Stage IV Melanoma Patients Treated with Radiation and Immunotherapy: Survival Rates and Analysis of Abscopal Effect

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INTRODUCTION

- Skin cancer is the leading cause of cancer in USA; **melanoma** carries the highest mortality rate of all skin cancers[3].
- **Immune checkpoint inhibitors** have been highly effective in the treatment of systemic melanoma cancers by blocking immune regulators **(PD-1 and CTLA-4**) and amplifying immune response[5].
- **Radiation therapy can be combined with immunotherapies** to potentially prolong survival, perhaps by stimulating antigen release and increasing response to immunotherapy; although little is understood about the best dose and timing of combination[4].
- Metastasized melanoma lesions have been shown to display **different treatment responses according to their location**; suggesting certain tissues may be more responsive to immune therapy[1].
- The **abscopel effect** describes the reduction in non-treated tumor sizes when another lesion is treated with radiation[2].
- Little is known about the mechanism behind the **abscopel effect**, but it has been postulated to be mediated by immune stimulation[2]. The hope is that immunotherapy can be enhanced through the abscopel effect.
- Our **goal** is to better characterize survival in Stage IV melanoma patients treated with both radiation therapy and immunotherapy and aid clinicians in the treatment of melanoma and other systemic cancers.

MATERIALS & METHODS

Selection

- **Institutional Retrospective Review** between 2008-2021
- **Criteria** included melanoma diagnosis + radiation treatment (RT) + immunotherapy treatment within 6 months of RT
- 20 total patients selected, 7 of which had multiple tumor lesions to follow

Data collection

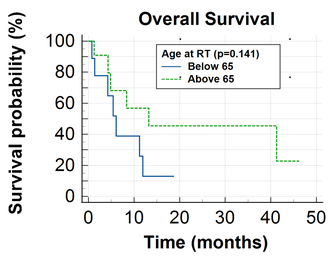
- **Patient characteristics** including age at RT, gender, and comorbidities
- **Immunotherapy treatment** type, timing in accordance to RT, and number of cycles
- **Radiation treatment** type, dosage amount, radiation biologically effective dose (BED), and radiation fraction number
- **Endpoints** include survival status, disease progression status, and radiographic response of lesions treated with radiotherapy and those not treated with radiation therapy that can be measured with abscopel effect
- Extracranial or intracranial melanoma index tumor lesions pre- and post radiation treatment measured according to **RECIST** or **PERCIST** criteria[6]

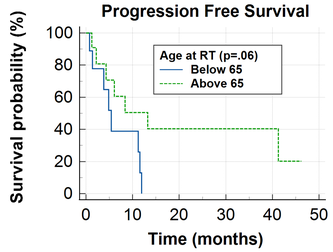
Analysis

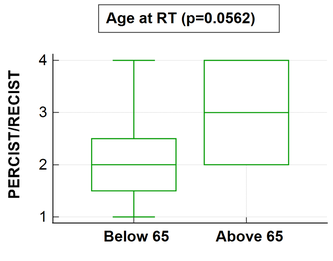
- **Kaplan-Meir survival curves** for both overall and progression-free survival using log-rank test
- **Mann-Whitney U Test** analysis against PERCIST/RECIST response for radiation-treated index tumor values[6]
- **Abscopel Effect**: For 7 patients with non-treated lesions, percent change was calculated for both the time before the start of treatment and after treatment. Percent change was normalized to time between scans, and subtracted to produce a **"delta-delta percent change"** to reflect the change in rate of tumor response to RT[2]

