Original article

Stereotactic ablative body radiotherapy (SABR) for bone only oligometastatic breast cancer: A prospective clinical trial

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ABSTRACT

Background: Stereotactic ablative body radiotherapy (SABR) is an emerging noninvasive approach for the treatment of oligometastases. Limited prospective evidence is available in breast cancer.

Objectives: To determine the safety and feasibility of single fraction SABR for patients with bone only oligometastatic breast cancer. Secondary endpoints were local and distant progression-free survival (LPFS and DPFS), toxicity and response assessment.

Methods and materials: In this single institution prospective trial we screened patients with computed tomography, bone scan, and sodium fluoride positron emission tomography. Eligible patients had one to three bone only oligometastases. All patients were treated at a dose of 20Gy in 1 fraction to each metastasis. Kaplan-Meier methods were used to determine local and distant progression free survival (LPFS and DPFS). Toxicity was graded using Common Terminology Criteria for Adverse Event version 4.0.

Results: 15 eligible patients were recruited to the study. Median follow-up time was 24 months. The treatment was feasible in 12 (80%) of patients with 3 (20%) of patients having treatment delayed by more than 3 days. 10 (67%) of patients experienced grade 1 treatment related toxicity, 4 (27%) experienced grade 2 toxicity and no patients experienced grade 3 or 4 treatment related toxicity. The two-year LPFS was 100%, DPFS was 67%.

Conclusion: We observed that SABR is feasible, well tolerated and effective in this cohort with two thirds of patients disease-free at two years. In selected patients with bone-only oligometastatic disease, SABR could be considered a treatment option. Randomised trials are required to assess the impact of SABR on overall survival when compared to the standard of care.

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1. Introduction

The treatment of patients with metastatic breast cancer predominantly involves the use of systemic therapies to control disease. Whilst outcomes are improving with modern therapies, achieving these outcomes requires continuous systemic therapy which over time has become more complex, expensive and burdensome on the patient and health system. It is therefore increasingly important to consider if alternative treatment strategies which entail less treatment burden can be utilised in breast cancer patients that are expected to have favourable long term outcomes.

By observing the natural history of breast cancer, Hellman and Weichselbaum [1] coined the state of "oligometastases" to describe the existence of a state of limited metastatic burden. There is some evidence that women with low volume oligometastatic breast cancer may be cured or experience improvement in progression-free survival if all the tumour cells can be removed or treated effectively [2–8].

Modern genomic techniques have confirmed that tumours are mixtures of different populations of tumour cells with differing phenotypes, termed subclones [9]. These subclones exist in discrete areas of tumour masses generating intra-tumour heterogeneity, and also are represented to a different extent in distinct metastatic sites (inter-tumour heterogeneity [10]). Systemic treatment is known to impose a strong selective pressure on tumour subclonal structure, with the phenomenon of acquired resistance - that is, progression after an initial response [11,12]. This has two implications. Firstly, reducing the reservoir of potentially resistant subclones by reducing tumour burden should curtail the emergence of

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resistant disease. Secondly, ablation of a progressing lesion has the potential to eliminate the resistant population prior to widespread dissemination. Thus, although evidence for cytoreductive or ablative therapies in the incurable disease setting is lacking in untreated populations [13,14], ablative therapies may have a role in maintaining the efficacy of systemic therapies when the disease burden is low.

Coleman et al. observed that patients with bone only disease have a longer survival than patients with visceral metastases — up to 20% alive at 5 years [15], with a median survival of over 72 months in selected patients [16,17]. Therefore, durable local control of bone metastases is increasingly recognised as important, and in selected patients local therapy is occasionally considered with the intent of improving survival outcomes.

Stereotactic ablative body radiotherapy (SABR) is an attractive option for metastasis-directed therapy conveniently delivered in one outpatient session. Currently there are limited publications in treatment of oligometastatic breast cancer using SABR treatment and none in bone only disease [18—21]. However, a recent publication with the use of SABR in the setting of oligometastatic disease from any tumour type has demonstrated a PFS and OS benefit in a randomised phase II study compared to standard of care alone [22].

We conducted a single institution prospective clinical trial in patients with one to three oligometastases from breast cancer. The primary objective of the study was to assess the feasibility and tolerability of the single fraction treatment. Secondary objectives included the assessment of treatment related toxicity, local progression free-survival (LPFS) and PET response assessment.

