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REVIEW

Is radical prostatectomy the best option for localized prostate cancer? Current opinion and research

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Abstract: Open radical prostatectomy is an effective treatment for prostate cancer with a 5-year biochemical recurrence-free survival rate of about 90% for localized disease. For men with organ confined disease, the 10 year disease-specific survival rate approximates 95% following retropubic prostatectomy. Attempts to improve survival rates by combining androgen deprivation therapy with radical prostatectomy have been unsuccessful. Erectile dysfunction and urinary incontinence are common complications following open radical prostatectomy. In an attempt to reduce morbidity, laparoscopic approaches have been developed with reported 8-year cancer control rates of about 70%. Robotic laparoscopic approaches yield a trifecta rate of achieving continence, potency and being prostate-specific antigen recurrence-free at 2 years of 74%. Comparative studies do not provide evidence that one surgical approach is superior. Few randomized trials have compared surgery with the other primary therapies for prostate cancer. A Scandinavian randomized study has reported that the metastatic rate and overall mortality are significantly better with surgery compared to watchful waiting. However, there are no published data from randomized trials comparing surgery with radiotherapy (external beam or brachytherapy), active surveillance or minimally invasive procedures. There are ongoing randomized trials comparing surgery with radiotherapy, brachytherapy, and active surveillance, but until these are published, there is no conclusive evidence that surgery is the best primary option for localized or locally advanced prostate cancer.

Keywords: prostatectomy, laparoscopic prostatectomy, radiotherapy, watchful waiting, active surveillance

Introduction

There are a number of treatment options for men with clinically localized or locally advanced prostate cancer and the debate as to which is superior spans decades. Options include watchful waiting, radiotherapy which may be external beam irradiation or brachytherapy (with or without hormone therapy), minimally invasive techniques such as cryotherapy and high intensity focussed ultrasound, and prostatectomy. A patient considering treatment will have to compare the procedural complexity, outcomes and quality of life associated with each modality to decide which is most suitable for them. This is a difficult task as the literature is extensive, complex and often biased.

The effectiveness of surgery (radical prostatectomy) as one of the standard treatments for localized prostate cancer is well established. The aim of radical prostatectomy is to provide cancer control by eradicating the entire prostate tumor whilst maintaining sexual and urinary function; collectively know as the 'trifecta' outcomes. The first prostatectomy was reported in 1867 by Billroth (as cited in Skrepetis et al[1]) and later

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described more fully by Young[2] in 1905. Millen[3] introduced the retroperitoneal approach in 1948 which provided a wider surgical field than the previous approach and allowed a simpler access to the pelvic lymph nodes. However, it was not until 1982 when Walsh[4] unravelled the prostate anatomy in detail, that radical prostatectomy was poised to make a major impact on the outcomes of men with prostate cancer.

Although radical prostatectomy is now a routinely performed operation, it remains a formidable procedure due to the location of the prostate gland deep within the pelvic cavity encircling the urethra. The complex vasculature surrounding the gland can result in a bloody surgical environment resulting in poor visualization and blood loss. In addition, the intricate network of the neurovascular bundle, responsible for erectile function, may not be anatomically distinct and requires intricate tissue manipulation to maintain potency. Therefore, it is not surprising that the outcomes following radical prostatectomy are strongly influenced by the experience of the surgeon. It has recently been reported that a surgeon does not reach optimum performance until 250 radical prostatectomies have been completed,[5] and that the surgeon's experience is strongly associated with cancer control.[6]

The two main approaches to open radical prostatectomy are retropubic and retroperitoneal and there is much current debate on the surgical superiority of one method over the other. The choice of procedure will often depend on the preference of the urologist rather than on anatomical considerations. At present there is minimal convincing evidence that one approach provides better surgical or oncological outcomes. However, one small randomized study suggests that the retropubic approach may be associated with more severe postoperative pain and analgesic requirement, whilst the retroperineal approach may induce less bleeding and a shorter hospital stay.[7] In experienced hands, there is little difference in the important outcomes for tumor control including surgical margin status, incontinence and potency between retropubic and retroperitoneal radical prostatectomy.

