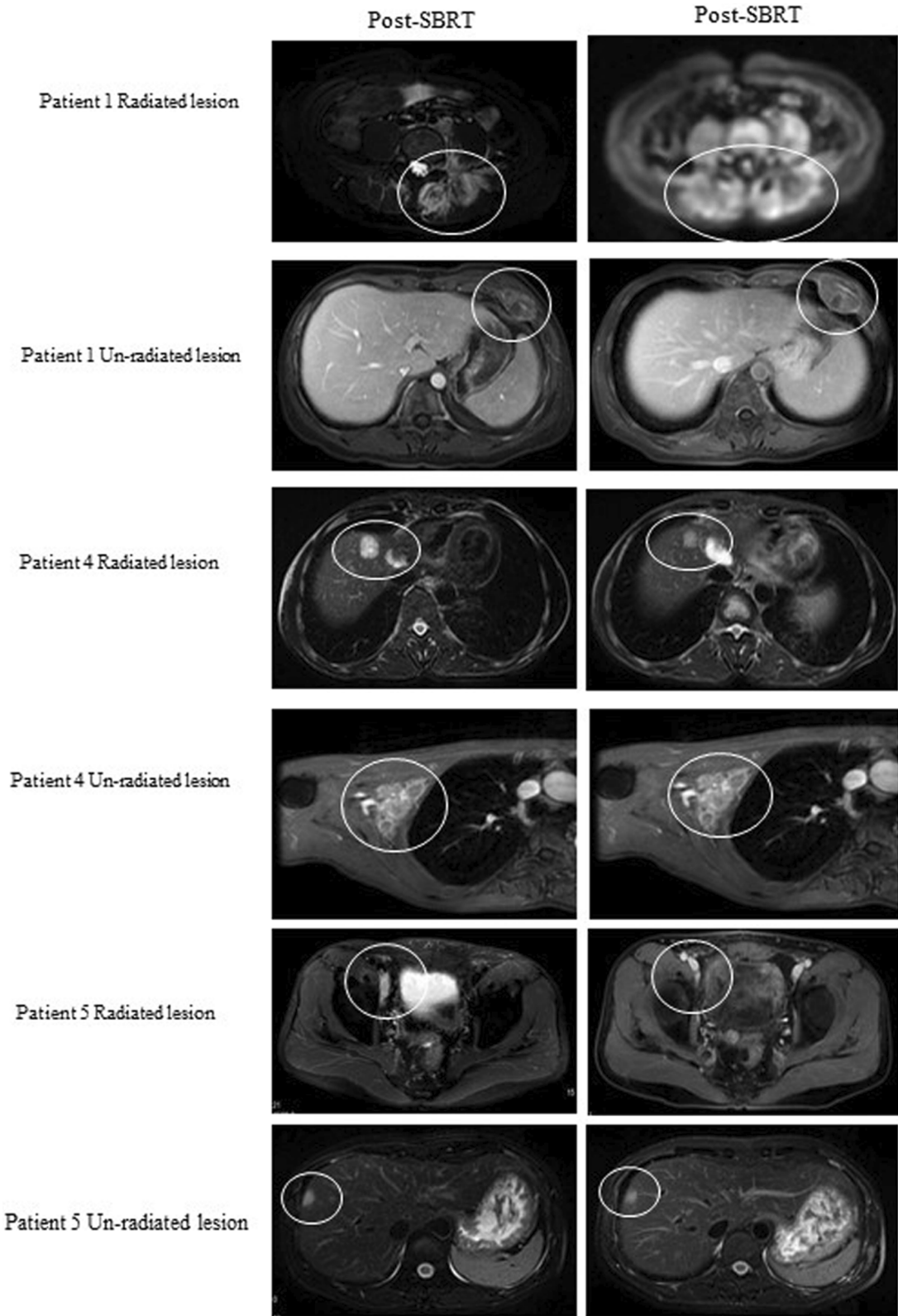
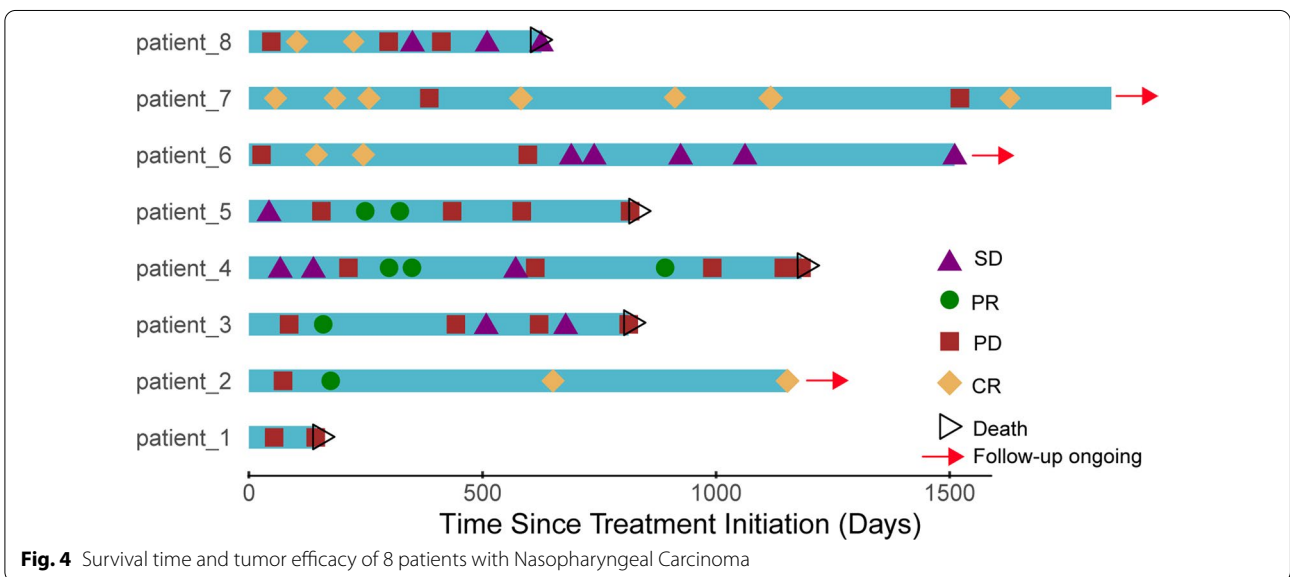
