Role of surgery in high-risk localized prostate cancer

N. Lawrentschuk PhD MB BS,† G. Trottier PhD MD,*† C. Kuk MSc,*† and A.R. Zlotta MD PhD*†‡*

ABSTRACT

Men with high-risk localized prostate cancer (PCa) remain a challenge for clinicians. Until recently, surgery was not the preferred approach, in part because risk of subclinical metastatic disease, elevated rates of positive surgical margins, absence of randomized studies, and suboptimal cancer control did not justify the morbidity of surgery. No randomized data comparing surgery with radiation therapy are yet available. Data for and comparisons between treatment options should therefore be analyzed with extreme caution.

When selecting the best treatment for patients with clinically localized high-risk PCa, considerations should include the life expectancy of the patient, the natural history of PCa, the curability of the disease, and the morbidity of treatment. High-grade PCa managed with noncurative intent greatly reduces life expectancy, but overall, it must also be remembered that radical prostatectomy (RP) and radiotherapy (RT) appear to have similar effects on quality of life. In this population, RP necessitates an extended pelvic lymph node dissection (PLND), but in selected cases, nerve-sparing is a therapeutic possibility and may offer a significant advantage over RT in terms of local control and—although absolutely not yet proved—maybe even in survival. One clear advantage is the ease of administering adjuvant or salvage external-beam RT (EBRT) after RP; conversely, salvage RP after failed EBRT is an exceedingly difficult surgery, with major complications. Surgery therefore has its place, but must be considered in the context of multimodality treatment and the risk of micrometastatic disease. Awaited trial results will help to further refine management in this group of patients.

KEY WORDS

Prostate neoplasm, pathology, prostatectomy, outcomes

1. INTRODUCTION

Men with high-risk localized prostate cancer (PCa) present a clinical dilemma. Until recently, surgery was not the preferred approach, in part because risk of subclinical metastatic disease, elevated rates of positive surgical margins, an absence of randomized studies, and suboptimal cancer control did not justify the morbidity of surgery. Some patients eventually received radiation therapy (RT), which was often cited as the "gold standard" for locally advanced PCa because of available studies [1,2]. However, no randomized data comparing surgery and RT are yet available. Data for and comparisons between treatment options should therefore be analyzed with extreme caution. Trial results from PIVOT [Prostate Intervention Versus Observation Trial (randomized)] [3] and PROTECT (Prostate Testing for Cancer and Treatment) are still anticipated [4]; hence, currently available data require a critical look when counselling such patients.

2. DISCUSSION

As Montie [5] wrote, if we are truly to progress further in lowering the mortality rate for men with high-risk localized PCa, we must develop innovative strategies leading to the complete elimination of local disease and unapparent metastatic disease. In light of that sentiment, surgery should not be overlooked, and a multimodality approach in such patients should be deemed feasible. Surgery is part of the multimodality approach; it should not be regarded as monotherapy in men with high-risk PCa. A multidisciplinary approach combining radical prostatectomy (RP), extensive lymphadenectomy, and when required, adjuvant external-beam RT (EBRT) and androgen deprivation therapy (ADT), is likely to offer local control and improved overall survival (OS). Another group increasingly presenting for help is high-risk men who, after failure of EBRT or other therapies (for example, cryotherapy, high-intensity focused ultrasound), are seeking salvage prostatectomy. They require special consideration before embarking on surgery.

2.1 Staging Is Suboptimal in Men with High-Risk Disease

Overstaging (pT2), overgrading, and understaging (pT4 or pN+) are common clinical errors in men

with high-risk disease. Nomograms can be useful in predicting the pathologic stage of the disease and the seminal vesicle invasion at RP [6]. In some series, up to half the patients thought to have extraprostatic extension harbour organ-confined disease and therefore could potentially have been denied surgery!

2.2 Radical Prostatectomy in Men with High-Risk PCa

The current recommendations of the European Urology Association (EAU) [7] for surgery in locally advanced PCa include men with prostate-specific antigen (PSA) below 20 ng/mL, clinical stage T3a, and Gleason score 8 or less on biopsy.

