Local control and radiological changes after stereotactic radiotherapy of sternal metastases using skin surface markers: A descriptive case series and mini-review of literature

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Abstract

Aim: To evaluate the local control, pain control and radiological response in patients with sternal metastases treated with stereotactic body radiation therapy (SBRT) with Cyberknife using skin surface markers.

Methods: Patients treated with SBRT for sternal metastases between 2017 and 2019 are retrospectively reviewed. The prescribed dose range from 24 – 35 Gy in 3 – 5 fractions. We analyze the radiological changes on different imaging modalities after SBRT and interpret the local control in correlation with clinical pain response.

Results: This series include five patients with oligo-metastatic/ progressive disease from different malignant pathologies. The median follow-up (FU) after SBRT was 12.6 months (range 6 – 24 months). Different changes on imaging modalities are reported, including sclerotic changes of lytic lesions on computer tomography (CT), signal alterations on magnetic resonance imaging (MRI) and altered FDG-activity on positron emission tomography (PET)-CT.

Conclusion: SBRT to sternal metastases showed a satisfactory local control with minimal toxicity profile. The radiological changes are described here for a better understanding of response assessment after SBRT for non-spine bone metastases. Those changes should be interpreted carefully as they vary between different modalities and tumor types.

Keywords: SBRT, Radiological response assessment, clinical outcome, Bone metastasis

Introduction

Bone metastases (BM) are common in patients with advanced cancer and may present with pain, neurologic deficits and pathologic fracture [1]. Vertebral column and pelvic bones are the most common sites for BMs. Conventional external beam radiotherapy (cEBRT) is the standard of care for bone metastases, mostly to relief pain and/ or prevent pathological fractures [2]. About two third of patients benefit from cEBRT with the mean duration of pain palliation of 4-6 months [3]. As the overall survival of cancer patients shows significant improvement in recent years, due to evolving therapies, SBRT could be a better option with applying ablative dose and provide better local control (LC) as well as improved pain response. Response assessment includes clinical presentation of BMs, alterations of biochemical markers like prostate specific antigen (PSA) or changes on different imaging modalities. Furthermore, radiological assessment after SBRT is challenging and there are only few reports addressing this topic. Recently, we have reported SBRT of sternal metastases using skin surface fiducial markers [4]. In the current study, we report about five cases with sternal metastases from different malignancies and describe the radiological changes after SBRT on imaging modalities. Furthermore, we provide a mini review of the literature for each case, addressing the behavior of BMs and their response to RT.

Case Series

Case 1: Follicular thyroid cancer with lytic metastasis of manubrium

The sternal metastasis was diagnosed in a patient with a history of eight years of follicular thyroid cancer. The patient was forty-eight years old at the time of first diagnosis and the treatment of primary tumor consisted of surgery followed by radioactive iodine therapy. Four years later, he had a relapse in the supraclavicular region, treated with neck dissection and EBRT up to 66 Gy. Three years after the first relapse, the 18F-fluorodeoxyglucose (18FFDG) PET/CT and MRI on T1w-/T2w sequences showed a solitary bone metastasis in the manubrium, causing mild pain (Visual Analog Scale, VAS 2-3). Considering oligometastatic disease, excellent general condition of the patient and previous irradiation, we performed a SBRT with 3 × 8 Gy to the sternal metastasis according the multidisciplinary recommendation. The SBRT was delivered at Cyber-Knife (CK) using skin surface markers, for technical details we refer to our previous publication [4]. The patient had three consecutive FUs with 18FDG-PET/CT, 3, 6 and 15 months after SBRT (Figure 1). At the time of first FU, PET/CT showed morphologic and metabolic tumor progression, although the sternal pain remained unchanged. We interpret these finding as pseudo-progression, the morphologic progress corresponds to PTV volume (Figure 2) and more metabolic FDG-activity might be explained due to short interval after SBRT with remaining inflammatory component. The second FU showed constant CT-changes while 18FFDG activity declined, which correlated with partial pain response. Unfortunately, by third FU, sternal metastasis showed metabolic progression on 18FFDG-PET/CT with more clinical sternal pain, although we did not observe morphological changes on CT. The multidisciplinary tumor-board recommended a surgical resection of the metastasis and pathological findings showed malignant cells only in a very tiny part of the sternum (2 mm), compatible with follicular thyroid cancer. Sternal pain with reduced intensity persisted at least for 9 months after the operation and obviously, PET/CT did not show any sternal FDG-activity.