2. Patients and methods

2.1. Study Design and participants

This prospective interventional clinical trial was approved by the Peter MacCallum Cancer Centre institutional review board, Melbourne, Australia (BOSTON, 'Bone Only STereotactic ablation for Oligometastatic Breast Neoplasia', Universal Trial Number U1111-1154-1830. All patients gave written informed consent. Inclusion criteria were pathologically confirmed breast cancer with the primary controlled with either surgery or radiotherapy (or a combination of both); bone scan or computed tomography (CT) evidence of 1—3 bone only metastases within 12 weeks of enrolment (including patients with pre-existing metastatic disease, de novo oligometastatic disease or patients that developed oligometastatic whilst on anti-cancer treatment); Eastern Cooperative Oncology (ECOG) status of 2 or less with a life expectancy of greater than 12 months. Patients were ineligible if they had previous high dose radiotherapy (BED > 20Gy) to an area to be treated, visceral metastases, treatment with any cytotoxic chemotherapy agent within 3 weeks of SABR, evidence of spinal cord compression or a Spinal Instability Neoplastic Score ≥ 7 in a vertebral body to be treated, a lesion in a long bone (femur or humerus) which involved the cortex (to minimise fracture risk). Histological confirmation of metastatic disease was not mandatory. All radiotherapy plans were reviewed at the peer reviewed SABR chart round. Clinician discretion with respect to change or commencement of endocrine or targeted therapy was permissible at the time of study entry.

Patients were secondarily screened with a sodium fluoride (NaF) positron emission tomography (PET)/CT scan as a more sensitive and specific imaging modality for detecting bone metastases [23]. Patients were excluded if more than three bone metastases were detected on PET. When discordance occurred between imaging modalities, subsequent review of all imaging occurred at our dedicated oncology imaging department for a consensus opinion and when recommended, additional investigations were ordered.

Symptoms were recorded using Common Terminology Criteria for Adverse Events version 4.0. Pretreatment spinal instability scores were recorded for spinal targets. Follow-up after SABR was every 3 months for 2 years with clinical evaluation, CT imaging and whole body bone scanning. A second NaF PET scan was performed at 12 months (Fig. 1).

2.2. Interventions

Eligible patients received a single fraction of SABR to all visible sites of disease. A single fraction of 20Gy was chosen based on a previous publication using SABR for breast cancer spinal metastases in which a mean dose of 19Gy (15—22.5 Gy) was used safely [24]. We also have institutional experience using a single fraction of 20Gy [25] which represents a biologically equivalent dose of 120 Gy (assuming an alpha beta ratio of 4 for breast cancer). All patients were immobilised using a commercial dual vacuum immobilization device (BodyFix, Stockholm, Sweden). Contouring of the gross tumour volume (GTV) was undertaken using all available imaging modalities including NaF PET, CT and/or magnetic resonance imaging. A margin of 5 mm was given to the gross visible tumour to define a planning target volume (PTV). A single fraction of 20Gy was prescribed to the 80% covering isodose, covering 95% of the PTV, resulting in peak doses of typically 125% within the target. Each lesion that received SABR had kV —kV pair image matching followed by soft-tissue verification with cone-beam CT scan before and midway through treatment delivery. The treatment planning system used was Varian Eclipse (version 13.6) using a Triple A calculation algorithm. All patients were treated with a Varian 2100 series linear accelerator.

Dose constraints found in Appendix 1 were met. An example of the dose distribution and dose volume histogram for a treated sternal metastasis is demonstrated in Appendix 2.

2.3. Outcome measures

The primary endpoints were both feasibility and tolerability. Feasibility for each patient was defined as: (1) successful completion of treatment within 3 days of intended treatment completion, and (2) image guidance verification of treatment delivery within 5 mm of planned delivery. Tolerability was defined as no greater than a 15% rate of Grade 3 or higher treatment-related toxicity and no Grade 5 toxicities related to SABR. Secondary outcome measures include local progression-free survival [LPFS], distant progression free survival [DPFS] and treatment-related adverse events. Local progression was defined as > 25% increase in size of measurable
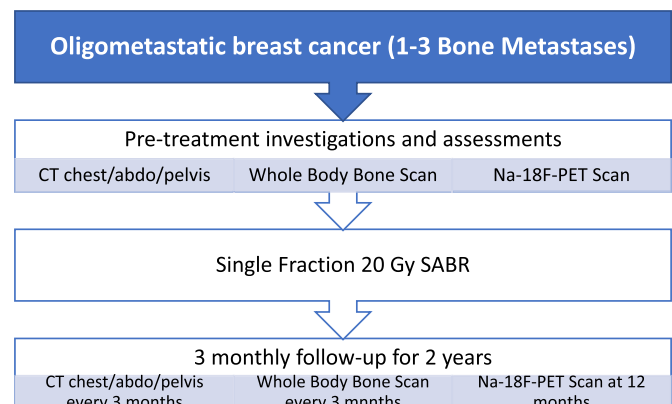