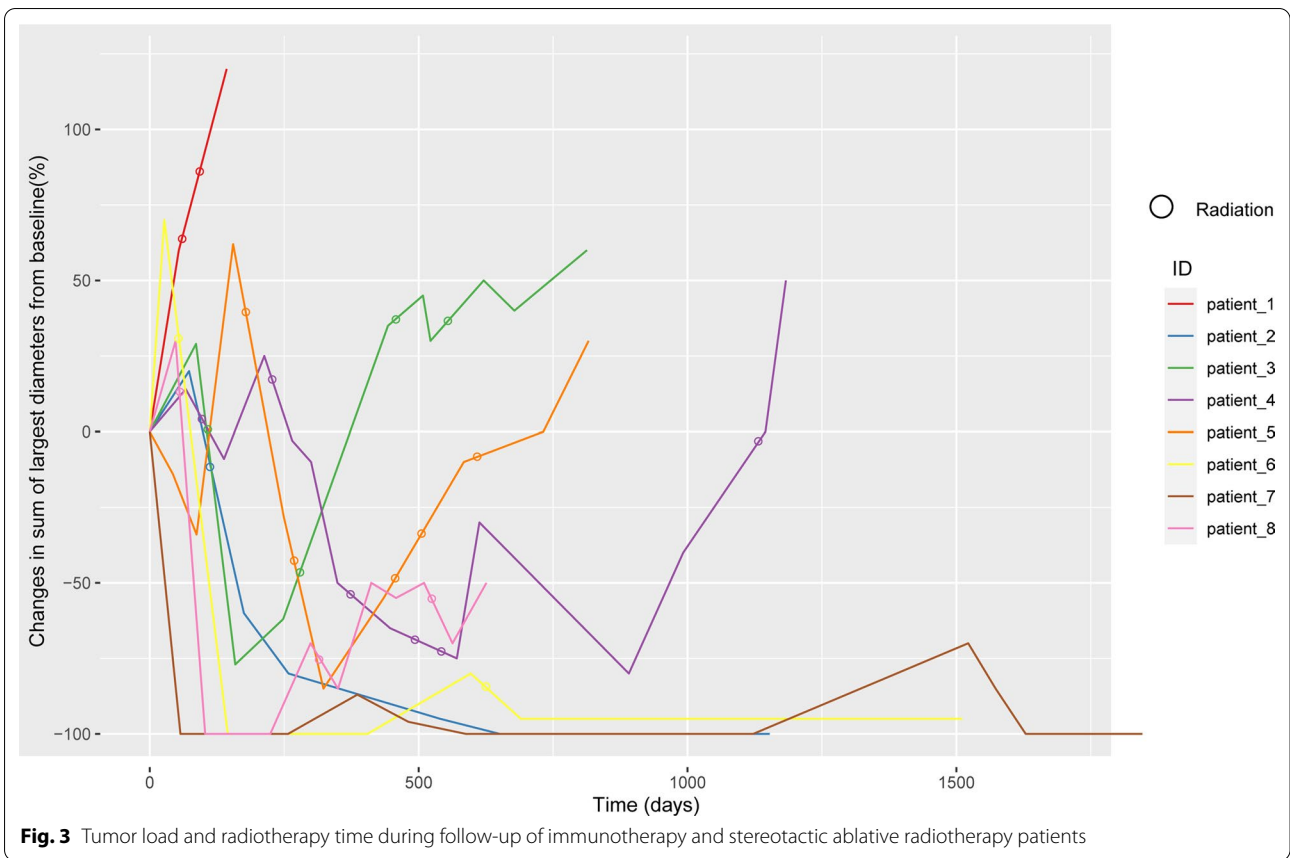