Outcomes following radical open prostatectomy

Due to the protracted natural history of prostate cancer, major outcomes such as disease progression and metastases may not be evident for some years following prostatectomy. The prostate cancer marker, prostate-specific antigen (PSA), is commonly used to follow the disease course and a rise in the serum level may predict clinical recurrence by several years giving rise to the concept of biochemical recurrence. Although highly dependent on stage of disease, the 5-year biochemical-free survival for men with localized or locally advanced disease following radical prostatectomy can be expected to approximately 90% (Table 1).[8–15]

A recent report of 1,150 men with localized prostate cancer, has demonstrated the excellent long-term outcomes following open retropubic prostatectomy.[15] For men with organ-confined disease, the 10-year disease-specific survival rate was 98%. In another large cohort study of 12,677 men, the 15-year prostate cancer-specific mortality and overall mortality following radical prostatectomy were 12% and 38%, respectively.[16] Similarly, out of 1,746 men with newly diagnosed localized prostate cancer, only 11% had died of prostate cancer at 15 years after surgery.[17] Survival outcomes for prostate cancer patients following radical retropubic prostatectomy appear not to be compromised in those men having previously received transurethral resection of the prostate[18] nor in selected elderly men aged over 70 years.[19]

In an attempt to improve outcomes of primary radical prostatectomy, a number of randomized trials have combined

Table 1 PSA recurrence following open radical prostatectomy

Study	Patient no. and stage	Follow up (years)	PSA recurrence
Han 2003[8]	2,091 T1c, T2	Median 5.9	17% recurred 5-year BRFS 84% 10-year 72% 15-year 61%
Helfand 2009[9]	1,886 T1a, T1b, T1c	Mean 4 (SD 3.3.)	8.7% recurred
Captanio 2008[10]	126 T1a, T1b	Not given	BFR 5-year: 10-year 92%:87%
Cronin 2010[11]	5,473 T2a–T2c	Not given	RFP 3-year: 5-year *86%–91%: 87%–91%
Caire 2009[12]	4,561 T2, T3, T4	>5 years	24% recurred at 5 years
Wood 2007[13]	1,915 T1, T2a–c, T3	Not given	BRFS 5-year 71%–88%**
Kordan 2009[14]	1,370 T2a T2c	Median 21 months	BRFS 96% 88%
Budaus 2009[15]	1,150 pT2 pT3a pT3b pT4	Not given	BRFS 10-year: 87% 53% 27% 6%

Notes: *Depending on definition of PSA recurrence; **Depending on race.
Abbreviations: BFR, biochemical-free recurrence; RFP, recurrence-free probability; BRFS, biochemical recurrence-free survival; PSA, prostate-specific antigen.

surgery with androgen deprivation therapy. This therapy exploits the growth retardation effect of lowering intraprostatic androgen levels. Current opinion on the use of androgen deprivation therapy prior to surgery (neoadjuvant) is divided. A recent meta-analysis of 10 randomized trials indicated that neoadjuvant androgen deprivation plus surgery, significantly reduced the rate of surgical margins but did not significantly improve the overall survival.[20] Although tumor volume is reduced with neoandrogen deprivation therapy, there does not appear to be an improvement in the surgical procedure of prostatectomy in terms of blood loss and operation time. In addition, androgen deprivation therapy is associated with significant side-effects, such as cardiac toxicity. As a result of these factors, neoadjuvant androgen deprivation therapy should not be routinely offered as a treatment option for men with localized prostate cancer. There are limited data from randomized trials on the use of adjuvant androgen deprivation therapy following surgery (adjuvant) and its use remains controversial. In a second meta-analysis of four randomized trials, adjuvant androgen deprivation therapy after surgery improved disease-free survival but not overall survival.[21] Consequently, the precise role of adjuvant androgen deprivation therapy combined with surgery has yet to be established.

