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Abstract (352 words)

Objectives: To report the outcomes of stereotactic ablative body radiotherapy (SABR) in men with oligometastatic prostate cancer (PCa) diagnosed on prostate-specific membrane antigen positron emission tomography/ computed tomography (PSMA PET/CT) based on a single institutional experience, and published literature.

Patients and methods: This is a retrospective cohort of the first 20 consecutive men with oligometastatic PCa treated with SABR in a single institution, who had: biochemical recurrence following previous curative treatment (surgery/ radiotherapy), no evidence of local recurrence, were not on palliative androgen deprivation therapy (ADT), and had PSMA-PET/CT confirmed oligometastatic disease (≤3 lesions). These men were treated with SABR to a dose of 30Gy in 3 fractions for bone metastases, and 35-40Gy in 5 fractions for nodal metastases. The outcomes of interest were: PSA response, local progression free survival (LPFS), distant progression free survival (DPFS), and ADT free survival (ADT-FS). A literature review was performed to identify published studies reporting on outcomes following PSMA PET/CT-guided SABR.

Results: In our institutional cohort, twelve men (60%) had a decline in PSA post-SABR. One man had local progression 9.6 months post-SABR, with 12-month LPFS of 93%. Ten men had distant progression outside of their SABR treatment field confirmed on PSMA PET/CT, with 12-month DPFS of 62% – 4 were treated with palliative ADT, 2 had prostate bed

radiotherapy for prostate bed progression (confirmed on magnetic resonance imaging), 4 had a further course of SABR (of which 1 had further progression and was treated with palliative ADT). At last follow-up, six men (1 who had LP, and 5 who had DP) had received palliative ADT; the 12-month ADT-FS was 70%. Men with longer intervals between local curative treatment and SABR had better DPFS (P=0.03) and ADT-FS (P=0.005). Four additional studies reporting on PSMA PET/CT guided SABR for oligometastatic PCa were identified with a total of 346 patients included in the review. PSA decline was reported in 60-70% of men post-SABR. The 2-year LPFS, DPFS, and ADT-FS were 76-100%, 27-52%, and 58-62% respectively.

Conclusion: PSMA PET/CT have an important role in identifying men with truly oligometastatic PCa who would benefit the most from metastases-directed therapy with SABR.

INTRODUCTION

Conventional treatment for men with metastatic prostate cancer (PCa) is systemic therapy. However, pooled analyses of several retrospective studies (1) and two prospective trials (2, 3) have shown that in men with oligometastatic (4) PCa, treatment of the oligometastatic lesions (i.e. metastasis directed therapy, MDT) with stereotactic ablative body radiotherapy (SABR) is feasible, and can delay disease progression and initiation of androgen deprivation therapy (ADT). In all these studies, oligometastatic disease was diagnosed on fluorodeoxyglucose (FDG), choline, or sodium-fluoride (NaF) PET scans (1-3, 5). The advent of prostate-specific membrane antigen positron emission tomography/ computed tomography (PSMA PET/CT) has allowed for better detection of oligometastatic lesions in men with PCa (6, 7). While there is an earlier study reporting on PSMA PET/CT-guided conventional fractionated radiotherapy for oligometastatic disease (8), to our knowledge, published studies on the outcomes of PSMA PET/CT-guided SABR for oligometastatic PCa are lacking (9-12). The aims of this study are to report our early institutional experience, and review the published literature, on the outcomes following PSMA PET/CT-guided SABR in men with biochemical recurrence following previous curative PCa treatment.

METHODS

Study population: This is a retrospective cohort of the first 20 consecutive men treated with SABR for oligometastatic PCa at our institution from January 2016 who fulfil the following criteria: biochemical recurrence following curative treatment for PCa (with surgery and/ or radiotherapy) with no PSMA PET/CT evidence of disease in the prostate bed (post-surgery)

or prostate (post-radiotherapy), PSMA PET/CT detected oligometastatic disease of ≤3 lesions (including either lymph nodes or bone), and not previously on palliative ADT (men who received adjuvant ADT as part of curative prostate radiotherapy were allowed). This study was approved by Austin Health Human Research Ethics Committee (LNR/19/Austin/05).

SABR planning: All men were treated with SABR to a total dose of 30Gy in 3 fractions for bone metastases and 35-40Gy in 5 fractions to nodal metastases. All men were simulated supine and immobilized with an Elekta Bodyfix cradle. Planning CT scans were fused with PSMA PET/CT for target delineation. Gross target volume (GTV) included gross disease visible on CT and PSMA PET/CT. A uniform 5mm expansion to planning target volume (PTV) was generated. Planning was undertaken on Elekta Monaco software with a Volumetric Modulated Arc Therapy (VMAT) technique. Dose was prescribed to cover 95% of the PTV with maximum doses of 120-135% of the prescribed dose within the GTV. Dose constraints applied to organs at risk followed the American Association of Physicists in Medicine (AAPM) guidelines relevant to each site, and were respected for all treatment (13).

SABR treatment: All treatments were delivered with an Elekta Versa HD linear accelerator. Treatments were delivered 2-3 times per week, on non-consecutive days. Pre-treatment image guidance was performed with Cone Beam CT (CBCT), or a combination of CBCT and Exactrac imaging to assess and correct patient positioning, using a six degree of freedom couch. Positional error corrections were applied to maintain patient accuracy within 2mm and 2 degree of planned position. Post-correction and post-treatment imaging was acquired for all treatment fractions.

