Surgical Management of Organ-Confined Prostate Cancer with Review of Literature and Evolving Evidence

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Abstract Prostate cancer is the most common solid organ malignancy in men in the USA with an annual incidence of 105 and an annual mortality rate of 19 per 100,000 people. With the advent of PSA screening, the majority of prostate cancer diagnosed is organ confined. Recent studies including the SPCG-4 and PIVOT trials have demonstrated a survival benefit for those undergoing active treatment for localized prostate cancer. The foremost surgical option has been radical prostatectomy (RP). The gold standard has been open radical retropubic prostatectomy (RRP); however, minimally invasive approaches including laparoscopic and robotic approaches are commonplace and increasing in popularity. We aim to describe the surgical options for the treatment of localized prostate cancer by reviewing the literature. A review of the literature was undertaken using MEDLINE and PubMed. Articles addressing the topic of radical prostatectomy by open, laparoscopic and robotic approaches were selected. Studies comparing the different modalities were also identified. These articles were reviewed for data pertaining to perioperative, oncological and functional outcomes. There is a paucity of randomized studies comparing the three modalities. The published data has demonstrated a benefit in favour of robotically assisted laparoscopic prostatectomy (RALP) over laparoscopic radical prostatectomy (LRP) and traditional open RRP in perioperative outcomes. When reviewing the best-reported outcomes for RALP compared to LRP and RRP, operative times are lower

(105 vs. 138 vs. 138 min), estimated blood loss rates are lower (111 vs. 200 vs. 300 ml) and blood transfusion rates are lower as in the length of stay (1 vs. 2 vs. 2.3 days) and overall complication rates (4.3 vs. 5 vs. 20%). Similarly, when reviewing functional outcomes, RALP compared to LRP was not inferior. At 12 months, the reported continence was 97 vs. 94 vs. 89% and potency was 94 vs. 77 vs. 90%. In comparative studies, however, these differences did not always meet statistical significance. With respect to oncological outcomes, there was no clear evidence of superiority of one modality over another. RALP is now the most common modality for surgical treatment of organ-confined prostate cancer. Individual series appear to support better perioperative outcomes and perhaps quicker return to functional outcomes. There does not appear to be a clear advantage to date in oncological parameters; however, RALP does not appear to be inferior to either LRP or RRP. It is anticipated that further high quality randomized studies will shed more light on the clinical and statistical significance in the comparison between these modalities.

Keywords Prostate cancer · Localized · Laparoscopy · Robotic surgery

Introduction

Prostate cancer is the most common cancer affecting men in the USA with an annual incidence of 105 and mortality of 19 per 100,000 [1]. With increased PSA screening and awareness, most cases are organ confined at the time of diagnosis [2].

A variety of treatment options exist for men diagnosed with localized prostate cancer. These include extirpative surgery, radiation treatment, observation (active surveillance or watchful waiting), hormone manipulation or combination

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therapy. Radical prostatectomy is an increasingly common treatment option [3].

The mainstay of active treatment is either radical prostatectomy (RP) or radiotherapy (RT). Currently, there are conflicting data on the superiority of either of these modalities as the primary treatment option. Sooriakumaran et al. found that RP was associated with improved outcomes when compared with radiotherapy [4]. In a large study comparing radical prostatectomy with observation, a survival benefit was demonstrated to be associated with radical prostatectomy for organ-confined prostate cancer, particularly in those aged <65 years with intermediate disease. Furthermore, surgery was also associated with a lower risk of metastasis in older men [5].

RP can be performed with a variety of approaches including open, laparoscopic and robotic. Open RP can be performed via a perineal or retropubic approach whilst laparoscopic RP can also be performed in an extraperitoneal approach or via a transperitoneal route. The aim of this paper is to describe the surgical options for the treatment of localized prostate cancer by reviewing the literature.

