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Invited Review

The role of surgery in high risk and advanced prostate cancer: A narrative review

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ABSTRACT

Patients with high-risk and advanced prostate cancer require safe and efficacious therapies likely to offer a survival advantage while minimizing the treatment-related toxicities. Improvements in the surgical technology, diagnostic modalities, radiological staging, and risk stratification have made surgery for high-risk and advanced prostate cancer a safe and feasible option. In this review, we outline the role of radical prostatectomy in high-risk localized, locally advanced, and metastatic prostate cancer. We overview available data evaluating the use of surgery in the context of a multi-modal approach and highlight ongoing trials in this area. Furthermore, the role of surgery as a non-systemic modality for metastasis-directed therapy (MDT) is also described. Emerging imaging modalities enabling more accurate staging and longer follow-up of clinical trials for prognostic endpoints are anticipated to help identify patient cohorts and treatment strategies, where the use of surgical treatments is likely to provide oncological benefits and acceptable toxicity.

Keywords: Cytoreductive prostatectomy; metastasis-directed therapy; metastatic disease; multi-modality approach; prostate cancer; radical prostatectomy.

Introduction

The management of advanced prostate cancer (PCa) is rapidly evolving. Risk stratification of the localized disease is based upon the risk of disease recurrence or progression. Therefore, high-risk PCa, by definition, bears an increased risk of biochemical failure, need for secondary therapy, metastatic progression, and death from PCa. Advanced prostate cancer generally refers to the disease state where PCa has established spread to either regional lymph nodes (N1) or distant sites (M1) and is therefore associated with an increased risk of cancer-related mortality. The national prostate cancer audit (NPCA) reports that a total of 40% and 17% of patients have high-risk and metastatic disease at diagnosis, respectively. High-risk N0M0 PCa and N1M0 treated with ADT alone, and *de novo* M1 PCa treated in the docetaxel era are associated with a 2-year overall survival in 97%, 93%, and 72% of patients, respectively.[1,2] This underpins the need to accurately identify and effectively treat patients with high-risk localized PCa, before its progression to a disseminated disease. Radical radiotherapy with adjuvant androgen deprivation therapy (ADT) has generally been regarded as the standard of care in the management of high-risk/locally advanced prostate cancer, supported by a level 1 evidence base. Recent technological advances, supported by the standardization of surgical techniques and improved disease staging using novel imaging modalities, however, has positioned surgical management as a viable option for men with high-risk disease. Additionally, the role of radical prostatectomy in metastatic prostate cancer has gained interest in recent years. Other areas of growing interest include surgical intervention for metastasis-directed therapy (MDT).

In this article, we review the role of surgery in three distinct settings: (i) high-risk localized PCa (N0M0), (ii) metastatic PCa (N1 or M1), and (iii) in the context of MDT. The review aims to appraise the available evidence and discuss controversies surrounding this developing area.

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High-risk prostate cancer

Defining "high-risk" prostate cancer

There are a variety of definitions of high-risk PCa. The National Institute of Clinical Excellence (NICE) guidance defines it as PCa with PSA >20, Gleason score 8, or stage ≥T2c. D'Amico, the American Urological Association (AUA), the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) all give slight variations on this with the key difference being stage of ≥T3 in AUA and NCCN definitions (Table 1).[3-7] Lack of standardization in criteria used to define high-risk PCa is associated with varying estimates of both prevalence and long-term outcomes.[8] For the purposes of this review, the authors have adopted the following criteria to define high-risk prostate cancer; PSA >20, Gleason score ≥8, or stage ≥T3.