Table I summarizes the RP trials in men with high-risk PCa. Acceptable positive surgical margins may be obtained, and yet adjuvant therapy is not infrequent (median: 40%; range: 0%–76%), emphasizing the multimodality nature of the approach. It is difficult to compare across series because selection criteria vary, as do the number of organ-confined cases. Rates of adjuvant therapy are misleading because they vary with the length of follow-up (for example, the Lavery *et al.* series [8] follow-up is 1 year; the Donohue *et al.* series [16], 10 years) and with institutional policy.

In patients with locally advanced disease, the review paper by Van Poppel and Joniau [23] showed average cancer-specific survival rates after RP of 85%–100% at 5 years of follow-up and 57%–91.6% at 10 years. The OS rate was more than 75% at 5 years and 60% at 10 years. In patients with high-grade prostate cancer (Gleason score ≥ 8), biochemical recurrence-free survival after RP was 51% at 5 years of follow-up and 39% at 10 years.

Keeping technical considerations for RP in mind is necessary because treatment must be individualized. Evidence is growing that the preoperative use of magnetic resonance imaging (MRI) can assist in preoperative planning [8,24]. In many instances, the sites, extent, and nature of extracapsular disease will be identified, altering nerve-sparing approaches and the extent of excision. At our centre, information from the preoperative MRI staging is used together with intraoperative frozen sections to assist in applying interfascial nerve-sparing to selected high-risk patients. We believe that special instruments (Barré instruments: Aesculap division, B. Braun Melsungen AG, Melsungen, Germany)—extra-thin scissors, dissectors, and loupes—assist in identifying anatomy and possible regions of extracapsular extension, and ensure the best possible surgical results.

The general approach has been to use open surgery. Even in the robotic-assisted laparoscopic RP (RALRP) era, patients at high risk are still predominantly offered open surgery because of the associated haptic feedback and ability to perform an extended PLND [25]. Three series (Table I) have used RALRP with

TABLE I Larger series (>50 patients) studying radical prostatectomy in men with high-risk prostate cancer

Reference	*Pts* (n)	*Pathologic*		*SV* + (%)	*Margins* + (%)	*Adjuvant therapy* (%)
		T2 (%)	*N+* (%)			
Lavery *et al.*, 2010[8,a]	123	42	2	32	31	26
Spahn *et al.*, 2010 [9]	372	15	37	43	57	80
Zlotta *et al.*, 2010 [10]	47	51	13	30	21	12.8
Ham *et al.*, 2009 [11,a]	121	21	24	—	49	—
Shikanov *et al.*, 2008 [12,a]	72	47	13	14	24	13
Freedland *et al.*, 2007 [13]	58	9	31	29	22	46
Bastian *et al.*, 2006 [14]						
Johns Hopkins University	220	25	17	25	29	73
SEARCH	149	51	6	22	47	72
Carver *et al.*, 2006 [15]	176	30	19	34	30	36
Donohue *et al.*, 2006 [16]	238	34	18	26	26	61
Ward *et al.*, 2005 [17]	842	27	27	—	56	76
Manoharan *et al.*, 2003 [18]	79	30	3	28	41	38
Van Poppel *et al.*, 2000 [19,b]	158	13	11	16	60	30
van den Ouden *et al.*, 1998 [20]	83	18	12	40	66	0
Gerber *et al.*, 1997 [21]	298	9	31	11	—	40
Lerner *et al.*, 1995 [22]	812	17	33	18	—	50

[a] Robot-assisted laparoscopic radical prostatectomy.
[b] cT3a: 47 patients; pathologic N+: 10%; SV+: 6%; margins+: 53%.
Pts = patients; N+ = lymph node–positive; SV = seminal vesicle; + = positive; SEARCH = Shared Equal Access Regional Cancer Hospital database.

acceptable results, but it must be noted that two series had a high proportion of organ-confined patients and undertook no extended PLND. Their follow-up was 1 year or less (or not reported), and longer studies are required for efficacy to be established. We agree that nerve-sparing is still possible in such patients, and those series, too, had good results with nerve-preservation and use of frozen sections.

