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Title:
Single-fraction stereotactic ablative body radiotherapy for sternal metastases in oligometastatic breast cancer: Technique and single institution experience

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Abstract

INTRODUCTION: Due to size and close proximity to skin, the sternum is a complicated target for stereotactic ablative body radiotherapy (SABR). This is a retrospective case series of single fraction SABR to sternal metastasis in patients with oligometastatic breast cancer.

METHODS: Between June 2014 and June 2018, ten breast cancer patients received 20Gy in 1 fraction to a solitary sternal metastasis. Eligible patients had Eastern Cooperative Oncology Group performance status of 0-2, oligometastatic disease (defined as 1-5 metastases) and a controlled primary site. Patients were treated with 3-dimensional conformal radiotherapy, each patient case comprising of >6 co-planar beams and 2-6 non-coplanar beams. Local control, pain response and adverse events were retrospectively reviewed.

RESULTS: The median planned target volumes was 84.75cc (range, 14.4–197.8cc). The median conformity index was 1.29 (range, 1.2-1.49). At a median follow-up of 32 months, nine patients achieved in-field control. Two patients had triple negative disease, one of them developed marginal recurrence, and the other had in-field recurrence. Seven patients had sternal pain prior to SABR, and within 3 months after SABR treatment the pain improved (n=3) or resolved (n=2). Four patients developed acute grade 1 and 2 skin reactions, and two patients had late grade 1 skin reactions. There were no grade 3 or 4 toxicities.

CONCLUSION: Our case series demonstrates safety of SABR with associated disease control and analgesic benefit in selected patients with oligometastatic breast cancer. The marginal recurrence observed in this cohort suggests wider margins could be beneficial to account for microscopic disease.

Key words: radiotherapy; stereotactic; breast cancer; sternal metastasis; oligometastases;

Introduction

Bone is the most frequent site of breast cancer metastasis with bone only metastases occurring in approximately 50% of patients with bone relapse[1]. Patients with bone only metastatic disease have a longer survival than patients with visceral metastases – up to 20% alive at 5 years[2], with a median survival of over 72 months in selected patients[3, 4]. Kozumi et al. found, the sternum was the most common metastatic site – occurring in 34% of patients with solitary bone metastases[5]. Furthermore, solitary sternal metastases remained solitary for longer than patients with solitary lesions at other sites. Additionally, a multivariate analysis suggests that solitary skeletal metastasis is a favourable independent prognostic factor to multiple skeletal metastases. It has been hypothesised that solitary sternal metastases may have a superior prognosis as they may be caused by local invasion from either the primary site or adjacent lymph nodes rather than via lymphatic or haematogenous channels[6].

Based on this hypothesis, previous attempts at achieving local control have included resection of isolated sternal metastases. Surgical management remains controversial with limited literature consisting of retrospective case reports and case series. Two case series have shown surgical resection is feasible, and could be curative in carefully selected patients[7, 8]. There were good long term local control, pain relief and improved cosmesis[7]. An aggressive treatment approach to solitary sternal metastases may provide a cure in patients with metastatic breast cancer[9]. Christopherson et al. suggest that curative intent treatment with chemotherapy, surgery and radiation for patients with breast cancer metastatic to the sternum and/or mediastinum has comparable outcomes similar to those of stage IIIC disease[10]. However, issues with the potential morbidity of surgical extirpation has tempered enthusiasm of this approach.

Stereotactic ablative body radiotherapy (SABR) has now emerged as a non-invasive technique to treat oligometastatic disease, utilising large doses of radiation in a highly conformal manner. A growing body of literature has

reported on the use of SABR for oligometastatic disease[11]. In particular, our institution has significant experience in utilising single fraction SABR for the treatment of oligometastases[12].

To our knowledge there are no reports describing SABR being used to treat sternal metastases in oligometastatic breast cancer. In this report we present our institutional experience with SABR to sternal metastases using a single-fraction approach in patients with oligometastatic breast cancer.

Methods and materials

Following approval by our ethics committee, we reviewed all patients with breast cancer who underwent SABR to a sternal metastasis between June 2014 and June 2018. All patients met the following criteria for receiving SABR; ECOG performance 0-2, oligometastatic disease (1-5 metastases) and a controlled primary site.