Considering the fact, that Response Evaluation Criteria in Solid Tumors (RECIST) and the modified form (RECIST 1.1) [5] use primarily the size measurement of the lesions, the tumor progression could not be properly assessed in above case. A more specific response Criteria for bone metastases is stablished at University of Texas MD Anderson (MDA) [6]. According to MDA-criteria, partial response (PR) for lytic lesions represents as a hyperdense border

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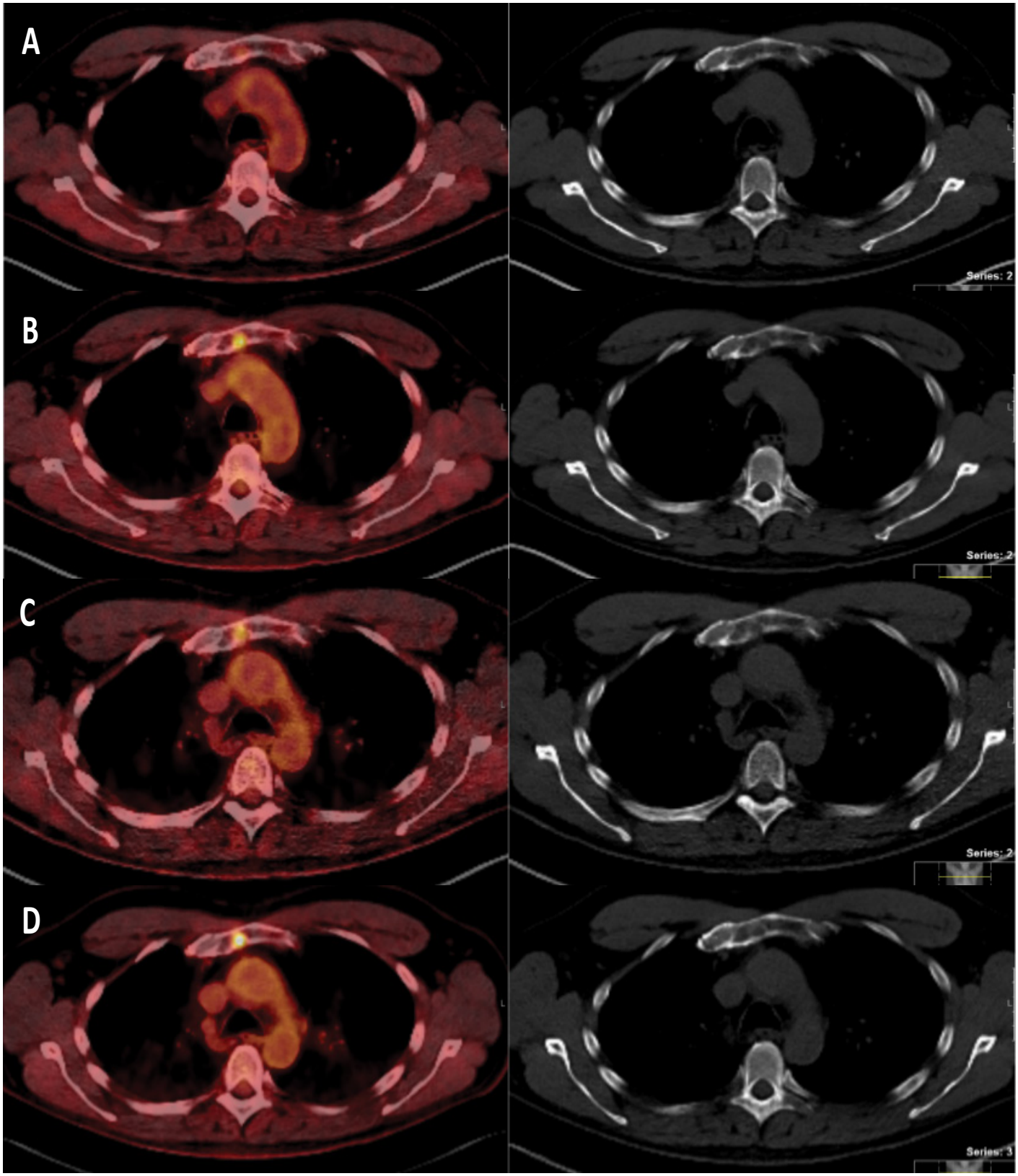

Figure 1. Baseline image (PET/CT) (A) and FUs 3, 6 and 15 months after SBRT respectively (B, C and D).

around the metastasis, while complete response (CR) forms as the lesion becomes sclerotic. In our case, there were no changes in bone density in FU-CTs. Focusing on FDG-activity, we know that in contrast to high negative-predictive value (NPV), PET-CT can have a poor positive-predictive value (PPV) after irradiation, due to inflammatory changes, which could increase FDG-uptake [7]. As RECIST, there is Positron Emission tomography Response Criteria in Solid Tumors (PERCIST), which considers changes in metabolic activity to assess the response [8]. However, these criteria are not routinely used in daily practice. Furthermore, the initial small size of the lesion (7 mm) makes the radiological response assessment even more difficult.

Figure 3 shows the MRI sequences before SBRT and directly before surgery. We observe an increase in size with no alteration in T2 signal intensity, indicating tumor progression [9]. Furthermore, diffusion-

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weighted (DW) sequence of MRI adds functional information to morphological changes and could be useful to assess the response after radiotherapy and differentiate between necrosis, especially after SBRT, and highly cellular residual tumor [9]. MRI-DW has similar sensitivity to PET/CT in detection of BMs in DTC and higher sensitivity as compared to standard MRI-sequences [10]. In our case, MRI-DW showed increased diffusion restriction, confirming the presence of tumor cells (Figure 3). However, apparent diffusion coefficient (ADC) mapping was not performed, which could have added more value to our assessment.