Follow-up: Following SABR, all men were followed-up with 3-monthly PSAs. Men who had PSA progression (i.e. PSA increase of more than 50% from pre-SABR PSA level, or 3 consecutive rises in PSA) were restaged with PSMA PET/CTs. In the absence of radiological progression on PSMA PET/CT, they continued to be observed with serial PSAs. Men with progressive oligometastatic disease detected on restaging PSMA PET/CT were considered for further SABR if deemed appropriate (i.e. ≤3 lesions) and technically feasible. Men in whom further courses of SABR were not feasible, or where there was evidence of extensive metastatic disease, were then started on palliative ADT. PSA progression alone without PSMA PET/CT progression was not an indication for ADT initiation.

Outcomes definition: The outcomes recorded were: PSA response, local progression free survival (LPFS), distant progression free survival (DPFS) and ADT free survival (ADT-FS). *PSA response* was defined as any drop in PSA following SABR, regardless of whether there was subsequent PSA progression. *Local progression* was defined as PSMA-avid disease progression within the 20% isodose line of the previous SABR treatment field. *Distant progression* was defined as any PSMA-avid disease progression outside the SABR treatment field. *ADT-FS* was defined as the time to initiation of palliative ADT. The LPFS, DPFS, and ADT-FS were estimated using the Kaplan-Meier methods. All time-to-events were defined from the date of completion of SABR to the outcomes of interest. Patient who did not develop the outcomes of interest were censored on the date of last follow-up. Differences in outcomes stratified by NCCN risk categories, pre-SABR PSA level, site of oligometastatic disease, and duration between local curative treatment and SABR (≤1 year, 1-2 years and >2 years) were evaluated using the log-rank test, with a two-sided P-value of <0.05 considered to be statistically significant. All statistical analyses were performed using STATA/IC 13 (STATA Corp, College Station TX).

Search strategies, data extraction and synthesis: A review of the literature was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISM) guidelines. Given the previous systematic review published by Ost et al (5) which included a search up to February 2014, we have limited our search on the PubMed and MEDLINE databases for publications from February 2014 onwards, using a series of keywords: 'stereotactic', 'prostate' and 'oligometastasis'. Additional reference lists of related journal articles, were hand-searched for additional studies. The systematic review included randomised and non-randomised, prospective and retrospective, original studies of men with oligometastatic PCa treated with SABR. Reviews, editorials or commentary articles were excluded. Full text articles were retrieved and reviewed by two authors (WLO and TLK). Only studies which reported on the use PSMA PET/CT for staging and confirmation of oligometastatic PCa were included. The primary outcomes of interest are those similar to our current study i.e. PSA response, LPFS, DPFS and ADT-FS – only studies reporting on at least one of these outcomes were included in this review. A narrative approach was adopted to synthesize the relevant findings of the studies, given the heterogeneity of the studies identified as well as inconsistency in outcome definition and reporting. Pooling of the studies in the form of meta-analyses was not possible.

RESULTS

Single institutional experience

Baseline characteristics: Table-1 shows the characteristics of the study cohort. The mean age at initial PCa diagnosis was 66 years (SD=6.0), with median PSA of 6.9 ng/mL (range: 3.4-22.2 ng/mL). Seventeen (85%) men had NCCN high risk PCa, while 3 (15%) had intermediate risk PCa. The majority of men (90%) had radical prostatectomies (RP), of which one-third had post-prostatectomy radiotherapy (PPRT) following RP. The median time from initial curative local treatment to oligometastatic PCa diagnosis was 34 months (range: 5-127 months), and the median PSA at the time of oligometastatic PCa diagnosis was 1.3 ng/mL (range 0.2-30 ng/mL). Most men (75%) had SABR to solitary lesions, 4 (20%) had 2 lesions treated and 1 (5%) had 3 lesions treated. Fifteen (75%) had SABR to pelvic nodal metastases alone, 3 (15%) to bone metastases alone, and 2 (10%) to both pelvic nodal and bone metastases. The median follow-up for the cohort was 15.9 months (range: 6.7-35.5 months).

PSA response: Twelve (60%) men had a PSA response following SABR, with the PSA response at 3 months (Figure-1A) and largest PSA changes compared to baseline PSA depicted as waterfall plot (Figure-1B).

LPFS: One patient had local progression within the SABR treatment field at 9.6 months post-SABR. The 12-month LPFS for the cohort were 93% (Figure-2). The number of events for local progression was too small for any meaningful stratified analyses.

DPFS: Ten (50%) men developed distant progression beyond the SABR-treated lesion, at a median of 8.7 months (range: 2.6- 30.4 months) post SABR (Table-2), including all 3 (100%) men who had SABR to bone metastases alone, all 2 (100%) men who had SABR to both nodal and bone metastases, and 5 of 15 (33%) men who had SABR to nodal metastases alone. The 12-month DPFS were 62% (95%CI= 36-80%) (Figure-3A). Of the ten men who developed distant progression, two (20%) had progression within the prostate bed, confirmed as macroscopic recurrences on magnetic resonance imaging (MRI), and were treated with salvage radiotherapy to the prostate bed; four (40%) had oligometastatic progression and were treated with further SABR (of these four men, one had a further progression and was treated with palliative ADT); and the remaining four (40%) had palliative ADT.

In stratified analyses, men who had shorter durations between curative local treatment and SABR had a higher likelihood of distant progression (P=0.03) – the 12-month DPFS for men who had SABR less than 1 year post curative local treatment was 29% (95%CI=9-67%), whereas for men who had SABR more than 2 years post curative local treatment, the 12-

month DPFS was 81% (95%CI=42-95%) (Figure-3B). There were no significant differences in DPFS, when stratified by NCCN risk categories (P=0.9), pre-SABR PSA levels (P=0.8) and sites of oligometastatic disease (nodal vs. bone metastases) (P=0.5).

ADT-FS: At last follow-up, there were 6 (30%) men who were on palliative ADT (1 who had local progression and 5 who had distant progression), initiated at a median of 8 months (range: 2.6-12.4 months) post completion of first SABR course. The 12-month ADT-FS was 70% (95%CI=40-87%) (Figure-4A).