Oligometastatic breast cancer (1-3 Bone Metastases)

Pre-treatment investigations and assessments

CT chest/abdo/pelvis   Whole Body Bone Scan   Na-18F-PET Scan

Single Fraction 20 Gy SABR

3 monthly follow-up for 2 years

CT chest/abdo/pelvis every 3 months   Whole Body Bone Scan every 3 mnnths   Na-18F-PET Scan at 12 months

Fig. 1. Study design.

lesion assessed using the MDA response criteria [26]. The investigator scored local progression of bony metastases, with progression typically confirmed with PET using Positron Emission Tomography Response Criteria in Solid Tumours (PERCIST 1.0) [27]. LPFS was measured from the date of treatment commencement to the date of first local progression or death due to any cause. DPFS was measured from the date of treatment commencement to the date of first distant progression or death due to any cause.

2.4. Statistical analysis

The worst grades of adverse events were tabulated as frequencies by grade for each toxicity type. The feasibility rate and response rate were estimated with an exact 95% confidence interval. Time-to-event endpoints were described using Kaplan-Meier method. Estimates at key time points were provided with 95% confidence intervals.

3. Results

Thirty-six patients were screened for the study between September 2014 and October 2016. 15 patients met all trial eligibility criteria and were recruited to the study. 21 patients were excluded during the screening period: Eight patients had no evidence of metastatic disease after further imaging and investigations, six patients had more than three metastases detected after NaF PET/CT (these additional metastases were subsequently visualised upon secondary review of the baseline CT scan two cases and confirmed with an MRI in one case), three patients declined participation, one patient had visceral metastases detected on CT scanning, three patients had metastases that were technically or clinically unsuitable for SABR treatment (two patients had disease that was too close to the spinal cord and one patient's plan was not safely achievable due to previous high dose radiotherapy close to the lesion to be treated). In total, 15 patients with 19 oligometastases received the trial intervention and were followed for 2-years.

The median age was 63 years. 18 (95%) of the metastases were treated with a single dose of 20Gy and 1 (5%) patient received a dose of 28Gy in 2 fractions for technical reasons. All 15 patients had their primary breast cancer surgically resected. The most common locations of the bone metastases were the spine - 9 patients (47%) and the sternum − 5 patients (26%). Thirteen (86%) patients had hormone receptor positive disease, 2 (14%) patients had Her-2 positive disease and 1 (7%) patient had triple negative breast cancer. The baseline patient and tumour characteristics are described in Table 1.

Four patients (4/15) had pre-existing and stable metastatic disease: One patient with triple negative disease had a solitary metastasis treated and did not receive systemic therapy during the study period. Another patient with ER positive and Her-2 positive disease received ongoing Trastuzumab, Pertuzumab and an aromatase inhibitor during the study period. A third patient with luminal breast cancer developed oligometastatic disease on an aromatase inhibitor and remained on it during the study period. The patient with ER negative and Her-2 positive disease did not receive systemic therapy before or during the study period.

Of the remaining eleven patients (11/15) with luminal disease (ER, PR positive, HER2 negative) receiving endocrine therapy: 8/11 developed oligometastatic disease. 6/8 patients remained on the same agent and 2/8 patients were switched to an alternative endocrine agent at the time of study entry.

3.1. Feasibility

All patients had image guidance verification of treatment delivery during treatment within 5 mm of planned delivery. The

Table 1
Baseline patient and tumour characteristics.

Variable	Result
Age (years)	
Mean (SD)	61 (6)
Median [range]	63 [43–71]
ECOG	
0	12 (80%)
1	2 (13%)
2	1 (7%)
Prior Surgery to the Primary	
No	0 (0%)
Yes	15 (100%)
Prior Chemotherapy	
No	3 (20%)
Yes	12 (80%)
Prior Radiotherapy	
No	5 (33%)
Yes	10 (67%)
Prior Hormonal therapy	
No	2 (13%)
Yes	13 (87%)
Prior Targeted therapy	
No	12 (80%)
Yes	3 (20%)
Time between primary treatment and SABR	
0 years (denovo)	2 (13%)
2 years	2 (13%)
3 years	3 (20%)
4 years	3 (20%)
5 years	1 (5%)
6 years	1 (5%)
7 years	1 (5%)
11 years	2 (13%)
Number of metastases	
1	11 (73%)
2	4 (27%)
3	0 (0%)
Tumour Location	
Acetabulum	1 (5%)
Hip	1 (5%)
Humerus	1 (5%)
Rib	1 (5%)
Skull	1 (5%)
Spine	9 (47%)
Sternum	5 (26%)
Subtype	
Luminal breast cancer	11 (73%)
Her2 enriched breast cancer	3 (20%)
Triple negative breast cancer (TNBC)	1 (7%)