2.3 Pelvic Lymphadenectomy in High-Risk PCa

The role of PLND in high-risk PCa has recently come under scrutiny. Burkhard and colleagues [26,27] have all emphasized the importance of an extended PLND, which is certainly a major undertaking of the procedure. Hence, RP in locally advanced PCa is not just the RP. Extended PLND requires removal of the obturator, external iliac, and hypogastric with or without the pre-sacral and common iliac nodes. Compared with a limited PLND (removal of the obturator with or without the external iliac nodes), the extended version has been reported to provide significant improvements in the detection of lymph node metastases [26].

Nomograms and tables have limited use in this high-risk group, because PLND will routinely be performed in all cases for staging. It is difficult to comment on the role of extended PLND, because few of the series (Table I) have reported nodal counts—a practice influenced by the habits of local pathologists. In one RALRP series, an extended PLND (obturator, external iliac, and internal iliac) removed a mean of 18.6 nodes.

2.4 External-Beam RT As Adjuvant Treatment After Surgery in High-Risk Patients

Although adjuvant treatment with RT after surgery is commonplace in malignancies such as breast cancer, PCa is treated differently because of the availability of PSA testing, which allows for the early detection of postoperative recurrence well before clinically symptomatic or palpable disease recurrence is found. The primary issue after RP for men with high-risk disease is that the possibilities of no therapy, early therapy, and delayed or salvage therapy at recurrence all seem feasible depending on an individual patient's risk. For example, at our institution, it is not uncommon for a patient with pT3a disease and negative surgical margins post RP to be observed, even after referral to the radiation oncology team. (Most would still be included in clinical trials.) At signs of recurrence, EBRT is then offered. Patients with T3a status and a positive surgical margin will likely be offered EBRT even without evidence of recurrence, being at higher risk, as demonstrated by a reanalysis by Van der Kwast *et al.* of the adjuvant data from the European Organisation for Research and Treatment of Cancer (EORTC) [28].

The question of whether immediate or early salvage RT at the first sign of biochemical recurrence achieves better long-term results has been the source of much debate. The ongoing U.K. Medical Research Council RADICALS (Radiotherapy and Androgen Deprivation in Combination After Local Surgery) study (see NCT00541047 at ClinicalTrials.gov) is aiming to recruit 4000 patients with pT3 disease who have not had biochemical failure post RP. Two randomizations are being done: one concerning the timing of RT, and the other concerning the use of ADT in conjunction with postoperative RT. Men may enter either or both randomizations. Hopefully, this study will make some contributions to the vexed question of hormones in such men; however, until RADICALS matures, an examination of other data may provide assistance.

Three randomized controlled trials addressing the timing or need for adjuvant EBRT after RP are available: the Arbeitsgemeinschaft Radiologische Onkologie (ARO-96-02) study [29] of the German Cancer Society, the Southwest Oncology Group (SWOG) 8794 study [30], and the EORTC 22911 trial [31]. In summary (Table II), all of those studies support adjuvant EBRT after RP for advanced localized PCa by demonstrating improved biochemical recurrence–free survival rates (and improved metastasis-free survival in one trial). Patients with positive surgical margins are most likely to benefit from adjuvant RT. Only modest toxicity occurred in the trials, which was encouraging.

One issue in the EORTC and SWOG trials is that patients could be included without having achieved a PSA nadir of less than 0.2 ng/mL postoperatively (30.5% EORTC, 27% SWOG). Those men were therefore likely to have had residual disease rather than to have been in an adjuvant situation. This case did not hold in the ARO trial, one of whose strengths was its requirement that participants have an undetectable postoperative PSA for enrolment, thus ensuring that the trial tested purely adjuvant RT. Further, the EORTC trial did not use three-dimensional RT, now considered to be standard care. Those issues probably have not changed the results, but they must be kept in mind.

The timely application of salvage RT in the control arms of both the EORTC and SWOG trials was also not undertaken. For example, in the SWOG trial, just 36 of 211 patients in the observation arm received salvage RT for PSA failure. It might then be considered that the trials were comparing a radical approach of immediate postoperative EBRT with a more palliative approach of observation with delayed hormones and only occasional salvage RT. Despite those shortcomings, both trials, together with the ARO trial, indicate the importance of adjuvant RT; however, exactly who should receive it, and when, remains debatable.