Evidence evaluating the role of radical prostatectomy in high-risk prostate cancer

The optimal management option for patients with high-risk PCa remains debatable. Historically, androgen deprivation therapy (ADT) with or without external beam radiotherapy (EBRT) have been favored. The European Association of Urology (EAU) guideline panel issues annual guidelines on all urological conditions.[4] This decade alone has seen some drastic changes in its recommendations on surgery in various settings, when used as part of multi-modal therapy. The level of evidence to support radical prostatectomy (RP) for high-risk PCa went from 3 in 2013[9] to 2a, with a grade A recommendation in 2016.[10] Current guidance includes a "strong" recommendation for use of RP for high-risk localized PCa.[4] Furthermore, among patients with locally advanced PCa, including cT3b-T4 N0 or any cN1, the EAU guidelines have shifted from 'grade C' recommendation in 2016 for RP to "strong" in 2018, which remains as such currently [4]. However, there remains a lack of randomized controlled trial (RCT) evidence comparing RP with other treatment modalities in the management of high-risk or locally advanced PCa. The ongoing SPCG-15 trial, led by the Scandinavian Prostate Cancer Group[11], aims to randomize 1,200 men with locally advanced PCa into either RT + ADT or RP + ePLND, with the primary outcome of cancer-specific survival. The results of this trial are expected in 2027.

Main Points:

- Radical prostatectomy, either as a monotherapy or as part of a multi-modality approach, is an option for patients with high-risk disease; however, level 1 evidence is lacking.
- Cytoreductive radical prostatectomy may be a realistic treatment option in patients with severe local symptoms or low-burden metastatic disease and may improve survival with the eagerly awaited results of the ongoing trials in this area.
- Salvage lymph node dissection is proposed as a form of non-systemic MDT in prostate cancer and may help delay or avoid the need for androgen deprivation therapy.

Currently, the reported outcomes following RP in patients with high-risk PCa are largely retrospective (Table 2). However, a number of studies have shown promise. The endpoints reported include biochemical failure-free survival (BFFS, i.e. post-operative PSA remains below a defined threshold), need for salvage treatment, cancer-specific survival (CSS), and overall survival. Reported outcomes vary depending on the parameters used to define recurrence or treatment failure. Serum PSA is commonly used for post-operative surveillance and reported biochemical progression-free outcomes, therefore, depend on the PSA threshold deemed to indicate biochemical failure, which varies between studies.

Ward et al.[12] studied outcomes for a cohort of 841 patients undergoing RP for clinical T3 PCa. They reported a 15-year CSS and BFFS (defined as PSA ≥0.4 ng/mL) rates of 79% and 38% of patients. In contrast, defining biochemical failure as PSA ≥0.2 ng/mL, Bastian et al.[13] reported a BFFS at 10 years of 28% in their cohort of 349 patients with high-risk PCa who underwent RP. Using a similar definition of biochemical recurrence (PSA ≥0.2 ng/mL), Donohue et al. [14] reported on a cohort of 238 patients with Gleason 8-10 PCa on initial biopsy and reported a BFFS of 39% at 10 years. Similarly, using a PSA threshold of >0.2 ng/mL, Spahn et al.[15] reported CSS and BFFS of 90% and 52% at 10 years, respectively. They also compared outcomes according to pre-operative risk factors and found that a biopsy Gleason score >7 with PSA >20 ng/mL was associated with significantly lower 10-year CSS than PSA >20 ng/mL alone (65% versus 95%, respectively). Zwergel et al.[16] reported a cohort of 275 patients with high-risk PCa (initial PSA >20 ng/mL) treated with RP. OS, CSS, and BFFS at 10 years were 70%, 83%, and 66.5%, respectively, with comparable BFFS rates in patients receiving ADT in either an adjuvant or salvage setting**.** Several retrospective case series have demonstrated CSS rates over 60% at 15 years after RP in the context of a multi-modal approach (adjuvant or salvage ADT and/or RT) for patients with a biopsy ISUP grade group 5.[17]