Materials and Methods

A review of the literature was conducted utilizing MEDLINE and PubMed. Queries were inserted, focussing on RP for prostate cancer by each of the modalities as well as comparative studies between modalities. Publications containing large numbers of cases were identified for each of the modalities as well as from high-volume surgeons. Oncological, perioperative and functional outcomes were also reviewed.

A review of the publications was undertaken. Each modality was reviewed individually as a treatment for localized prostate cancer. Attention was also directed to any technical aspects of each modality which may play a role in the dissemination of a particular modality or technique into mainstream practice. Following this, we analysed publications comparing the modalities to each other. The objective was to identify randomized control studies comparing each of the modalities. This proved to be challenging with the majority of data being single-institution, non-randomized studies.

Results and Discussion

Open Radical Prostatectomy

The first RP was first described in 1905 by Hugh H. Young and was undertaken as a radical perineal prostatectomy (RPP) [6]. Millen subsequently described the radical retropubic prostatectomy (RRP) in 1947 [7]. There has been constant revision and optimization of this technique over the last 20 years, and it still serves as the gold standard

for the treatment of localized prostate cancer [7, 8]. Important milestones in the refinement of the technique have come about, following a greater understanding of the anatomy of the prostate and the surrounding structures. Identification of the dorsal venous complex led to a reduction in the rates of blood loss [9]. Urinary continence was improved with identification of the external sphincter [10], and similarly, improvements in the potency rates were possible following the identification and preservation of the neurovascular bundles [11].

RPP has largely been supplanted by RRP in the arena of open surgery. Evaluating the Surveillance, Epidemiology, and End Results (SEER) program and Medicare-linked data between 2003 and 2007, approximately 4.9% of RPs were performed via a perineal approach and 74.3% of all RPs were performed via a retropubic approach [12]. The perineal approach had been traditionally favoured for the intraoperative proximity to the prostate as well as reduced blood loss and requirement for blood transfusion. Particularly in obese men, this approach offered easier access to the prostate compared to RRP. Postoperative pain scores and length of stay in hospital have been found to be lower when compared with RRP. The 30-day complication has also been demonstrated to be lower than that in the RRP group [12]. Despite these advantages of RPP over RRP, it is suspected that the need for a second incision for lymph node dissection and loss of familiarity of the perineal anatomy, improved understanding of the surgical anatomy and refinement of the retropubic technique has resulted in the decline in the utilization of RPP.

Operative times have diminished over the years with optimization of the surgical technique, improved understanding of the anatomy and higher volume of cases in large institutes. Mean operative times for RRP have been reported at 163 min [13] with mean volumes of intraoperative blood loss of 350 ml (range of 300–500 ml) [14], and further studies demonstrated mean transfusion rates of 7.7% [15]. With regard to oncological outcomes, Ficarra et al. reported on their RRP positive margin rates of 12% in localized prostate cancer [16]. Biochemical recurrence (BCR) is often used as a surrogate for oncological control. Mullin et al. reported on their BCR-free survival at 4 years being 93.2% in $\leq$ T2 stage cancer with RRP [17]. The rates of continence have improved with authors publishing a continence rate of 89% at 2 years (complete control or occasional leak) [18]. It must be noted that there is heterogeneity in the definition and documentation of continence post RP. With respect to the rate of erectile dysfunction, once again, the trend has indicated an improvement in potency rates with bilateral nerve-sparing procedures producing up to 90% potency rates at 12 months [19]. Higher continence and potency rates are often associated with increased surgical experience in higher-volume centres.

Laparoscopic Radical Prostatectomy

The first described laparoscopic radical prostatectomy (LRP) was described in 1992 [20], but due to the technically challenging nature and extended operative time, it was not readily adopted. It was only after the publication of experience from Schuessler in 1997 [21] and other European centres in 1998 that other skilled laparoscopic surgeons began utilizing this approach [22–25]. The approaches to LRP can be divided into an entirely extraperitoneal approach akin to the traditional RRP and the transperitoneal approach.