Radical prostatectomy for patients at high risk of recurrence or progression is controversial and major guidelines recommend radiotherapy with androgen deprivation for this group. However, some series have reported that major oncological outcomes may be favorable after radical prostatectomy for high-risk prostate cancer; with 5–15 year cause-specific survival of 80%–90% (Table 2).[22–31] These data suggest that radical prostatectomy in select high risk patients should be considered a feasible treatment option. However, many of the published surgical series were retrospective and uncontrolled

Table 2 Outcomes for men with high risk prostate cancer following prostatectomy

Study	Patients	Risk factors	Outcomes
Inman 2009[22]	236 T1–T4	Preoperative PSA > 50 ng/mL	PSA 50–99 >100 ng/mL 10 year BRFS 43% 36% 10 year PFS 83% 74% 10 year CSS (combined) 87%
Kawamorita 2009[23]	252	GS 8–10 PSA > 20 ng/mL T3a–T3b	PSA FFS 65% at 39 months
Loeb 2007[24]	288	cT2b GS 8–10, PSA > 15 ng/mL	7 year 10 year PFS 39% 35% CSS 92% 88% OS 91% 74%
Carver 2006[25]	176	T3 (mean follow up 6.4 year)	Recurrence 48% BRFS 5 year 48%, 10 year 44% CSM 5 year 6%,10 year 15%,15 year 24%
Ingaki 2009[26]	106	pT3 (mean follow up 18 months)	1 and 3 year recurrence 54% and 34% Biochemical progression 57%
Xylinas 2008[27]	100	T3 (median follow up 69 months)	5 year BRFS 45% 5 year CSS 90%
Freedland 2007[28]	58	T3a	15 year BRFS 49% 15 year MFS 73% 15 year CSS 84%
Ward 2005[29]	842	cT3 (median follow up 10.3 year)	Freedom from local or systemic disease: 5 year 10 year 15 year 85% 73% 67% CSS 95% 90% 79%
Loeb 2010[30]	175	>T2c GS 8–10 PSA > 20 ng/mL	10 year BRFS 68% MFS 84% CSS 92%
Pierorazio 2010[31]	1061 T1–T3	GS 8–10	15 year RFS 20.7% CSS 57.4% OS 45.4%

Abbreviations: PSA, prostate-specific antigen; BRFS, biochemical recurrence-free survival; PFS, progression-free survival; CSS, cause-specific survival; GS, Gleason score; FFS, failure-free survival; CSM, cause-specific mortality; MFS, metastasis-free survival; OS, overall survival.

and the impact of surgical management for high risk patients, either alone or in combination with other modalities, can only be accurately assessed in prospective randomized studies. In men with positive lymph nodes undergoing radical prostatectomy and lymphadenectomy, recurrence-free survival disease-specific survival and overall survival may be influenced by the diameter of the metastatic lesions; the larger metastases being associated with poorer outcomes.[32]

Complications of open radical prostatectomy

An improved awareness of the autonomic innervation of the corpora cavernosa and preservation of the neurovascular bundle has resulted in a high proportion of men maintaining erectile function following radical prostatectomy. In experienced hands, surgical preservation of the neurovascular bundle correlates positively with an improved recovery of erectile function and does not appear to increase the rate of positive surgical margins nor biochemical recurrence.[33]Approximately 80% of men undergoing prostatectomy are eligible for complete sparing of the neurovascular bundle and modern surgical approaches for this procedure have been described.[34–36]

There are a number of published series reporting potency after nerve-sparing surgery. The most commonly used intrafascial technique is that originally described by Walsh.[37] A recent study reported that at one year following intrafascial nerve-sparing open prostatectomy, 53% to 92% of men aged over 60 years had erections suitable for intercourse, depending on whether nerve sparing was uni- or bilateral.[15] Other advances in surgical technique suggest that the use of high anterior release of the levator facia during nerve-sparing open radical retropubic prostatectomy considerably improves sexual potency.[38] Using the Sexual Health Inventory for Men, patients with clinically localized prostate cancer and undergoing high release of the levator fascia were more likely to score 16 or higher compared to those not receiving high release levator fascia surgery (93% versus 77%; $P = 0.007$). Return to baseline sexual activity was also superior for those men in the treatment group (78% versus 52%; $P < 0.05$). The rate of positive surgical margins in this study was low (1.3%–1.5%) and was not significantly different between the two groups. Other centers have confirmed an improved sexual function using this surgical technique.[39]