As pointed out by McVey and Parker [32], nonrandomized trials cannot help with the specific questions of RT timing and the benefits of adjuvant versus salvage timing, because a fundamental difference (and therefore flaw) will always remain: inherent selection bias. Many patients receiving adjuvant RT will already

TABLE II Randomized controlled trials addressing the timing or need for adjuvant radiotherapy after radical prostatectomy

	ARO 96-02 (*Wiegel* et al., *2009* [29])	*SWOG 8794* (*Thompson* et al., *2009* [30])	*EORTC 22911* (*Bolla* et al., *2005* [31])
Variables			
Patients (*n*)	307	431	1005
TNM stage	pT3N0	pT3N0	pT2R1–pT3N0
Positive surgical margin at radical prostatectomy (%)	68	67 (with EC extension)	63
Postoperative PSA > 0.2 ng/mL (%)	0	16	11
Radiation dose (Gy)	60	60–64	60
Control arms			
Median follow-up (months)	54	152	60
Patients in control arm receiving salvage RT (%)	—	33	55
PSA at salvage in control arm (ng/mL)	—	1	—
Interval to salvage treatment (years)	—	2.2	2
Results			
Primary endpoint	BCR	Metastasis-free survival	BCR
BCR definition [PSA (ng/mL)]	0.1	0.4	0.2
Median follow-up (months)	54	152	60
BCR [% adjuvant/% control (follow-up)]	28/46 (5-year)	47/70 (10-year)	21/44 (5-year)
Overall survival [% adjuvant/% control (follow-up)]	—	74/66 (10-year)	90.8/91.5
Metastasis [% adjuvant/% control (follow-up)]	—	18/9 (12.6-year)	—
Grade 3 toxicity (%)	0.3	9.8 (6%>control)	4.2 (1.9%>control)

ARO = Arbeitsgemeinschaft Radiologische Onkologie; SWOG = Southwest Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; EC = extracapsular; PSA = prostate-specific antigen; RT = radiation therapy; BCR = biochemical recurrence.

have been cured by surgery alone, and all patients receiving salvage RT will by definition have recurrent disease after surgery. Outcomes in patients who have received adjuvant EBRT will therefore always be better than those in patients who have received salvage RT, colouring any recommendations. It appears that the message from the studies is that men with a rising PSA after RP should receive salvage RT as early as possible, and that waiting for the PSA to reach some arbitrary threshold is not appropriate. As a final note, caution about giving EBRT too near to surgery is warranted, because of the risks to continence from fibrosis [5], which also must be balanced in any decision on the timing of adjuvant EBRT.

The prospective EORTC 22911 trial [31] randomized 503 men to immediate postoperative EBRT (60 Gy conventional EBRT delivered over 6 weeks) or observation. Eligible patients had pN0M0 tumours and one or more pathologic risk factors: capsule perforation, positive surgical margins, invasion of seminal vesicles. The revised primary endpoint was biochemical progression-free survival. Analysis was by intention to treat. After a median follow-up of 5 years, biochemical progression-free survival was significantly improved in the irradiation arm (74.0%) as compared with the observation arm (52.6%). Side effects were significantly more common in the irradiated group, but they were rarely severe.

2.5 High-Risk Patients with Positive Lymph Nodes

It remains true that RP is still commonly abandoned if suspicious pelvic lymph nodes are detected during PLND. This practice is based on the theory that no survival benefit accrues to lymph-node-positive patients from surgical removal of the prostate because they have systemic disease. This thinking was supported by many authors. A large European study that started in 1988 of early versus delayed endocrine treatment of pN1–3 M0 PCa without local treatment of the primary tumour [33] confirmed the likelihood of the hypothesis and influenced a generation of urologists.

