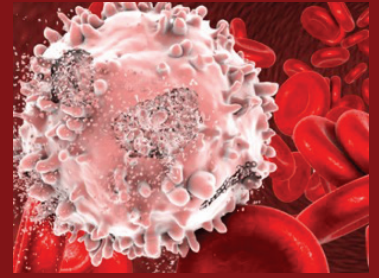


**Case Report : Epidural tumor
pseudoprogression after spine SBRT:
A case report and a mini review of the
literature**

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License, which permits unrestricted use,
distribution, and reproduction in any
medium, provided the original work is
properly cited.**Abstract:****Introduction**

Stereotactic body radiotherapy (SBRT) to the spine is becoming a more common form of treatment. Response assessment is challenging because pseudoprogression (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 a 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 spine¹. 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 applied²⁻⁵. Response assessment after SBRT is challenging because radiation-induced tissue alterations (Fibrosis, radiation-induced necrosis, vertebral compression fracture, etc.) can either mimic pseudoprogression (PP) or disguise true local tumor progression (TTP)⁶⁻¹¹.Aminiet al.¹² and Bahig et al.¹³ 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%¹² and 18%¹³, respectively. Jabejdar et al. analyzed 43 spinal segments from 31 patients with prostate cancer or renal cell carcinoma and detected an incidence of PP of 37%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 (¹⁸FDG-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 progression¹⁵.

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 retrotrachealtumorectomy followed by adjuvant chemo radiotherapy with 66 Gy in 33 fractions to the tumor bed and elective cervical lymph nodes with a sequential boost to the R2 locations with additional 6 Gy in 3 fractions, 72 Gy in total. Weekly epirubicin was given concomitantly. At the time of diagnosis, an asymptomatic lesion in the left transverse process/vertebral arch of T-7 was detected in ¹⁸FDG-PET/CT (Fig. 1A). This was suspicious for an osteolytic bony metastasis with a baseline Bilsky-Score of 0¹⁶ and a Spine Instability Neoplastic Score (SINS) of 4¹⁷. A biopsy was not performed due to high possibility of sampling error. Nevertheless, we carried out the above-mentioned treatment in curative intention and did regular f/u for the bony lesion, which remained unchanged for 18 months after first diagnosis, until the indication for SBRT was given by interdisciplinary tumorboard in the setting of oligometastatic disease. SBRT for thyroid metastases in primary or adjuvant/salvage settings is well tolerated and show high rates of local control¹⁸. We treated T-7 using Cyberknife spine tracking system (XSight Spine, Cyberknife, Accuray, Sunnyvale, CA, USA) with 24 Gy in 3 fractions to the 70% isodose based on common delineation guidelines¹⁹ (Fig. 1B). Following SBRT a radioiodine therapy was performed. The 8 months f/u with MRI after SBRT revealed a pathologic fracture of the left transverse process with a corresponding high ¹⁸FDG-

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^{12,13} and the consensus from the SPINO group¹⁵, 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 SBRT²⁰.

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 Bilsky 1c) (Fig. 1G). The ¹⁸FDG 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 marrow 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.