All patients underwent computer tomography (CT)-based planning. Patients were immobilised with a personalised foam cradle, a commercial vacuum immobilization device (BodyFix, Stockholm, Sweden), or a 5-points head, neck and shoulders immobilisation mask (Efficast, Antwerp, Belgium). A free breathing three-dimensional CT planning scan (3DCT) or a four-dimensional CT planning scan (4DCT) with 3mm slice spacing was obtained for each patient (Philips Brilliance Widebore). The 4DCT scans were obtained under free breathing and with respiratory monitoring (RPM ,Varian Medical Systems, Palo Alto CA). An average CT and maximum intensity projection (MIP) CT were reconstructed. All planning CT scans were then fused with PET scan, and were fused with MRI if available.

The gross tumour volume (GTV) included the tumour seen on all available imaging. For patients who had a 4DCT planning scan, an internal target volume (ITV) combined volumes of GTV at various phases of respiration. There was no clinical target volume (CTV) delineated in patients treated between 2014 and

2016. The two patients treated in 2017 and 2018 had a margin of 5mm given to the GTV to define a CTV. A margin of 5 mm was given to the GTV, ITV or CTV to define a planning target volume (PTV).

Patients were treated with 3-dimensional conformal radiotherapy (3DCRT). Beam arrangement was customised and selected based on clinical experience, each patient case comprising of at least 7 co-planar beams and 2-6 non-coplanar beams (
Figure 1). 3DCRT was used because it was quick to plan and deliver, allowed easy incorporation of non-coplanar beams, achieved good PTV coverage and met organs at risk (OAR) dose constraints.

A single fraction of 20Gy was prescribed to the isodose line covering ≥99% of the PTV. The dose constraints for the organs at risk were informed by QUANTEC recommendation guidelines, completed RTOG protocols, and the AAPMTG101 working party consensus guidelines[13, 14]. The dose constraint for the spinal canal was 0.03cc ≤ 12Gy, skin was 0.03cc ≤ 24Gy, combined lungs was 1000cc ≤ 7.4Gy, oesophagus was 0.03cc ≤ 15.4Gy and heart was 15cc ≤ 16Gy. All the target volumes were located close to the skin surface, and most were long and cylindrically shaped. As a result, the skin dose constraint was the most difficult to achieve.

Varian Eclipse computer software (Version 11 and 13 with AAA dose calculation algorithm) was used to develop the treatment plans. The treatments were delivered by Varian linear accelerators (21 series and TrueBeam with 5mm MLC width) using 6MV photons. A kilovoltage cone beam CT scan was acquired for localisation prior to treatment delivery, and repeated mid-treatment.

Patients received concurrent and/or adjuvant endocrine, targeted or immune therapy as per the treating oncologist. No patient received concurrent or adjuvant cytotoxic chemotherapy within three weeks of the SABR fraction.

All patients were assessed one month after treatment for acute side effects and pain response. They were then reviewed every three months up to 24 months to assess for events using NCI CTCAE V4.0. A routine FDG PET scan within 12 months after SABR was used for response assessment. Local control defined as the absence of progression at the treatment site per PERCIST 1.0 criteria[15]. In-field recurrence was defined as any recurrence occurred within the isodose line corresponding to the prescription dose and marginal recurrence as any recurrence occurred between the prescription isodose line and the line corresponding to the 50% of the prescription dose. Additional CT scans were typically organised every three to six months by the treating oncologist. Treated sternal metastasis control at the time of last follow-up was determined by the patient's most recent radiological investigations using MDA classification of bone response[16] and/or PET scan. The radiological investigations completed after SABR were also used to determine the time to distant relapse. Distant relapse was defined as any recurrence occurred outside of the line corresponding to the 50% of the prescription dose.

Descriptive statistics were used to analyse the collected data.

Results

A total of ten breast cancer patients with solitary sternal metastasis treated with SABR were identified and included in this case series. The baseline demographic and clinical data of these patients are detailed in Table 1. The median patient age was 56 years old and the median gross tumour volume was 26.65cc (range, 3.0cc - 103.4cc). The mean duration from the time of initial breast cancer diagnosis to the development of sternal metastasis was six years. Six of the ten patients had solitary sternal metastases. Eight patients had previous radiotherapy to the breast or chest wall. None of the patients had concurrent chemotherapy or immunotherapy during SABR.

The treatment plan details for each patient are detailed in Table 2. The median planned target volume was 84.75cc (range, 14.4 – 197.8cc), and the median

length was 6.1cm (range, 3.5 - 12.2). The median conformity index was 1.29 (range, 1.2 - 1.49). The maximum skin dose ranged from 8.6Gy to 24.5Gy.