When considering the efficacy of RP in management of high-risk PCa, we can refer to the available evidence comparing RP with EBRT and ADT. Although this is largely non-randomized, there is no evidence to indicate that EBRT produces better outcomes and there is, in fact, evidence to suggest that outcomes may be better for patients managed with RP as monotherapy or as part of a multi-modality approach. Berg et al.[18] reported an observational study in 2018, using data from the USA National Cancer Data Base (NCDB), comparing outcomes in a cohort of 13,985 men <65 years old with high-risk PCa treated with ERBT and

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Table 1. Definitions of "high-risk" prostate cancer

Factor	NICE[6]	D'Amico[3]	AUA[7]	EAU[4]	NCCN[5]
PSA	>20 ng/mL	>20 ng/mL	>20 ng/mL	>20 ng/mL	>20 ng/mL
	or	**or**	**or**	**or**	**or**
Gleason score	8-10	8-10	8-10	8-10	8-10
	or	**or**	**or**	**or**	**or**
Clinical stage	≥T2c	≥T2c	≥T3	≥ T2c	≥T3

NICE: National Institute for Clinical Excellence; AUA: American Urological Association; EAU: European Association of Urology; NCCN: National Comprehensive Cancer Network.

Table 2. Summary of cohort studies reporting outcomes following radical prostatectomy in patients with high-risk prostate cancer

					BFFS[b] (%)			CSS (%)			OSS (%)		
Study[a] (Year published)	Timeframe	Location	N	Inclusion criteria	5 y	10y	15y	5y	10y	15y	5y	10y	15y
Ward et al. (2005)[12]	1987-1997	USA	841	T3 disease	58	43	38	95	90	79	90	76	53
Bastian et al. (2006)[13]	1982-2004	USA	349	Gleason 8-10	40	28	-	-	-	-	-	-	-
Donohue et al. (2006)[14]	1983-2004	USA	238	Gleason 8-10	51	39	-	-	-	-	-	-	-
Zwergel et al. (2007)[16]	1986-2005	Germany	275	PSA >20 ng/mL	53-76[c]	25-59[c]	25-41[c]	93	83	71	87	70	58
Spahn et al. (2010)[15]	1987-2005	European multi-center	712	PSA >20 ng/mL	65	52	-	-	89	85	-	74	58

[a]The cohort for Donoghue et al.'s study was derived from a prospective database. All other studies were retrospective. [b]Ward et al. defined BF as PSA >40 ng/mL, all others defined BF as PSA >20 ng/mL, [c]data is stated for group receiving hormone therapy immediately post-prostatectomy and group with deferred hormone therapy.
BF: biochemical failure; BFFS: biochemical failure-free survival; CSS: cancer-specific survival; N: number of patients in cohort; PSA: Prostate-Specific Antigen; USA: United States of America.

brachytherapy (BT) versus those treated with RP alone. RP was associated with significantly better overall survival, with median follow-up of 92 months (p<0.008). Another observational study from Sooriakumaran et al.[19] compared outcomes for PCa patients treated with RP versus those treated with EBRT and ADT, using data from a number of national Swedish registers. They reported better outcomes in terms of CSS following RP in patients treated for high-risk PCa. However, substantial benefit was only noted among younger patients (<64 years old) and those with no comorbidities. Both studies are therefore limited by small numbers of older men and those with comorbidities. This leads us to a common criticism in studies comparing surgical outcomes and those of non-surgical treatment modalities for PCa. Are these "better outcomes" related to patient selection rather than treatment modality? A majority of studies reporting surgical outcomes in high-risk PCa have young, fit patient cohorts, likely reflecting the demographic of patients who tend to be offered surgery in the first place. There is, therefore, limited evidence available for outcomes in the older or more comorbid patients treated with RP. Conversely, it can be argued that younger, fitter patients with high-risk PCa are actually more likely to die from PCa, rather than other causes, at the outset. To assist in this dilemma, we can refer to a study by Rajan et al.[20] who found that comorbidity does not affect CSS following primary curative treatment in patients with prostate cancer. They performed a large observational study (n=118,543) analyzing PCa-specific and other-cause mortality in patients with PCa. Using unadjusted data, they found that increased comorbidity was associated with increased PCa- and other-cause mortality. Upon adjusting for patient, tumor and treatment characteristics, the association between increased comorbidity and PCa-specific mortality was lost. These findings suggest that younger, fitter patients are not less likely to die from PCa following RP than more comorbid patients undergoing RP. Thus, the findings of Berg et al.[18] and Sooriakumaran et al.[19], aforementioned, remain valid.