However, against that trend, the Mayo Clinic published their landmark 1999 paper on high-risk PCa patients with positive lymph nodes. They concluded that, compared with ADT treatment only, treatment with RP and ADT significantly improved the probability of OS in a carefully matched group of patients with similar age, T stage, number of positive nodes, and preoperative PSA (if available). The 10-year OS probability was approximately 65% for patients treated with RP and ADT as compared with only approximately 30% in the matched patients receiving ADT alone. The study may certainly be criticized for being retrospective and nonrandomized, but the patients were well matched, strengthening the persuasiveness of the conclusions. Too often these data are forgotten in favour of EBRT, particularly after the Bolla *et al.* study [1] was published; and yet that study was not designed around the treatment of node-positive patients. However, in 2010, Engel *et al.* [34] published data from the Munich Cancer Registry supporting the Mayo data because patients who underwent RP despite the presence of positive pelvic lymph nodes experienced better survival than did those in whom surgery was aborted after positive lymph nodes were found. The difference from the Mayo data is the larger numbers (approximately 700 with RP and 250 with no RP, compared with approximately 100 in both arms in the Mayo study) and the fact that no matched comparisons were available. Of course, the Munich data are also retrospective and nonrandomized, but they again challenge the notion of abandoning RP in node-positive patients [34].

Thus, a body of evidence is emerging from the Mayo and Munich data to support the theory that removing the prostate is true local control, but at the same time to raise the spectre that metastasis perhaps depends more on the primary tumour than on nodal disease as previously thought [34]. That understanding would of course involve RP in such patients, but it is also supported in the radiation literature where local control is obtained. In a study of outcomes after EBRT, Cohen *et al.* [35] demonstrated a significantly better outcome in patients with negative prostate biopsies than in patients with positive biopsies (a sign of local treatment failure). The incidence of metastasis decreased significantly after a few years in the patients with apparent local disease control (negative biopsy), but it progressively increased in the group of patients without local control (positive biopsy). That trend is supported by a Scandinavian prospective randomized trial in which patients treated with ADT alone had significantly poorer cancer-specific survival and OS than did patients treated with combined ADT and RT [36]. Overall, when combined with the RP data, such trials suggest that the primary tumour continues to shed PCa cells into the blood circulation; thus, removal or definitive treatment seems logical [37].

2.6 Androgen Deprivation in Men Undergoing RP with Positive Lymph Nodes

The issue of immediate versus delayed ADT in men undergoing RP with histologically proven positive nodes has been addressed in two prospective randomized trials: the Eastern Cooperative Oncology Group (ECOG) 3886 trial [38] and the EORTC 30846 trial [33]. Interestingly, the ECOG trial, reported by Messing *et al.* [38], showed a statistically significant difference in favour of immediate ADT; the larger EORTC trial did not.

Many tend to remember the ADT part of the Messing trial, but in looking at the study from another angle, the 5- and 10-year survival rates in these men with bulky disease (the mean PCa volume was more than 15 mL) and positive nodes may also tell us that removal of the primary tumour helped to achieve surprisingly good long-term cancer control [38]. Comparing these trials is impossible despite their similarities (operable patients turned out to have positive nodes, with a similar median PSA), but in an interesting article, Studer *et al.* [37] noted that the 10-year survival of patients in whom the prostate had been removed (ECOG trial) was again approximately 65%. If the prostate was not removed (EORTC trial), then the 10-year survival of the whole patient cohort was approximately 30%. That perspective gives further support to the notion that, as already discussed, the primary site harbours disease. And so the question remains: When to administer ADT?

The EORTC trial is underpowered to show equivalence or superiority, and so many clinicians fall back to the Messing data for early ADT. That fallback approach is challenged by some who feel that it is an example of overtreatment. Another possibility is to use the data demonstrating the association between short postoperative PSA doubling time and poor prognosis to stratify patients into subgroups for a determination of need for adjuvant treatment regimens [39].

A final point about the ECOG trial is that the study did not have a centralized pathology review, and not many patients were included in the study, thereby raising questions about its generalizability.

