Stereotactic ablative body radiotherapy in patients with prostate cancer

Andrew Loblaw[1,2,3], Stanley Liu[1,2], Patrick Cheung[1,2]

[1]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [2]Department of Radiation Oncology, [3]Institute for Health Care Policy, Measurement and Evaluation, University of Toronto, Toronto, ON, Canada

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study material or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Andrew Loblaw. Institute for Health Care Policy, Measurement and Evaluation, University of Toronto, Sunnybrook Health Sciences Centre, Rm T2-161, 2075 Bayview Ave, Toronto, ON, M4N 3M5, Canada. Email: Andrew.loblaw@sunnybrook.ca.

Abstract: Prostate is the most common non-cutaneous cancer diagnosed among men in North America. Fortunately most prostate cancers are screen detected and non-metastatic on diagnosis. Treatment options for men with localized prostate cancer include surgery ± postoperative radiation or radiation ± androgen deprivation therapy (ADT). Brachytherapy ± external beam radiation treatment (EBRT) appears to have superior long-term disease control over EBRT alone likely because of higher biologic effective dose delivered. Stereotactic ablative body radiation (SABR) is a novel, non-invasive, high-precision EBRT technique that allows safe delivery of biologic doses similar to brachytherapy with similar or lower side effects [measured using toxicity or quality of life (QOL) scales]. Efficacy for SABR appears to be similar to brachytherapy including positive biopsy rates 2–3 years post treatment, biochemical failure (BF) rates out to 10-year and incidence of metastases. SABR dose escalation reduces biopsy positivity and prostate-specific antigen (PSA) nadirs but increases genitourinary (GU) and gastrointestinal (GI) toxicity—no effect on BF has been realized yet. The overall treatment time (OTT) varies in many protocols. Phase 2 randomized data shows that QOL is better in the acute setting with a weekly course of treatment compared to an every other day treatment regimen with no difference in late setting. Follow-up data are immature and likely underpowered to determine efficacy differences. SABR is cheaper and uses less resource than any other radiation technique. Given the healthcare resource challenges (including financial resources), SABR would be a welcomed addition if studies show non-inferiority to other radiation techniques. For patients with de novo or metastatic disease on relapse, there is much enthusiasm regarding the use of SABR in the setting of oligometastatic prostate cancer. SABR appears to be feasible to deliver, well tolerated and may delay the next line of therapy. However, until adequately powered randomized studies confirm a benefit, such an approach cannot be considered standard of care treatment at this time. Enrollment of eligible prostate cancer patients onto SABR clinical trials should be encouraged.

Keywords: Prostatic neoplasms; radiosurgery; stereotactic body radiotherapy (SBRT); randomized controlled trial (RCT); quality of life (QOL); toxicity

Introduction

Prostate cancer is the most commonly diagnosed non-cutaneous in North American men. Approximately 250,000 will be diagnosed in 2017 (1,2); the Canadian Cancer Society estimates that due to increasing life expectancy, the incidence of prostate cancer could double by 2030 (3).

While the incidence of screening has dropped over the last decade (4), over 90% of men are still diagnosed with localized (i.e., non-metastatic) disease. There are moderately strong data supporting the use of radiotherapy (RT) for node positive prostate cancer (5) and the role of radiotherapy for metastatic disease are currently being addressed in randomized controlled trials (RCTs). The hypothesis and preliminary data supporting this latter concept will be discussed later in this document.

Radiobiology

External beam radiation treatment (EBRT) for prostate cancer has traditionally employed conventional fractionation, where a daily dose of 1.8–2 Gy is delivered, 5 days a week for several consecutive weeks. This fractionation was largely predicated upon the assumption that prostate cancer possesses a fractionation sensitivity similar to other carcinomas, which is described by the linear-quadratic equation. Specifically, many rapidly proliferating carcinomas and acutely-responding normal tissue (e.g., skin epithelium and mucosa), have a high α/β ratio and their response to radiation is largely insensitive to fraction size. In contrast, slower proliferating cancers and late-responding normal tissue (e.g., spinal cord) have a low α/β ratio, and are intrinsically sensitive to fraction size.

