Combination of Stereotactic Radiosurgery with Immunotherapy: Is It a New Treatment Option for Brain Metastases?

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

ABSTRACT

Brain metastases (BM) represent the commonest intracranial tumours which occur approximately 30% of all adult patients presenting with solid cancers. The BMs do not only reduce the survival expectations but negatively alter the quality of life measures as well. For decades, surgery and whole-brain radiotherapy (WBRT) constituted the traditional treatment options with limited efficacy for the BMs. However, the unsatisfactory local control and ultimate survival outcomes led to a paradigm change, and stereotactic radiosurgery (SRS) has been executed as an alternative to surgery and WBRT or to augment the outcomes of each treatment when used in conjunction with them. In spite of the impressive improvements in the local control rates, yet the desired survival
results were not achieved with SRS mainly due to the deaths ascribed to the extracranial systemic disease progression or unavoidably fatal distant brain recurrences. In this regard, as of late, numerous immunotherapeutics have been shown to improve the outcomes of various cancers, such as the locally advanced non-small-cell lung cancers. Recognizing the fact that the immunotherapy is becoming one of the indispensable components of standard treatment protocols for many tumour primaries, this review aimed to evaluate the efficacy and safety of the use of novel immunotherapeutics with standard SRS for BMs.

Keywords: Brain metastases; stereotactic radiosurgery; immunotherapy; efficacy; safety.

**ABBREVIATIONS**

ICI : Immune checkpoint inhibitor;  
LC : Local control;  
OS : Overall survival;  
MM : Malignant melanoma;  
SRS : Stereotactic radiosurgery;  
IPI : Ipilimumab;  
NIVO : Nivolumumab;  
Pembro : Pembrolizumab;  
ATEZO : Atezolizumab;  
NR : Not reported;  
NSCLC : Non-small-cell lung cancer;  
RCC : Renal cell carcinoma;  
WBRT : Whole-brain radiotherapy;  
PTS : Patients.

**1. INTRODUCTION**

Brain metastases (BM) are the most common intracranial tumours occurring in up to 30% of adult patients with solid cancers [1]. Practically, many cancers metastasize to the brain, yet most BMs typically originate from the lung (small- and non-small-cell) and breast cancers which is trailed by the malignant melanomas, renal cell carcinomas, and other relatively uncommon tumors [2]. Contrasting with the recent notable advances in the diagnosis and treatment of BMs, the patients presenting with BMs have a dismal prognosis with a median survival of a few weeks if untreated, and just about 6 months after whole-brain radiotherapy (WBRT) [3].

The ionizing radiation utilized in WBRT principally acts by causing double-strand DNA damage in tumor cells, fixation of the damage with oxygen, and the formation of cytotoxic free radicals. Notwithstanding, when utilized in a hypofractionated way, the ionizing radiation in the form of high-precision stereotactic radiosurgery (SRS) exerts additional vital actions by altering the local and systemic immune responses against the tumor cells via triggered immunogenic cell death, improved neoantigen presentation, and cytotoxic T-cell activation. For BMs, SRS further offers fundamentally prevalent local control rates with reduced risk of neurocognitive deterioration related to the conventional WBRT. Recently, in light of this basic knowledge, various authors reviewed their experience on the different combinations of SRS and immune checkpoint inhibitors (ICIs) in patients presenting with BMs of a variety of cancer primaries. In this regard, the present review aimed to comparatively summarize the accessible evidence on this hot topic with regards to the tumor control-, survival-, toxicity outcomes to highlight the best sequencing and combination of various ICIs and SRS regimens.

**2. IMMUNE CHECKPOINT INHIBITORS**

Monoclonal antibodies, also known as ICIs, act by blocking the inhibitory immune pathways. Recently, the utilization of these antibodies in conjunction with other anti-cancer modalities has been proposed to improve the therapeutic efficacy of conventional chemotherapy and or SRS, which incited another territory of research in cancer treatment. Opening a new therapeutic window for patients presenting with BMs, coming for the most part from the BMs of malignant melanoma, early proof appeared to support this proposition exhibiting fundamentally upgraded tumor control rates and survival durations with the expense of only slightly increased risk of neurologic toxicity after the various blends of SRS and ICIs.