overall feasibility rate was 80% (95% CI [52–96]) Treatment was delayed by more than 3 days for 3 patients: Two patients required replan due to contour change after quality assurance review at SABR chart round (6 and 12 days, respectively); One delay was by patient choice (28 days). All patients received SABR treatment as the reasons for the delays were deemed clinically acceptable by the treating physician.

3.2. Safety and tolerability

Treatment related adverse events were observed in 14 patients (93%). There were no Grade 3 or 4 toxicities. Treatment related adverse events within 24 months of SABR are described in Table 2.

3.3. Local progression free survival and distant progression free survival

None of the patients sustained local progression or died during the study (100% LPFS at 2 years). As there were no deaths or local progression during the study, the DPFS, freedom from distant

Table 2
Acute adverse events (worst grade) related to treatment.

Adverse Event	Grade 1	Grade 2	Total (%)
Bone Pain	7		7 (47%)
Back Pain	4	1	5 (33%)
Skin Hyperpigmentation	3		3 (20%)
Chest Wall Pain	1	1	2 (13%)
Esophagitis	1	1	2 (13%)
Lethargy	1	1	2 (13%)
Nausea	2		2 (13%)
Skin Induration	2		2 (13%)
Abdominal Pain		1	1 (7%)
Alopecia	1		1 (7%)
Atelectasis	1		1 (7%)
Radiation Dermatitis		1	1 (7%)
Gastrointestinal Disorders - Other (Reflux)	1		1 (7%)
Neuralgia	1		1 (7%)
Pain (Neuropathic)	1		1 (7%)
Skin Atrophy	1		1 (7%)
Telangiectasia	1		1 (7%)
Any adverse event¥	**10**	**4**	**14 (93%)**

¥ Number of patients whose worst AE was grade 1 or 2.

progression and progression free survival estimates are the same. These estimates at 1-year were 80% (95% CI 62–100) and at 2-years were 65% (95% CI 45–95) (Fig. 2).

Of the 5 patients who experienced progression at distant sites, 3 relapsed with further bone disease. Two hormone positive patients required a change in systemic therapy and one with triple negative disease received further SABR. Two of 5 patients developed isolated brain metastases, requiring palliative surgery and radiotherapy.

Ten patients (67%) did not relapse distantly. Of these, all eight hormone receptor positive and Her-2 negative were on endocrine therapy prior to SABR and did not require a change to systemic treatment during the study period. One further patient with hormone receptor negative and Her-2 positive disease remained off all systemic therapies due to drug toxicity with SABR delivered to a lung and bone metastasis. One patient with hormone receptor positive, Her-2 positive disease remained on endocrine therapy, trastuzumab and pertuzumab during the study period.

3.3.1. Response table

Response was assessed at 12 months post SABR treatment using MDA classification of bone response and correlated with NaF PET scans (PERCIST 1.0). In instances where there was disagreement
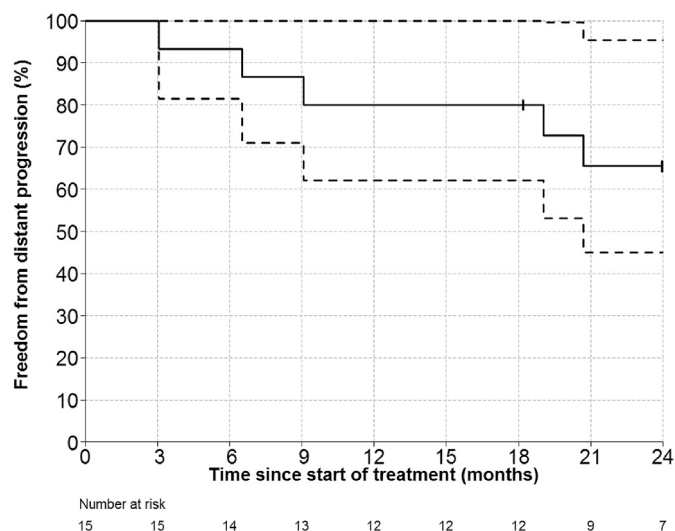

Fig. 2. Kaplan-Meier estimate of distant progression free survival (solid line). Dashed line represents 95% confidence interval.

between MDA classification and PERCIST 1.0, it was PERCIST 1.0 that was used as the confirmatory assessment tool. Response was assessed for each lesion (lesion response) and for each patient (patient overall response) Table 3.