Modeling studies using data from prostate patients treated with conventionally fractionated RT (CFRT) or low-dose rate brachytherapy led Brenner and Hall to conclude that prostate cancer has a low α/β ratio of 1.5 and they postulated that use of larger dose per fraction (i.e., hypofractionation) treatments over a shorter period of time, should result in equivalent tumor control and comparable late side-effects relative to CFRT (6). Advances in radiotherapy planning, image guidance and dose delivery have facilitated the clinical implementation of hypofractionated radiation treatment for prostate cancer (7). Randomized clinical trials such as the CHHiP and PROFIT studies, have demonstrated non-inferiority of hypofractionated treatment (60 Gy in 20 fractions; 3 Gy fraction size) compared to CFRT (74 Gy in 37 fractions or 78 Gy in 39 fractions; 2 Gy fraction size) both in terms of biochemical control and late toxicity (8,9). This has resulted in the adoption of hypofractionated treatment as a standard regime for localized prostate in many cancer centres.

In agreement with prior studies, the estimation of α/β ratios from these randomized trials are similarly low (α/β ratio of 1.9 in CHHiP, α/β ratio of 1.3 in PROFIT) (10).

Clinical investigators have now investigated the use of even larger fractions of radiotherapy in prostate cancer (e.g., 36.25 Gy in 5 fractions; 7.25 Gy fraction size or 35 Gy in 5 fractions; 7 Gy fraction size) which has been referred to as stereotactic body radiotherapy (SBRT) or stereotactic ablative body radiation (SABR) (11-14). The clinical outcomes reported to date have been very promising, with excellent biochemical control and no considerable increase in acute or late toxicities, discussed in detail later in this manuscript.

The linear-quadratic equation may inaccurately predict cancer cell kill at the higher doses of radiation used in SABR (15) although this remains a contested point (16). This has led to the hypothesis that biological mechanisms other than the classic five determinants of radiation response (DNA repair, redistribution through the cell cycle, reoxygenation, repopulation and intrinsic cellular radiosensitivity) may enhance the therapeutic effect of SABR. Indeed, there has been considerable research interest over the past decade and a half elucidating the contribution of the tumor microenvironment on radiation response, specifically within the context of high doses of radiation. The tumor vasculature has been postulated to be a major determinant of radiation response, whereby the endothelial acid sphingomyelinase (ASMase) pathway generates the pro-apoptotic second messenger ceramide, which in turns induces apoptosis of endothelial cells, microvascular dysfunction and secondary tumor cell death (17). Kolesnick and colleagues reported that activation of this ASMase pathway is dose-dependent, being triggered with single doses of more than 8–10 Gy (18). In contrast, lower doses of radiation such as those used in CFRT, are not believed to induce significant endothelial apoptosis.

Preliminary clinical support for induction of apoptotic mediators by high dose radiotherapy was observed in a pilot study of 11 patients with large bulky tumors treated initially with a single 15 Gy dose of irradiation (19). They observed a statistically significant increase in serum ceramide in patients who experienced a complete or partial response. More recently, Dubois *et al.* reported the results of an ancillary study investigating ceramide as a potential predictive biomarker for colorectal patients with lung or liver metastases treated with SABR and irinotecan (20). A statistically significant increase in total ceramide in serum at 3 and 10 days following SABR correlated with tumor response to SABR. It remains to be determined if circulating bioactive lipid products such as ceramide will be clinically useful predictive biomarkers for SABR response.

Accumulating evidence indicates that SABR may also play an important role in activating the host immune system. SABR ablation of tumor cells can induce the release of tumor antigens, and when this occurs in conjunction with immune checkpoint inhibitors, this has been hypothesized to serve as an 'in situ' anti-tumor vaccine to prime the immune system (21). There have been several clinical reports of abscopal responses, where SABR treatment of one metastatic lesion in combination with checkpoint agents, results in resolution of distant metastatic deposits in a systemic manner (21,22). It should be noted that almost all the data on abscopal effects has been reported on tumors other than prostate cancer. There are currently many phase 1 and 2 clinical trials investigating SABR with different immune checkpoint inhibitors, which will address the potential importance of SABR as an adjuvant player in the era of immunotherapy.

Androgen deprivation therapy (ADT) has been routinely administered with radiotherapy in high-risk prostate cancer for decades, and this combined treatment approach has been well established to improve overall survival when combined with EBRT. Mechanistically, ADT is now known to promote radiosensitization through impairment of DNA double-stranded break (DSB) repair in prostate cancer (23-25). However, recent studies are beginning to provide provocative evidence that with extreme dose-escalation to the prostate through high dose rate (HDR) or low dose rate (LDR) brachytherapy, the added benefit of ADT on disease-control may be limited compared to EBRT. Thus, it will be of interest to determine the relative benefit provided by ADT within the context of SABR for prostate cancer.