Putting altogether, we interpret these radiological/PET changes as tumor progress, which was confirmed by histopathological examination. Interestingly, we observe more FDG-activity on FU PET-scan compared to initial examination and this FDG-uptake corresponds apparently to a very small residual tumor. An explanation could be inflammatory components due to malignant process and/or radiation-induced, which could represent as increased metabolic activity. The differentiated thyroid cancer (DTC) consists of follicular, medullary and papillary subtypes and bone metastases are more common in the former two pathologies than papillary thyroid cancer, possibly due to more blood vessel invasion and hematologic spread [11]. Patients with osseous metastasis have a poor prognosis, and the situation gets even worse in patients with undifferentiated tumors [12]. Furthermore, patients with synchronous BMs have poorer prognosis than patients with metachronous BMs or patients who developed metastases after radioactive iodine (RAI) therapy [13]. BMs from DTC are generally osteolytic with frequent infiltration of surrounding soft tissue components and like other solid tumors; the most common involved sites are vertebral column and pelvic bones. Interestingly, sternum is the third common osseous metastatic site in DTC [14]. There are few studies, reporting the role of SBRT in treatment of BMs in DTC, among them a prospective study with limited number of spinal metastases, which showed high rates of local control (88% and 79% at 2- and 3 years respectively) as primary or adjuvant/salvage therapy [15]. For non-spine BMs, there are even less data available. In a retrospective study, Ishigaki et al. showed excellent results with 97.1% LC rate after 1-year in 60 bone metastases (both spine and non-spine) from 13 patients treated with SBRT at CK [16]. Most of the patients had FU with CT-scan using RECIST criteria for response assessment. Of interest, the majority of lesions (92.5%) showed stable disease and only 5% of lesions had radiological partial response with >=30% decrease in diameter of the metastases [16].

Case 2: Breast cancer with mixed lytic/blastic metastasis of manubrium

A 52-year-old patient with the history of metastatic breast cancer

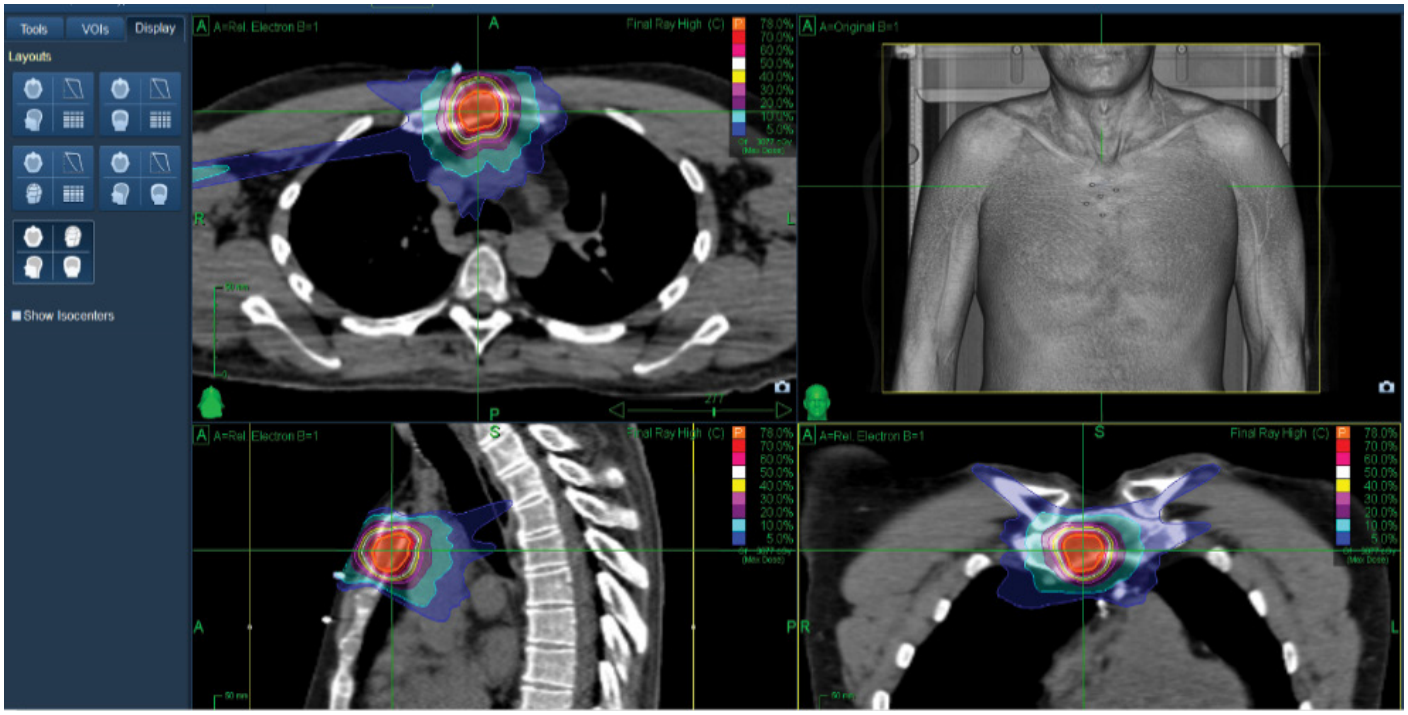

Figure 2. Cyberknife SBRT plan for case 1 with 3x8 Gy and dose prescription to 80% isodose lines.