Fig. 2 The dynamic imaging responses of all irradiated and non-irradiated lesions (patients # 1, # 4 and #5)



Discussion

Although a PD-1/PD-L1 blockade has resulted in impressive clinical responses in some RM-NPC cases, its effectiveness is still far from satisfactory in most patients. Optimal results will require combination with

other treatment modalities (immune-modulating treatments), such as SBRT, to enhance a systemic clinical response. The ORR to ICIs alone in our cohort is only 12.5% at first evaluation, while radiation therapy produced an excellent response in PD-1 inhibitor-resistant

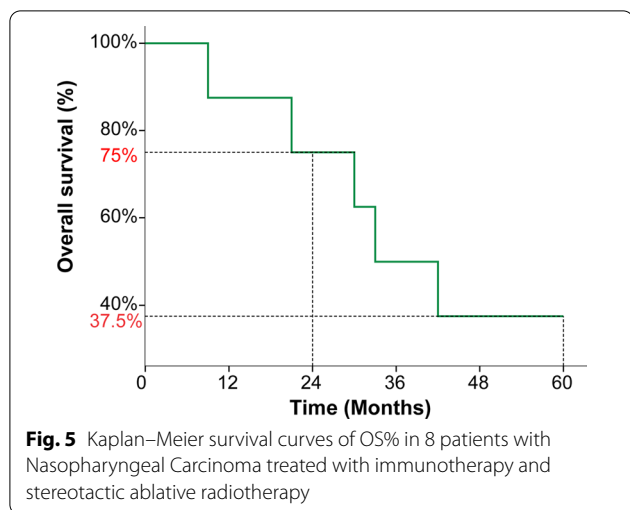


Table 3 Treatment related toxicities

Treatment-related AE	No. (%) of events	
	Any Grade	Grade 3–4
Any	8(100%)	3(37.5%)
Fatigue	6(75.0%)	0
Asthenia	5(62.5%)	0
Nausea	3(37.5%)	1(12.5%)
Decreased appetite	5(62.5%)	1(12.5%)
Diarrhea	2(25.0%)	0
Dry mouth	5(62.5%)	0
Vomiting	3(37.5%)	1(12.5%)
Rash	7(87.5%)	0
Pruritus	6(75.0%)	0
Anemia	2(25.0%)	0
Pneumonia	1(12.5%)	0
Neutropenia	1(12.5%)	0
Myalgia	0	0
Autoimmune hepatitis	0	0
Dyspnoea	0	0