When stratified by duration between curative local treatment and SABR, men who had SABR less than 1 year post curative local treatment were more likely to be started on palliative ADT – 12-month ADT-FS was 38% (95%CI=1-81%) for men who had SABR less than 1 year post curative local treatment, compared to 89% (95%CI=43-98%) in men who had SABR more than 2 years post curative local treatment (P=0.005) (Figure-4B). There were no significant differences in ADT-FS when stratified by NCCN risk categories (P=0.2), pre-SABR PSA level (P=0.8), and site of oligometastatic disease (nodal vs. bone metastases) (P=0.4). The reasons for initiation of palliative ADT were: widespread metastatic disease (n=3), infeasibility of SABR given proximity to previous radiotherapy field (n=2) and patient's preference (n=1).

Literature review

Baseline characteristics: A total of four published studies reporting on the use of PSMA PET/CT-guided SABR for oligo-metastatic PCa were identified (Figure-5). Five studies, including our institutional data, with a total of 346 men were included in this review (Table-3). The median age of men at the time of SABR were 67-72 years, and the median PSA at the time of SABR were between 1.3 and 3.35 ng/mL (Table-3). A large majority of the men had radical prostatectomies as primary treatment – 67% had radical prostatectomies alone, and 22% had radical prostatectomies followed by adjuvant/ salvage radiotherapy – while only 10% had definitive radiotherapy. Most men had up to three oligometastatic sites treated – more than half of the men (54%) had single sites of oligometastases, while 23% and 12% had 2 and 3 sites of oligometastases respectively. More than half of all men included in the review had nodal oligometastases alone, while the other 39% had bone metastases alone, and 5% had mix of nodal and bone metastases. Varying dose and fractionations regimens of SABR were reported in all studies (Table-3).

Oncological outcomes: Different oncological outcomes were reported, with varying outcome definitions used across studies (Table-4). Of the studies reporting PSA responses,

60-70% patients were documented to have PSA declines following SABR (Table-5). Only the study by Kneebone et al reported complete biochemical response (i.e. undetectable PSA) in 14% of patients. Overall, the 2-year LPFS was reported to range between 76% and 100%. The 1-year and 2-year biochemical progression free survival (bPFS) were reported to be 46-51% and 13-16% respectively, while the 1-year and 2-year DPFS were reported to 55-62% and 27-52% respectively. Only three studies reported ADT-FS, of which one reported median ADT-FS of 9 months (10), and the other two reported 2-year ADT-FS of 58-62% (11). Only two studies reported on treatment-escalation free survival (TE-FS) – median TE-FS of 12.3 months in the study by Habl et al (10), and 2-year TE-FS of 51.7% in the study by Bowden et al (11). Only three studies reported toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE), and none reported grade 3 and above acute or late toxicities.

DISCUSSION

While there has been a surge in publications on PSMA PET/CT (14) and SABR for oligometastatic PCa (1-3, 5), only a few studies have reported the outcomes of SABR for PSMA PET/CT-defined oligometastatic PCa (9-12) (Table-3).

The LPFS outcomes in our institutional experience is comparable to earlier studies, despite the use of varying SABR dose and fraction regimens, depending on the treatment site (i.e. bone/ node). Nonetheless, these are all recognized schedules for SABR, with biological effective doses (BED) of more than 100Gy. In the pooled retrospective study by Ost et al however, it was noted that men treated with lower BED had lower LPFS – 3-year LPFS of 79% with BED $\leq$100Gy vs. 99% with BED >100Gy (1). In the review of published literature, most of the studies reported excellent 2-year LPFS of more than 90%; the 2-year LPFS was reported to be lower at 73% in the study except the study by Fanetti et al - it is however, important to note that only 5 of the 77 treated lesions (6%) were treated to BED of >100Gy, and there were 17 lesions whereby the dose and fractionation were not reported (12).

Despite the excellent local control, approximately half of the patients in our institutional cohort developed distant progression at 2 years. Nonetheless, our findings of 12-month DPFS of 62% however appear slightly better than that reported in earlier studies in the non-PSMA PET/CT era. The use of PSMA PET/CT has likely improved our selection of men with truly early, low-volume oligometastatic disease. This is evident on the much lower pre-SABR PSA level, and lower proportion of men who had bone metastases in our cohort, compared to earlier studies based on non-PSMA PET/CT staging. Of note, in the twelve men who had pre-SABR PSA levels of less than 2ng/mL, only two (17%) had bone metastases, while the

remaining (83%) had pelvic nodal metastases alone. The study by Kneebone et al using PSMA PET/CT staging also reported a higher proportion of men (65%) with nodal metastases alone (9) – of these, 33% and 20% who had SABR to solitary and multiple nodal metastases had no distant failure respectively, as compared to only 15% in those who had SABR to bone metastases. This highlighted the lower likelihood of distant progression following SABR in men with early nodal oligometastatic PCa.

Also, not surprisingly, in the 4 men who had node-only distant progression after SABR in our institutional series, the nodes involved were the next echelon of nodal stations beyond the SABR treated nodes. In our cohort, we observed that men who had a short interval between previous local curative treatment and SABR were more likely to have distant progression. This likely reflects that this group of men have more extensive micro-metastatic disease beyond that detected on PSMA PET/CT at the time of SABR. One could then argue in favour of offering these men radiotherapy to the nodal field instead of SABR to the PSMA-avid oligo-metastatic node alone, in order to maximise loco-regional control. Those with longer interval between curative local treatment and SABR on the other hand were likely to have more dormant and potentially truly oligo-metastatic disease, and thus would benefit most from SABR to the oligometastatic nodal disease. It is therefore important to consider the natural history of underlying PCa in each individual patient when selecting men who are appropriate for SABR.

