Case Report: Epidural tumor pseudoprogression after spine SBRT: A case report and a mini review of the literature

Abstract:
Introduction
Stereotactic body radiotherapy (SBRT) to the spine is becoming a more common form of treatment. Response assessment is challenging because pseudoprogession (PP) is difficult to distinguish from true tumor progression (TTP).

Methods
We report the case of a patient with anaplastic thyroid carcinoma and a bony metastasis to T-7. The MRI 22 months after the first SBRT to this location showed radiological tumor progression to the epidural space resulting in a re-SBRT. The three and six months MRI after re-SBRT showed again progressive epidural growth. After T-7 vertebrectomy, obtained tissue specimens were histopathologically evaluated.

Results
Although the MRI sequences after second SBRT were highly suspicious of tumor progression into epidural space, only a small cluster of carcinoma cells of 1mm diameter was found within the bony structure near the disc, not belonging to the radiologically highly suspicious epidural mass.

Conclusion
To our knowledge, we report the first case of radiographic tumor progression to the epidural space following primary SBRT and re-SBRT, which histopathologically revealed a PP after spine surgery. Based on the “epidural progression criterion” from the SPINO-consensus, the first and the second progression after SBRT should have been classified as TTP. Due to the challenge in distinguishing TTP from PP, reporting of such cases are essential to share experiences and thereby improve the understanding of PP after spine SBRT.

Keywords: SBRT, Response Assessment, Pseudo-progression, Spine Metastasis

Introduction
Skeletal metastases are common in cancer patients and they involve mostly the spine. As the life expectancy of these patients is increasing, not just local short-lasting palliation but local ablative treatment is demanded. Due to the potential of superior local control and pain response rates compared with conventional radiotherapy, spine stereotactic body radiotherapy (SBRT) is increasingly applied. Response assessment after SBRT is challenging because radiation-induced tissue alterations (Fibrosis, radiation-induced necrosis, vertebral compression fracture, etc.) can either mimic pseudoprogession (PP) or disguise true local tumor progression (TTP). Aminiet al. and Bahig et al. showed that 37.8% and 46.9% of patients with multiple tumor sites, respectively, exhibited tumor volume progression on magnetic resonance imaging (MRI) after spine SBRT. This has to be distinguished between...
TTP and PP. Based on MRI follow-up (f/u) they revealed a PP rate of 14%\textsuperscript{12} and 18%\textsuperscript{13}, respectively. Jabehdar et al. analyzed 43 spinal segments from 31 patients with prostate cancer or renal cell carcinoma and detected an incidence of PP of 37%\textsuperscript{14}.

Misdiagnosing tumor progression can result in unnecessary salvage spine surgery or re-SBRT with a high risk of consecutive morbidity or myelopathy. Therefore, the differentiation of PP and TTP is most relevant to clinical practice.

The spine response assessment in neuro-oncology (SPINO) group consensus recommends MRI as the best imaging modality for response assessment. In case of ambiguity about local tumor response in MRI, other imaging modalities like 18F-fluorodeoxyglucose positron emission tomography/ computed tomography (\textsuperscript{18}FDG-PET/CT) could be useful. Local progression is defined as gross unequivocal increase in tumor volume and/or either new tumor progression within the epidural space or, if already, pre-existing, neurological deficits deteriorate due to further epidural progression\textsuperscript{15}. To the best of our knowledge, we hereby report the first case of a histopathological proven PP to the epidural space in a non-operated patient after re-SBRT.

Case report

We present the case of a 78-year-old man diagnosed with an anaplastic thyroid carcinoma (pT4b pN0 cM0, UICC stage IVB). Initial treatment consisted of hemithyroidectomy and retrotracheal tumorectomy followed by adjuvant chemo radiotherapy with 66 Gy in total. Weekly epirubicine was given concomitantly. At the time of diagnosis, an asymptomatic lesion in the left transverse process with a corresponding high 18\textsuperscript{FDG-}

avidity in the PET/CT (Fig. 1C). The subsequent f/u by MRI 22 months after SBRT showed a progression in the left transverse process/vertebral arch extending into the epidural space on level T-7 (Bilsky 1b) (Fig 1D). The patient was asymptomatic.