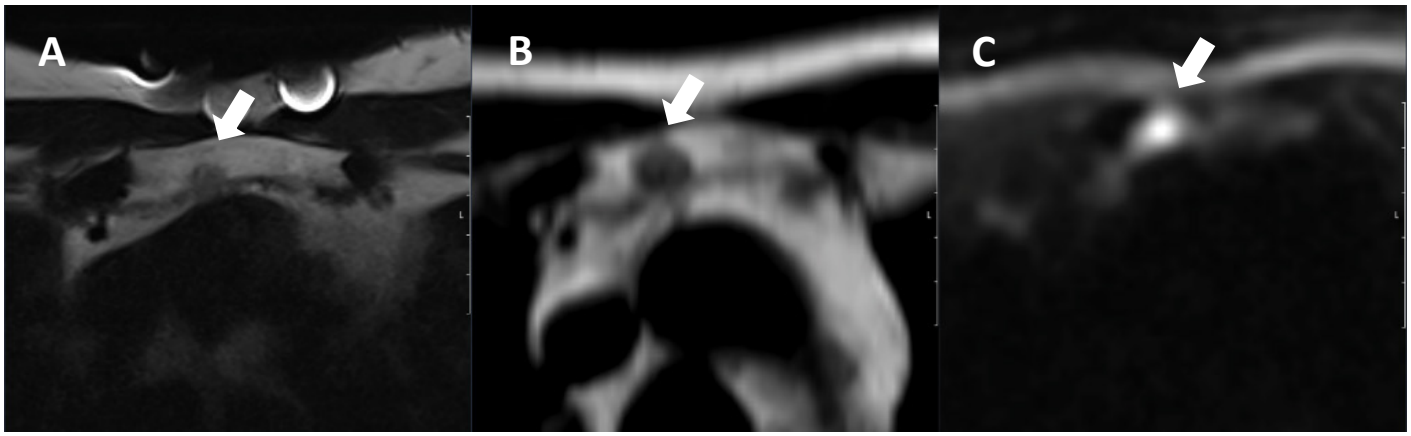

Figure 3. Baseline T2-MRI (A) compared to FU T2-/DW-MRI (B, C) 15 months after SBRT. White arrow shows the BM.

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was referred to our radio-oncological department to evaluate SBRT for the singular BM in the manubrium. The patient was diagnosed with breast cancer 2.5 years before referral, initially the cancer was localized and treated with mastectomy plus adjuvant chemo-/hormone therapy. Almost 15 months after the first diagnosis, PET/CT showed multiple hepatic and pulmonary metastases, plus singular BM in sternum manubrium. Therefore, systemic therapy was changed to new hormone therapy plus kinase inhibitor (KI). Under this systemic treatment, the sternal metastasis showed progression while hepatic and pulmonary metastases remained unchanged. The patient presented with light burning pain and pressure in the manubrium (VAS 2 – 3), however there was no need for painkillers. According to multidisciplinary tumorboard with considering the situation as oligo-progressive, we treated the sternal metastasis with 3 × 8 Gy using SBRT with skin surface markers at CK. Four weeks after SBRT, patient presented in our clinic with complete pain relief. Further FUs using PET/CT and contrast-enhanced chest CT showed almost complete response and the patient remained clinically asymptomatic (Figure 4). The FDG-activity decreased already at first FU and became negative in following PETs. The CT-findings correlated to PET-changes as the primary lytic lesion showed re-mineralization and bone density increased. According to MD Anderson Cancer Center criteria [17], we interpret these results as response to therapy. Furthermore, a descriptive study validated sclerotic changes as response to SBRT for non-spine lytic BMs [18].

Bone is the most common metastatic site in breast cancer with vertebral column and pelvis as preferential localizations. Mostly, BMs from breast cancer are osteolytic, but could be osteoblastic or mixed pattern. This heterogeneity of BMs makes the response evaluation even more difficult, for example lytic lesions could re-mineralize after SBRT and present as osteoblastic BMs [19]. Some guidelines recommend CT or skeletal scintigraphy (SS) as initial examinations for diagnosis of BMs, however comparing different imaging modalities, Hamaoka et al. showed that radiological changes may appear earlier on CT and MRI as compared to SS [20]. Especially for BMs, the sensitivity of bone scans are not inferior compared to FDG-PET, however showing higher specificity, FDG-PET could be helpful as a confirmatory test in case of uncertainties. Moreover, it has been shown that modern imaging modalities such as PET and whole body MRI are better options to visualize BMs as SS is related to osteoblastic activity and therefore could not reflect the changes in bone marrow [21]. An interesting study demonstrated signs of progressive disease on bone scans 3 months after treatment of BMs in BC, however these changes were flare reactions and the lesions healed subsequently [22]. Although bone scan still plays a role in initial diagnosis of BMs in BC, it is not recommended to assess the response to treatment [23]. As mentioned above, sclerotic changes on CT scans could be interpreted as radiological response to RT; however, these findings should be interpreted cautiously in patients under anti-osteoclastic therapy [24]. Considering the role of PET/CT, Daniel et al. reported the value of PET and CT of the PET/CT in response assessment after palliative radiotherapy of BMs in small number of patients from different pathologies [25]. Most of the lesions were lytic (61%) and only one lesion (6%) was sclerotic [25]. Interestingly, on FU-CT, the majority of lesions (88%) became sclerotic and the rest (12%) showed no radiological changes. The metabolic activity was decreased after RT and only two sclerotic metastases had higher FDG-activity, 3 months after therapy [25]. Another possibility for response assessment are breast cancer specific tracers such as Her-2-neu for PET examination [24]. According to international guidelines for management of metastatic BC (mBC), PET/CT is not recommended for routine re-staging in Mbc [26]. Furthermore, the use of PET/CT shortly after start of therapy is recommended only as a part of prospective trial, as the results might present pseudo-progression and should be carefully interpreted [26]. Finally, the role of PET/CT in response assessment for BMs from BC has been shown in some studies, however we need supporting level I evidence to establish its clinical utility [26].