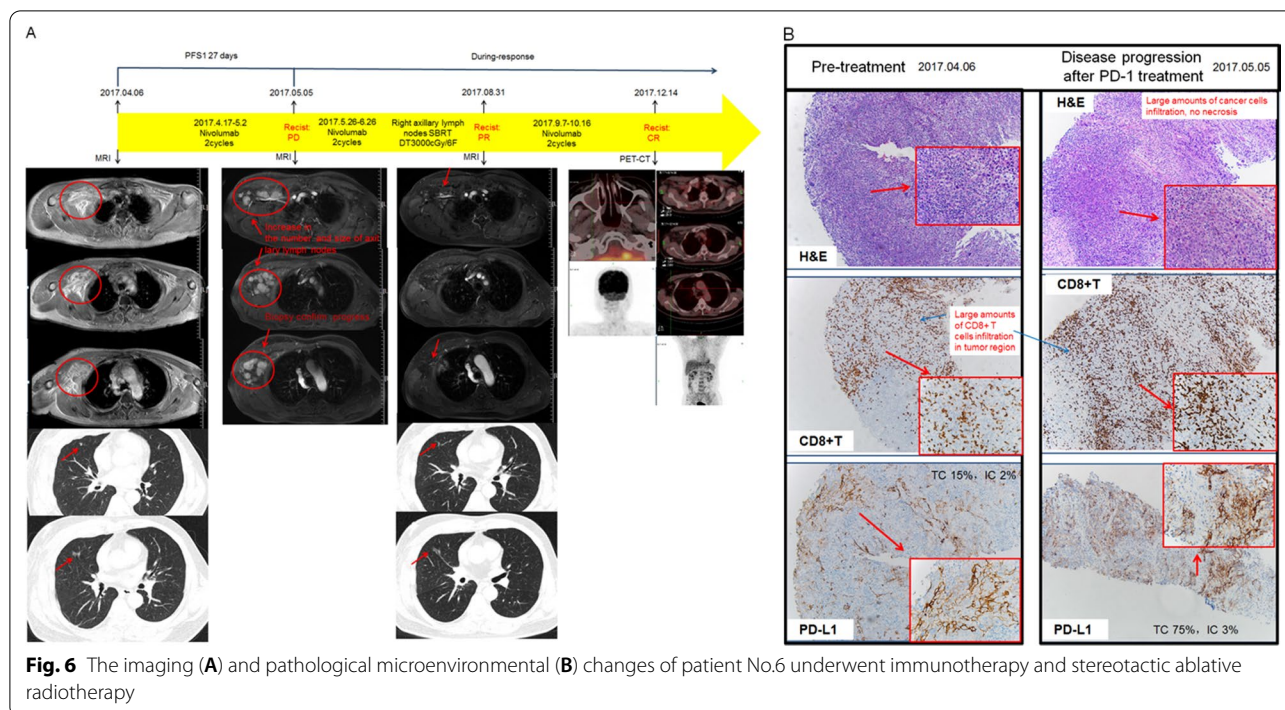
patients, with the confirmed ORR and CR reported to be of 85.7% and 28.6%. Notably, neither an abscopal effect nor pseudoprogression were observed in our study. Our results are of paramount importance in that this is the first report on the combination of PD-1 inhibitors and radiotherapy in refractory RM-NPC. Our results are consistent with the stimulation of anti-tumor activity by a combination of SBRT with anti-PD-1 treatment and may maximize the clinical benefit of PD-1 inhibitors in this subset of patients.

NPC tumors are characterized by an abundant immune infiltration, the ORR for refractory RM-NPC

treated with PD-1 alone, however, was not by the mechanism we expected. As reported in the current study, only an ORR of 12.5% was achieved at first evaluation. This may be a consequence of low tumor mutation burden and limited specific antigens that could be recognized by immune cells that would be insufficient for effectively eliminating tumor cells [37]. Likewise, results of published studies with refractory RM-NPC indicated less than satisfactory, but slightly higher ORR (ranging from 19 to 34%) than ours [13–15]. This might be due to different assessment time point, as all patients underwent their first response evaluation just after 2–3 cycles of PD-1 inhibitors. If PD-1 inhibitors continue to be used alone, the ORR might increase. The retrospective nature and relatively small sample size of our study may be other reasons contributing to this dissimilarity.

The most exciting finding of this study was that radiotherapy can effectively reverse drug-resistance of PD-1 inhibitors. Of the seven patients who were resistant to PD-1 inhibitors, 85.7% (6/7) of them experienced an ORR after receiving radiation, with the median PFS and 2-year OS of 8 months and 71.0%. Indeed, preclinical evidence had clearly indicate that radiotherapy might increase response rates to immune checkpoint inhibitors (ICIs) by creating a more permissive tumor microenvironment [32, 38, 39]. Combining anti-PD-1 treatment with radiotherapy can result in improved clinical response rates and prolong survival [33, 40–42]. However, radiotherapy intervention in those studies were integrated into the treatment plan in advance, either before or during the treatment with ICIs. Masini et al. have reported from the phase II NIVES clinical trial that radiotherapy before ICI therapy did not improve outcome in Renal Cell Carcinoma patients [43]. Whereas in our cohort radiotherapy was given only when PD-1 inhibitor-resistance appeared and was intended to start an immune response by radiation. What was strikingly noticeable was that all irradiated lesions achieved ORR (CR or PR) at second evaluation, but an abscopal effect was not observed in unirradiated lesions.