2.7 Salvage Prostatectomy in High-Risk Patients After Failure of Other Primary Therapies

With the increasing use of EBRT and other therapies (for example, cryotherapy, high-intensity focused ultrasound), urologists are increasingly being consulted about the prospects of salvage RP. The first realization about such patients is that they are undoubtedly oncologically compromised, but also often functionally compromised from their first therapy, which may have been repeated. Compared with function in men presenting for primary RP, sexual and urinary function in these late RP patients are particularly affected and less than ideal. Those problems, combined with the problem of surgery in a previously treated field, have

led to reports of increased morbidity after open RP, and even after RARLP, in such high-risk men.

Although the series tend to be smaller, some common themes emerge. Overall, rates of erectile dysfunction are high because of previous therapy, and in any case, nerve-sparing is compromised. Transient urine leaks may occur after surgery; bladder neck contractures are more frequent; and posterior urethral distraction and even rectal injuries with recto-urethral fistula development have been reported [40–42]. Because of such consequences, implantation of artificial urinary sphincters and inflatable penile prostheses produces better outcomes in patients with postoperative urinary incontinence or erectile dysfunction and should be part of any discussion about salvage RP. The cancer-specific mortality after salvage RP has been reported to be 27% at 10 years and 40% at 15 years [42]. Therefore, in counselling such patients, RP is definitely possible, with acceptable oncologic control and positive margin rates of approximately 30%, but at a higher cost. Moreover, the need for accurate preoperative staging to exclude men without local disease cannot be overemphasized [40]. Also, if undertaken, the RP should be done closer to the time of local failure to improve oncologic control [42].

2.8 Radiotherapy in High-Risk Patients as an Alternative to RP

Suffice to say, an alternative to RP and PLND in high-risk patients is RT. The EORTC study reported by Bolla *et al.* [1] of approximately 400 patients was a prospective randomized trial comparing EBRT with EBRT plus a luteinizing-hormone releasing-hormone agonist (goserelin) in patients with locally advanced PCa. Selection involved patients with clinical stage T1 or T2 disease and Gleason scores of 8–10, and also patients with T3 or T4 lesions who were N0 Nx M0. Thus node-positive patients were few (7%), with most having T3 disease (82%). The proportion of surviving patients who were free of disease at 5 years was 85% in the combined-treatment group and 48% in the RT group (95% confidence interval: 38% to 58%; $p < 0.001$). Those results are acceptable, but as yet, no head-to-head comparison of multimodality treatment has included surgery. High-dose brachytherapy is also an option in high-risk men, and data are accumulating on this approach when combined with ADT [43].

3. SUMMARY

Locally advanced PCa remains very challenging. In selecting the best treatment for patients with clinically localized PCa, the life expectancy of the patient, the natural history of the PCa, the curability of the disease, and the morbidity of treatment should all be considered. High-grade PCa managed with noncurative intent greatly reduces life expectancy. It must also be remembered that, overall, RP and three-dimensional conformal RT appear to have similar effects on quality of life [44]. In selected cases, RP with extended PLND, and even nerve sparing, is a therapeutic possibility and may offer a significant advantage over RT in terms of local control and—although absolutely not yet proved—perhaps survival. One clear advantage is the ease of administering adjuvant or salvage EBRT after RP; conversely, salvage RP after failed EBRT is an exceedingly difficult surgery, with major complications. Surgery therefore has its place, but must be considered in the context of multimodality treatment and the risk of micrometastatic disease. The role of extended PLND in this paradigm is also of utmost importance. Finally, we recommend the importance of an experienced, high-volume center in this type of advanced disease. Awaited trial results will help to further refine management in this group of patients.

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Corresponding author: Nathan Lawrentschuk, Division of Urology, Department of Surgical Oncology, Princess Margaret Hospital, 3-130 – 610 University Avenue, Toronto, Ontario M5G 2M9.
E-mail: lawrentschuk@gmail.com

* University Health Network, University of Toronto, Department of Urology and Surgical Oncology, Princess Margaret Hospital, Toronto, ON.
† University of Melbourne, Department of Surgery, Austin Hospital, Urology Unit, Melbourne, Victoria, Australia.
‡ University Health Network, University of Toronto, Department of Urology and Surgical Oncology, Mount Sinai Hospital, Toronto, ON.