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Jason Naziri BS

Samuel Adediran MD

Lehigh Valley Health Network, Samuel.Adediran@lvhn.org

Suresh G. Nair MD

Lehigh Valley Health Network, suresh.nair@lvhn.org

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Metastatic Cancers Treated with Concurrent PD-1 Inhibition and Stereotactic Ablative Radiotherapy (SABR)

Jason Naziri BS, Samuel Adediran MD, Suresh Nair MD

Lehigh Valley Health Network, Allentown, Pennsylvania

Introduction

- Metastatic solid tumor disease portends poor outcomes and is often refractory to first line therapy. Immune therapy has become a viable alternative
- In recent years, check point inhibitors have become a paradigm shifting modality of treatment in malignancy trailblazing a new class of cancer treatment. Ablative radiotherapy has been shown to increase response rates by virtue of creating a more penetrative tumor microenvironment thus exposing certain malignant-specific antigens and further recruitment of immune responsive cells
- Novel evidence has shown the synergistic effect of checkpoint inhibitors and ablative radiotherapy. Our institution has been treating patients with concurrent SABR and PD-1 therapy for multiple solid tumor malignancies including renal, melanomatous, and lung cancers

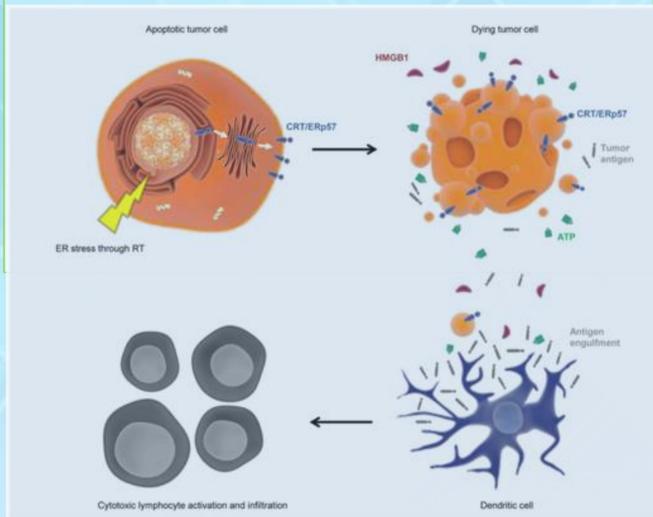


Figure 1 Immunogenic Cell Death
Stress Induced by Radiation Leads to Antigen Exposure to the Adaptive Immune System

Problem Statement

- The purpose of this study is to assess the toxicities and health outcomes in all patients concurrently treated with SABR and anti-PD-1 therapy for solid tumors

Methods

- This was an IRB approved retrospective cohort study of patients with solid tumor metastases
- We gathered tumor registry data of patients who received concurrent SABR and anti-PD-1 between January 1 2015 and December 31 2016
- Local progression was assessed using response evaluation criteria in solid tumors (RECIST) and categorized as partial, stable, or progressive
- Overall survival was also calculated using the Kaplan–Meier method, with the log-rank test, Tarone-Ware, and Breslow used to test differences between groups. Cox proportional hazard model analyses were also carried out

Results

- We identified 12 patients who have received concurrent therapy with SABR and PD-1 inhibitors
- All patients had metastatic disease of various sites and refractory to at least a first line chemotherapeutic agent. No patients were lost to follow up. Of the 12 patients, three (25%) were treated with concurrent therapy twice. Of the 15 total PD-1 inhibitor treatments, 10 (67%) were with nivolumab while 5 with pembrolizumab (33%)
- Median time from initial cancer diagnosis was 21 months (range: 11-38 months) with a median follow-up of 14 months (range: 6-19 months). The median treatment dose and fractions were 40.5 Gy (range 24-54 Gy) and 5 fr (range 3-9) respectively
- Four lesions (27%) were noted to undergo local progression at time of analysis. In these patients, local progression was noted a median of 3.5 months following radiation (range 1-8 months)
- A total of five patients had died at the time of study analysis (42%). Median OS for all patients from the date of primary cancer diagnosis was 72 months