The 1-year ADT-FS of 70% observed in our cohort is also comparable to earlier studies (2, 3). However, ADT-FS is not a widely used outcome, and was reported in only 2 of the 4 studies in the literature review. This is especially in the setting of increasing interest in early initiation of systemic therapy (15) and novel anti-androgen treatment (16-19) in men with metastatic PCa. While we do not routinely start ADT with PSA progression alone without PSMA PET/CT confirmation of disease progression, there is no strict trigger for ADT initiation, and this is often at the discretion of the treating clinicians in consultation with men. In fact one of the men in our cohort was started on ADT due to patient preference, despite him being appropriate for a further course of SABR. Nonetheless, given the multiple side effects associated with ADT (20), and the fact that men who progress will eventually be treated with palliative ADT, a delay in ADT initiation, we believe, may be an appealing option to most men.

One of the limitations of our institutional study is the lack of comprehensive reporting of toxicities in our cohort. Nonetheless, to be best of our knowledge, there were no reported toxicities requiring medical intervention or hospitalizations (i.e. CTCAEv4 grade 3 and above

toxicities) during the follow-up period in our series. Of the studies included in the literature review, none reported any grade 3 and above toxicities. Earlier prospective studies have also consistently reported the feasibility of SABR for oligometastatic PCa with overall low toxicities (2, 3), and there was only one (3%) grade 3 toxicity (vertebral fracture) reported in the POPSTAR study of patients treated with 20Gy in 1 fraction (3).

PSMA PET/CT will most likely continue to revolutionize PCa care, in the primary staging (21), as well as in the recurrent setting (6, 7). Recently, the Australian and New Zealand Faculty of Radiation Oncology Genito-urinary Group (FROGG) has also recommended the use of PSMA PET/CT staging in men with recurrent PCa considered for SABR for oligometastatic disease, in order to select men who have truly oligometastatic disease who may benefit most from such an approach (22). With increasingly easy access to PSMA PET/CT in Australia, there are also concerns that there may be inappropriate and overuse of PSMA PET/CT. There is however evidence to suggest that a clinician-centred education program may lead to appropriate utilisation of staging investigations (23).

CONCLUSION

In conclusion, we reported the oncological outcomes in men with oligometastatic PCa diagnosed on PSMA PET/CT treated with SABR in a single Australian institution and published literature. The use of PSMA PET/CT has allowed for better selection of men with truly oligometastatic PCa. It is also important to take into account the underlying natural history of PCa in each individual men to select those who will benefit the most from metastatic directed treatment. Nonetheless, such approach remains investigational at this stage, and eligible men should be encouraged to be enrolled in clinical trials such as the CRUK 14-038/ TROG 16-03 CORE trial (24).

CONFLICT OF INTEREST

Nil to disclose

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Table 1 | Baseline patient-, tumour-, treatment-details of study cohort (n=20)

Age at PC diagnosis (year)	
Mean (SD)	66 (6.0)
Median (IQR)	67 (51-74)
PSA level at PC diagnosis (ng/mL)	
Mean (SD)	8.5 (4.5)
Median (IQR)	6.9 (3.4-22.2)
ISUP Grade Group at initial PC diagnosis	
2 (3+4)	3 (15%)
3 (4+3)	11 (55%)
5 (4+5/ 5+4/ 5+5)	6 (30%)
Clinical stage/ Pathological stage at PC diagnosis	
T2	3 (15%)
T3	17 (85%)
NCCN risk category at PC diagnosis	
Intermediate risk	3 (15%)
High risk	17 (85%)
Previous curative treatment for PCa	
RP	12 (60%)
Definitive RT + ADT	2 (10%)
RP + PPRT	5 (25%)
RP + PPRT + ADT	1 (5%)
Surgical margin status in patients who had previous RP	
Clear/ negative	11 (61%)
Positive	7 (39%)
Time from curative treatment to diagnosis of oligometastatic disease (months)	
Median (range)	34 (5-127)
PSA level at diagnosis of oligometastatic disease, ng/mL	
Mean (SD)	4.1 (7.0)
Median (IQR)	1.3 (0.2-30)
Number of oligometastatic lesions treated with SABR per patient	
1	15 (75%)
2	4 (20%)
3	1 (5%)
Sites of SABR treated oligometastatic lesions	
Lymph node only	15 (75%)
Bone only	3 (15%)
Lymph node and bone	2 (10%)
Sites of nodal metastases (total 21 lymph nodes treated)	
External iliac lymph nodes	9 (43%)
Internal iliac lymph nodes	8 (38%)
Peri-rectal/ pre-sacral lymph nodes	4 (19%)

Dose and fractionation of SABR (N=24)	
30Gy/ 3#	6 (25%)
35Gy/ 5#	2 (8%)
40Gy/ 5#	16 (67%)

*RP=Radical prostatectomy; RT=radiotherapy; PPRT =Post-prostatectomy radiotherapy; ADT=androgen deprivation

Table- 2 | Patients who had local progression (n=1) or distant progression (n=10) following SABR to oligometastatic disease