The anti-tumoral immune response typically incorporates numerous immune cells including the macrophages, natural killer (NK) cells, dendritic cells, and T- and B-lymphocytes. Among those immune cells, certainly, the T-cells embrace the greatest anti-tumour immune burden. The final magnitude and quality of the immune responses initiated by the recognition of the specific antigens by T-cells are properly regulated by the established harmony between the costimulatory and inhibitory (immuno-checkpoint) signals [4,5]. The appropriate immune response can occur in the lymph nodes
as well as in the peripheral tissue or tumor, namely the final target. However, T-cells remain unresponsive unless they recognize similar antigens through their receptors. In the specific context of cancer immunotherapy, the two most effectively contemplated immuno-checkpoints are the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1): both being inhibitory receptors those regulating the immune response at diverse levels with particular mechanisms [6-15]. The antibodies blocking these inhibitory receptors (ipilimumab for CTLA-4, and nivolumab and pembrolizumab for PD-1 receptor) on T-cells demonstrate anti-tumoral efficacy, and in this way, are routinely utilized in the treatment of numerous cancers.

3. INTERACTIONS OF RADIOTHERAPY WITH IMMUNE SYSTEM

Over the most recent two decades, various studies investigating the impact of RT on the immune system exhibited that the local RT was increasing the systemic immune response through its anti-tumoral immune stimulant actions. The apoptotic and necrotic tumour cell debris release excessive levels of tumour-associated antigens following the RT, those introduced to the CD8+ cytotoxic T cells by the dendritic cells (DCs). Thusly, recognition of these antigens activates the immune system against the tumor cells all through the affected body [16]. Supporting this essential information, outcomes of preclinical and clinical studies showed that the therapeutic radiation (particularly when used in conjunction with ICIs) was augmenting systemic immune response in a significant manner with resultant immunogenic tumor cell death [17-20].

Research surveying the interactions between the RT and immune system provided some additional vital information on the importance of dose and fractionation of RT and the optimum timing of RT that exert maximum anti-tumor immune stimulation. Firstly, examines indicated that the immune modulatory ionizing radiation was increasing the number of CTL cells while at the same time diminishing the number of regulatory T-cells in a dose- and fraction-dependent manner through which an optimal tumour-specific immune response become provoked. In a mouse melanoma model, Schauer et al. [21] evaluated the impact of the total dose, per fraction dose, and the number of fractions of RT on the RT-induced immune response and the resultant outcomes. The authors reported that the single fraction doses of 7.5 to 15 Gy had an immune stimulatory effect that proficiently impeded the tumor growth with an accompanying LC advantage. The superior LC rates with single-fraction SRS was also found to be associated with the size of radiation dose and the number of tumor-reactive T cells. Interestingly, simultaneous increments in Treg quantities were observed to offset these beneficial actions. On the other hand, 2 fractions of 7.5 Gy gave off an impression of being related with low Treg numbers and resultant best LC and anti-tumor immunity rates. Therefore, a multifractionated medium-size radiation dose scheme was superior over a single fraction of large-dose radiation in terms of stimulation of a favourable anti-tumoral immunity and tumor control rates. In an older mouse model, Dewan et al. [22] investigated the impact of per fraction doses on the tumor control rates and induction of an abscopal effect with and without administration of an anti-CTLA-4 antibody. Treatment with anti-CTLA-4 antibody alone was shown to have no detectable effect on either primary or secondary tumors. All RT alone regimens produced comparable significant growth delay in the primary tumor but not in the secondary tumors outside the RT portal. Starkly contrasting with these single modality treatments, the combination of RT and anti-CTLA-4 antibody significantly regressed the primary (P<0.001) and secondary (abs copal effect) tumors’ growth only when given in 3 fractions of 8 Gy and 5 fractions of 6 Gy, but not single-dose 20. Therefore, the results of these studies indicate that different RT regimens might lead to similar direct growth inhibitory effects on the irradiated tumor, which may significantly differ in terms of exerting abscopal effects at distant metastatic foci when combined with CTLA-4 inhibitors.

In addition, the addition of anti-CTLA-4 antibody following RT has been reported to be associated with decreased therapeutic efficacy [22-25].