RESULTS

Age of Radiation Treatment

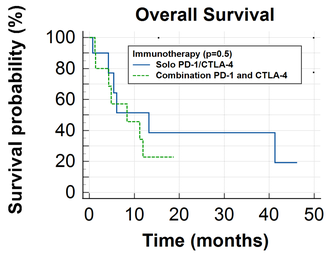


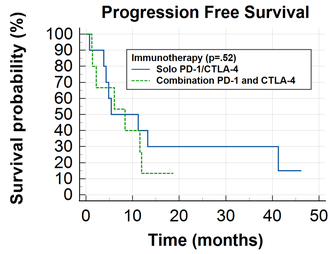


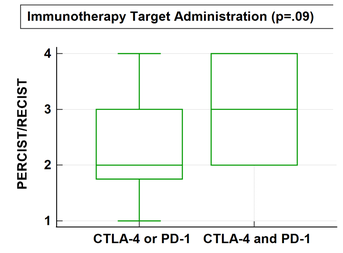


- **Younger patients** displayed **lower overall survival and progression free survival times** than older patients treated with radiation
  - **Older patients** trended towards **responding better to radiation treatment** than younger patients

Immunotherapy Administration Type

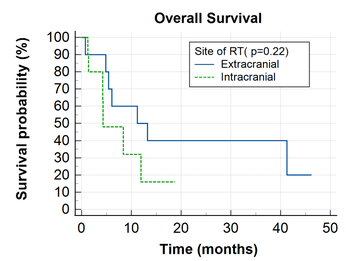


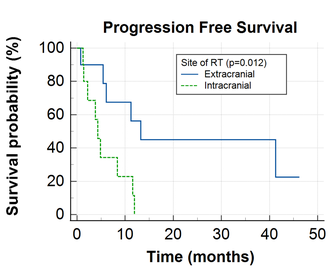


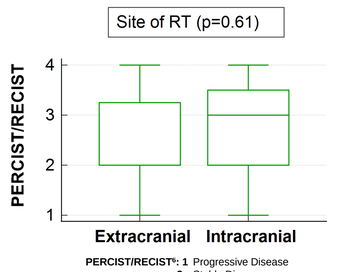


- Patients receiving **combination PD-1 and CTLA-4 inhibitors** displayed **better PERCIS/RECIST** tumor responses than those only receiving only PD-1 or CTLA-4 inhibitors
- Patients who received **both PD-1 and CTLA-4 inhibitors did not** display significant differences in **overall or progression free survival times** compared to patients receiving either PD-1 or CTLA-4 inhibitors

Site of Radiation Treatment





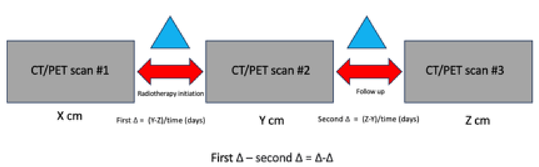


PERCIST/RECIST[6]: 1 Progressive Disease
2 Stable Disease
3 Partial Treatment Response
4 Complete Treatment Response

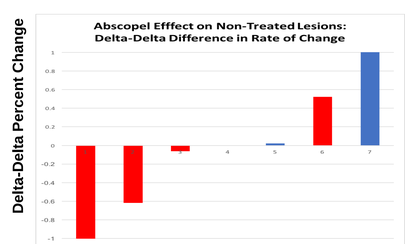
- Patients with **intracranial** irradiated melanoma lesions exhibited **lower overall and progression free survival** times than those with extracranial-treated melanoma lesions

Both extracranial and intracranial radiation-treated lesions **did not display significant differences in tumor response to treatment**

Abscopel Effect



- In 7 patients with non-treated lesions present at the time of radiation treatment, patients with **extracranial** treated lesions trended to exhibit a **less favorable rate of change in tumor size (p=.16)**



Red: Patients with extracranial treated lesions
Blue: Patients with intracranial treated lesions

Cohort Characteristics/Response

Table 1: Patient and tumor characteristics (n=20)