The overall disease control rate (DCR) at 12 months measured as CMR/PMR/SMD was 87%. In the 7 patients that achieved a CMR on PET and were disease free at 12 months, all 7 remained disease free at 24 months, as shown in the progression event history chart, Fig. 3.

4. Discussion

In this paper we report the final results of a prospective trial, in which breast cancer patients with bone only disease successfully underwent SABR to all oligometastatic sites. To our knowledge this is the only study using single fraction SABR radiotherapy in breast oligometastatic disease. SABR was feasible and tolerable in the treatment of bone lesions in oligometastatic breast cancer. Patients had excellent local control (100% at 2-years) and 65% of study participants were alive and free from progression at 2 years. Milano [28] reported a 2-year PFS of 44% in patients with 1–5 metastatic deposits. The superior PFS in our study is perhaps explained by the broader inclusion criteria in the Milano study (up to 5 metastases, including visceral disease). The preferred fractionation schedule in the Milano study was 50 Gy in 5 fractions to each lesion and only 8 patients had bone only metastatic disease, with the majority of patients having liver or lung metastases (70%). In the Milano study a subgroup analysis of bone only patients demonstrated there were no local failures, one distant failure and no deaths. Overall, the local control of those patients treated with curative intent in the Milano study was 89%, with no lesions failing locally after 18 months. An observational study also using a multi-fraction approach of between 49 and 75 Gy in 3–4 fractions in patients with either lung or liver metastases demonstrated 1 and 2 year local control rates of 98% and 90% respectively [29]. All of the local progressions occurred in patients with liver metastases. These 2 studies together with our paper indicated that bone only oligometastatic disease is perhaps the most favourable target to achieve long term disease control and potentially cure.

The single fraction SABR strategy used in our study has obvious advantages for patient convenience. Furthermore, it was very well tolerated with no patient experiencing grade 3 or 4 treatment related toxicities during the study period, with only 4 (27%) of patients experiencing grade 2 toxicities. Equivalence of single fraction SABR compared to a multi-fraction approach has previously been reported in the treatment of primary lung cancer [30,31]. In the context of metastatic disease, the use of single fraction SABR is not only convenient but minimises the potential duration of interruption to systemic therapy.

Despite developing progressive disease, 8 of the 11 (72%) ER + HER2-patients continued the same endocrine therapy after SABR and remained disease free during the study period. This suggests that SABR may have a role in extending the benefit of a given endocrine therapy. In contrast, the standard approach for these patients would be a change in therapy. Therapies with evidence of benefit following progression on initial endocrine therapy include fulvestrant, CDK4/6 inhibitors, and everolimus with exemestane. Although fulvestrant and CDK4/6 inhibitors are in general well tolerated, significant rates of grade 3 or adverse events are reported [32–34], and everolimus appears less well tolerated than chemotherapy [35]. The estimated rate of PFS in the first line setting with CDK4/6 inhibitors in combination with aromatase inhibitors is approximately 50% at 2 years in patients who were untreated or recurred at least 12 months after adjuvant therapy and thus selected for endocrine sensitivity [32,34]. These trials included

Table 3
PET Response assessment at 12 months.

Response type	Response	n (% [95% CI])
PET overall response	CMR	7 (47% [21−73])
	PMR	5 (33% [12−62])
	SMD	1 (7% [0−32])
	PMD (distant progression)	2 (13% [2−40])
	CMR/PMR	12 (80% [52−96])
	SMD/PMD	3 (20% [4−48])
PET response (per lesion)	CMR	10 (59% [33−82])
	PMR	6 (35% [14−62])
	SMD	1 (6% [0−29])
	No PET (distant progression prior to scan)	2
	CMR/PMR	16 (94% [71−100])
	SMD/PMD	1 (6% [0−29])
	No PET (distant progression prior to scan)	2