	NCCN risk category of primary PCa	Curative treatment	Time from curative treatment to oligometastases (month)	PSA level at oligometastases (ng/mL)	Sites of SABR treated oligometastases	Time to progression (month)	Site of progression	Management for progression
1*	High risk (GS5+4, pT3a, PSA7.7)	RP	5.3	0.7	Pre-sacral node (x1)	9.6	Pre-sacral node (x2) L) internal iliac node (x1)	Palliative ADT
2	High risk (GS4+3, pT3a, PSA13.7)	RP + PPRT	105	30.2	T8 spine (x1)	30.4	Rib (x1)	SABR
3	Intermediate risk (GS4+3, pT2c, PSA6.9)	RP	58	0.23	S4 spine (x1)	24.6	Prostate bed alone	PPRT
4	High risk (GS4+5, pT3b, PSA6.7)	RP	5.6	0.54	R) external iliac node (x1)	3.3	Prostate bed alone	PPRT
5	High risk (GS 4+5, pT3a, PSA 9.7)	RP	18.3	0.83	R) internal iliac node (x1) L) internal iliac node (x1) L) external iliac node (x1)	4.5	Widespread (pelvic and para-aortic node)	Palliative ADT
6	Intermediate risk (GS4+3, pT2c, PSA 5.4)	RP	26.6	1.7	T6 spine (x1) L) external iliac node (x1)	21.0	L) external iliac (x1)	SABR
7	High risk (GS4+3, pT3a, PSA4.8)	RP + PPRT	44.3	12.9	Right humerus (x1)	8.7	Bone: clavicle (x1) Seminal vesicle	SABR; then palliative ADT
8	High risk (GS4+5, pT3a, PSA12.5)	RP + PPRT	53.5	2.7	L) internal iliac node (x1)	10.9	Widespread (inguinal node and bone)	Palliative ADT
9	High risk (GS3+4, pT3b, PSA 9.1)	RP	9.1	1.01	R) perirectal node (x1)	3.9	Widespread (bone)	Palliative ADT
10	High risk (GS4+3, pT3b, PSA 6.2)	RP	7.6	2.55	L) ASIS (x1) R) external iliac node (x1)	5.7	R) internal iliac node (x1)	SABR
11	High risk	RP	21.8	0.4	R) external iliac node (x1)	2.7	R) internal iliac node (x1)	Palliative ADT

	(GS4+3, pT3b, PSA?)				R) internal iliac node (x1)			(patient's preference)

*patient who had local progression

Abbreviation: RP=Radical prostatectomy; RT=radiotherapy; PPRT =Post-prostatectomy radiotherapy; ADT=androgen deprivation

Table 3 | Characteristics of published literature on SABR in patients with PSMA-PET confirmed oligometastatic prostate cancer

	Institution	Study design	Study period	No. of patients	Type of primary treatment	Age at SABR (years)	PSA at SABR (ng/mL)	No. of oligometastases	Site of oligometastases	SABR dose/ fractionation
Habl et al, 2017	Technical University of Munich, Germany	Single institution, retrospective	2012-2016	15	RP: 15 (100%)	Median: 72 (range: 56-78)	Median: 1.99 (Range: 0.44-11.7)	1: 11 (73%) 2: 3 (20%) 3: 1 (7%)	Bone: 15 (100%)	25-40Gy/ 5#
Kneebone et al, 2018	Royal Northshore Hospital, Australia	Single institution, prospective	2014-2016	57	RP: 20 (35%) EBRT: 7 (12%) RP+EBRT: 30 (53%)	n/a	Mean: 2.12# (Range: 0.15-8.9)	1: 44 (77%) 2: 10 (18%) 3: 3 (5%)	Nodes: 37 (65%) Bone: 18 (31%) Nodes & bone: 2 (4%)	20Gy/1#, or 24Gy/2# (bone); 50Gy/5#, or 30Gy/3# (node)
Fanetti et al, 2018	European Institute of Oncology, Italy	Single institution, retrospective	2012-2016	55	RP+/-EBRT: 39 (71%) EBRT: 16 (29%)	Median: 72 (range: 45-85)	Median: 3.35 (Range: 0.43-33)	1: 37 (67%) 2:14 (25%) 3: 4 (7%)	Bone: 55 (100%)	15Gy/1# 18-30Gy/3# 10Gy/4# 20-25Gy/5# Other (not specified)
Bowden et al, 2019	Epworth Healthcare, Australia	Single institution, prospective	2014-2016	199	RP: 185 (93%) EBRT 9 (4.5%) BT: 3 (2%) Not stated: 2 (1%)	Mean: 67.4 (SD: 6.5)	Median: 1.8 (Range: 0.8-4.6)	1: 81 (41%) 2: 50 (25%) 3: 34 (17%) 4: 24 (12%) 5: 10 (5%)	Nodes: 126 (63%) Bone: 45 (23%) Nodes & bone: 12 (12%) Other (4 (2%)	50Gy/10# (all)
Current study	Austin Health,	Single institution,	2016-2017	20	RP: 12 (60%) EBRT: 2	Median: 67 (range: 51-	Median: 1.3	1: 15 (75%) 2: 4 (20%)	Nodes: 15 (75%) Bone: 3 (15%)	30Gy/3# (bone)

	Australia	retrospective			(10%) RP+EBRT: 6 (30%)	74)	(Range: 0.2-30)	3: 1 (5%)	Nodes & bone: 2 (10%)	35-40Gy/5# (nodes)

Abbreviation: PSMA = Prostate-specific membrane antigen; PET = Positron Emission Tomography; RP = Radical prostatectomy; EBRT = External beam radiotherapy; BT = Brachytherapy; Gy = Gray; # = fraction

#mean

Table – 4 | Outcomes definitions following PSMA PET/CT-guided SABR for oligometastatic prostate cancer in the published literature

