Survival Rates in Stage IV Melanoma Patients Treated Immunotherapy and Radiation Differ According to Age and Radiation Treatment Site

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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

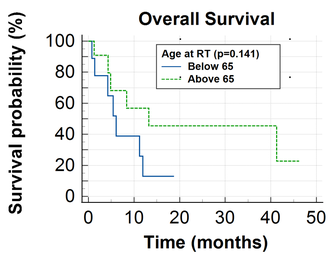
- **Patient characteristics** including age at RT, gender, and comorbidities
- **Immunotherapy treatment** type, timing in accordance to RT, and number of cycles
- **Radiation treatment** type, dosage amount, radiation biologically effective dose (BED), and radiation fraction number
- **Endpoints** include 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]

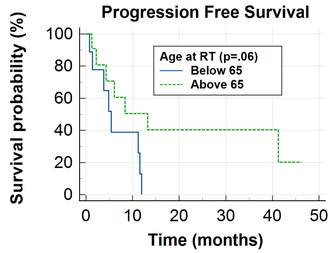
Analysis

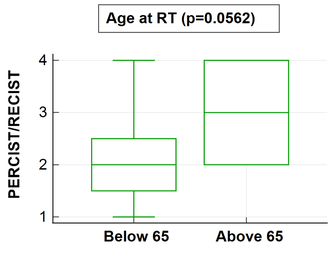
- **Kaplan-Meir survival curves** for both overall and progression-free survival using log-rank test
- **Mann-Whitney U Test** analysis against PERCIST/RECIST response for radiation-treated index tumor values[6]
- **Abscopel Effect**: For 7 patients with non-treated lesions, percent change was calculated 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

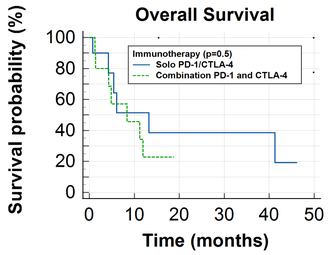


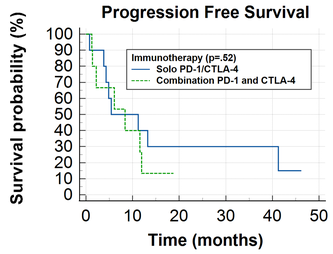


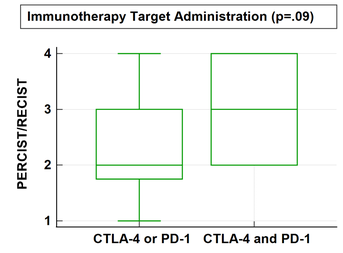


- **Younger patients** displayed **lower overall survival and progression free survival times** than older patients treated with radiation
  - **Older patients** trended towards **responding better to radiation treatment** than younger patients

Immunotherapy Administration Type

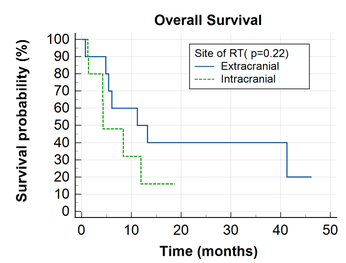


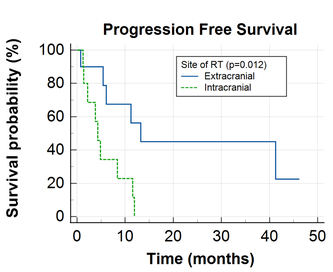


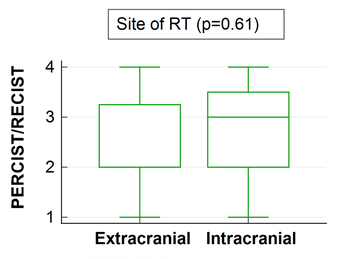


- Patients receiving **combination PD-1 and CTLA-4 inhibitors** displayed **better PERCIS/RECIST** tumor responses than those only receiving only PD-1 or CTLA-4 inhibitors
- Patients who received **both PD-1 and CTLA-4 inhibitors did not** display significant differences in **overall or progression free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

Site of Radiation Treatment







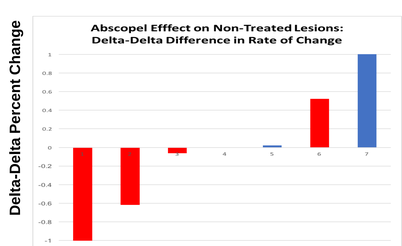
PERCIST/RECIST[6]: 1 Progressive Disease
2 Stable Disease
3 Partial Treatment Response
4 Complete Treatment Response

- 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	6 (30%)
RECIST	12 (60%)
Unable to evaluate	2 (10%)
Longest Tumor Dimension	
Median (cm)	2.7
Range (cm)	0.9-12
Location of Treated Metastasized Lesion	
Intracranial	10 (50%)
Extracranial	10 (50%)
Charlson Comorbidity Index (age-factored)	
Median	9
Range	6-11

Table 2: Treatment Characteristics (n=20)

Immunotherapy Type	
Combination Therapy	10 (50%)
Solo Therapy	10 (50%)
Immunotherapy Administration Timing	
Concurrent with Radiation	9 (45%)
Before or After Radiation	11 (55%)
Radiation BED	
Median (Gy)	49
Range (Gy)	22-132
Radiotherapy Modality	
SBRT/SRS	17 (85%)
WBRT	2 (10%)
IMRT	1 (5%)

Table 3: Patient Response (n=20)

Overall Survival Time	
Median (months)	5.75
Range (months)	.75-46.2
Progressive Free Survival Time	
Median (months)	5.75
Range (months)	.75-46.2
PERCIST/RECIST Response	
Patient Number	18
CMR/CR	4
PMR/PR	5
SMD/SD	6
PMD/PD	3
Recurrence	
Local Tumor Recurrence	6
Distant Failure	12
Unknown	2

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.

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