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Immunoradiotherapy

Stereotactic radiosurgery and immunotherapy in melanoma brain metastases: Patterns of care and treatment outcomes

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ABSTRACT

Purpose: Preclinical studies have suggested that radiation therapy (RT) enhances antitumor immune response and can act synergistically when administered with immunotherapy. However, this effect in melanoma brain metastasis is not well studied. We aim to explore the clinical effect of combining RT and immunotherapy in patients with melanoma brain metastasis (MBM).

Materials and methods: Patients with MBM between 2011 and 2013 were obtained from the National Cancer Database. Patients who did not have identifiable sites of metastasis and who did not receive RT for the treatment of their MBM were excluded. Patients were separated into cohorts that received immunotherapy versus patients who did not. Univariable and multivariable analyses were performed using Cox model to determine predictors of OS. Kaplan–Meier method was used to compare OS. Univariable and multivariable analyses using logistic regression model were used to determine the factors predictive for the use of immunotherapy. Propensity score analysis was used to account for differences in baseline patient characteristics between the RT and RT + immunotherapy groups. Significance was defined as a P value ≤ 0.05.

Results: A total of 1104 patients were identified: 912 received RT alone and 192 received RT plus immunotherapy. The median follow-up time was 6.4 (0.1–56.8) months. Patients with extracranial disease (OR 1.603, 95% CI 1.146–2.243, $P = 0.006$), and patients receiving SRS (OR 1.955, 95% CI 1.410–2.711, $P < 0.001$) as compared to WBRT, had a higher likelihood of being treated with immunotherapy. The utilization of immunotherapy had nearly doubled between 2011 and 2013 (12.9–22.8%). On multivariable analysis, factors associated with superior OS were younger age, lower medical comorbidities, lack of extracranial disease, and treatment with immunotherapy and SRS. The median OS was 11.1 (8.9–13.4) months in RT plus immunotherapy vs. 6.2 (5.6–6.8) months in RT alone ($P < 0.001$), which remained significant after propensity score matching.

Conclusions: An increase in trend for the use of immunotherapy was noted, however, an overwhelming majority of the patients with this disease are still treated without immunotherapy. Addition of immunotherapy to RT is associated with improved OS in MBM. Given the selection biases that are inherent in this analysis, prospective trials investigating the combination of RT, especially SRS and immunotherapy are warranted.

Malignant melanoma is one of the leading causes of cancer and cancer related mortality in the United States. In its metastatic setting, melanoma is a devastating disease with a 5-year survival of approximately 20% [1]. At diagnosis, approximately 4% of the patients present with metastatic disease [2]. The frequency of metastases to various organs varies, however, approximately 5–20% patients present with brain metastasis [2]. In patients with brain metastases, the 5-year survival is often less than 10% [1]. Historically, these patients have been treated with palliative whole brain radiation therapy (WBRT). More recently, prospective randomized trials have demonstrated that use of more focal radiation therapy (RT), such as stereotactic radiosurgery (SRS), is non-inferior to WBRT with the additional benefit of preservation of

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neurocognitive function [3–5]. Despite this benefit, a recent population based study in the United States showed that SRS is only being used in approximately 25% of brain metastases patients, while the vast majority receive WBRT [6].

Since the FDA approval of ipilimumab in 2011 for metastatic melanoma, the therapeutic landscape of systemic therapy is also rapidly changing. Recent prospective trials on checkpoint inhibitors of cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) have shown significantly improved overall survival (OS) in patients with metastatic melanoma compared to other cytotoxic agents [7–10]. However, long-term follow up and effectiveness of such immunotherapeutic agents, when given with RT, in patients with brain metastases is lacking [11,12]. Unfortunately, the early randomized clinical trials with longer follow-up investigating immunotherapy for metastatic melanoma largely excluded patients with brain metastasis [13]. Several retrospective trials have suggested that the combination of RT with immunotherapy results in increased intracranial control [14–17]. However, studies evaluating the impact of immunotherapy in combination with RT and the association with OS remain controversial with multiple studies reporting mixed results [12,14,18]. A recent population based study excluding patients with brain metastases, however, showed that RT combined with immunotherapy did not appear to have a survival advantage compared to immunotherapy alone in patients with extracranial metastatic melanoma [19].