There has been a systematic review that reported that the mean incident for an distant/abscopal response was 41% in 1736 non-small-cell lung cancer patients treated with an ICIs-SABR combination [44]. However, some investigators argued that this so-called distant response of non-irradiated lesions cannot be called a real abscopal response, since ICIs are systemic broad-spectrum anti-tumor drugs [45]. Thus, these patients may have a systemic anti-tumor effect, even if they were not irradiated. The real abscopal effect should be defined as treatment of ICIs being ineffective, and the irradiation of major or progressive lesions can mediate tumor regression at a remote site. Recently, Elisa Funck-Brentano et al.



[45] reported a retrospective study that correctly analyzed the abscopal effect, in which 26 melanoma patients who failed anti-PD-1 monotherapy were included. The abscopal effect was seen in 35% of patients who received hypo-fractionated radiotherapy combined with the anti-PD-1 monoclonal antibody regimen. This surprisingly high incidence of an abscopal effect in melanoma may be explained by the strong immunogenicity of melanoma, owing to which radiotherapy may more easily stimulate an overall immune response.

There are currently two main theories for how radiotherapy activates immunity that are supported by experimental data from animal models. One view is abnormal proteins caused by radiotherapy irradiation play the role of in situ vaccines, generating systemic anti-tumor immunity and an abscopal effect [46]. The other is that broken double-stranded DNA (dsDNA) could be produced in large quantities by irradiated tumor cells that would trigger the cGAS-STING signaling pathway after entering the cytoplasm, and mediate the elimination of damaged tumor cells by immune cells [47]. Results from our study suggested that the latter mechanism may play a greater role. The current study indicated that all irradiated lesions achieved good local control, but no obvious abscopal effect was observed in unirradiated lesions. As Prof. Chang from MD Anderson Cancer Center has proposed, it is time to abandon single-site irradiation for inducing abscopal effects [26]. Perhaps it is necessary for

radiation oncologists to rethink how to use our effective weapons (i.e., SBRT) to provide local consolidative therapy (LCT) for all lesions or as many lesions as possible, but solely rely on an abscopal effect to control tumors. Data from phase III trials testing the combination of radiotherapy with ICI have shown that patients who derived benefits either had good prognostic factors and a smaller disease burden (oligometastatic disease) or received irradiation to all sites of gross disease [48, 49]. Furthermore, in melanoma patients the benefit of ICI and the ability to maintain robust antitumor immunity seems to be greatest for patients with a lower total tumor burden [50]. This suggests that a reduction in tumor burden, which could be obtained using comprehensive (but not single site) radiotherapy, could help to potentiate ICI and extend overall survival. Thus, we contend that using comprehensive radiotherapy (i.e., LCT) in combination with ICIs is an important, albeit unexplored, strategy for the optimization of approaches that combine radiotherapy with ICIs.

Published data have confirmed that LCT can effectively improve disease control and overall survival of oligometastasis in various types of cancer [34, 35, 51], its combination with ICI in patients with oligometastasis has shown meaningful clinical outcomes as well [52, 53]. However, there is no relevant report assessing the definite clinical benefit of LCT for ICI in patients with multiple metastases who have more treatment difficulty than

oligometastasis. For such a particular subset of patients with a high tumor burden, ICIs alone may not yield a satisfactory clinical response, except for the few cases with a high mutation load or microsatellite instability (MSI). Of note, two multiple metastatic NPC cases who did not response to ICIs alone (patient #2 and #6) achieved an exciting response (CR) after LCT when SBRT was delivered to all visible lesions, suggesting that tumor debulking by LCT could create conditions to ignite local immunity and then enhance tumor response.

In the current study, toxicities associated a PD-1 inhibitor combined with SBRT were generally tolerable, with no lethal toxicity occurring. Grade 3–4 toxicities appeared in 37.5% of patients including nausea, decreased appetite, and vomiting, but did not cause treatment interruption. Our results suggest that this combined modality is feasible and is consistent with data reported by other investigators.