LRP is a challenging procedure and requires advanced laparoscopic skill. There is a recognized learning curve during which there is an expected improvement in the total operating time, complications, blood loss and rates of blood transfusion. Of note, there was no change to the length of stay or duration of catheterization with greater experience [26]. The mean operating time for LRP has ranged from 225 to 328 min in the literature [27]. Studies have reported that there was no appreciable difference between the transperitoneal and extraperitoneal approaches in LRP. The intraoperative blood loss rates have been disclosed at 200 ml (10–1300 ml) [28]. Similarly, the mean rate of blood transfusion was at 0% [29]. Positive surgical margin rates have been reported between 5 and 23% [30–32]. Soares et al. commented on length of stay, duration of catheterization, complications and functional outcomes. They reported the mean hospital length of stay was 3 days (2–14 days) with a mean duration of catheterization of 14 days (1–35 days). Complications were uncommon at 5.3%. Of the functional outcomes, continence has been reported at 93.8%. With regard to potency, LRP has been reported to achieve a potency rate of 76.6% with bilateral nerve-sparing procedures [28].

Robotic Radical Prostatectomy

Robotically assisted laparoscopic prostatectomy (RALP) was first performed in 2000. Since then, there has been improvement in the technology and in the proportion of RP performed robotically. The three-dimensional view, magnification, articulated instrumentation and minimally invasive nature of the procedure have led to rapid popularity of this modality. In 2010, approximately 80% of all RPs were performed robotically [33]. The vast majority of studies looking at RALP are retrospective in nature with some prospective studies now available and even fewer randomized controlled trials. At present, only two notable RCTs have compared RALP with LRP or RRP [34, 35].

There is a learning curve associated with RALP. With increasing numbers, there is evidence of improvement in the operating time, blood loss, positive margin, urinary continence and potency rates [26, 36]. Among high-volume centres, the mean operating time has been reported at 105 min

(range of 55–300 min). This was calculated from skin incision to fascial closure. The blood loss rates were low at 111 ml (50–500 ml) and blood transfusion requirements as low as 0.4%. The rates of positive surgical margins for $\leq$ pT2 cancers were 4%. The mean hospital length of stay was reported at 1 day with a mean catheterization duration of 6.3 days (4–28 days) [37]. Continence rates at 12 months have been reported at 70–97% whilst 94% of men were reported as being potent at >18 months [16]. Early continence has been reported as 92.8% at 3 months with the use of a periurethral suspension stitch as described by Patel et al. [38]. Reported complication rates associated with RALP have been as low as 4.3% [37]. Ficarra et al. reported that in their series, RALP was associated with an 81% potency rate compared to 49% in the RRP cohort [16]. Unlike LRP, the financial cost associated purchasing and maintaining the equipment as well as the cost of consumables per case for RALP are high.

Comparison Between the Modalities

As stated, there is a paucity of randomized controlled studies comparing these three modalities (open, laparoscopic and robotic prostatectomies). There are, however, prospective, non-randomized studies with large numbers of patients. From published data, the following comparisons have been noted.

Perioperative Outcomes

Among the modalities, RALP has been reported as the favoured modality when addressing perioperative outcomes. A mean duration of 105 min for RALP is much shorter than that reported for RRP or LRP. Similarly, RALP was associated with a lower rate of blood loss, the need for blood transfusions, length of stay and complication rates.

In a meta-analysis performed by Parsons and Bennett, both LRP and RALP were associated with significantly lower blood loss compared to RRP [39]. Asimakopoulos et al. [34] and Porpiglia et al. [35] reported on similar blood loss rates between the LRP and RALP groups. Regarding blood transfusions, Trinh et al. [15] as well as Healey et al. [40] found that compared to RRP, RALP patients were less likely to receive a blood transfusion.