Based on retrospective analyses\textsuperscript{12,13} and the consensus from the SPINO group\textsuperscript{15}, this radiological progress was considered as TTP (see discussion section below). After multidisciplinary tumorboard discussion, we decided against a histologic verification due to the possibility of a sampling error. Because there was no instability of the spine (SINS 4) and an operation seemed possible even after re-SBRT, we decided for an active approach and a salvage re-SBRT. A “watch and wait” strategy was rejected in this still asymptomatic patient, because patients with neurologic symptoms are deemed unsuitable for SBRT\textsuperscript{20}.

T-7 was retreated using SBRT at CyberKnife with 30 Gy in 5 fractions to the 77% isodose (Fig. 1E). The 3 months f/u MRI after re-SBRT revealed a tumor progression ventrally into the left pedicle and posteriorly into the contralateral vertebral arch of T-7 and further progressive epidural space infiltration (Bilsky 1b) (Fig. 1F). The subsequent MRI 6 months after re-SBRT showed again a progressive tumor in all directions and as well into the epidural space (nearly Bilsky1c) (Fig. 1G). The \textsuperscript{18}FDG PET/CT revealed high avidity in the epidural tumor mass and in the spinous process (Fig. 1H).

The patient remained asymptomatic during f/u time. This progress was again classified as local TTP based on the same above-mentioned reasons and the tumorboard decided for a surgical intervention. Therefore, T-7 vertebrectomy and a XRL-Cage implantation (XRL vertebral body replacement device, DePuySynthes, West Chester, PA, USA) were performed. Obtained tissue specimens were formalin-fixed, decalcified, and stained with H & E. The histopathological analysis of the fragments of T-7 showed a loose, myxoid fibrosis in the narrow cavity of T-7 with rarified trabeculae. Only a small cluster of residual carcinoma cells with a diameter of 1 millimeter surrounded by fragments of trabeculae was evident (Fig 2A,B). Outside and not inside the bone marrow, regions with paucicellular fibrous tissue were noted (Fig 2C,D). By immunohistochemistry the carcinoma focus presented positivity for TTF1 und pax8, corresponding to a metastasis of the thyroid primary.

The patient recovered well from the operation and was not restricted in walking. The cervical region showed persistent complete remission. In the meantime, the patient developed further bone and lymph nodes metastases in the mediastinum. Six months after vertebrectomy he is in a reduced general condition due to systemic cancer disease and secondary illnesses.
Fig. 1: The lines A, C, D, F, G and H show the followup with corresponding T2 sagital, T1/T2 axial MRI and FDG-PET/CT images. The corresponding level of the treatment plan with the isodoses are depicted on line B (1st SBRT) and E (re-SBRT). SBRT was applied using Cyberknife (Accuray, Sunnyvale, CA, USA).

Fig 2. Photomicrographs of H&E stainings:
A: Vertebral body with a carcinoma focus of 1mm (arrowheads ▲) surrounding adjacent bone trabeculae; part of the vertebral disc (cartilaginous tissue [asterisk *]); magnification 20x.
B: Carcinoma focus (arrowheads ▲) as in A; higher magnification 100x.
C: Paucicellular fibrous tissue outside bony structures; magnification 20x.
D: Fibrous tissue outside bony structures with blood; magnification 100x.
Discussion

The response assessment after spine SBRT is challenging, as we already know from stereotactic radiosurgery in intracranial lesions23. For the first time, Al-Omair et al. reported two cases with an intravertebral, biopsy-confirmed PP after spine SBRT6. Without biopsy, these lesions would have been considered radiographically as local TTP.

Two retrospective analyses investigated predictive factors to distinguish between PP and TTP based on radiologic examination. Bahig et al. revealed earlier time to tumor enlargement (mean 5 months [PP] vs. 15 months [TTP]) as predictive marker for PP13. This is consistent with the data of Amini et al12, who found the time-to-peak-size to be between 3-6 months with following tumor volume regression.