Although this is the first study showing that PD-1 inhibitors combined with SBRT can achieve encouraging results in the treatment of refractory RM-NPC, the retrospective nature and small sample size limits the extensive applicability. Thus, the benefits elicited by this combination are not yet formally established. In addition, additional tumor biology analysis of the ICI-resistant mechanism was not performed in our study and need to be considered in further studies.

Conclusions

The treatment was well tolerated, with clinical activity supporting the augmentation role of SBRT upon PD-1 inhibitors. Much remains to be learned regarding the optimal dose and/or fractionation schedules of radiotherapy and the mechanism by which SBRT stimulates an immune response. Further well-designed prospective studies are warranted to confirm the complementary role of radiotherapy and PD-1 inhibitors.

Abbreviations

NPC: Nasopharyngeal carcinoma; RM-NPC: Recurrent/metastatic nasopharyngeal carcinoma; SBRT: Stereotactic body radiation therapy; ISABR: Immunotherapy and stereotactic ablative radiotherapy; ECOG PS: Eastern Cooperative Oncology Group performance status; TIL: Tumor infiltration lymphoma; GTV: Gross Target Volume; PFS: Progression free survival; OS: Overall survival; ORR: Objective response rate; PTV: Planning Target Volume; DCR: Disease control rate; AE: Adverse event; ICIs: Immune checkpoint inhibitors; LCT: Local consolidative therapy; CR: Complete response.

Acknowledgements

Not applicable.

Author contributions

JP, ZG contributed to the conception of the study; GC, JL, LT performed the experiment; TL, SL, MC, JZ contributed to data curation; JL, QG, YC contributed significantly to manuscript preparation, and performed the data analyses and wrote the manuscript; CC, ZG, JP helped perform the analysis with constructive discussions. All authors read and approved the final manuscript.

Funding

The project was supported by Fujian Provincial Clinical Research Center for Cancer Radiotherapy and Immunotherapy (Grant No. 2020Y2012), the National Natural Science Foundation of China (Grant No. U1705282).

Availability of data and materials

The datasets analyzed during the current study are not publicly available.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors have no potential financial competing interests.

Author details

¹Department of Medical Oncology, Fujian Medical University Cancer Hospital and Fujian Cancer Hospital, Fuzhou 350014, Fujian Province, China. ²Cancer Bio-Immunotherapy Center, Fujian Medical University Cancer Hospital & Fujian Cancer Hospital, No. 420 Fuma Road, Fuzhou 350014, Fujian Province, China. ³Department of Radiation Oncology, Fujian Medical University Cancer Hospital & Fujian Cancer Hospital, Fuzhou 350014, Fujian Province, China. ⁴Fujian Provincial Key Laboratory of Translational Cancer Medicine, Fuzhou, Fujian, China. ⁵Department of Pathology, Fujian Medical University Cancer Hospital & Fujian Cancer Hospital, Fuzhou, Fujian Province, China. ⁶Department of Ultrasound, Fujian Medical University Cancer Hospital & Fujian Cancer Hospital, Fuzhou, Fujian Province, China. ⁷College of Chemistry, Fuzhou University, Fuzhou, China.