Median follow-up duration after SABR was 32 months (range, 11 – 55 months) (Table 3). The PET restaging scan within 12 months after SABR showed that six patients achieved complete metabolic response within the PTV, two patients had stable metabolic disease and one patient had partial metabolic response. One of the ten patients had the post treatment PET scan at 18 months after SABR instead of 12 months. The PET scan for this patient showed complete metabolic response of the treated site. At 13 months, one of these patients had in-field recurrences superiorly and inferiorly (

Figure 2). Another patient at 2 months developed a marginal recurrence inferior to the PTV. Both of these patients had triple negative breast cancer. At last follow-up, nine patients achieved in-field control of their treated sternal metastasis. Seven patients had distant relapse after SABR and the median time to distant relapse was 11 months (range, 2 - 20 months). At the time of analysis, one patient had died two weeks after their last follow-up.

Seven patients had pain from their sternal metastasis prior to treatment (Table 3). Two of these patients were pain-free within three months after their SABR treatment. Three patients had an improvement in their pain after SABR treatment. One of these patients had a pathological fracture of the sternum prior to SABR and the pain improved within three months after SABR. The remaining two patients' charts did not include information about their sternal pain after SABR.

There were no grade 3/4 acute or grade 3/4 late toxicities (Table 4). Four patients developed acute grade 1/2 skin reactions, and two patients had late grade 1 skin reactions. Two patients who had pain prior to treatment reported acute grade 1 pain in the treated area.

Discussion

Our case series demonstrates that single fraction SABR to the sternal metastases is a safe and effective treatment for pain and local control in

patients with oligometastatic breast cancer. It is a non-invasive alternative to radical surgical resection, with less morbidity and cost.

The optimal dose and fractionation schedule for treating bone metastases remains controversial. We found that SABR with a dose of 20Gy in 1 fraction to sternal metastases provides good local control. Nine patients had in-field control of their treated sternal metastasis after the completion of SABR, with a local control rate of 90% at 12 months. This is consistent with existing literature showing that SABR is an effective treatment for local control of bone metastases[12, 17]. Spencer et. al conducted a systematic review of 57 studies which showed pain response rates of >75% and local control rates >80% following SBRT for bone metastases[18].

In our case series, one patient had marginal recurrence and one patient had in-field recurrence, both patients had a PTV size >90cc. We postulate that the marginal recurrence can be attributed to subclinical disease extension not detectable on imaging. Our current institutional policy based on practical consensus is to add a 5mm to GTV and crop within anatomical boundaries to create a CTV. The CTV is then expanded by 5mm to create a PTV. An additional method of reducing the rate of marginal recurrence might be to routinely also use MRI to help delineate bone metastases[19]. However the only patient in this case series who had a CTV of 5mm still developed a marginal recurrence inferior to the PTV. This suggests there might be other contributing factors such as size of sternal metastasis and breast cancer phenotype.

The two patients in the study who recurred locally were the only patients with triple negative disease. Both developed distant relapse within 6 months after the completion of SABR. and one of them died at 13 months due to distant disease. This is consistent with triple negative breast cancer behaving more aggressively compared to other breast cancer phenotypes. Our case series raises the question on whether there is any additional benefit for SABR to oligometastatic disease in triple negative breast cancer patients. Further studies

are needed to determine which subset of patients with oligometastatic breast cancer would benefit from aggressive local therapies.

Nine out of ten patients in this case series were alive at the time of analysis, with a median follow-up of 32 months. Milano et al. found that some patients with oligometastatic breast cancer treated with hypofractionated stereotactic radiotherapy can survive more than 10 years[20]. Recent trials suggest that treating all sites of oligometastatic disease with SABR is associated with an improvement in progression free survival and overall survival[21, 22].

SABR to bone metastases is known to provide good and durable pain control[18, 23]. Most of the symptomatic patients in our case series had an improvement in their pain beyond 12 months. A recent prospective randomized single institution phase 2 non-inferiority trial indicated that patients with painful bone metastases who underwent high-dose single fraction SABR (12 or 16Gy) had better pain response than patients who had conventional 30Gy in 10 fractions[24]. Additionally a review on the published cost-effectiveness studies on stereotactic radiosurgery (SRS) and SABR has shown that they are cost-effective management strategies when compared with conventional treatment[25]. This further supports the notion of considering SABR in the palliative setting.