SABR requires delivery of high precision IGRT to achieve safe and effective treatment. Dedicated non-coplanar (Cyberknife) SABR systems were the first to be used but similar outcomes can be used with gantry-based planar IGRT systems found in virtually all modern RT centres. This review article will briefly cover the following topics for SABR prostate: oncologic outcomes, quality of life (QOL)/toxicity, dose escalation, overall treatment time (OTT), cost effectiveness/system impact, and treatment of oligometastatic disease.

Oncologic outcomes

The group with the largest cohort and longest median follow-up is the Flushing New York Centre. Katz et al., published the outcomes of 515 localized prostate cancer patients treated with SABR using a non-coplanar system.

Sixty-three percent, 30% and 7% had low-, intermediate- or high risk disease (26). All patients had a 5 mm planning target volume (PTV) margin around the prostate (3 mm posteriorly) and MRI fusion (no MRI nodule dose painting). The prescribed dose was 35–36.25 Gy delivered in 5 daily fractions to >95% of PTV; 14% had ADT. Amifostine, daily laxatives and fleet enema were also used. With a median follow-up of 84 months, the 8-year biochemical disease-free survival (bDFS) was 94.6%, 94.3% and 65.0% for patients with low-, intermediate- and high-risk prostate cancer. Longer follow-up was published in 2017 for the 232 low-risk patients in this cohort; 10-year bDFS was 93.6% (27).

Our group has exclusively studied SABR outcomes using gantry-based systems. Our two earliest prospective SABR studies (pHART3, pHART6) examined 114 patients with low- or intermediate-risk prostate cancer delivering 35 or 40 Gy in 5 weekly fractions. PTV margin was 4–5 mm isometrically and daily electronic portal imaging (EPID) with gold seed fiducials were used for image-guidance. No bowel preparation or amifostine was used.

Early outcomes of SABR look very promising. In the pHART3 study, routine biopsies were done 3 years post-treatment. Seventy-one of 74 (96%) of eligible patients agreed to biopsy and of those, 3 (4%) had positive biopsies. Zelefsky et al., presented data from Memorial Sloan Kettering's SABR experience showing that biopsy positivity was inversely associated with dose. In a phase 1 prospective dose escalation study (32.5, 35, 37.5, and 40 Gy in 5 fractions), the biopsy positivity rate was 45%, 12%, 17% and 5%, respectively (28).

In a pan-Canadian propensity-based analysis of biochemical and survival outcomes, SABR, LDR brachytherapy and EBRT were compared for low-risk patients. The pre-matched cohort contained 602 patients; the median follow-up was >5.0 years for each cohort. There were no significant differences in biochemical failure (BF) before or after matching for SABR vs. LDR but the prostate-specific antigen (PSA) nadir was lower after LDR (0.47 vs. 0.05 ng/mL, P<0.001). For the SABR versus EBRT, SABR had a trend towards lower BF before matching (P=0.08), which became significant after matching (P<0.001) (29).

Despite higher PSA nadirs, the long-term biochemical outcomes continue to be excellent with SABR. With a median follow-up of 102 months, the 8-year BF rate for the pHART3 and pHART6 cohorts was 5.0% (30). It was notable that of the 9 BF patients, 3 are still being observed without treatment, 4 had local salvage therapy and 2 were

Table 1 Medium term outcomes of SABR prostate

Study [year]	Dose (Gy)/F/ week	EQD2 (Gy)	n	G6 (%)	Med FU (mo)	5 y bDFS (%)	Acute G3 + (%)		Late G3 + (%)		
							GU	GI	GU	GI	ED
Pham *et al.* [2010] (32)	34/5/1	82	40	100	60	93	2	0	3	0	50
Katz *et al.* [2013] (33)	35–36.3/5/1	86.5–92.2	303	73	60	95	0	0	2	0	25
Kupelian *et al.* [2013] (34)	35–40/ 4–5/1–2	86.5–110.6	135	80	60	97	NR	NR	NR	NR	NR
Mantz [2014] (35)	40/5/2	110.6	102	69	>60	100	2	0	NR	0	NR
Hannan *et al.* [2016] (36)	45-50/5/2	138–168	91	47	54	99	0	2	5.4	6.8	26
Musunuru *et al.* [2016] (37)	35/5/4	86.5	84	100	74	97	1	0	0	1	43
Zimmerman *et al.* [2016] (38)	45/9/9	84.7	80	100	83	96	NR	NR	4	13%	NR
Total*	–	–	835	77	63	97	0.6	0.3	2.6	1.0	30