Monotherapy versus multi-modality approach (MMA)

Surgery offers the advantage that, as a monotherapy, the possible adverse effects of ADT or EBRT are avoided. Our understanding of the side effects of ADT is ever evolving, with a growing body

Table 3. Ongoing RCTs evaluating RP in metastatic prostate cancer

Trial	Number of patients	Comparisons	Primary objective	Volume of metastasis
ISRCTN15704862 *(TROMBONE)*	Pilot: 50 *(study closed)*	RP versus RT	Feasibility to randomize	Oligomet
NCT03655886 *(LOMP-II)*	Pilot: 86	RP versus RT	Feasibility to randomize	Any
NCT01751438	Phase II: 180 *(study closed)*	SoC versus SoC + RP/RT	PFS	Oligomet
NCT02454543 *(G-RAMPP)*	Phase II: 452 *(closed early)*	SoC versus SoC + RP	CSS	Oligomet
NCT02742675 *(FUSCC-OMPCA)*	Phase II: 200 *(study closed)*	ADT versus ADT + RP/RT	PFS	Oligomet
NCT03988686	Phase II: 120	SoC versus SoC+ CRP	Time to castrate-resistance	Oligomet
NCT03456843 *(SIMCAP)*	Phase II: 180 Phase III: 860	SoC versus SoC + RP + ePLND	Phase II: 2y FFS Phase III: OS	Any, but no visceral metastasis
ISRCTN58401737 *(ATLANTA-IP2)*	Pilot: 80 Phase II: 918	SoC versus SoC + MIAT versus SoC + local RT/RP	Pilot: (1) Feasibility to randomize; (2) Safety; (3) Complete pathological response Phase II: PFS	Any
NCT03678025 *(SWOG 1802)*	Phase III: 1273	SoC versus SoC + RP/RT	OS	Any

SoC: Standard of care; RP: Radical prostatectomy; RT: Radiotherapy; ADT: Androgen deprivation therapy: PLND: Pelvic lymph node dissection; MIAT: Minimally invasive ablative therapy; Oligomet: Oligometastatic disease

of literature highlighting concerns regarding cardiovascular adverse effects[21] and dementia.[22] A recent systematic review by Moris et al.[23] compared outcomes for various treatment modalities in patients with high-risk PCa. They reported that although no primary treatment modality has, as yet, shown superiority over others in terms of survival, evidence for RP is encouraging given the possible advantage of avoiding ADT in some patients. They did, however, suggest that at present RP should be employed as part of a multi-modality approach (MMA) in patients with high-risk PCa, as monotherapy is curative in only a minority of patients.

Level 1 evidence has demonstrated better outcomes for patients treated with ADT in combination with ERBT versus either therapy alone.[24,25] There is limited evidence to suggest the best options for MMA, including RP in patients with high-risk PCa. Post-operative adjuvant EBRT is associated with better biochemical control, though RCT evidence suggested inconsistent survival outcomes, resulting in variable uptake of adjuvant EBRT. Recent meta-analysis of the three RCTs evaluating adjuvant versus early salvage EBRT found both modalities to result in comparable event-free survival.[26] Therefore, EBRT can be safely delayed in the vast majority of men treated with RP for high-risk PCa. Nevertheless, due to the relatively low proportion of men included in these trials with very high-risk features (Gleason score 8-10, pT3b or higher) resulting in a greater risk of disease progression, selected patients may be considered for adjuvant radiotherapy, while longer term follow-up data for this patient sub-group are awaited.