This case series outlines a technique on treating sternal metastasis with stereotactic radiotherapy with excellent local control, using a single dose which is very convenient for patients. There is no reported literature on SABR in sternal metastases. SABR is typically used for spherically shaped volumes, most commonly in the lung. Our data demonstrates that it is also a safe and effective technique for atypically shaped and large volume metastases (PTV range, 14.4cc - 197.8cc).

Previous publications have indicated that severe toxicity from SABR to bone metastases is rare[18, 23]. Our patients had minimal grade 1 or 2 acute and late

toxicities and there were no grade 3 or 4 toxicities. Interestingly the asymptomatic patient with the largest GTV of 103.4cc developed an acute grade 2 skin reaction and no pain. Whereas the patient with the smallest GTV of 3.0cc had pain prior to treatment and had ongoing but improved grade 1 pain since treatment.

Our case series has several limitations. It includes a small number of patients, with varying breast cancer phenotypes and disease burden. Acute and late toxicities were collected retrospectively based on clinical records. Additionally, most of the patients received endocrine and systemic therapy, which would influence the progression and survival outcomes recorded. Given that most breast cancer patients with bone only oligometastatic disease will survive more than 10 years[20], a prospective study with longer follow-up to assess late toxicities and treatment benefit is required. However this small series demonstrates that SABR to sternal metastasis was feasible and has minimal toxicity with medium term local control in all ten patients with median follow-up of 32 months.

Conclusion

Our case series is the first to provide safety and efficacy data on SABR as a management strategy of sternal metastases in patients with oligometastatic breast cancer. It supports the notion that single fraction SABR is a safe treatment that provides effective pain control and local control of bone metastases in selected patients.

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Nil

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Figure legends

Figure 1 – Transverse view of a patient's treatment plan with the field arrangements

Figure 2 – Sagittal view of Patient 2's treatment plan with the follow up PET scan fused showing in-field recurrence

Tables

Table 1 - Patient Characteristics

1	43	ER+ / PR- / HER2+	Right hip	7	Yes	Traztuzumab Pertuzumab
2	63	TNBC	Nil	3	Yes	-
3	28	ER+ / PR+ / HER2-	Nil	1	No	Aromatase inhibitor Ribociclib
4	59	ER+ / PR+ / HER2-	Nil	11	No	Aromatase inhibitor
5	52	ER+ / PR+ / HER2-	9th rib, T9, scapula	5	Yes	Pembrolizumab Denosumab
6	55	ER+ / PR+ / HER2-	Nil	13	Yes	Aromatase inhibitor

						Denosumab
7	66	ER+ / PR+ / HER2-	T7, axilla	16	Yes	-
8	57	ER+ / PR- / HER2+	Nil	2	Yes	Pembrolizumab Denosumab
9	42	TNBC	Lungs	15	Yes	Atezolizumab Denosumab
10	65	ER+ / PR+ / HER2-	Nil	3	Yes	-

Table 2 – Treatment details

1	No	31.6	5.2	3	3	1.49	124	1	8.6	9	2
2	No	96.4	10	5.5	1.6	1.28	127	2.6	23	9	4
3	No	87	3.9	4.4	2.6	1.38	120	10.7	24.2	8	2
4	No	14.4	2.1	2.6	1.6	1.32	126	1.4	23.5	8	6
5	No	130.1	12.2	5.6	2.8	1.6	117	2.3	23.5	11	6
6	No	197.8	9.4	8.6	3.8	1.23	132	7.2	22.5	11	2
7	No	39.5	3.5	2.8	2	1.2	127	1.8	23.1	7	5
8	No	38.8	3.7	4.5	1.8	1.2	118	1.8	16	10	6
9	Yes	90.2	8.8	6.5	2.3	1.2	130	5.9	24.5	8	6
10	No	82.5	7	5.6	2.8	1.3	120	2.6	21.6	8	6