*, weighted average. SABR, stereotactic ablative body radiation; EQD2, equivalent dose in 2 Gy; GU, genitourinary; GI, gastrointestinal; ED, erectile dysfunction; NR, not reported; Med FU, median follow-up; mo, months; bDFS, biochemical disease-free survival.

treated with ADT alone. No patient has progressed to metastatic disease or developed castrate-resistance. These results are similar to the observations from other SABR studies with medium-term follow-up (31).

QOL/toxicity

Overall SABR appears to be tolerated very well. *Table 1* shows the studies with more than 48 months median follow-up reported in the literature. Of the 835 patients and a median follow-up of 63 months, the proportion of patients with grade 3 or higher toxicities in the GU or GI domains was 0.6% and 0.3% acutely and 2.6% and 1.0% in the late term, respectively.

Health-related QOL is felt to be more sensitive to meaningful changes to patients after treatment and may be more important since it reflects the patient's true experience (39). There are various ways to describe QOL changes over time. In terms of longitudinal change, *Figure 1* shows the bowel, bladder and sexual domain scores (transformed from 0–100 point scale with 100 representing the best QOL) from the pHART3 protocol (40). These were measured with the expanded prostate index composite (EPIC-50) at baseline and every 6 months until 5 years. Bowel and bladder scores remain stable while sexual QOL falls over

time. The proportion of patients experiencing a minimally clinically important change (MCIC) on average over the 5 years of follow-up was 17.9%, 26.2% and 38.5%, respectively. On multivariate analyses, bladder volume >260 cc, rectal D1cc >35 Gy and penile bulb V35 Gy >4% independently predicted for having an MCIC in urinary, bowel and sexual domains.

Dose escalation

A number of RCTs have shown that a higher dose of conventionally fractionated radiotherapy has a lower incidence of BF (41). In the largest study, RTOG 0126, an extra 9 Gy of radiation (70.2 *vs.* 79.2 Gy to PTV) decreased BF from 43% to 26% at 10 years (42). It is notable that this was a trial of low and low-tier intermediate risk patients. However, this BF improvement came at the cost of higher late grade 2+ gastrointestinal (GI) toxicity (16% *vs.* 22%, P=0.0063) and genitourinary (GU) toxicity (10% *vs.* 15%, P=0.001) in the dose escalated arm. Brachytherapy boost, considered by many to the ultimate in dose escalation, also decreased BF at the cost of higher late GU toxicity. In the ASCENDE-RT study where high-tier intermediate and high-risk patients were randomized between ADT, EBRT ± LDR brachytherapy boost, 9-year BF was 37.6% for EBRT
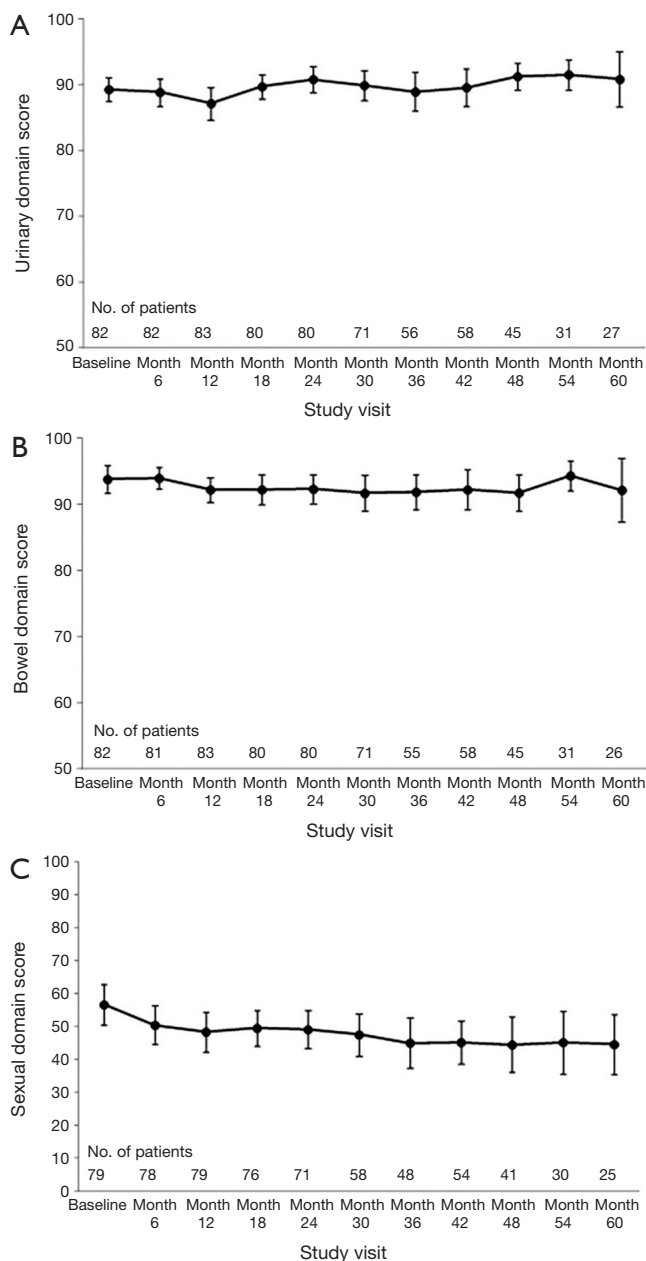
Figure 1 Health-related QOL measured by the EPIC-50. (A) urinary domain; (B) bowel domain; (C) sexual domain (40). Permission obtained from Elsevier to reproduce Figures. QOL, quality of life; EPIC-50, expanded prostate index composite.