4. CLINICAL EVIDENCE FOR COMBINATION OF SRS AND ICIS

In light of the discerning hypothetical and preclinical proof recommending a synergistic connection between the SRS and ICIS prompted the conduction of clinical examinations researching the different combinations of these two treatment modalities in patients presenting with BMs (Table 1). However, the vast majority of these investigations were retrospective and consolidated BMs of malignant melanoma, an exceptionally immunogenic tumor.
Table 1. Clinical trials of combination stereotactic radiosurgery and immun checkpoint inhibitors in patients for brain metastases

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Design</th>
<th>ICI</th>
<th>Primary</th>
<th>1-yr LC (%</th>
<th>Median OS (mo)</th>
<th>1-yr OS (%)</th>
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<td></td>
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<td>11</td>
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</tr>
<tr>
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<td></td>
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<td>19.7</td>
</tr>
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<td>16</td>
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<td>IPI</td>
<td>MM</td>
<td>NR</td>
<td>4</td>
<td>NR</td>
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<td>NR</td>
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<td>IPI</td>
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<td>56 (6-mo)</td>
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<td>54 (all pts.)</td>
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<tr>
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<td>2016</td>
<td>22</td>
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<td>17</td>
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<td>NSCLC</td>
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<td>MM</td>
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<td>MM</td>
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<td>NR</td>
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<td></td>
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<td>11.9</td>
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<tr>
<td>Reference</td>
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<td>Patients (n)</td>
<td>Design</td>
<td>ICI</td>
<td>Primary</td>
<td>1-yr LC (%)</td>
<td>Median OS (mo)</td>
<td>1-yr OS (%)</td>
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<td>Chen et al. [42]</td>
<td>2018</td>
<td>51</td>
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<td></td>
<td></td>
<td>28</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
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<td>2018</td>
<td>29</td>
<td>Non-concurrent Concurrent</td>
<td>NIVO or PEMBRO ATEZO</td>
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<td>17.6 (all pts.)</td>
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<td></td>
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<td>Nardin et al. [45]</td>
<td>2018</td>
<td>25</td>
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<td>MM</td>
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<td>NIVO</td>
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<td>IPI</td>
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<tr>
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<tr>
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<td>18</td>
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<td></td>
<td></td>
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<td>5</td>
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In one of the earliest studies, Knisely et al. [26] reviewed the retrospective data of 77 malignant melanoma patients who underwent SRS for BMs to evaluate the impact of ipilimumab on survival. Reassuringly, the median overall survival (OS) was 21.3 months in patients receiving ipilimumab plus SRS versus 4.9 months in the SRS alone group. Similarly, the 2-year survival rate also favored the combination treatment over the SRS alone (47.2% versus 19.7%), and the addition of ipilimumab to SRS emerged to be an independent factor associated with a significant reduction in the risk for death (P=0.03). In a comparative retrospective report, Silk et al. [27] compared the outcomes of 70 malignant melanoma patients who underwent WBRT/SRS with or without ipilimumab for BMs. Once more, the outcomes of this retrospective survey affirmed that the addition of ipilimumab to RT was associated with significantly improved median survival times (5.3 versus 18.3 months). The results of subsequent studies in malignant melanoma, non-small-cell carcinoma, and renal cell carcinoma BMs altogether confirmed the superiority of the combination of SRS with either of ipilimumab, or pembrolizumab, or nivolumab over the SRS alone in terms of LC rates and median survival durations [28-48].

Qian et al. [32] conducted a critical observational study to determine the effect of the relative timing and type of ICIs on the response of malignant melanoma BMs to treatment with SRS. The outcomes of a total of 75 malignant melanoma patients with 566 BMs who received SRS and ICIs were analyzed. The authors considered the SRS and ICI as concurrent if SRS was administered within 4 weeks of ICI administration. In this study, the concurrent use of SRS and ICIs yielded an essentially more prominent median percent reduction in the lesion volume at 1.5 (-63.1% versus -43.2%, P<0.0001), 3 (-83.0% versus -52.8%, P<0.0001), and 6 months (-94.9% versus -66.2%, P<0.0001) in comparison with nonconcurrent treatment. Critically, proposing a comparably higher efficacy of the anti-PD-1 agents, the researchers also noticed that the median volume reduction was fundamentally more noteworthy with anti-PD-1 than anti-CTLA-4 drugs at all intended time points (p<0.05). Kiess et al. [29] retrospectively investigated the safety and efficacy of single-fraction SRS in 46 patients who received ipilimumab for malignant melanoma BMs. A total of 113 BMs were treated with a median dose of 21 Gy (range: 15-24 Gy) and a median of 4 doses of ipilimumab (range: 1-21). Patients received SRS during ipilimumab (N=15), before ipilimumab (N=19), and after ipilimumab (N=12). The sequence of SRS and ipilimumab was significantly associated with OS outcomes (P=0.035). SRS during or before ipilimumab demonstrated significantly superior 1-year OS (65% versus 56% versus 40%, P=0.008) and regional recurrence rates than the SRS after ipilimumab (69% versus 64% versus 92%; P=0.003). Importantly, the authors reported that SRS during ipilimumab also yielded a numerically superior but not significant 1-year LC rates (100% versus 87% versus 89%; P=0.21) over the SRS before or after ipilimumab sequences. These results were later confirmed by Ahmed et al. [34] and Cohen-Inbar et al. [36] in similarly designed further studies. Skrepnik et al. [37] also retrospectively investigated the same question in a group of malignant melanoma patients and reported that the administration of ipilimumab within 30 days of SRS was more compelling than its use >30 days of SRS in terms of regional brain control and time to progression endpoints. The authors furthermore announced that the radiation necrosis (RN) was more common with SRS and ipilimumab combination compared to older SRS alone arrangement, however strikingly, the occurrence rate of the RN was significantly connected with improved OS outcome, which should be affirmed with further investigations.