Received: 29 January 2022 Accepted: 27 May 2022

Published online: 05 July 2022

References

- National Comprehensive Cancer Network. (NCCN) Clinical Practice Guidelines in Oncology. Nasopharyngeal carcinoma. Version 1. 2019.
- Chan AT, Teo PM, Leung TW, Johnson PJ. The role of chemotherapy in the management of nasopharyngeal carcinoma. *Cancer*. 1998;82(6):1003–12.
- Au E, Ang PT. A phase II trial of 5-fluorouracil and cisplatin in recurrent or metastatic nasopharyngeal carcinoma. *Ann Oncol*. 1994;5(1):87–9.
- Chua DT, Sham JS, Au GK. A phase II study of docetaxel and cisplatin as first-line chemotherapy in patients with metastatic nasopharyngeal carcinoma. *Oral Oncol*. 2005;41(6):589–95.
- Leong SS, Wee J, Tay MH, et al. Paclitaxel, carboplatin, and gemcitabine in metastatic nasopharyngeal carcinoma: a Phase II trial using a triplet combination. *Cancer*. 2005;103(3):569–75.
- Zhang L, Huang Y, Hong S, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *Lancet*. 2016;388(10054):1883–92.
- Airoldi M, Pedani F, Marchionatti S, et al. Carboplatin plus taxol is an effective third-line regimen in recurrent undifferentiated nasopharyngeal carcinoma. *Tumori*. 2002;88(4):273–6.
- Chua DT, Sham JS, Au GK. A phase II study of capecitabine in patients with recurrent and metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. *Oral Oncol*. 2003;39(4):361–6.
- Ngan RK, Yiu HH, Lau WH, et al. Combination gemcitabine and cisplatin chemotherapy for metastatic or recurrent nasopharyngeal carcinoma: report of a phase II study. *Ann Oncol*. 2002;13(8):1252–8.
- Seiwert TY, Burtneis B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol*. 2016;17(7):956–65.
- Sanmamed MF, Chen L. A paradigm shift in cancer immunotherapy: from enhancement to normalization. *Cell*. 2018;175(2):313–26.

12. Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations. *Sci Transl Med*. 2016;8(328):328rv4.
13. Hsu C, Lee SH, Ejadi S, et al. Safety and antitumor activity of pembrolizumab in patients with programmed death-ligand 1-positive nasopharyngeal carcinoma: results of the KEYNOTE-028 study. *J Clin Oncol*. 2017;35(36):4050–6.
14. Fang W, Yang Y, Ma Y, et al. Camrelizumab (SHR-1210) alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma: results from two single-arm, phase 1 trials. *Lancet Oncol*. 2018;19(10):1338–50.
15. Ma B, Lim WT, Goh BC, et al. Antitumor activity of nivolumab in recurrent and metastatic nasopharyngeal carcinoma: an international, multicenter study of the mayo clinic phase 2 consortium (NCI-9742). *J Clin Oncol*. 2018;36(14):1412–8.
16. Wang Y, Liu ZG, Yuan H, et al. The reciprocity between radiotherapy and cancer immunotherapy. *Clin Cancer Res*. 2019;25(6):1709–17.
17. Demaria S, Golden EB, Formenti SC. Role of local radiation therapy in cancer immunotherapy. *JAMA Oncol*. 2015;1(9):1325–32.
18. Demaria S, Ng B, Devitt ML, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *Int J Radiat Oncol Biol Phys*. 2004;58(3):862–70.
19. Reits EA, Hodge JW, Herberts CA, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J Exp Med*. 2006;203(5):1259–71.
20. Kalbasi A, June CH, Haas N, Vapiwala N. Radiation and immunotherapy: a synergistic combination. *J Clin Invest*. 2013;123(7):2756–63.
21. Weichselbaum RR, Liang H, Deng L, Fu YX. Radiotherapy and immunotherapy: a beneficial liaison. *Nat Rev Clin Oncol*. 2017;14(6):365–79.
22. Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest*. 2014;124(2):687–95.
23. Sharabi AB, Nirschl CJ, Kochel CM, et al. Stereotactic radiation therapy augments antigen-specific PD-1-mediated antitumor immune responses via cross-presentation of tumor antigen. *Cancer Immunol Res*. 2015;3(4):345–55.
24. Zeng J, See AP, Phallen J, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. *Int J Radiat Oncol Biol Phys*. 2013;86(2):343–9.
25. Gerber SA, Lim JY, Connolly KA, et al. Radio-responsive tumors exhibit greater intratumoral immune activity than nonresponsive tumors. *Int J Cancer*. 2014;134(10):2383–92.
26. Brooks ED, Chang JY. Time to abandon single-site irradiation for inducing abscopal effects. *Nat Rev Clin Oncol*. 2019;16(2):123–35.
27. Chakraborty M, Abrams SI, Coleman CN, Camphausen K, Schlom J, Hodge JW. External beam radiation of tumors alters phenotype of tumor cells to render them susceptible to vaccine-mediated T-cell killing. *Cancer Res*. 2004;64(12):4328–37.
28. Formenti SC, Demaria S. Radiation therapy to convert the tumor into an in situ vaccine. *Int J Radiat Oncol Biol Phys*. 2012;84(4):879–80.
29. Zhang H, Liu L, Yu D, et al. An in situ autologous tumor vaccination with combined radiation therapy and TLR9 agonist therapy. *PLoS ONE*. 2012;7(5):e38111.
30. Bernstein MB, Garnett CT, Zhang H, et al. Radiation-induced modulation of costimulatory and coinhibitory T-cell signaling molecules on human prostate carcinoma cells promotes productive antitumor immune interactions. *Cancer Biother Radiopharm*. 2014;29(4):153–61.
31. Schaeue D, Ratikan JA, Iwamoto KS, McBride WH. Maximizing tumor immunity with fractionated radiation. *Int J Radiat Oncol Biol Phys*. 2012;83(4):1306–10.
32. Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature*. 2015;520(7547):373–7.
33. Desideri I, Francolini G, Scotti V, et al. Benefit of ablative versus palliative-only radiotherapy in combination with nivolumab in patients affected by metastatic kidney and lung cancer. *Clin Transl Oncol*. 2019;21(7):933–8.
34. Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol*. 2019;37(18):1558–65.
35. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet*. 2019;393(10185):2051–8.
36. Szoln M, Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. *Clin Cancer Res*. 2013;19(5):1021–34.
37. Pérez-Ruiz E, Melero I, Kopecka J, Sarmiento-Ribeiro AB, García-Aranda M, De Las RJ. Cancer immunotherapy resistance based on immune checkpoints inhibitors: targets, biomarkers, and remedies. *Drug Resist Updat*. 2020;53:100718.
38. McLaughlin M, Patin EC, Pedersen M, et al. Inflammatory microenvironment remodelling by tumour cells after radiotherapy. *Nat Rev Cancer*. 2020;20(4):203–17.
39. Sharabi AB, Lim M, DeWeese TL, Drake CG. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. *Lancet Oncol*. 2015;16(13):e498–509.
40. Yamaguchi O, Kaira K, Hashimoto K, et al. Radiotherapy is an independent prognostic marker of favorable prognosis in non-small cell lung cancer patients after treatment with the immune checkpoint inhibitor, nivolumab. *Thorac Cancer*. 2019;10(4):992–1000.
41. Schapira E, Hubbeling H, Yeap BY, et al. Improved overall survival and locoregional disease control with concurrent PD-1 pathway inhibitors and stereotactic radiosurgery for lung cancer patients with brain metastases. *Int J Radiat Oncol Biol Phys*. 2018;101(3):624–9.
42. Chen L, Douglass J, Kleinberg L, et al. Concurrent immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in non-small cell lung cancer, melanoma, and renal cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2018;100(4):916–25.
43. Masini C, Iotti C, De Giorgi U, et al. Nivolumab in combination with stereotactic body radiotherapy in pretreated patients with metastatic renal cell carcinoma. Results of the phase II NIVES study. *Eur Urol*. 2022;81(3):274–82.
44. Chicas-Sett R, Morales-Orue I, Castilla-Martinez J, et al. Stereotactic ablative radiotherapy combined with immune checkpoint inhibitors reboots the immune response assisted by immunotherapy in metastatic lung cancer: a systematic review. *Int J Mol Sci*. 2019;20(9):11458.
45. Funck-Brentano E, Baghdad B, Fort M, et al. Efficacy of late concurrent hypofractionated radiotherapy in advanced melanoma patients failing anti-PD-1 monotherapy. *Int J Cancer*. 2020;147(6):1707–14.
46. Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S, Formenti SC. Using immunotherapy to boost the abscopal effect. *Nat Rev Cancer*. 2018;18(5):313–22.
47. Sato H, Okonogi N, Nakano T. Rationale of combination of anti-PD-1/PD-L1 antibody therapy and radiotherapy for cancer treatment. *Int J Clin Oncol*. 2020;25(5):801–9.
48. Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2014;15(7):700–12.
49. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377(20):1919–29.
50. Huang AC, Postow MA, Orlowski RJ, et al. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. *Nature*. 2017;545(7652):60–5.
51. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOL phase 2 randomized clinical trial. *JAMA Oncol*. 2020;6(5):650–9.
52. Bauml JM, Mick R, Ciunci C, et al. Pembrolizumab after completion of locally ablative therapy for oligometastatic non-small cell lung cancer: a phase 2 trial. *JAMA Oncol*. 2019;5(9):1283–90.
53. Luke JJ, Lemons JM, Karrison TG, et al. Safety and clinical activity of pembrolizumab and multisite stereotactic body radiotherapy in patients with advanced solid tumors. *J Clin Oncol*. 2018;36(16):1611–8.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.