and 16.7% for the brachytherapy boost arm (43). While there was no difference in grade 3–4 late GI toxicity, there were more grade 3–4 late GU toxicities in the experimental arm (21% *vs.* 6%, P<0.001).

In the Flushing NY series, Katz looked at 35 Gy in

5 fractions (n=147) versus 36.25 Gy in 5 fractions (n=283) and found no difference in bDFS with a median follow-up of 84 months (4.7% *vs.* 6.5%, P=0.67) (26). With an equivalent dose in 2 Gy (EQD2) of 86.5 $Gy_{1.4}$ versus 92.2 $Gy_{1.4}$ perhaps this lack of difference isn't surprising.

When our group looked at 35 Gy in 5 fractions *vs.* 40 Gy in 5 fractions (EQD2 110.6 $Gy_{1.4}$), there were still no differences in BF (P=0.97) but we noted that PSA nadir was lower with the higher dose (0.39 *vs.* 0.11 ng/mL) (30). Perhaps not surprisingly, we did observe that 48-month cumulative incidence of grade 2+ late GI toxicity (26.2% *vs.* 7.6%, P=0.017) and grade 2+ GU toxicities (24.2% *vs.* 5.0%, P=0.049) were higher with the higher dose level (44).

Timmerman's group also observed similar dose-toxicity relationships. In their multicenter, phase 2 dose escalation trial of 45, 47.5 and 50 Gy in 5 fractions, the cumulative incidence of late grade 2+ GI toxicity was 6.7%, 33.3% and 32.8% while risk of grade 3–4 GI toxicity was 0%, 1.6% and 8.2%. Grade 3+ late GI toxicity was strongly correlated with volume of rectal wall receiving 50 Gy > 3 cm^3 (P<0.0001), and treatment of >35% circumference of rectal wall to 39 Gy (P=0.003) (45).

Assuming there is a benefit to dose escalated SABR, how can that be achieved without significantly increasing the side effects of treatment? There appears to be strong relationship between the volume of normal tissues (especially the anterior rectum) in the high dose region and toxicity/QOL deterioration. Four possibilities to improve the dosimetry include using one or more of: stricter planning objectives, hydrogel spacer (46), intrarectal immobilization (47), and/or focal boosting to the dominant intraprostatic nodule (DIL) (48).

OTT

The impact of OTT has been shown to be important in prostate cancer radiotherapy from both a disease control perspective as well as toxicity. In a multi-institutional study involving 4,839 patients treated with conventionally fractionated radiotherapy, Thames *et al.* found a statistically significant improvement in bDFS when patients receiving 70–72 Gy completed treatment in less than 52 days (49). They estimated a 0.9% increase in BF for each day the OTT was >52 days.