Between the LRP and RALP groups, however, there was no significant difference between the rates of transfusion according to Allan and Ilic [49]. The overall complication rates have been reported to be lower in both LRP and RALP when compared to RRP [41, 42]. Tewari et al. reported a complication rate four times higher in RRP than compared to RALP (20 vs. 5%) [13]. The perioperative outcomes are summarized in Table 1.

Table 1 Perioperative outcomes

	Number	Operative time (min)	EBL (ml)	BTR (%)	LOS (days)	Complications (%)
Open						
Menon et al. [43]	30	138	970	30	2.3	60
Tewari et al. [13]	100	163	910	67	3.5	20
Bhayani et al. [44]	24	168	1473	Not reported	3.04	21
Laparoscopic						
Soares et al. [28]	1138	177	200	0.5	3	5
Porpiglia et al. [35]	60	138	234	Not reported	4.8	12
Papachristos et al. [45]	100	195	300	1	2	14
Robotic						
Patel et al. [37]	1500	105	111	0.4	1	4.3
Badani et al. [46]	2766	154	142	2	1.14	12
Zorn et al. [47]	744	234	222	1.20	1.2	Not reported

N number of patients in the study group, *EBL* estimated blood loss, *BTR* blood transfusion rate, *LOS* length of stay

Oncological Outcomes

It must be noted that the margin status can be affected by other factors including tumour characteristics, nerve-sparing attempt as well as surgeon's experience. Looking at the data published from individual series, RALP appears to be associated with better outcomes. For pT2 or lower-stage tumours, RALP was associated with a low surgical margin rate of 4% compared to 5% in the LRP series and 12% in the reported open series. When reviewing the positive surgical margin (PSM) in RALP, rates between 15.5 and 21.2% have been reported [27]. The learning phase accounts for a number of the higher PSM rates reported. Tewari et al. [13] and Smith et al. [48] both reported that progressing through the learning curve for RALP, the PSM rate fell from 23 to 6% and from 35.7 to 15%, respectively. It must be noted, however, that in comparative studies, there has been no demonstrated significant differences in the PSM between the LRP and RALP groups [29, 34, 35, 49]. The BCR-free survival rates appear to favour RALP when compared to LRP and RRP if single series is compared to each other. However, in comparative studies, the rate of BCR-free survival was not statistically different between LRP and RALP groups (RR 1.01; 95% CI 0.91, 1.12) [49, 50]. Porpiglia et al. [35] found no significant difference in biochemical-free survival between LRP and RALP groups (92.5 vs. 98%, $p = 0.19$). See Table 2 for comparisons.

Functional Outcomes

The functional outcomes between these modalities are summarized in Table 3. With regard to continence, it is well recognized that there is marked heterogeneity in the definition, quantification and documentation. Similarly, the description

and definition of potency varies from publication to publication. This makes drawing direct comparisons challenging.

Once again, RALP has been demonstrated to have superior outcomes compared to LRP and RRP. At 12 months, the best quoted data for both continence and potency has been in the RALP series. The reported rates were 97, 94 and 89% for the RALP, LRP and RRP groups, respectively. Similarly, the best reported rates for potency were 94, 77 and 90% for RALP, LRP and RRP, respectively. With regard to the rate of return of potency, it has been reported that an earlier recovery was noted in the RALP group compared to the LRP group (RR 1.51; 95% CI 1.19, 1.92). This trend was seen at the 3-, 6- and 12-month follow-up periods [49, 54]. The advantage of RALP vs. LRP in potency rates was also noted in other studies [34, 35].