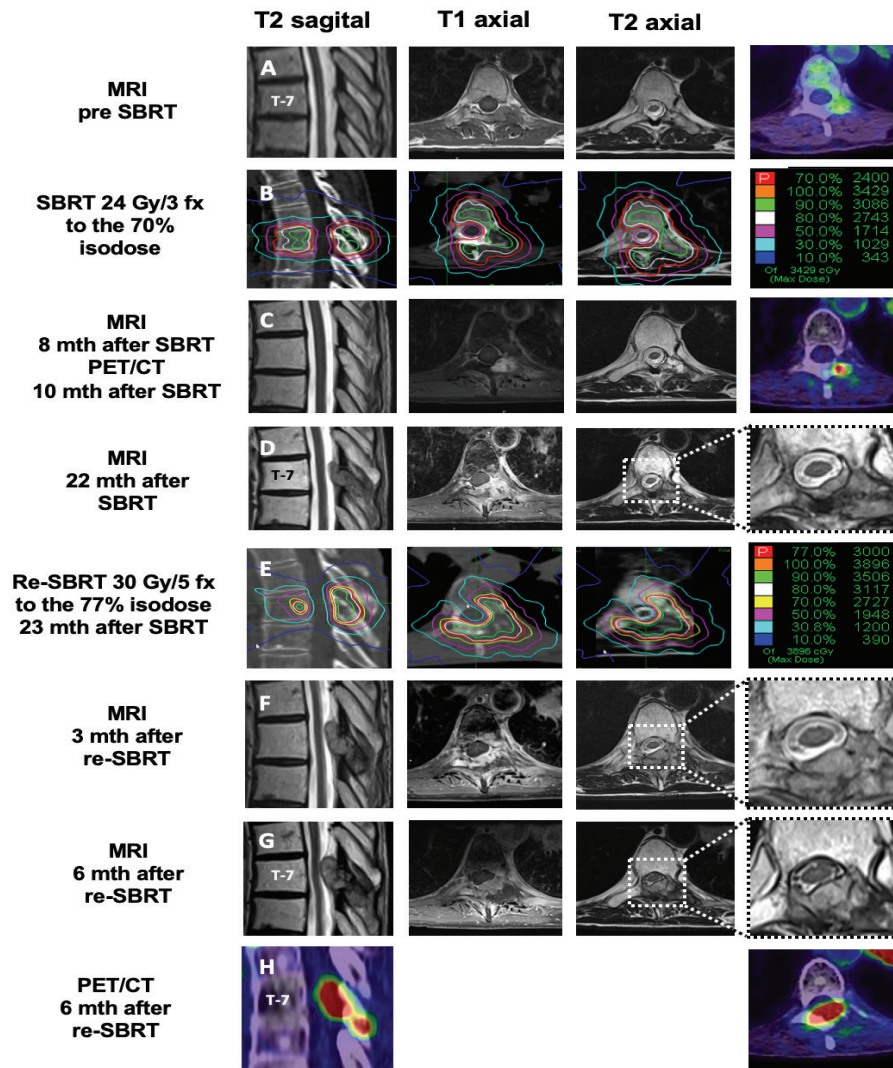


Fig. 1: The lines A, C, D, F, G and H show the followup with corresponding T2 sagittal, T1/T2 axial MRI and FDG-PET/CT images. The corresponding level of the treatment plan with the isodoses are depicted on line B (1st SBRT) and E (re-SBRT). SBRT was applied using Cyberknife (Accuray, Sunnyvale, CA, USA).

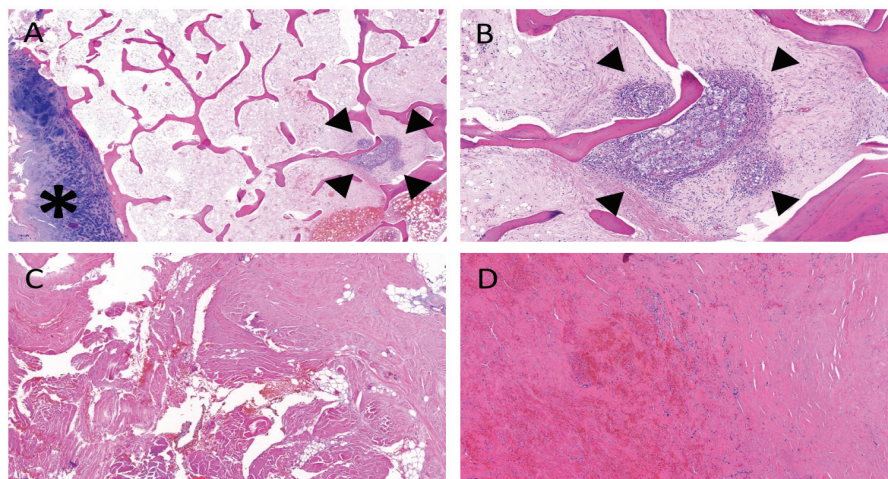


Fig 2. Photomicrographs of H&E stainings:

- 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: Carcinomafocus (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 lesions²¹. 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 al.¹², who found the time-to-peak-size to be between 3-6 months with following tumor volume regression.

Initially, Al-Omair 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 progression¹⁵.

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 analyses^{12,13}, 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 exists^{6,8-11}. 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.

Publication	Specification	Extension to ES (pre-SBRT)	Post-OP SBRT	PP within ES	PP diagnosis based on:	Short time* to progression
Taylor, 2015 [6]	Case 1 Case 2	yes yes	yes yes	yes yes	MRI f/u Histology (surgery)	yes (3 weeks) yes (7 weeks)
Bahig, 2016 [12]	1 case [#]	yes	N.A.	yes	MRI f/u	yes (3 mths)
Present case	1 st SBRT (24 Gy/3 fx) [‡] Re-SBRT (30 Gy/5 fx)	no [‡] yes	no [‡] no	no [‡] yes	--- [‡] Histology (surgery)	no (18 mths) [‡] yes (3 mths)

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.

|| 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 TTP¹⁵ 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.

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