	PSA response	LPFS	bPFS	DPFS	ADT-FS	TE-FS	Toxicities
Habl et al, 2017	N/A	Tumour progression within the irradiated PTV	(i)Rising PSA level out of post-SABR nadir to >0.2ng/mL; or (ii) drop in PSA, but above 0.2ng/mL and rise again; or (iii) continuously rise PSA post SABR, or (iv) clinical progression	Absence of new metastatic lesion	N/A	N/A	N/A
Kneebone et al, 2018	Initial PSA decline after SABR; Complete biochemical response = PSA<0.03ng/mL	Radiological progression of treated lesion within the radiation field assessed using CT imaging	PSA increase >0.2ng/mL above the nadir response	N/A	N/A	N/A	CTCAEv4 acute: ≤3 months; late: > 3 months
Fanetti et al, 2018	N/A	Diagnosis of in-field relapse (morphologic or metabolic increase in PTV)	Time to PSA increase after SABR	Radiologically detected local progression or distant progression	Time from SABR to initiation of palliative ADT	NR	CTCAE v3
Bowden et al, 2019	Change in PSA post-SABR	N/A	N/A	N/A	N/A	Commencement of ADT in ADT-naïve patients; Commencement of 2nd line ADT/ chemotherapy in patients already on ADT	CTCAE v4

Current study	Any drop in PSA following SABR, regardless of whether there was subsequent PSA progression	PSMA-avid disease progression within 20% isodose line of SABR treatment field	N/A	PSMA-avid disease outside of the SABR treatment field	Time from SABR to initiation of palliative ADT	N/A	N/A

Abbreviation: LPFS = Local progression free survival; bPFS = biochemical progression free survival; DPFS = Distant progression free survival; ADT-FS = Androgen deprivation therapy free survival; TE-FS = Treatment-escalation free survival; NR = not reported; PTV = Planning target volume; CTCAE = Common Terminology Criteria for Adverse Event

Table- 5 | Outcomes following PSMA PET/CT-guided SABR for oligometastatic prostate cancer in the published literature

	Follow-up period, (months)	PSA response	LPFS	bPFS	DPFS	ADT-FS	TE-FS	Acute Toxicity	Late toxicity
Habl et al, 2017	Median: 22.5 (Range: 7.0-53.7)	NR	2yr: 100%	Median: 6.9 month (range: 1.1-28.4)	Median: 7.4 month (range: 1.8-54.4)	Median: 9.3 month* (range: 2.6-36.1)	Median: 12.3 month (range: 2.6-36.1)	NR	NR
Kneebone et al, 2018	Median: 16 (Range: 5-31)	70% (14% complete PSA response)	100%	Median: 11 month 1yr: 46% 2yr: 16%	NR	NR	NR	G1: 7% G2: 2% G3: 0%	G1: 4% G2: 0% G3: 0%
Fanetti et al, 2018	Median: 24.6 (Range: 3-67.2)	NR	1yr: 83% 2yr: 76%	1yr: 51% 2yr: 13%	1yr: 55% 2yr: 27%	NR	NR	G1: 1.8% G3: 0%	n/a
Bowden et al, 2019	Median: 35.1 (Range: 6.5-51.3)	75%	n/a	n/a	n/a	2yr: 58%*	Median: 27.1 month 2yr: 52%	G3: 0%	G3: 0%
Current study	Median: 15.9 (Range: 6.7-35.5)	60%	1yr: 93% ~~2yr: 93%~~	n/a	1yr: 62% ~~2yr: 52%~~	1yr: 70% ~~2yr: 62%~~	NR	NR	NR

Abbreviation: LPFS = Local progression free survival; bPFS = biochemical progression free survival; DPFS = Distant progression free survival; ADTFS = Androgen deprivation therapy free survival; TE-FS = Treatment-escalation free survival; NR = not reported

*subset of patients who did not have prior ADT

Figure-1 | PSA waterfall plot of PSA response at 3 months (A), and maximal changes in PSA compared to baseline (B)