In their randomized trial, Porpiglia et al. [35] demonstrated that the continence rate was higher in the RALP group (80%) compared to the LRP group (61.6%) particularly at the 3-month follow-up ($p = 0.04$). Allan and Ilic [49] also noted this

Table 2 Oncological outcomes

	Positive surgical margins (%)	BCR-free survival, % (years)	Overall survival, % (years)
Open			
Han et al. [51]	10.30	84 (5)	96 (10)
Bianco Jr. et al. [52]	12.37	83 (6)	95 (CSS at 10)
Laparoscopic			
Hruza et al. [31]	6.8	70.3	93.2
Guillonneau et al. [53]	12	90.5 (3)	Not reported
Porpiglia et al. [35]	15.8	92.50	Not reported
Robotic			
Papachristos et al. [45]	2.9	95	Not reported
Porpiglia et al. [35]	13.2	98	Not reported

Table 3 Functional outcomes

	Continence, % (years) ^a	Potency, % (months) ^a
Open		
Ficarra et al. [16]	88	49
Bianco Jr. et al. [52]	91	63 (18)
Laparoscopic		
Soares et al. [28]	94 (5)	77
Porpiglia et al. [35]	83	54
Asimakopoulos et al. [34]	83	32
Robotic		
Papachristos et al. [45]	93	46
Asimakopoulos et al. [34]	94	77
Porpiglia et al. [35]	95	80

^a Values are calculated at 12 months unless otherwise stated

finding where a significantly higher rate of return to continence was seen in the RALP group compared to the LRP group (RR 1.14; 95% CI 1.04, 1.24). Although Asimakopoulos et al. [34] had a similar finding, their study did not attain statistical significance.

Learning Curve

It is evident that surgeon's experience and higher surgical volume are factors that influence patient outcomes [27, 36]. The learning curve is generally referred to as the number of cases required to be completed during which there is an improvement in the surgeon's skill at performing the procedure. With RP, this is generally manifest as an improvement in measurable outcomes such as operating time, blood loss, positive surgical margins, urinary continence rates, potency rates, peri-operative mortality, complications and length of stay. Whilst many of these outcomes have multiple contributing factors, surgical experience has been identified to influence at least some of them [55].

In line with this, a decrease in the overall likelihood of complications was noted with the doubling of caseload (OR 0.84 [0.82–0.87], $p < 0.001$) [56]. There was no difference in the 30- or 90-day mortality with increasing surgeon's experience [57].

LRP is a challenging procedure to master and requires significant time investment. An advanced level of laparoscopic skill is required as well as a skilled assistant [58]. Allan et al. found that the PSM plateaued after approximately 200–250 cases, suggesting this as the learning curve for LRP [49].

In another study, when comparing the rates of PSM and continence from an experienced RRP surgeon embarking on performing RALP, between 170 and 200 cases were needed before the outcomes were comparable [59].

Conclusion

RP is an increasingly common treatment option for localized prostate cancer. With long-term follow-up available and short learning curves, as well as minimally invasive modalities not proving to be superior to RRP in oncological outcomes or resulted in anticipated benefits to patients, RRP remains the gold standard technique for surgical removal of the prostate [60].

Recent trends, however, indicate growing numbers of cases being performed robotically. Whilst a great number of publications are available addressing the technique and outcomes of RRP, LRP and RALP, only a small number of randomized controlled trials have been attempted. This is likely due to patients being unwilling to be randomized to a surgical modality when confronted with the diagnosis of cancer. The perception of newer is better, and the more technologically advanced the equipment, the better it must be is likely to play a role in the patient's decision making.

Analysis of the literature thus far demonstrates minimally invasive surgery is associated with lower blood loss and transfusion rates, shorter operating times and shorter hospital stays. There is also a trend of an earlier return to continence and potency. There is no demonstrable improvement in PSM or in BCR-free survival in open vs. minimally invasive techniques. However, it must be noted that there is a learning curve with both LRP and RALP. The rates of blood loss, positive surgical margins, incontinence and potency are surgeon dependent.

RALP is a constantly evolving modality with improving oncological and functional outcomes. Surgical skill and technique remain to be important factors in successful outcomes more so than the modality utilized. Associated financial costs remain to be an inhibitor to the dissemination of the technology.

It is hoped that good quality randomized studies, utilizing consistent validated outcome measures, will be undertaken to support the growing body of evidence in support of minimally invasive RP.

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