Case 3: Breast cancer with lytic BM of manubrium

A 49-year-old woman with mBC and solitary sternal metastasis was referred to our department for evaluation of SBRT. BC was initially diagnosed 15yr ago and treated with mastectomy, chemotherapy and hormonal therapy. 11 years later, patient had chest wall relapse and a BM in manubrium. According to multidisciplinary tumorboard, chest wall relapse was treated with surgical resection plus intraoperative RT (IORT), adjuvant external beam RT and hormonal therapy. The RT fields included the sternal metastasis as well (50 Gy in 25 fractions). The disease was stable until 3 years after relapse, when patient experienced sternal pain and PET/CT showed increased FDG-uptake in previously known sternal BM. The sternal pain was diffuse (VAS 5 – 6) and did not correlate exactly to the location of metastasis. Looking exactly at CT from PET/CT, the part

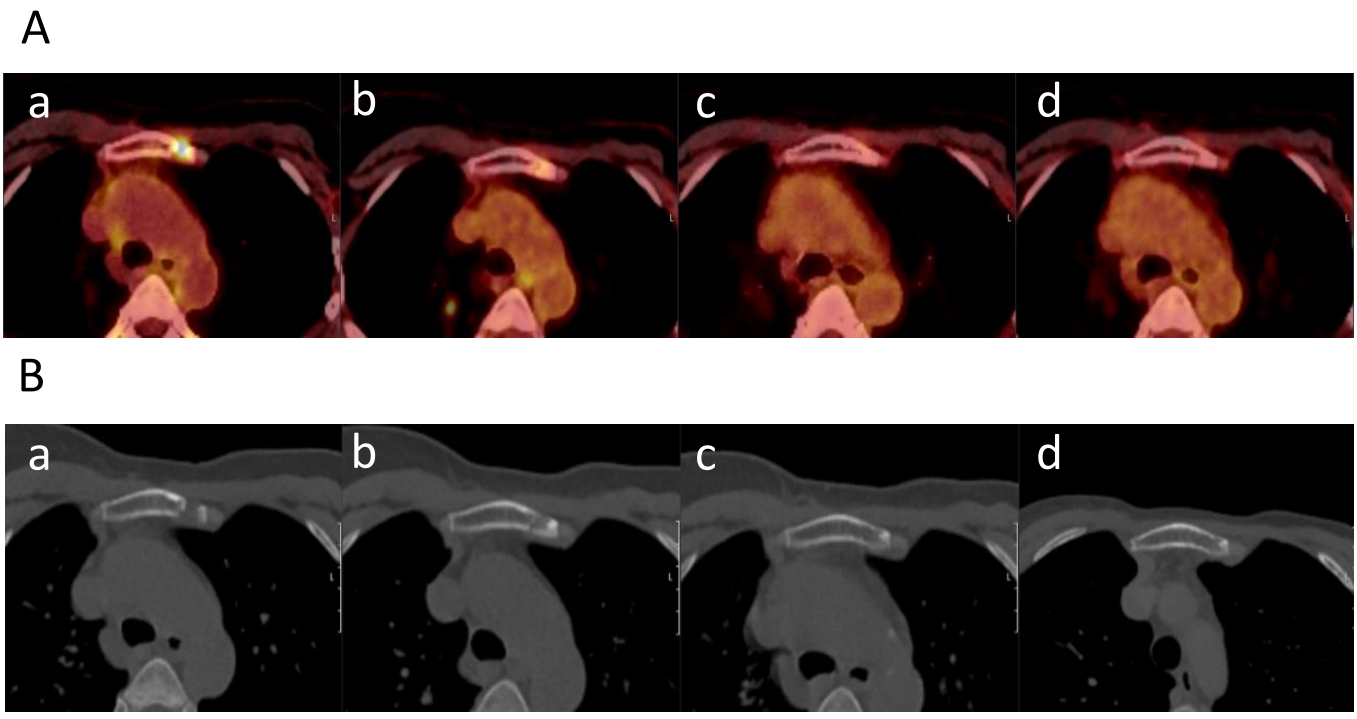

Figure 4. A) Baseline (a) PET compared to FUs 5, 8 and 12 months (b, c, d) after SBRT. B) Baseline (a) CT from PET/CT and FUs at 5, 12 and 18 months (b, c, d) after SBRT.