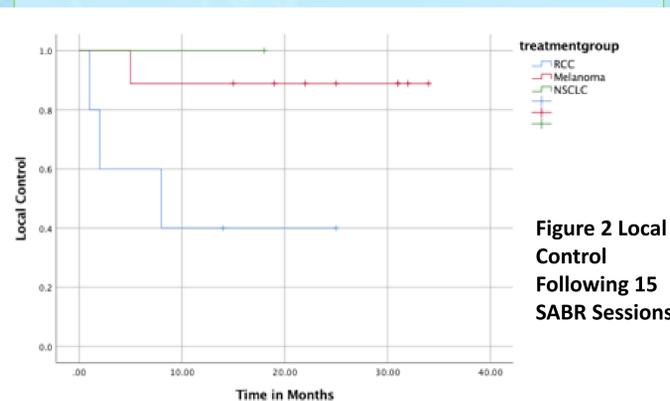


Figure 2 Local Control Following 15 SABR Sessions

| Variable | n | % |
|-----------------------------------|-------|-------|
| No. of Patients | 12 | |
| No. of PD-1 Treatments | 15 | |
| Type of PD-1 Inhibitor | | |
| Pembrolizumab | 5 | 33% |
| Nivolumab | 10 | 67% |
| Age (years) | | |
| Median | 65.5 | |
| Range | 44-83 | |
| Gender | | |
| Male | 7 | 58.0% |
| Female | 5 | 42.0% |
| Primary Tumor Resected | | |
| Y | 6 | 50.0% |
| N | 6 | 50.0% |
| Alive | | |
| Y | 7 | 58.0% |
| N | 5 | 42.0% |
| Enrolled on clinical trial | | |
| Y | 5 | 42% |
| N | 7 | 58% |

Table 1 Patient Characteristics

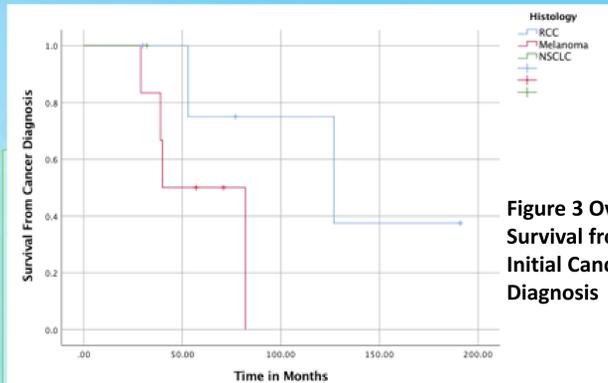


Figure 3 Overall Survival from Initial Cancer Diagnosis

| Variable | n | % |
|---|-------|---|
| FU from Radioembolization | | |
| Median (months) | 14 | |
| Range (months) | 6-19 | |
| Time from Primary Diagnosis to Radioembolization | | |
| Median (months) | 21 | |
| Range (months) | 11-38 | |
| Treatment Dose (Gy) | | |
| Median | 40.5 | |
| Range | 24-54 | |
| Number of Fractions | | |
| Median | 5 | |
| Range | 3-9 | |
| Treated Site | | |
| Segmental | 7 | |
| Lobar | 19 | |

Table 2 Lesion Characteristics

Discussion

- In this novel analysis of solid tumor oligometastases treated with SABR concurrently with anti-PD-1 therapy, we found no increased toxicity with combination therapy
- Studies using mouse models in the preclinical setting have provided strong evidence to support combination treatments in patients with multiple solid tumors
- This potential immunogenic effect of ablative radiation doses may potentially a path to improve overall survival and progression free survival in future cancer therapies. Given our remarkable OS with such dismal malignancies, we find that treatment in the concurrent setting has the potential to upregulate the tumor specific antigenic exposure and improve both local control and potentially distal control
- Multiple other recent clinical studies have confirmed improved OS with the use of PD-1 therapy and radiation. Nevertheless, the optimal sequence and dosage of both SABR as well as PD-1 inhibitors has yet to be established. Given our findings as well as the promising data of other cohorts, further prospective analyses should be pursued

Conclusions

- In the setting of oligometastatic disease for solid malignancies including renal cell carcinoma, melanoma, and NSCLC, SABR and PD-1 inhibitor concurrent therapy may offer improved outcomes without significant additional toxicity. Given the poor outcomes of these patients, randomized clinical studies are needed to clarify and better define the most appropriate combination of RT with check point inhibitors

References

Available upon request

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