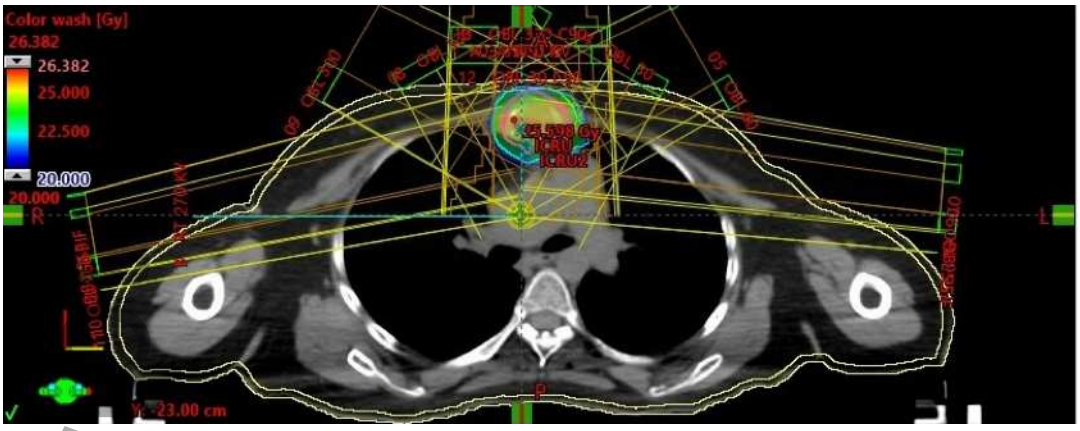
Table 3 – Treatment outcomes

1	49	Resolved	No	No	Not applicable	20
2	55	Recurred	Yes	No	Not applicable	6
3	11	Resolved	No	Yes	No	No relapse
4	31	Stable	No	Yes	Yes	No relapse

5	30	Stable	No	Yes	Unknown	19
6	48	Stable	No	Yes	Unknown	No relapse
7	33	Resolved	No	No	Not applicable	20
8	22	Stable	No	Yes	Yes	11
9	12	Stable	Yes	Yes	No	2
10	34	Stable	No	Yes	Yes	19

Table 4 – Toxicity

1	31.6	8.6	0	0	0	0
2	96.4	23	1	0	0	0
3	87	24.2	0	0	0	0
4	14.4	23.5	0	1	1	1
5	130.1	23.5	1	0	0	0
6	197.8	22.5	1	0	1	0
7	39.5	23.1	0	0	0	0
8	38.8	16	0	1	0	1
9	90.2	24.5	0	0	0	0
10	82.5	21.6	2	2	0	1



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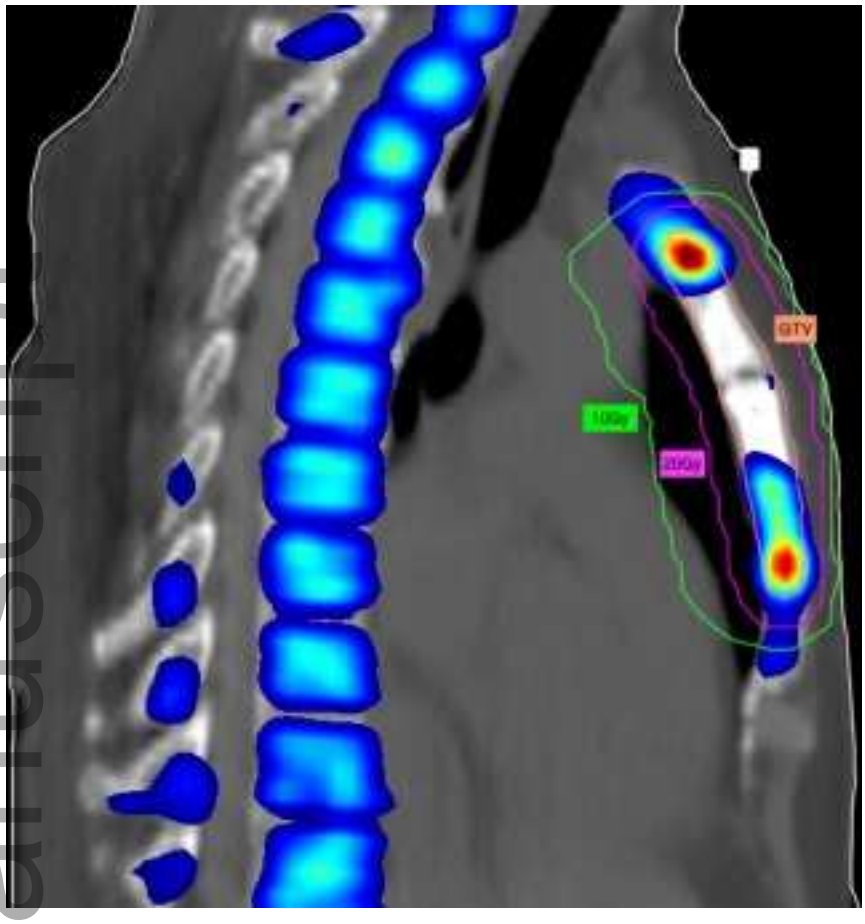

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