CMR − complete metabolic response, PMR − partial metabolic response, SMD − stable metabolic disease, PMD progressive metabolic disease.
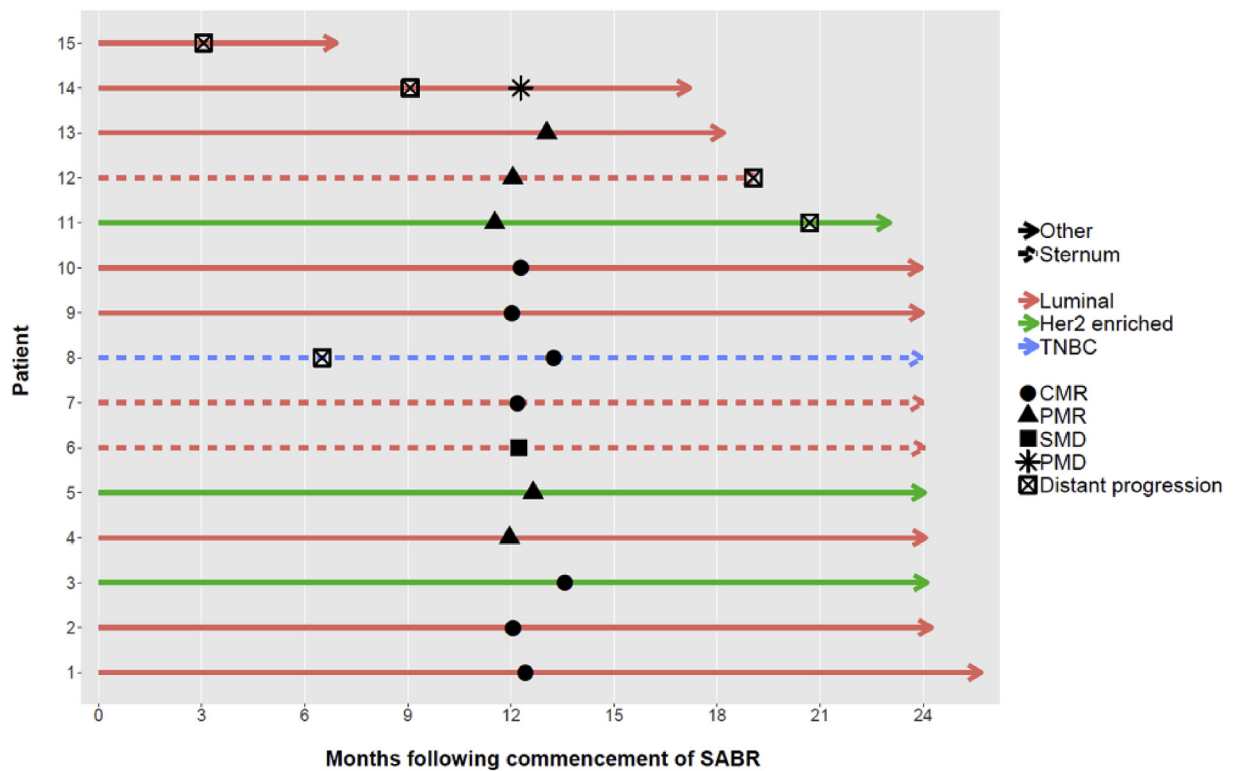

Fig. 3. Progression event history chart with PET response at 12 months (CMR − complete metabolic response, PMR − partial metabolic response, SMD − stable metabolic disease, PMD progressive metabolic disease)*Patient 14, recorded PMD due to uptake at a distant bone site.

patients with visceral metastases, whereas our study cohort was highly selected with bone only oligometastases. A more salient comparison are trials of subsequent therapy following progression on initial endocrine therapy. In two phase 3 trials in this setting, the use of the CDK4/6 inhibitor palbociclib with fulvestrant resulted in a median PFS of 9.2 months [33,36], and everolimus with exemestane of 10.6 months. In both these studies, there were no significant differences in PFS for patients with or without visceral disease. The PFS for patients in our study that would otherwise have been candidates for second line therapy on these trials compares favourably, acknowledging the severe limitations of cross-trial comparisons.

Our data indicates the potential utility of SABR in ablating localised metastatic sites and rendering patients disease free for 2 years without changing endocrine therapy. In this context. SABR may be an attractive treatment option for patients with limited bone only metastasis, potentially delaying the introduction of more toxic systemic therapies.

Of 19 treated metastatic sites, five (26%) were sternal metastases that were all safely and successfully treated with SABR. Sternal metastases are considered a separate entity of metastatic disease with perhaps a better prognosis as there is no systemic connection with the paravertebral venous plexus through which further spread may occur. Noguchi reported on radical resection in 9 patients with sternal metastases with a median survival of 30 months [37]. SABR provides a significantly less invasive and less toxic alternative to this radical approach in selected patients.