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with increased metabolic activity appeared as lytic lesion, while the non-active part showed mixed pattern of lytic/sclerotic BM (Figure 5). To eliminate uncertainty, the lesion was biopsied under CT-navigation and the pathology confirmed metastasis of BC. Taking into account the previous RT to chest wall, we performed SBRT with 5 × 6 Gy to BM in manubrium. In clinical FUs, the metastasis showed metabolic and morphologic response, as the lesion became FDG-inactive with increased bone density/sclerotic changes (Figure 5). The patient experienced a partial pain response (VAS 2 – 3) at FUs. We interpret that as partial pain response, however the patient was severely stressed mentally and the residual pain might be due to psychosomatic components.

Case 4: Hepatocellular carcinoma (HCC) with oligo-progression of sternal metastasis

A 77-years old man with the diagnosis of metastatic HCC was referred to us for evaluation of SBRT to sternal metastasis. At the time of first diagnosis, the tumor was confined to liver segment III and was removed surgically. 2.5 years later, patient had tumor recurrence with metastases to abdominal wall, adrenal gland, sternum and lungs. A systemic targeted therapy was started; the tumor showed further progress and the therapy was changed to immunotherapy. The immunotherapy was effective and all metastases showed regression. 18 months after initiation of immunotherapy, the sternal metastasis showed progression, while all other metastases remained controlled. The patient had no symptoms regarding sternal lesion and SBRT was performed with 5 × 7 Gy to BM. In FUs, 3 and 6 months after therapy, the patient presented himself in good performance status and was asymptomatic without sternal pain [27]. Figure 6 shows the radiological changes after SBRT on MRI-sequences. Here the significant reduction in diffusion restriction and alterations on T2-sequences with mixed hyper- and hypo-intense signals are parameters, which indicate radiological response after SBRT.

BMs from HCC are increasingly reported as the OS for these patients has improved in recent years and bone appears to be one of most common extrahepatic metastatic sites [28]. However, HCC patients with BMs have poor prognosis and the quality of life (QOL) is reduced among their population [29]. BMs from HCC have frequently soft-tissue components and are hyper-vascularized [30]. The majority of BMs present as osteolytic lesions, but could be osteoblastic or a mixed pattern of both [31]. Chen et al. described the radiographic characteristics of BMs in HCC with bone matrix destruction mainly due to osteolytic process [31]. Furthermore, more than two third of BMs were located in vertebral column and are susceptible to form soft tissue mass [31]. Soft tissue mass formation could cause variety of clinical manifestations, from spinal cord compression at vertebrae to swelling of lower limbs and deep vein thrombosis [31]. Most interestingly, the formation of soft tissue mass was not seen with pure osteoblastic lesions [31]. A study from Velloni et al. evaluated the appearance of HCC-BMs (spine and non-spine) on MRI [32]. They showed that most of the BMs are hyper-intense on either T1- or T2-weighted fat suppressed sequences and about one third of the metastases have arterial ring enhancement, which could be characteristic for HCC-BMs [32]. Of interest, more than half of the lesions presented with early washout on MRI-sequences [32]. Like BMs from other malignancies, here is the palliative RT the treatment of choice for symptomatic BMs and could be applied conventionally or as SBRT, depending on disease and patient situations. In a randomized trial, He et al. demonstrated lower treatment failure and earlier pain relief with hypo-fractionated RT compared to conventional RT [33]. Furthermore, other studies reported improved LC and better radiological response with RT dose escalation for spine metastases from HCC [34-36].

Case 5: Malignant melanoma with sternal metastasis

A case of 84-year-old male patient with malignant melanoma and solitary sternal BM was referred to our clinic to evaluate the SBRT. The first diagnosis of melanoma was 26 years ago, which was operated and the patient had no relapse until one year before his presentation in our department. The relapse site was the same as initial manifestation of the tumor and the surgeon did the resection. Quickly after first relapse, the second relapse occurred in the same year, which was treated again surgically with adjuvant immunotherapy. Under immunotherapy, a solitary sternal metastasis was diagnosed on PET/CT and the patient was sent to us. At the time of presentation in our clinic, the patient had no symptoms regarding the metastasis. A SBRT with 3 × 8 Gy was performed and the patient tolerated the RT very good and without any side effects. Unfortunately, a half year after SBRT to sternal metastasis and under immunotherapy the patient developed systemic progression with bilateral pulmonary metastases, lymph nodes and multiple BMs and died soon after. Figure 7 demonstrates the FUs for sternal metastasis with PET/CT and CT-Thorax, four and six months after SBRT respectively. The BM showed progression on both imaging modalities with bigger diameters and increased FDG-activity. As the last FU was only 6 months after SBRT and the patient did not have pain regarding sternal metastasis, the radiological changes might be due to pseudo-progression, which mimics the true tumor progression on imaging modalities.