For SABR, OTT has been variable with fractions delivered in consecutive days, every other day (QOD), twice per week, and once per week (QW) (13,50-53). These

single arm studies have shown good bDFS rates as discussed above. With respect to toxicity, however, small differences in treatment times can have a significant impact. King *et al.* delivered 36.25 Gy in 5 fractions, initially treated in 5 consecutive days (54). However, they observed a higher than expected rate of late GI toxicity which improved when SABR was delivered QOD (38% *vs.* 0% reported moderate-severe rectal symptoms on EPIC for QD *vs.* QOD, P=0.0035) (54).

To our knowledge there are 2 RCTs formally testing OTT for patients receiving prostate SABR. Mirabell and colleagues have conducted a multicenter study in Europe (NCT01764646) on prostate cancer patients receiving 36.25 Gy in 5 fractions, randomizing 170 patients between a 9- and 28-day treatment regimen. Miralbell's study has reached its accrual goal and the results are maturing. PATRIOT (NCT01423474) was a multicentre, Canadian study which randomized 152 low- or intermediate-risk patients receiving SABR 40 Gy in 5 fractions to QOD *vs.* QW treatment frequency (OTT 11 *vs.* 29 days). QOL and toxicity results have been presented for PATRIOT at GU Cancers Symposium 2015 (55) (*Figure 2*).

With a median follow-up 13.1 months, mean bowel and urinary QOL declined after treatment but recovered by 3 months. The proportion of patients with acute MCIC in bowel (90.0% *vs.* 69.6%, P<0.01) and urinary (95.7% *vs.* 74.6%, P<0.01) summary scores for the QOD and QW arms, respectively. No differences were found in acute sexual (P=0.38) or hormonal (P=0.48) QOL. An updated analysis has been submitted for publication (median follow-up 47 months). Between 6–48 months there were no differences in late bowel or bladder QOL between the two arms.

From a toxicity perspective, worst acute GI grade 1, 2, 3 toxicities were 64%, 18%, 0% *vs.* 41%, 11%, 0% (P<0.01) for QOD *vs.* QW arms. Worst acute GU toxicities were 38%, 32%, 1% *vs.* 30%, 34%, 3% (P=0.69), respectively. In the late setting, there were no late grade 3+ GI toxicities. Late grade 3 GU toxicity occurred in 1 (1.3%) *vs.* 0 patients in the QOD and QW day arms (P=0.32). Time trend analysis of PSA revealed no significant differences between the two groups (P=0.44).

Oligometastatic disease

The standard treatment for stage IV prostate cancer is ADT as the first line option for hormone sensitive disease. ADT can be delivered continuously or intermittently, with no definitive evidence that one approach being better than the other (56,57), but many believe that a continuous approach yields the most benefit. Recently, upfront chemotherapy with ADT has been shown to improve survival compared to ADT alone, especially in patients with high volume metastatic disease (58). In subgroup analysis, adding chemotherapy to ADT for patients with low volume oligometastatic disease (fewer than 4 bone metastases) was not associated with a survival advantage, so the practice of adding chemotherapy to ADT has been variable in this setting. More recently, combining ADT with abiraterone has also been shown to improve overall and failure free survival compared to ADT alone in patients with hormone sensitive metastatic prostate cancer (59,60). These data are expected to change the standard of practice as it is anticipated that patients will be offered combination ADT and 2nd generation hormone therapy (such as abiraterone), even in the low volume oligometastatic setting. Nonetheless, castration resistant prostate cancer (CRPC) eventually develops, at which point the median survival is 2–3 years.

The use of radiotherapy (RT) in patients with metastatic cancer has historically been limited to low dose treatment with "palliative intent". Eradication or long term control of the primary tumour and visible metastases was never a goal since these patients likely harboured more widespread microscopic disease that will become apparent with time. However, this dogma is being challenged, as the use of SABR for metastatic cancer is increasingly being considered, especially in the setting of oligometastatic disease (61,62). Since metastatic tumours may themselves seed further metastases, eradication of oligometastatic tumours with SABR may increase progression-free and overall survival in some patients. Even if cure is not achieved, long term control of gross tumour disease may increase time to radiographic/symptomatic progression and need for subsequent lines of systemic therapy. Randomized phase 2 trials have shown that such a strategy improves progression free survival significantly in patients with oligometastatic non-small cell lung cancer (63,64).