In addition to conventional staging the study explored the utility of NaF PET/CT as a superior staging modality for bone metastasis. 6 patients deemed eligible on conventional imaging became ineligible after more than three metastases were detected on the NaF PET/CT scan. Furthermore, NaF PET/CT provided response

assessment information that may correlate with longer term LPFS. In the 6 patients that had not progressed and achieved a CMR on a 12 month NaF PET/CT and were disease free at 12 months, all 6 remained disease free during the study follow up period of 2 years. Of the 5 patients with PMR, two developed distant progression. This suggests that NaF response could have important prognostic implications. It may be worthwhile to consider using NaF PET in both staging and as a potential predictive prognostic biomarker. In addition, this finding supports the theory that metastases seed metastases [12] and as such aggressive metastasis directed radiotherapy may benefit some patients in the longer term.

Limitations of this study include a limited sample size, two-year follow-up, single institutional dataset, variability in use of systemic therapies and heterogeneity in the breast cancer histological subtypes. Furthermore, although NaF PET/CT is considered more sensitive and specific than conventional imaging [23], there are reports of false positives with this modality [38]. Given tissue confirmation was not mandatory, this is a potential limitation of this study. Despite these limitations we observed that this patient cohort may benefit from prolonged PFS with this approach. The challenge remains to confirm this finding (particularly, luminal cases) in larger studies comparing SABR to the standard of care, which is currently the subject of large randomised trials [39]. Our current approach is to offer SABR in selected breast cancer patients with limited oligometastatic disease after comprehensive review in a multidisciplinary setting. We are currently investigating the immune stimulating effects of SABR in different dose fractionation schedules when combined with immunotherapy in 2 prospective clinical trials: AZTEC (ClinicalTrials.gov Identifier: NCT03464942) and BOSTON II (ClinicalTrials.gov Identifier: NCT02303366). Further work also needs to be performed to clarify the subgroup of patients that may best benefit from such an approach and how clinicians will integrate it into patient care. To add to the body of evidence for this emerging treatment option, the author suggests that eligible patients are entered onto randomised trials or clinical registries when feasible, including the EORTC OligoCare registry.

5. Conclusions

Single fraction SABR for oligometastatic bone only breast cancer is safe, feasible and convenient with excellent local control. In selected patients with up to two bone only oligometastases, the majority of patients do not progress at 2 years, remained alive without the need for further systemic treatment. Therefore it is worthwhile to conduct larger studies with longer follow-up to further assess the efficacy of SABR compared to the standard of care.

Funding source

Ethical approval

This prospective interventional clinical trial was approved the Peter MacCallum Cancer Centre institutional review board, Melbourne, Australia.

Declaration of competing interest

I have no conflict of interest.

Appendix 1

Normal tissue contouring and dose constraints (institutional single fraction guideline - informed by QUANTEC recommendation guidelines [40], and the AAPM TG101 working party consensus guidelines [41].

Organ	Contouring	Parameter	Dose/Fractionation
Kidney	Entire kidney	V10	33%
Spinal canal	Spinal Canal − 1 cm above and below the target volume	Maximum dose	$0.03\,cc \leq 12\,Gy$
Brain Stem	Including midbrain, pons and medulla	Maximum Dose	$0.03\,cc < 12.5\,Gy$
Skin (5 mm subcutis)	Body surface − 5 mm	Maximum Dose	$0.03\,cc \leq 24\,Gy$
Small Bowel	Entire peritoneal Sac	Maximum Dose/Volume	$30\,cc \leq 12.5\,Gy$
Stomach	Entire Stomach	Maximum Volume	$5\,cc \leq 22.5\,Gy$
Liver	Entire liver	Maximum Dose/Volume	$700\,cc \leq 15\,Gy$
Lung	Combined Left and right Lung - GTV	Maximum Dose/Volume	$1000\,cc \leq 7.4\,Gy$
Oesophagus	Cricoid to gastro-oesophageal junction	Maximum Dose	$0.03\,cc \leq 15.4\,Gy$
Rectum	Recto-sigmoid to anal canal (solid structure)	Maximum Dose/Volume	$20\,cc \leq 14.3\,Gy$
Bladder wall	Entire structure	Maximum Dose/Volume	$15\,cc \leq 11.4\,Gy$
Heart/Pericardium	Entire Structure	Maximum Dose/Volume	$15\,cc \leq 16\,Gy$
Brachial Plexus	Entire Structure	Maximum Dose	$0.03\,cc \leq 15.4\,Gy$