Similarly, the use of systemic chemotherapy has also been proposed as part of an MMA, among men undergoing RP for high-risk PCa.[23] However, recent RCT data in both the neo-adjuvant[27] and adjuvant settings[28], have both failed to show a clinically significant improvement in biochemical recurrence, and longer term follow-up data regarding MFS, CSS, and OS endpoints are awaited. In view of severe toxicity associated with systemic chemotherapy, ongoing efforts such as the PROTEUS trial[29] have started to shift current focus to investigating the use of neo-adjuvant hormonal therapies.

Treatment-related toxicity

Another aspect of PCa treatment modalities to consider is treatment-associated morbidity. It is generally reported that patients treated with RP experience less gastrointestinal toxicity than EBRT, though they can have more problems with urinary incontinence and erectile dysfunction.[23] EBRT risks both short and long-term genito-urinary (GU) and gastrointestinal (GI) toxicities. ADT carries additional systemic risks, having been associated with increased risk of cardiovascular disease and diabetes mellitus.[25] Additionally, the cumulative toxicity of individual treatment modalities when RP is offered as part of MMA cannot

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be underestimated. The functional outcomes following an RP have been reported to be promising with novels techniques such as NeuroSafe and Retzius-sparing radical prostatectomy. However, radiotherapy techniques have also shown improvement in recent years with fewer treatment-related adverse side effects.

Potential Benefits with Radical Prostatectomy

Radical prostatectomy does offer some notable benefits in the management of high-risk prostate cancer. Despite improvement in PCa diagnostics with pre-biopsy mpMRI, standardization of reporting and biopsy techniques, accurate quantification of grade and volume of cancer is not possible in a proportion of patients.[30] RP provides a large sample for histopathological analysis and thereby accurate local tumor staging & grading. The Gleason score is the strongest predictor of all outcomes for patients with high-risk PCa, with reduced cancer-specific survival in patients with Gleason score >7 irrespective of clinical stage.[15] Donohue et al.[14] reported downgrading of poorly differentiated PCa to Gleason 7 after RP in 45% of patients deemed high risk following initial prostate biopsy. Similarly, there remains subjective variation in determining presence of extra-prostatic extension on MRI, which may also impact risk stratification at the time of diagnosis. Ward et al.[12] also noted that 23% of patients staged as T3 on pre-operative imaging (cT3) were eventually downstaged to pT2 following histopathological evaluation of the radical prostatectomy specimen. Furthermore, given the non-specific nature of serum PSA, some patients may also be incorrectly classed as 'high risk,' due to factors other than malignancy, such as infection and recent instrumentation, which lead to an artefactually raised PSA level. Thus, given the above inaccuracies in assessment of risk features, some patients may unnecessarily receive ADT and adjuvant therapy, with associated treatment-related morbidity.[12,31] Accurate staging and grading from the pathological specimen following RP, may therefore help guide a more reliable estimate of long-term prognosis and counsel patients regarding the need for secondary therapies.

Notably, RP may be particularly well suited for men with bothersome voiding or storage lower urinary symptoms. Symptomatic improvement in such patients following RP, may be greater than that following EBRT alone[32], and obviate the need for ancillary bladder outlet surgery prior to undergoing definitive therapy. Additionally, radiotherapy is an unsuitable option in men with inflammatory disease and previous pelvic radiotherapy.

Radical Prostatectomy for Metastatic Prostate Cancer

The use of RP in management of metastatic PCa is a less well-trodden field and one which has only recently gained interest. The concept of radical treatment of the primary tumor in the presence of known metastatic disease is based on Paget's "seed and soil" hypothesis from 1889.[33] PCa is consistent with this model in its preponderance for hematogenous spread from the 'seeds' of the metastatic prostate cells to the "soil" microenvironment of bone, with spread generally only occurring elsewhere if metastatic tumor burden is particularly high.[34]

The STAMPEDE trial (Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy) provided RCT evidence for the use of local EBRT in the management of metastatic PCa.[35] Although there was no improvement in OS in the EBRT group versus control across unselected patients in the overall cohort, it demonstrated a significant improvement in OS, CSS, and BFFS in a pre-specified cohort of patients with low metastatic disease burden (also referred to as oligometastatic disease).