The SRS and ICI combination has like manner been tested at various other tumor sites. In one such study, Chen et al. [42] retrospectively reviewed the outcomes of a total of 260 patients who got SRS for 623 BMs for non-small cell lung cancer, malignant melanoma, and renal cell carcinoma primaries from 2010 to 2016 in absence of WBRT. Of these patients, 79 received SRS and ICI (35% of whom received concurrent SRS and ICI concurrently) while the remaining 181 were treated with SRS alone. The SRS with concurrent ICI group had significantly superior median OS than the groups treated with SRS with nonconcurrent ICI, and SRS alone groups [24.7 versus 14.5 (P=0.006) versus 12.9 (P=0.002) months; P<0.05], respectively. The authors further reported that the survival gain was offered by the SRS with concurrent ICI was with no excessive increment in the neurologic toxicity rates. In another study, Schapira et al. [44] reviewed the medical records of non-small cell lung cancer patients with BM consecutively treated with PD-1 pathway inhibitors and SRS at Massachusetts General Hospital from 2012 to 2017. A total of 37 patients were treated with
mostly a single fraction dose of 18 Gy SRS for 85 lesions and all patients received PD-1 pathway inhibitors (83.8% nivolumab, 10.8% atezolizumab, and 5.4% pembrolizumab). Concurrent SRS and PD-1 pathway inhibitors demonstrated higher benefit in terms of 1-year OS (87.3% versus 70.0% versus 0%; P=0.008) and distant brain failure (38.5% versus 65.8% versus 100%, P=0.042) rate compared with SRS before or after PD-1 pathway inhibitor schemes. Similarly, the 1-year LC rate of 100% in the SRS concurrent with or after the PD-1 pathway inhibitor therapy group was significantly superior to the 72.3% observed in the SRS before the PD-1 pathway inhibitor therapy group (P=0.016).

Since the SRS and ICI studies were small retrospectives observational cohort series incorporating various SRS schemes and ICIs, two meta-analyses examined the impact of ICI on SRS outcomes to evaluate the true value of this approach in statistically more powered patients gatherings [49,50]. In the first meta-analysis, Lu et al. [49] compared the survival outcomes of BM patients receiving concurrent ICI with SRS against the non-concurrent ICI administered before or after SRS. A total of 8 retrospective observational cohort studies incorporating 408 patients were included. Concurrent ICI with SRS conferred a significant 1-year OS benefit (P=0.011) over the non-concurrent protocols. The more recent meta-analysis published by Lehrer et al. [50] included a sum of 534 patients with 1,570 BMs who participated in 17 studies. The 1-year OS rate was 13% higher in the concurrent SRS and ICI group than the non-concurrent treatment group (64.6% versus 51.6%; P<0.001). The LC rates at 1-year also trended to favor the SRS and ICI group over its non-concurrent treatment counterpart (89.2% versus 67.8%; P=0.09). The overall RN incidence was only 5.3% for all studies.