Initially, Al-Omaire et al. recommended ruling out PP by biopsy, if the radiographically suspected local progression appeared within the treated location with no new epidural or paraspinal disease extension6. The SPINO group consensus defines local TTP as unequivocal increase in tumor volume and/or either new tumor progression within the epidural space or, if already, pre-existing, neurological deficits deteriorate due to further epidural progression 15.

In our case, after the primary SBRT, the MRI at 6 months showed a pathologic fracture of the left transverse process/vertebral arch. After 22 months, a tumor extending into the epidural space was evident. Thus, fulfilling the above-mentioned criterion of new epidural growth of the SPINO group15 and the timefactor criterion of the two retrospective analyses12,13, we suggested TTP. After the re-SBRT, progressing infiltration into the epidural space was evident in the following f/u MRI at 3 and 6 months. The 18FDG-PET/CT showed a high avidity in the area of the epidural progression but not in the area of the lytic transverse process/vertebral arch indicating local progression for a second time.

Surprisingly, after vertebrectomy only a residual cluster of carcinoma cells of 1mm diameter were found in bony structures, which was neither consistent with the expected tumor mass assumed from the MRI nor the PET/CT. Unfortunately, due to surgery technique, it was not possible to define the specific localization of the tissue infiltrating the epidural space for further histopathological analysis or the exact location of the tumor cells within T-7 to correlate with MRI and PET/CT. The residual carcinoma cells were associated to bone trabeculae near the vertebral disc proving that they do not belong to the epidural tumor mass but to the vertebral body (Fig2. A, B). The dynamic of the vital tumor cells remain unclear.

Histopathological correlation of PP with imaging is rare but data of PP within the vertebral body without tumor extension into the epidural space exists63-11. Taylor et al.7 and our present case report the rarer histopathological correlation of PP within the epidural space.

Considering that PP to bony structure of the spine is a known phenomenon, together with case 2 of Taylor et al.7, our case is the only published case of an unequivocal PP in the epidural space allowing a correlation of radiological and histopathological findings not only from biopsies but also from a complete surgical specimen (Tab. 1).

In our case, the tumor did not infiltrate the epidural space initially, but showed radiological evidence of epidural involvement after SBRT. Further, not only the first spine SBRT but also the re-SBRT were applied to a non-operated location.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Specification</th>
<th>Extension to ES (pre-SBRT)</th>
<th>Post-OP SBRT</th>
<th>PP within ES</th>
<th>PP diagnosis based on:</th>
<th>Short time* to progression</th>
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<td>Case 1 Case 2</td>
<td>yes yes</td>
<td>yes yes</td>
<td>yes yes</td>
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<td>no† no</td>
<td>no†</td>
<td>---† Histology (surgery)</td>
<td>no (18 mths)§ yes (3 mths)</td>
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<tr>
<td></td>
<td>Re-SBRT (30 Gy/5 fx)</td>
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Tab. 1. Reported cases in the literature with pseudoprogression within the epidural space with further information about the setting of SBRT and on which investigation the diagnosis of pseudoprogression was based.

Abbreviations:

ES: Epidural space; fx: Fractions; f/u: Follow-up; N.A.: Not available; PP: Pseudoprogression; SBRT: Spine stereotactic body radiotherapy

* ≤ 6 months [11, 12]  # Within the investigated cohort  † Details about the 1st SBRT of this case is provided to show the complete situation. Particularly, after 1st SBRT true tumor progression was suspected based on several criteria (for details see text) but not proven.

1 One cluster of 1mm with carcinoma cells in the bone

Conclusion

Based on the “epidural progression criterion”, the tumor volume progression of our case should have been classified as TTP 13 but histopathologically revealed an epidural PP.

We hereby report the first case of a histopathologically proven epidural PP after re-SBRT to a non-operated location.

We think that reporting of such cases are essential and shed more light on the challenging topic of distinguishing TTP from PP after spine SBRT.
References