Gender	
Female	6 (30%
Male	14 (70%
Age at treatment	
Median	65
Range	27-96
Overall survival at time of analysis	
Living	7 (35%
Dead	13 (65%
Progressive free survival at time of analysis	
Progressed or Dead	15 (75%
Living without Progression	5 (25%
Tumor criteria	
PERCIST	8 (40%
RECIST	12 (60%
Longest tumor dimension	
Median (cm)	2.7
Range (cm)	0.9-12
Location of treated metastasized lesion	
Cranial	10 (50%
Extracranial	10 (50%
Charlson comorbidity index (age-factored)	
Median	9
Range	6-11

Table 2: Treatment Characteristics and Patient response (n=20)

Immunotherapy type	
Dual therapy	10 (50%)
Single therapy	10 (50%)
Immunotherapy treatment	
Before radiation	6 (30%)
After radiation	3 (15%)
Before and after radiation	11 (55%)
Radiation BED	
Median (Gy)	49
Range (Gy)	22-132
Radiotherapy modality	
SBRT/XRT	17 (85%)
WBRT	3 (15%)
Overall survival time	
Median (months)	5.75
Range (months)	0.75-46.2
Progressive free survival time	
Median (months)	5.75
Range (months)	0.75-46.2
PERCIST/RECIST Response	
Patient Number	18
CMR/CR	4
PMR/PR	5
SMD/SD	6
PMD/PD	3
Time to post-Treatment PET/CT	
Median (months)	1.7
Recurrence	
Local tumor recurrence	6
Distant failure	12
Unknown	2
Abscopal response	
Patients	7
Median age at RT	76
Alive	4
Dead	3

DISCUSSION/CONCLUSIONS

- **Younger patients had worse survival** as well as less favorable PERCIST/RECIST response to RT compared to older patients. This was an unexpected, novel finding not seen in patients receiving immunotherapy alone. This may reflect differences in immunotherapy response in patients receiving both radiotherapy and immunotherapy that needs to be further investigated.
- Combination CTLA-4 and PD-1 therapy was correlated with better PERCIST/RECIST tumor response, but did not significantly affect survival times, and **further research is needed to understand the interaction of immune therapy and radiation.**
- There was significantly **lower survival among intracranial lesion** patients. This is most likely explained by **lower expectancy in brain metastasis** compared to other metastasized sites. **No difference** was found in **PERCIST/RECIST response** in the **irradiated lesions** between the groups. One possible explanation is that there is worse immunogenic response in the brain[1].
- However, the trend of our patients with irradiated intracranial lesions exhibiting a more favorable delta-delta in un-irradiated tumors **challenges the understanding as the brain as a less immunogenic tissue.** Further research in larger cohorts and better tools to radiographically assess abscopel response is needed.

REFERENCES

1. Barker CA, Postow MA. Combinations of radiation therapy and immunotherapy for melanoma: a review of clinical outcomes. Int J Radiat Oncol Biol Phys. 2014 Apr 1;88(5):986-97. doi: 10.1016/j.ijrobp.2013.08.035. PMID: 24661650; PMCID: PMC4667362.
2. Chandra RA, Wilhite TJ, Balboni TA, et al. A systematic evaluation of abscopal responses following radiotherapy in patients with metastatic melanoma treated with ipilimumab. *Oncoimmunology*. 2015;4(11):e1046028. 2015 May 28. doi:10.1080/2162402X.2015.1046028
3. Gruber P, Zito PM. Skin Cancer. [Updated 2020 Nov 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441949/
4. Schoenfeld JD, Mahadevan A, Floyd SR, et al. Ipilmumab and cranial radiation in metastatic melanoma patients: a case series and review. *J Immunother Cancer*. 2015;3:50. 2015 Dec 15. doi:10.1186/s40425-015-0095-8
5. Tang, C., Wang, X., Soh, H., Seyedin, S., Cortez, M.A., Krishnan, S., Massarelli, E., Hong, D., Naing, A., Diab, A., et al. (2014). Cancer Immunol Res *2*, 831–838.
6. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. *J Nucl Med*. 2009;50 Suppl 1(Suppl 1):122S-50S. doi:10.2967/jnumed.108.057307