5. DISCUSSION

As discussed in detail above, one significant inquiry that should be urgently addressed is the optimal sequencing of SRS and ICIs. In most studies, the concurrent use of both modalities was defined as the administration of ICIs 2 to 4 weeks before or after the SRS, which offered the best LC and OS outcomes. Currently, basing on this clinical proof, it is typically recommended that the interval between the SRS and ICIs ought not to exceed 4 weeks [52]. However, suggesting a differential sequence-dependent distinct efficacy for different ICIs, recently Young et al [53] investigated the timing and influence of different ICIs in a mouse colorectal cancer model. All the mice received either CTLA-4 orOX-40 blockade delivered 7 days before or either 15 or 19 days after a 20-Gy SRS dose. Strikingly, though the CTLA-4 blockade was most efficient when utilized 7 days before SRS, the anti-tumor efficacy of the OX-40 inhibitor was optimal when delivered within 1 day after the SRS as opposed to its delivery 7 days after the SRS. Hence, Young's outcomes emphatically underline the prerequisites for extra work on the ideal timing of administration of different ICIs discredit the equivalent sequencing for all ICIs.

Though the ipilimumab is the most common ICI to be combined with SRS, particularly in BMs originating from malignant melanomas, yet, the results of studies reporting the comparative efficacy of ipilimumab relative to other ICIs are scarce. In a recent study comprising 38 patients with BMs of malignant melanoma, Robin et al. [54] compared the outcomes of anti-CTLA4 alone (N=25) versus anti-PD-1 alone or anti-PD-1 + CTLA-4 combination (N=13) delivered within 8 weeks before or after the SRS. The authors reported that the anti-PD-1 alone or anti-PD-1 + CTLA-4 combination group had superior out-of-field brain progression (P=0.049), extracranial progression (P=0.015), and progression-free survival (P=0.043) rates than the anti-CTLA4 alone group. Hence, these results provide the preliminary evidence for the likelihood that ICIs other than the ipilimumab may have better viability with SRS for BMs, either alone or in blend form, than the ipilimumab plus SRS, which will be addressed in future trials.
While the current evidence, for the most part, supports the improved LC and OS rates with the concurrent administration of ICIs and SRS, this sequence has all the earmarks of being related with higher rates of perilesional brain edema and RN [55]. In the previously mentioned study by Cohen-Inbar et al. [36], overall the post-SRS perilesional edema was observed in 26.3%, 27.9%, 21.8%, and 24.1% of lesions at 3, 6, 9, and 12 months. The authors noticed that the incidence of perilesional edema was significantly higher in the concurrent than the sequential treatment group at 3 months (31.3% versus 15.3%; P=0.011) and 12 months (30.2% versus 0%; P=0.048), individually. However, the overall intracerebral hemorrhage and 12 months RN rates were not different between the two groups, though both tended to be higher in the concurrent treatment arm. The previously detailed Lehrer's meta-analysis provided the most reliable toxicity data on the RN incidence following various ICIs combined with SRS [50]. As indicated by this large meta-analysis, the overall RN incidence was fortunately only 5.3%, suggesting a distinctive RN risk with different ICIs, the authors called attention to that the RN risk was more pronounced in patients treated with ipilimumab than the pembrolizumab or nivolumab.

6. CONCLUSION

Preclinical and clinical evidence indicates that SRS induces both local and systemic immune responses that can be synergized with ICI to increase the effectiveness of these therapies and thereby improve patient outcomes. Nonetheless, mechanisms in which the SRS schedule and ICI agent can be synergized to provide anti-tumor effects may likewise overlap in terms of toxicity profiles. Albeit most proof originates from single-institution retrospective cohort studies, yet, their results indicate higher efficacy of SRS and ICI combination compared to either modality alone with the cost of modest increments in severe toxicity rates. Therefore, considering the fact that all accessible studies are retrospective in nature, the currently available results ought to be interpreted with caution in absence of phase III randomized trials, and treatment should be decided on per-patient basis, rather than recommending the immunotherapy for all patients undergoing SRS for BMs. Moreover, as the present literature, in general, reflects the results accomplished in patients primarily presenting with the highly immunogenic malignant melanoma BMs, treatment decisions for other primaries and BMs of unknown primary should be carefully evaluated for the appropriateness of the immunotherapy and SRS combination for such patients until the results of future research addressing these tumor types become available. In this respect, ongoing research on the optimal dose, fractionation, and timing of SRS with different ICI types and dosages, and particularly the non-melanoma histologies will without a doubt give basic insights for the maximization of the benefit of this combination with desired minimum toxicity risks.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


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