The idea that local therapy improves survival despite metastatic disease indicates that other local therapies, such as surgery, may provide the same benefit. Data from retrospective studies, though limited by relatively small sample size, have confirmed feasibility of RP in this setting, and report 67-80% 5-year overall survival following cytoreductive RP (cRP), among well-selected patients.[36,37] However, the only prospective study evaluating cRP did not find a significant benefit on overall survival.[38] Nevertheless, cRP may provide an additional symptomatic advantage in comparison to the use of non-surgical approaches, wherein one-third of the patients progress to develop symptomatic local progression within 3 years, which may be avoid in surgically treated patients.[39] In light of these conflicting data, a number of Phase II/III RCTs are in progress to investigate the efficacy of RP in the management of metastatic PCa (Table 3).

The TRoMbone (Testing Radical prostatectomy in men with prostate cancer and oligoMetastases to the bone) study, based in the United Kingdom, is a feasibility trial that randomized patients with low metastatic disease burden to either standard care (currently ADT with or without other systemic therapies) or standard care with additional use of RP and extended lymph node dissection. Inclusion criteria were limited to patients with 1-3 bony metastases and no visceral spread, with a locally resectable tumor (T1-T3).[40] Interim outcomes have suggested safety and feasibility in randomizing to systemic therapy either with or without RP. Pending additional funding, the TRoMbone study is expected to the offer surgical treatment of men with low metastatic disease burden as a new arm of the STAMPEDE trial.

The ATLANTA trial, also UK-based, is another ongoing multicenter RCT comparing outcomes following standard treatment (ADT), radical radiotherapy, radical prostatectomy, and minimally invasive ablative therapies (such as cryotherapy or focal high intensity focused ultrasound) in the management of patients with metastatic PCa. This study does not exclude patients with high burden of metastatic disease, and uses progression-free survival as its primary outcome.[41] All patients are eligible

to receive MDT in the form of stereotactic all-body radiotherapy (SABR) or pelvic lymph node dissection (PLND). Randomization is stratified by metastatic burden, intent to treat pelvic lymph nodes, intent to treat metastasis, and intent to commence chemotherapy.

A number of additional RCTs are in progress assessing the efficacy of radical prostatectomy in patients with metastatic PCa, including the SWOG 1802 and SIMCAP trials, both using overall survival as their primary outcome measure in a Phase III setting. The results of these trials are eagerly awaited and likely to result in a change in current practice.

Given that low metastatic burden predicted response to local radiotherapy in the STAMPEDE and HORRAD trials, it is expected that cRP may similarly result in variable outcomes dependent on metastatic burden. Nevertheless, there remains a lack of consensus regarding the definition of oligometastatic PCa. Among available retrospective data comparing cRP to best systemic therapy, cRP is associated with improved survival (55% versus 21%) and lower local complication rate (<10% versus 25-30%).[42] The majority of ongoing trials therefore focus on patients with low metastatic burden, apart from the SWOG 1802, ATLANTA-IP2, and LoMP-2 trials, which additionally include men with high metastatic burden.

Metastasis-Directed Therapy

Finally, surgery, in the form of salvage lymph node dissection (SLND), may also be used as a form of non-systemic MDT in PCa, in parallel to the growing use of stereotactic ablative radiotherapy (SABR) in the management of oligometastatic PCa recurrence (low-burden metastasis).