There is increasing interest world-wide in exploring the use of SABR for treatment of oligometastatic prostate cancer, especially in the hormone sensitive setting (65-68). One approach is to deliberately withhold ADT by delivering SABR to all tumour sites. Such a strategy may significantly delay the need to start ADT. Decaestecker *et al.*, reported on 50 recurrent hormone sensitive metastatic prostate cancer patients with ≤3 metastases which were treated with SABR alone without any systemic therapy (69). Repeat courses of SABR were allowed if further new metastases
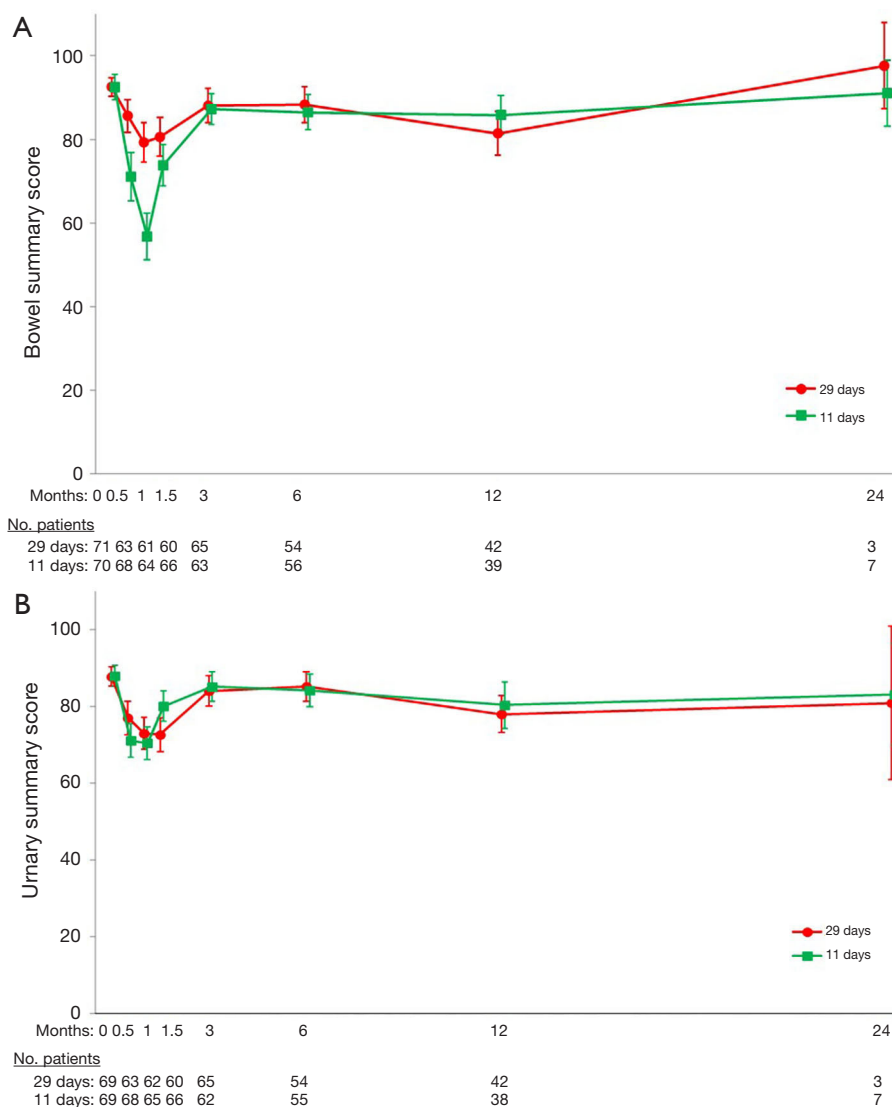
Figure 2 Mean (95% confidence interval) (A) bowel and (B) urinary QOL scores over time. From Quon GU Cancer Symposium 2015 (55). QOL, quality of life.

developed in a limited fashion during follow-up. ADT was not started until polymetastatic disease developed (defined as >3 new metastases). With a median follow-up of 2 years, local control of the irradiated tumours was 100%, while the median ADT free survival was 25 months in this prospective study. Another approach is to combine SABR to all metastases with upfront ADT, which may result in prolonged progression free survival and delay the onset of CRPC. Schick *et al.*, (70) reported on 50 patients with hormone sensitive oligometastatic prostate cancer (≤5 metastases) which were treated with high dose RT to all tumour sites along with upfront concurrent ADT (most patients

receiving ≤12 months of ADT). After a median follow-up of 31 months, 3-year biochemical relapse free survival was 54.5% (BF defined as PSA >1 ng/mL or Phoenix definition for those who had synchronous oligometastatic disease). At the University of Toronto, a phase 1 trial (ClinicalTrials.gov Identifier: NCT02563691) has completed accrual where SABR was delivered to all sites of disease in the setting of hormone sensitive oligometastatic prostate cancer. Patients also received ADT for 1 year before moving to a planned intermittent approach. This trial has now been expanded to a single arm phase 2 study where the sample size has been increased to better evaluate efficacy.