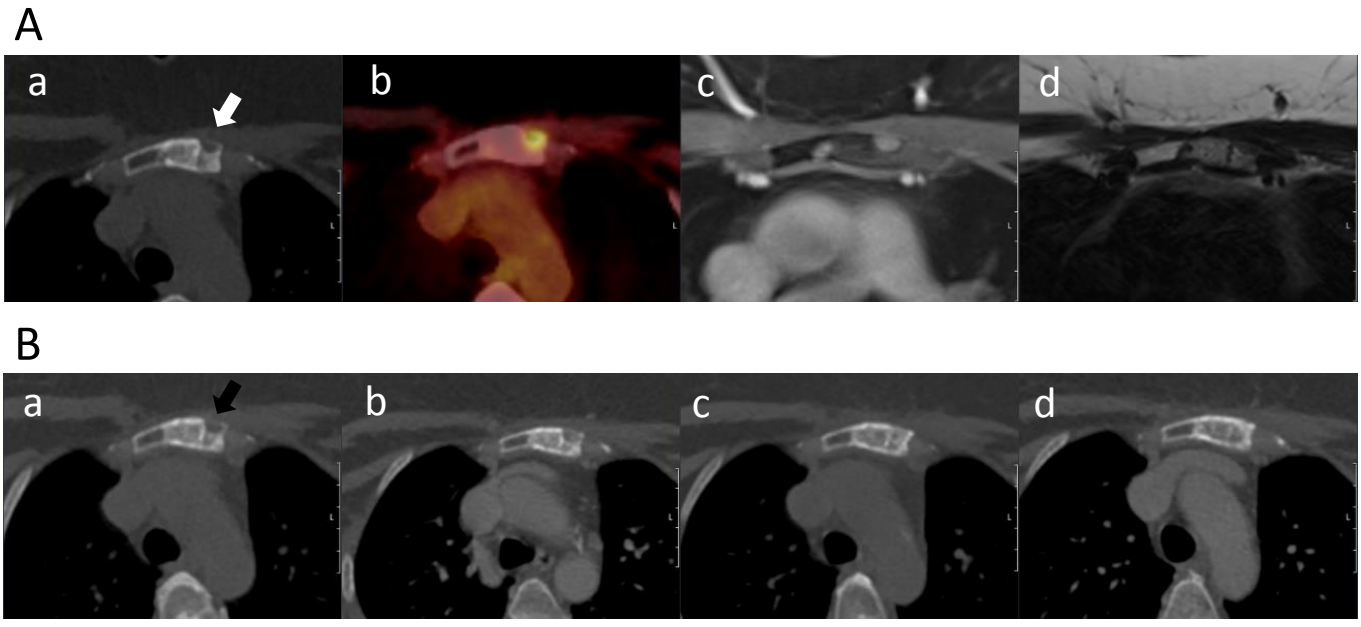

Figure 5. A) Baseline PET/CT (a, b) and MRI (T1w-contrast and T2w) (c, d). The white arrow shows the lytic and metabolic active part of the metastasis. B) Baseline CT (a) compared to FU-CTs 2, 8 and 15 months after SBRT respectively (b, c, d).

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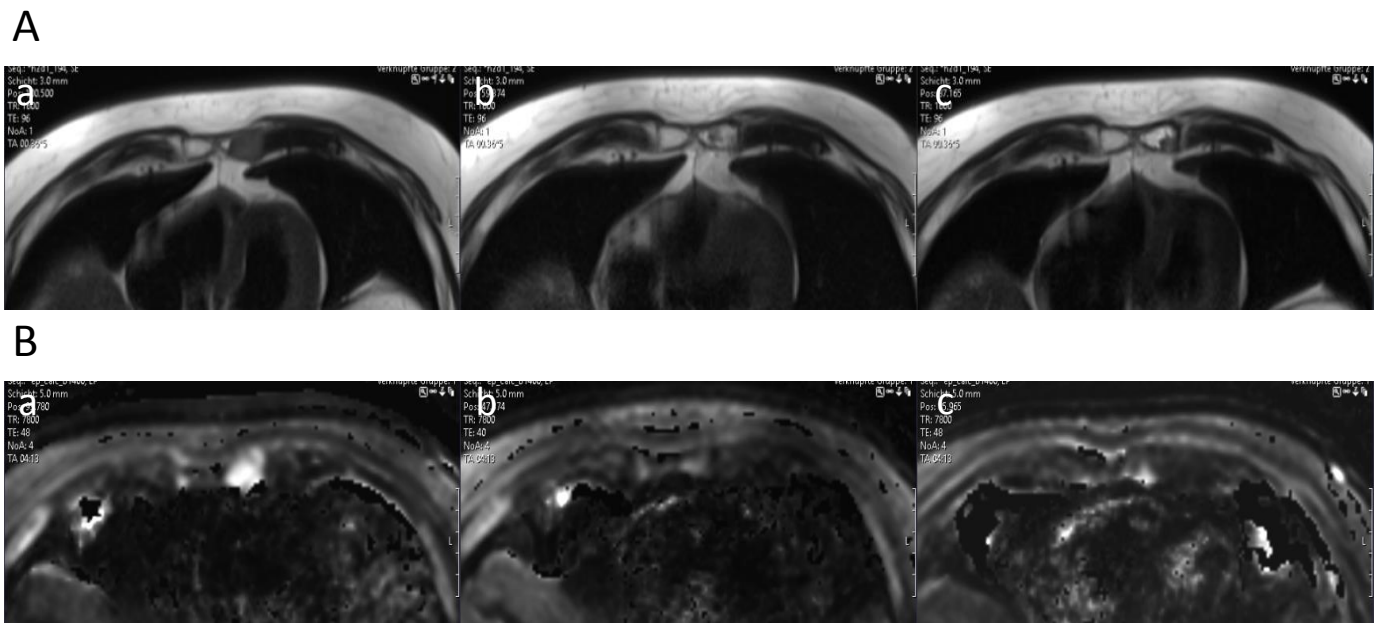

