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Introduction

• In 1953, RH Mole first described the abscopal effect as regression of tumor remote from the irradiated tissue.

• Despite the spinal column representing one of the most common sites of metastases, the abscopal effect in the context of spinal oncology has been poorly described.

• We present the first systematic review of the abscopal effect after radiation therapy to metastatic spinal cancer.

• The objective of this systematic review is to identify unique features that may increase abscopal successes after irradiating spinal lesions.
Methods

• Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in the Enhancing the QUALity and Transparency Of health Research (EQUATOR) resources, a systematic review identified relevant studies via a computer-aided search of MEDLINE (1946 – October 18, 2018) and Embase (1947 – October 18, 2018).

• This PRISMA paradigm selected for specified articles: (1) cases with metastatic cancer to the spine; AND (2) “abscopal” in the title, abstract, and/or keywords.
Results

• Ten publications that met the inclusion and exclusion criteria from the PRISMA flow diagram described a total of thirteen patients.

Figure 1. (right) PRISMA Flow Diagram.
Results (2)

• Tumor pathology included 4 melanoma (30.7%), 2 renal carcinoma (15.3%), 2 invasive ductal breast carcinoma (15.3%), 1 hepatocellular carcinoma (7.6%) 1 urothelial bladder cancer (7.6%), and 1 endometrial adenocarcinoma (7.6%).

• Two patients in two separate articles observed the abscopal effect following radiation therapy to the spine alone.

• The remaining eight articles commented on the abscopal effect in the setting of both systemic and radiation therapy.

• Three authors failed to observe an abscopal effect.
Table 1. Systematic Review. Publications commenting on the abscopal effect after metastatic cancer to the spine.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Primary</th>
<th>Metastatic Areas</th>
<th>Systemic Therapy</th>
<th>Radiation Therapy</th>
<th>Surgical Resection</th>
<th>Abscopal Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ishiyama et al, 2012 [9]</td>
<td>1</td>
<td>61</td>
<td>M</td>
<td>Renal cell carcinoma, clear type</td>
<td>- L3 spinal metastasis</td>
<td>- Brain metastases: stereotactic radiosurgery (SRS) to dose of 18 Gy</td>
<td>- Left nephrectomy</td>
<td>Almost complete disappearance of untreated multiple lung metastases and lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>Crimlinski et al, 2014 [6, 7]</td>
<td>Only 2/10 patients were treated with spinal radiation</td>
<td>N/A</td>
<td>N/A</td>
<td>Melanoma</td>
<td>Lung and vertebral metastases</td>
<td>Ipilimumab</td>
<td>Vertebral radiation therapy: 30Gy/10 fractions</td>
<td>None</td>
<td>Abscopal effect to the lung lesion</td>
</tr>
<tr>
<td>Hardy et al, 2015 [8]</td>
<td>Only 1/10 patients were treated with spinal radiation</td>
<td>25</td>
<td>F</td>
<td>Hodgkin’s Lymphoma</td>
<td>Lumbar 3 - S</td>
<td>Donor Lymphocyte Infusion (DLI)</td>
<td>8 Gy radiation therapy</td>
<td>None</td>
<td>No abscopal effect</td>
</tr>
<tr>
<td>Levy et al, 2016 [11]</td>
<td>Only 2/10 patients were treated with bony radiation</td>
<td>65</td>
<td>M</td>
<td>Squamous cell lung carcinoma</td>
<td>Lymph node, bone, and liver</td>
<td>The entire study population of 10 patients were treated with durvalumab</td>
<td>Spine C7-T4, T7-T10, L5-S1, L2: 28 GY/5 fractions</td>
<td>None</td>
<td>Systemic immune responses suggested by T-cell proliferation in the peripheral blood as well as upregulation of interferon (IFN)-inducible genes and tissue damage receptors in non-irradiated tumor</td>
</tr>
<tr>
<td>Ribeiro et al, 2016 [14]</td>
<td>Only 2/16 patients were treated with spinal radiation</td>
<td>58</td>
<td>F</td>
<td>Urothelial Bladder carcinoma</td>
<td>Lymph node, bone, lung, and liver</td>
<td></td>
<td>Lung and liver treatment regimens cannot be specified.</td>
<td>None</td>
<td>No abscopal effect was observed in the entire study population of 10 patients</td>
</tr>
<tr>
<td>LaPlant et al, 2017 [10]</td>
<td>Only 2/16 patients were treated with spinal radiation</td>
<td>54</td>
<td>M</td>
<td>Both with melanoma</td>
<td>Lung</td>
<td>Ipilimumab then nivolumab</td>
<td>For the study population of 16 patients, the median total dose was 245 Gy (1–400 Gy), and the doses were: in general, given in 3 fractions (1–30 fractions)</td>
<td>None</td>
<td>Abscopal effect to non-irradiated pulmonary nodules</td>
</tr>
<tr>
<td>Leung et al, 2018 [15]</td>
<td>Only 2/10 patients were treated with bony radiation</td>
<td>65</td>
<td>F</td>
<td>Invasive ductal carcinoma</td>
<td>- Thoracic lymph nodes</td>
<td>- Pelvic mass excision</td>
<td>- Dose-painting stereotactic body radiation therapy: 18 Gy to the center of the lesion over 3 fractions concurrent with immunomodulators</td>
<td>None</td>
<td>No evidence of pulmonary or nodal metastases and unchanged residual treated tissue in the sacrum</td>
</tr>
<tr>
<td>Oh et al, 2018 [13]</td>
<td>1</td>
<td>64</td>
<td>F</td>
<td>Endometrial adenocarcinoma</td>
<td>- Left thigh cutaneous metastases</td>
<td>Nivolumab.</td>
<td>None</td>
<td>Total abdominal hysterectomy</td>
<td>Strong partial response not only in the targeted lesions but also throughout metastatic tumor burden</td>
</tr>
<tr>
<td>Azami et al, 2018 [5]</td>
<td>1</td>
<td>67</td>
<td>F</td>
<td>Invasive ductal Breast carcinoma</td>
<td>- Femur, lumbar vertebral and sacrum</td>
<td>Anastrozole</td>
<td>Right breast: 60 Gy</td>
<td>Complete remission in all sites exhibiting 18F-Fluoro-deoxy-glucose (FDG) uptake on Positron emission tomography (PET)</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 1. Systematic Review. Publications commenting on the abscopal effect after metastatic cancer to the spine.
Discussion

- Cell death by ionizing radiation is linked to an “immune-mediated” component: an increase in the CD8+ T-cells.
- Immunomodulators likely enhance the “immune-mediated” component by increasing the CD8+ T-cell:Treg cell ratio.
- Ngwa et al found in preclinical trials that substantial abscopal responses occur when immunotherapies follow (or at least simultaneously administered with) radiotherapy.
Summary Points

• Abscopal effect is more commonly observed when systemic therapy includes immunomodulators.

• Abscopal effect has a higher likelihood of success when immunomodulators are administered in conjunction with or after radiation therapy to the spine.

• Higher doses of radiation in a smaller number of fractions likely increase the abscopal success.

• Ionizing radiation to the bone marrow of the spinal column may increase circulating lymphocytes that attack cancerous lesions elsewhere in the body.

• These trends still require further investigation with experimental and clinical studies.