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Original article

Use of extracranial radiation therapy in metastatic melanoma patients receiving immunotherapy

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ABSTRACT

Purpose: Explore the patterns of use of extracranial radiation therapy (RT) in metastatic melanoma patients receiving immunotherapy, its potential association with OS, the impact of the site and timing of RT on clinical outcomes when combined with immunotherapy.

Materials and methods: Patients with extracranial metastatic melanoma who received immunotherapy with or without extracranial RT from 2004 to 2013 were obtained from the National Cancer Database. Multivariable Cox regression analysis was used to evaluate factors associated with overall survival (OS). Subset analyses comparing outcomes in patients receiving RT to bone metastases versus soft tissue metastases were also performed. OS was compared using the Kaplan–Meier and log-rank statistics.

Results: A total of 1675 patients were identified: 1387 received immunotherapy alone and 288 received immunotherapy plus RT. An increase in the utilization of RT as well as SBRT was noted over time. The rate of RT use was 11.5% (0% with SBRT) in 2004 and gradually rose to 19.8% (27.0% with SBRT) in 2013 (P = 0.04). The median OS was 15.4 vs. 19.4 months in the immunotherapy plus RT and immunotherapy alone groups, respectively (P = 0.02). However, on multivariable analysis, RT was not associated with worse OS. The poor OS in the RT group was confined to the patients who received RT to bone metastases, but not in patients who received RT to soft tissue metastases. In subset analyses of patients irradiated to soft tissue, RT administered at least 30 days before immunotherapy was associated with a higher OS than RT administered within 30 days or 30 days after immunotherapy: median 26.1 months vs. 16.0 months (P = 0.009) vs. 15.4 months (P = 0.004), respectively.

Conclusions: This study demonstrates that extracranial RT plays an increasing role in the management of metastatic melanoma patients in the era of immunotherapy. The site and the timing of RT may have important interaction with immunotherapy, and need to be carefully considered in future clinical trials.

Malignant melanoma is the fifth leading cause of cancer in adults and the tenth leading cause of cancer-related death in the USA [1]. At diagnosis, 84% of the patients present with localized disease, 9% present with spread to regional lymph nodes, and 4% present with metastatic disease. The frequency of metastases to certain organs in patients who present with stage IV disease varies in literature: approximately 5–20% with CNS metastasis at the time of diagnosis, 15–20% liver metastasis, 20–40% lung metastasis, and 5–15% bone metastasis [2]. In the metastatic setting, melanoma is a devastating disease with a 5-year survival of approximately 20%, and less than 10% in patients with brain and liver metastases [1,2].

The therapeutic landscape for this disease has rapidly changed with recent development of targeted and immunotherapeutic agents. In particular, checkpoint inhibitors of cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) have been shown to significantly improve overall survival (OS) in patients with metastatic melanoma [3–6]. However, a proportion of metastatic melanoma patients do not respond to these immune checkpoint blockade agents [3]. One proposed mechanism of resistance to immunotherapy is that cancer cells possess various mechanisms of inducing immunosuppression allowing for subversion of the host anti-tumor immune response [7–9]. Therefore, there is a clinical need to identify strategies that can potentially increase the response rate to these agents in order to further improve the outcomes of patients with metastatic melanoma.

Pre-clinical studies have suggested that local irradiation of tumors releases tumor-associated antigens, activates dendritic

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cells, and expands tumor-specific cytotoxic T-cells to stimulate a systemic anti-tumor immune response. Based on the preclinical data, several institutional studies have investigated the impact of radiation therapy (RT) when administered in combination with immunotherapy [10]. Case studies have also reported an abscopal phenomenon in melanoma and lung cancer patients with previously refractory disease after adding focal RT to immunotherapy [11,12]. To date, retrospective studies have suggested possible improved clinical outcomes with RT and immunotherapy for melanoma, but confirmation of survival benefit from large prospective studies is lacking [13].

We aim to use the National Cancer Database (NCDB), a large hospital-based cancer registry, to explore the patterns of use of extracranial RT in patients with metastatic melanoma receiving immunotherapy, its potential association with OS, and the impact of the site and/or timing of RT on clinical outcomes when combined with immunotherapy.

Materials and methods

The NCDB is a joint project of the American Cancer Society and the American College of Surgeons Commission on Cancer. The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer accredited hospitals. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the US annually. Data elements are collected and submitted to the NCDB from commission-accredited oncology registries using standardized coding and data item definitions, including details not available from Surveillance, Epidemiology, and End Results (SEER) registry, such as RT dose/technique, chemotherapy use/timing, and comorbidities [14].