Figure 6. A) Baseline T2-MRI-sequences (a) and FUs (b, c) 3 and 6 months after SBRT. B) Baseline DW-MRI-sequences (a) and FUs (b, c) 3 and 6 months after SBRT.

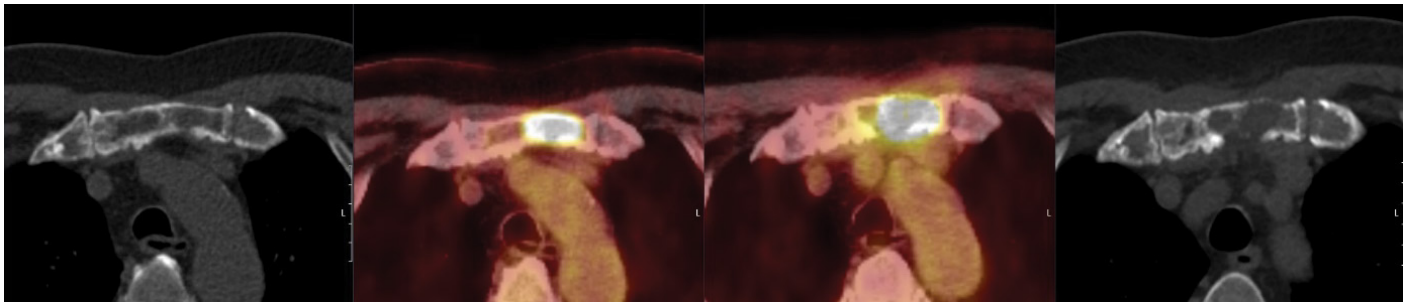

Figure 7. Baseline PET/CT (a, b) compared to FUs with PET (c) and CT (d) 4 and 6 months after SBRT.

Skeletal system metastases are common in patients with malignant melanoma; however, BMs occur mostly in patients with disseminated disease and only a small proportion of patients present with bone lesions as first metastatic site [37]. Therefore, patients with BMs have limited survival of approximately 6 months with reduced QOL. Zekri et al. showed more morbidity and mortality of BMs in melanoma patients as compared to breast and prostate cancers, indicating the substantial need for bone modifying agents in this group of patients [38]. BMs are mostly osteolytic with medullary origin and invasion of surrounding soft tissue is common [39]. Considering the osteolytic nature of bone lesions and lack of osteoblastic activity, PET/CT is superior to BS for diagnosis of BMs [40]. As the soft tissue involvement is a common feature of BMs in melanoma patients, MRI plays an important role in the diagnosis and treatment of such lesions, especially for spine metastases [41]. There are some reports regarding response assessment after treatment for melanoma patients, here the quantitative monitoring of FDG-uptake in metastatic lesions does not show reliable correlation with clinical outcomes [39]. As expected, immune modulations play a role in developing BMs in melanoma with elevated expression levels of programmed death-ligand-1 (PD-L1) [42]. The BMs present as hyper-intense lesions on T1-weighted sequences, however on T2-weighted images they could appear as either hyper- or hypo-intense lesions [43]. As for BMs from other malignancies, RT plays an important role in palliating pain, reducing neurologic deficits and improving QOL in patients with BMs from melanoma. A multicenter retrospective study from Tucci et al. demonstrated improved OS under immunotherapy and palliative RT, which might be due to additive effect [44]. There are several retrospective studies indicating the role of SBRT for pain palliation and local control for BMs from different tumors, including melanoma, which demonstrate superior LC and improved pain response with SBRT compared to conventional RT [45]. Regarding the radiological response assessment after SBRT, we refer to the discussions of above cases with sternal metastases, as there are no specific reports describing such evaluation for malignant melanoma.

Discussion and Conclusion

As the utilization of SBRT for non-spine metastases has increased remarkably in the recent years, the response assessment on imaging modalities is still a challenging topic. Here we describe the radiological changes of five cases with sternal metastases from thyroid, breast and hepatocellular cancer as well as for malignant melanoma. Furthermore, we report the clinical pain response after irradiation with correlation to radiological evaluations. We observe different patterns of alterations on imaging modalities after SBRT to sternal metastases. These changes might represent pseudo-progression with inflammatory components after SBRT and need careful assessment to avoid unnecessary further therapies. Another important factor is the time between SBRT and imaging modalities, as pseudo-progression might exist several months after SBRT. We believe that such reports are necessary for better understanding of tumor behavior after SBRT, might help us to distinguish between true and pseudo-progression and shed more light to the still unclear era of response assessment after SBRT.

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Conflicts of Interest

None.

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