We aim to use the National Cancer Database (NCDB), a large hospital-based cancer registry, to explore the patterns of care for the use of immunotherapy and SRS in the modern era after the FDA approval of ipilimumab. Additionally, we also analyze whether the combination of immunotherapy and RT in melanoma brain metastases improves overall survival, and explore whether the technique of RT (SRS vs. WBRT) impacts 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 [20].

De-identified data for patients with histologically confirmed melanoma with brain metastases from 2011 to 2013 were obtained from the NCDB participant user file. Patients prior to 2011 were not included as this marked the FDA approval of ipilimumab for the treatment of metastatic melanoma. Patients with unknown RT status, unknown anatomic site of RT, those who received radioactive implant and radioisotope, or unknown vital status were excluded. Given that this cohort only includes patients treated during and after 2011, the majority of the patients were likely treated with CTLA-4 agent ipilimumab. 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 [20]. Treatment groups were categorized as WBRT, WBRT + immunotherapy, SRS, and SRS + immunotherapy. SRS was defined as fraction size $\geq$5 Gy per fraction and receiving $\leq$5 fractions of RT. Patients not meeting these criteria were defined as receiving WBRT. Performance status

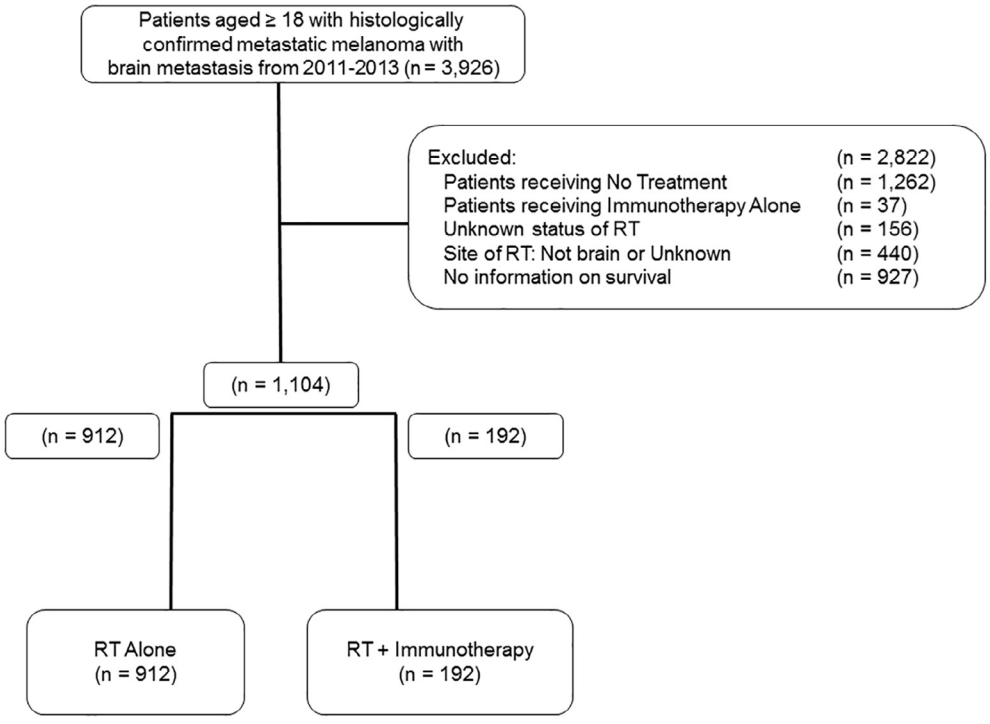

Fig. 1. CONSORT diagram. RT, radiation therapy.