De-identified data for patients with newly diagnosed metastatic melanoma with extracranial metastases from 2004 to 2013 were obtained from the NCDB participant user file. Eligible patients were required to have received immunotherapy. In the NCDB, immunotherapy agents were defined as on https://seer.cancer.gov/seertools/seerrx/, which included IL-2, vaccines, ipilumumab, pembrolizumab, and nivolumab. The initial sites of metastasis were documented for approximately 25% of metastatic melanoma patients in the NCDB and included brain, lung, liver, and bone, while the rest were coded as other "not otherwise specified (NOS)". Patients with coded brain metastasis at the time of initial diagnosis or those treated with RT to the brain (as not all of the patients were coded for their initial site of metastasis) were excluded since RT for brain metastasis is standard of care and would interfere with our analysis of studying the benefit of combining RT and immunotherapy given the paucity of patients that would have received immunotherapy alone for brain metastasis. Patients with unknown RT status, unknown anatomic site of RT, those who received radioactive implant and radioisotope, or unknown vital status were excluded. Inclusion and exclusion criteria are summarized in the CONSORT diagram (Fig. 1). Patient, tumor, and treatment information were extracted and dichotomized when necessary as previously described using categories defined in the NCDB data dictionary [14]. Stereotactic Body RT (SBRT) was defined as patients receiving $\geq$5 Gy per fraction and receiving $\leq$5 fractions of RT. Biologically equivalent dose in 2 Gy

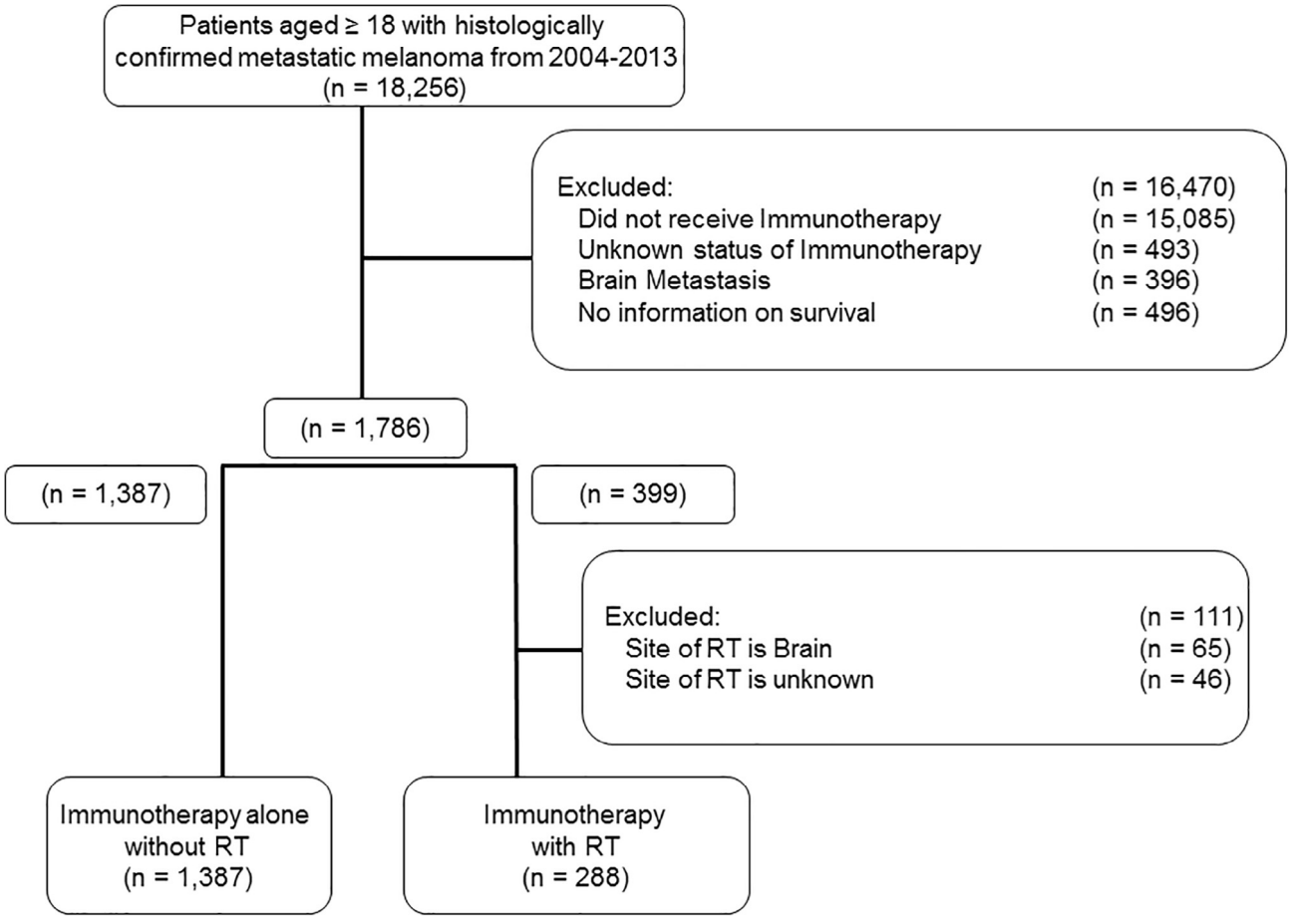

Fig. 1. CONSORT diagram. RT, Radiation Therapy.

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