Note: Maximum dose is defined to a point. The minimum meaningful volume for a point is 0.035 cc.
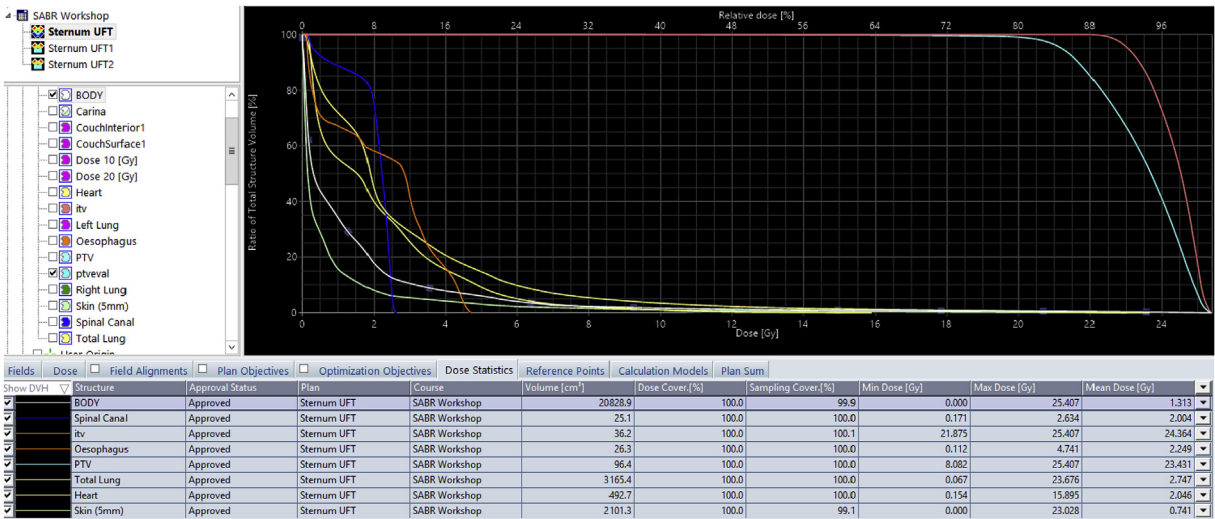
When planning more than one lesion a summary plan must be created. The dose constraints apply to the summary plan.

Appendix 2

Axial SABR dose distribution for a sternal metastasis (9 field conformal) Figure a.
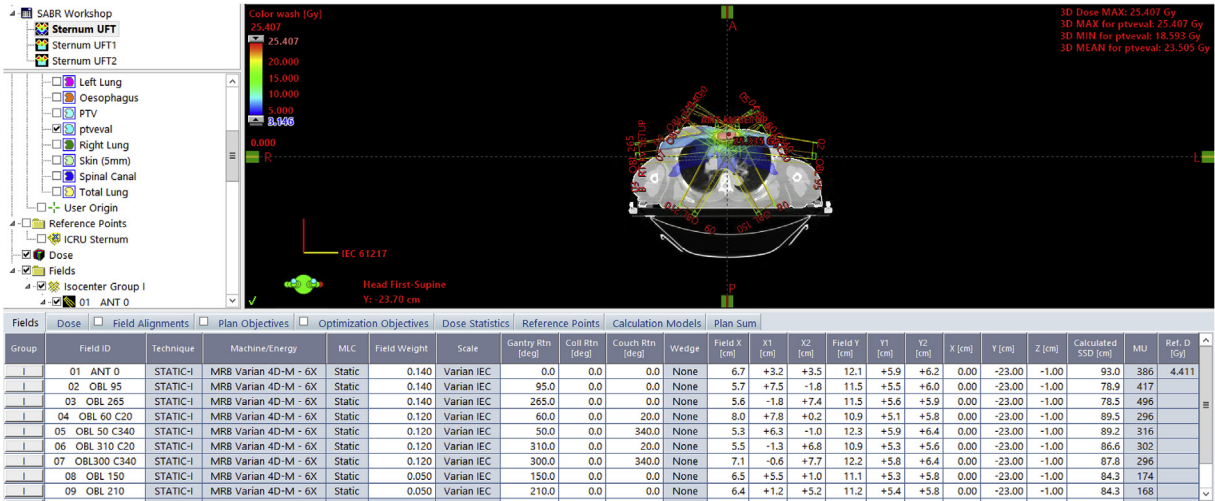
Dose Volume Histogram Figure b.

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