However, there are no published randomized data to support the routine use of SABR in the setting of oligometastatic prostate cancer, although data are forthcoming. In Belgium, the STOMP randomized phase 2 trial (Clinicaltrials.gov identifier: NCT01558427) (71) has completed its accrual of 62 patients. This study compared surveillance versus surgery/SABR to all sites of disease in patients with metachronous hormone sensitive oligometastatic prostate cancer. In both arms of the study, ADT was deliberately withheld until the development of polymetastatic disease. The primary endpoint was ADT-free survival. The hope is that surgery/SABR can delay the onset of more widespread metastatic cancer and symptoms associated with ADT. However, such an approach denies these patients upfront systemic therapy, which would be considered standard of care treatment. The SABR-COMET randomized phase 2 trial (ClinicalTrials.gov Identifier: NCT01446744) (72) is a study comparing standard of care treatment versus standard of care treatment plus SABR to all metastases in patients with recurrent metachronous oligometastatic cancer. This study has completed its planned accrual of 99 patients. All solid cancer histologies were eligible. The primary endpoint was overall survival and preliminary results may be available in 2018. In the United Kingdom, the CORE randomized phase 2 trial (ClinicalTrials.gov Identifier: NCT02759783) is a very similar study comparing standard of care therapy versus standard of care therapy plus SABR to all sites of disease in patients with recurrent metachronous oligometastatic breast cancer, NSCLC, and prostate cancer with progression free survival as the primary endpoint. This study is still accruing with a target sample size of 206 patients. Both the SABR-COMET and CORE studies allow multiple cancer histologies with different natural histories and systemic therapies. As such, it is unlikely these studies will provide a definitive conclusion about any specific malignancy such as prostate cancer.

In Canada, a national multi-centre randomized phase 3 trial has been proposed to compare best systemic therapy (continuous ADT ± 2nd generation hormone therapy or chemotherapy) versus best systemic therapy plus local ablative therapy (choice of surgery/SABR/RT) to all sites of disease in patients with synchronous and metachronous hormone sensitive oligometastatic prostate cancer with the primary endpoint being failure-free survival. It is anticipated that the study will open in 2018. A similar study concept is also being considered in France (73).

Most of the published literature and the completed/ongoing prospective trials investigating SABR in oligometastatic prostate cancer have targeted the hormone sensitive phase of the disease. For CRPC, there is even less published retrospective data (74), so it represents yet another clinical scenario to investigate the use of SABR. The use of SABR may potentially offer better palliation of symptomatic bone pain compared to conventional palliative RT. In Canada, a national multi-centre randomized phase 2/3 trial (ClinicalTrials.gov Identifier: NCT02512965) comparing conventional palliative RT versus SABR for symptomatic spine metastases is being conducted through the Canadian Clinical Trials Group. The primary endpoint is the proportion of patients with a complete pain response at 3 months after treatment and it is hypothesized that SABR will be superior.

Another evolving issue is the role of novel imaging in the routine staging and identification of patients with oligometastatic prostate cancer. Positron emission tomography (PET) scanning with prostate cancer membrane antigen (PSMA) based tracers appear to the most promising novel imaging to detect prostate cancer recurrence/metastases given its relatively high sensitivity and specificity compared to standard computed tomography (CT) scans and bone scans. However, large validation studies with tissue endpoints are missing from the literature for this promising imaging modality, and PSMA PET scanning is still not widely available in the world (75).

Despite the enthusiasm regarding the use of SABR in the setting of oligometastatic prostate cancer, such an approach cannot be considered standard of care treatment at this time. Adequately powered randomized studies showing differences in meaningful outcomes will need to be completed and reported before SABR for oligometastatic prostate cancer should be offered outside of clinical trials. As such, enrollment of potential oligometastatic prostate cancer patients onto clinical trials should be encouraged.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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