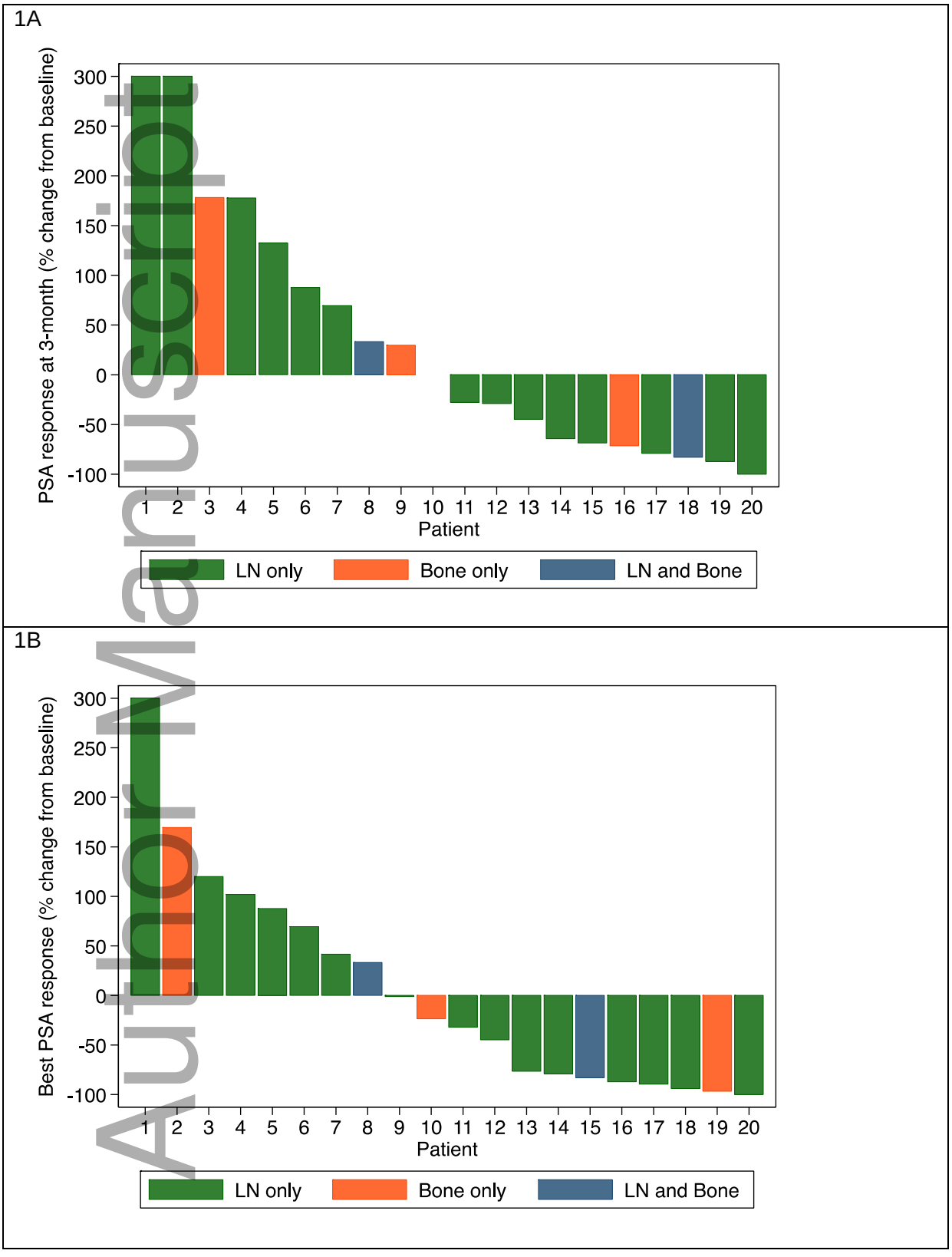


Figure-2 | Kaplan Meier plot for local progression free survival (LPFS)

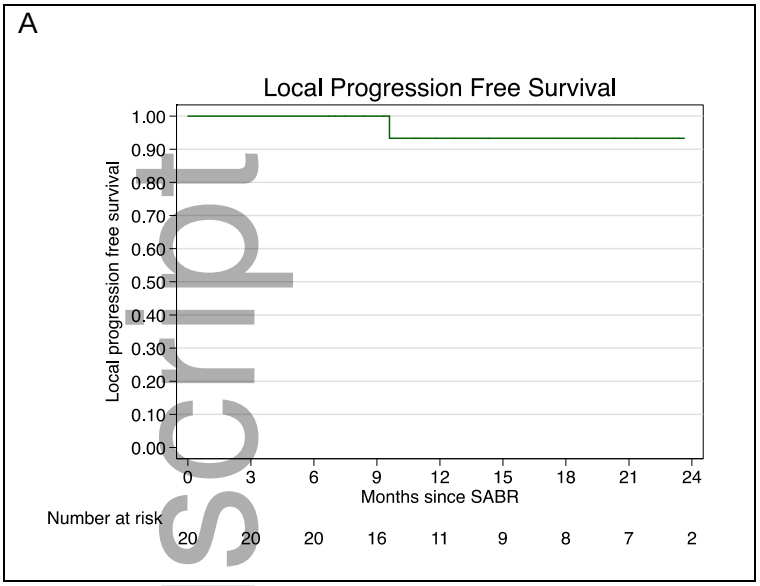


Figure-3 | Kaplan Meier plot for distant progression free survival (DPFS) (A); DPFS stratified by duration between curative local treatment to SABR (B)

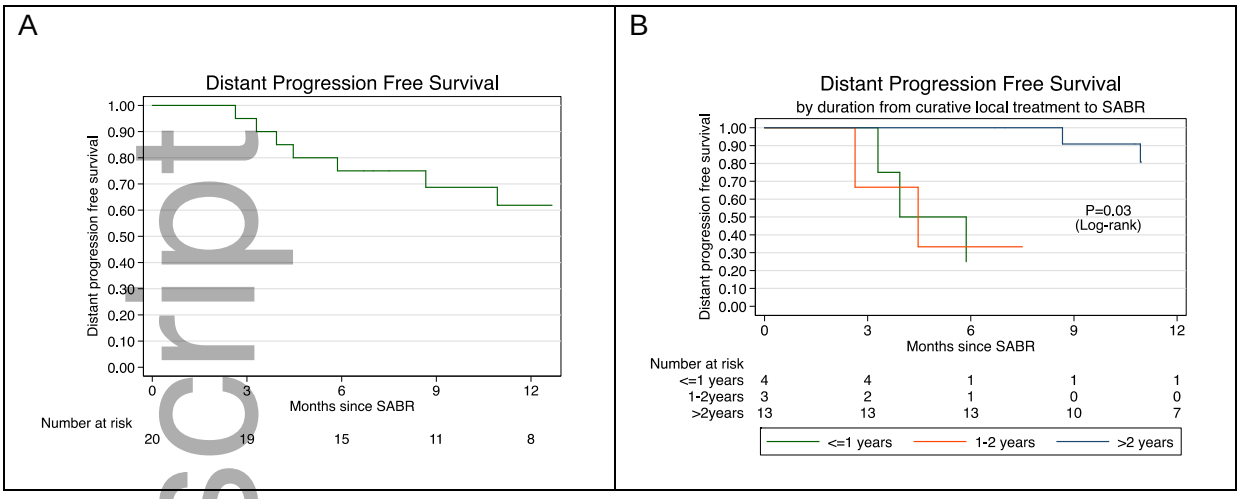


Figure-4 | Kaplan Meier plot for ADT free survival (ADT-FS) (A); ADT-FS stratified by duration between curative local treatment to SABR (B)