Non-systemic MDT has a number of advantages, including possible delay to the need for ADT and thereby reducing ADT-associated morbidity. Early identification of oligometastatic disease may also allow curative treatment in disease where this would previously not have been possible. Choline PET (positron emission tomography)-CT scans have traditionally been used to identify metastatic disease. However, choline PET-CT has low sensitivity and specificity at low PSA levels and low metastatic disease burden (oligometastatic disease). More recently, imaging with radio-labeled prostate-specific membrane antigen (PSMA) has shown promise in identifying metastatic disease on PET-CT not detected on choline PET-CT[43] or conventional imaging.

A systematic review by Moghul et al.[44] reported on findings from three studies comparing choline PET-CT with PSMA PET-CT. The latter had a significantly greater rate of detection on per-lesion analysis. Exclusive detection (lesions identified by one imaging modality but not by the other) was also significantly greater for PSMA PET-CT than choline PET/CT. Identifying oligometastatic disease in these patients, where it may have otherwise been undetected may therefore allow earlier and potentially curative use of non-systemic MDTs.

Even though the oligometastatic disease is not fully understood, accumulating clinical evidence suggests that, in comparison to high burden metastatic disease, oligometastatic PCa may be a biologically different entity and be associated with improved clinical responses from MDT.[45] Use of pelvic SLND to manage nodal recurrence following primary PCa treatment has reasonable outcomes. A systematic review by Ploussard et al.[46] in 2018 reported outcomes following SLND in 27 series. They found a complete biochemical response (PSA <0.2 ng/mL) in up to 79.5% of cases (mean 44.3%) and 5-year overall survival of approximately 85%. Major complication rate was less than 10% overall.

Early clinical recurrence (eCR), defined as recurrence within the first year after SLND, and PSMA-PET findings may be used as a risk stratification tool to identify optimal candidates for SLND. Patients with eCR have significantly greater risk of a 3-year CSM as compared with those who did not develop eCR (20% versus 1.4% 3-year CSM).[47] Patients with three or more PET-avid lesions or retroperitoneal involvement, ISUP grade group 5 disease, concurrent use of ADT, and high PSA were also noted to be an increased risk of eCR and therefore should be considered for SLND. The choice of radiotracer also impacts the sensitivity of PET-CT, with PSMA PET outperforming choline PET helping reliably determine unilateral versus bilateral SLND. While two or more PET-avid LN lesions within ipsilateral LN using either modality was associated with increased likelihood of contralateral node involvement, the presence of a single PET-avid ipsilateral LN on PSMA PET more reliably avoided the need for contralateral SNLD, as compared with choline PET. Thus, unilateral SLND may be sufficient in the context of a single PET-avid lesion on PSMA, and therefore minimize morbidity associated with SLND.[48]

Although surgical MDT may reduce the need for ADT and thereby reduce ADT-associated treatment toxicity, there is no clear evidence as to whether it improves survival and RCT evidence comparing MDT with ADT in the management on oligometastatic disease is awaited. This is in fact a rapidly evolving area of interest with approximately 41 ongoing trials across North America and Europe.[49]

Conclusions

The above discussion provides an overview of the emerging evidence evaluating the role of RP in management of high-risk and advanced PCa. RP either as monotherapy or as part of MMA is an option for patients with high-risk disease, however, level 1

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evidence is lacking. Therefore, it is important that the clinicians offer individualized patients treatment strategies with a multidisciplinary approach, offering RP appropriately in selected cases. It is important to take into consideration life expectancies, competing illnesses and individual patient factors taking into account oncological benefit and treatment-related toxicity of available treatment options. For patients with metastatic disease, RP may be a realistic treatment option in patients with low-burden metastatic disease and may improve survival, with results of ongoing trials in this area eagerly awaited. Nevertheless, further research is required to support careful selection of patients with high-risk and metastatic PCa who are most likely to benefit from surgical treatment. Furthermore, surgery is also an emerging modality for non-systemic MDT in patients with oligometastatic disease, in the context of rapid advances in molecular imaging technology resulting in improved early detection of recurrent PCa.

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Turk J Urol 2020; 47(Supp. 1): S56-S64
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