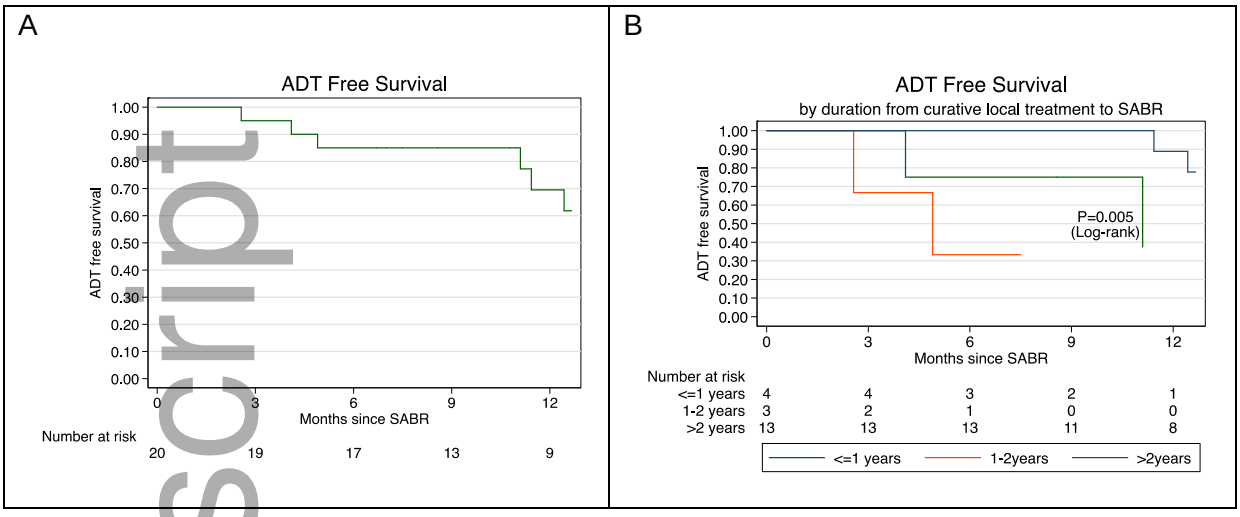
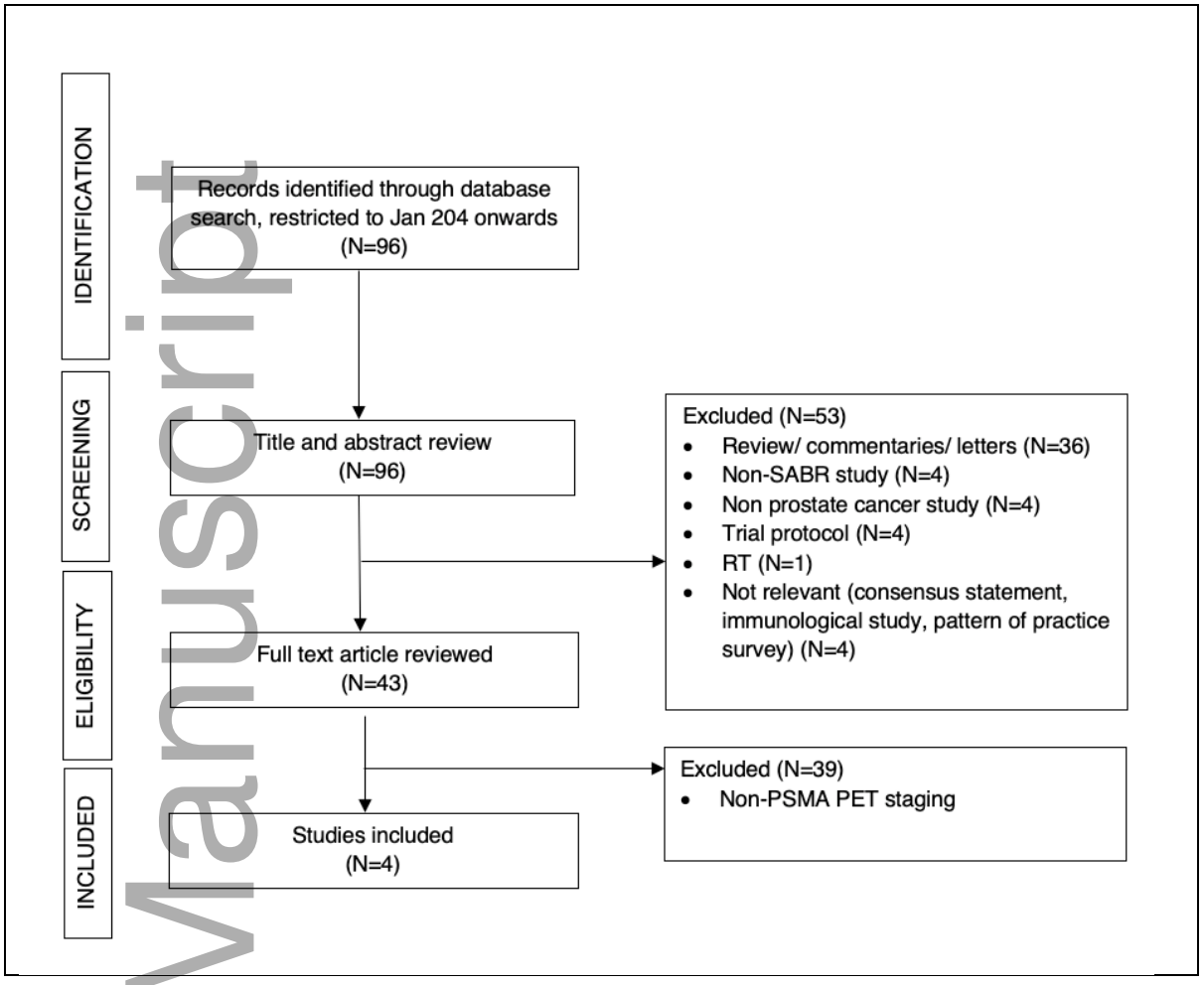


Figure-5 | Flow diagram of search strategies adapted from PRISMA



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Title:
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