Urinary incontinence is a common complication following prostatectomy and can severely impact on a patient's quality of life. However, a better appreciation of the anatomy and function of the external urinary sphincter over recent years has resulted in improved urinary control for many men following surgery. At one year following intrafascial nerve-sparing open prostatectomy up to 97% of men aged over 60 years may have complete urinary continence.[15] A review of surgical series demonstrates that urinary control continues to improve with time after prostatectomy and most men plateau at 1–2 years.[40,41] Factors influencing the return of urinary control include increasing patient's age, preservation of the neurovascular bundle, incidence of an anastomotic stricture and definitions of incontinence.

Laparoscopic radical prostatectomy

In an attempt to reduce the morbidity associated with open radical prostatectomy, minimally invasive laparoscopic approaches have been developed. Many reports on laparoscopic radical prostatectomy have appeared in the literature since the introduction of this technique in 1992 by Schuessler and colleagues.[42] In many centers worldwide laparoscopic radical prostatectomy is currently being introduced as a feasible surgical option for localized prostate cancer. The patient may perceive laparoscopic radical prostatectomy as a simpler and potentially less morbid procedure consequently favoring this option compared to open radical prostatectomy. A number of studies from Europe, USA and Canada have reported favorable short-term outcomes for laparoscopic radical prostatectomy.[43–46] Intraoperative complications were low ranging from 8% to 12%. The ranges for the positive surgical margin rate increased with stage and for pT2 and pT3 tumors were respectively 0%–20% and 39%–67%, with an overall rate of 27% in one study. The PSA recurrence-free rate at one year was 95%, with PSA recurrence-free survival rates of 72%–95% at 1–5 years. Clinical progression was seen in 4% at 3 years with a low mortality rate of 0.3% and overall survival of 99%.

Longer follow up was reported in a recent study of 1564 consecutive patients with localized disease.[47] Laparoscopic radical prostatectomy achieved 5 year and 8 year cancer control in 78% and 71%, respectively, with 5 year results of 53% for high risk patients. However, this report was from two high volume centers in Paris and New York and the data were from one or two surgeons, therefore whether these data can be generalized is debatable.

As seen with open prostatectomy, adequately supervised training for the laparoscopic approach is essential to maintain surgical competence with acceptable oncological outcomes. A study of 1,000 cases in the UK suggested that there were several learning curves depending on the outcome of interest.[48] The plateau for reducing blood loss was reached

following 150 procedures, whereas up to 200 laparoscopies were required for optimum control of complications and continence. Maximum surgical competence for maintaining potency in patients was not achieved until 700 procedures had been performed. A large retrospective study of 4,702 men undergoing laparoscopic radical prostatectomy reported that a patient's risk of recurrence at 5 years, decreased from 17% to 9% when treated by surgeon who had preformed either 10 or 750 laparoscopies.[49] This has important implications for patients deciding to accept the laparoscopic surgical approach to prostatectomy. It should also be noted that the variation in surgical ability may be a confounding factor when comparing studies, both within the same technique and between different surgical approaches.

Robotic assisted laparoscopic radical prostatectomy

The use of robotic assistance for minimally invasive radical prostatectomy was first reported in 2001 by Binder.[50] Since then advances in robotic technology have dramatically increased its use, especially in the United States where today over 60% of radical prostatectomies are performed robotically. The attractions of robotic laparoscopic radical prostatectomy for the surgeon include the magnified 3D visualization, reduced tremor, instrument articulation and improved ergonomics. However, there are disadvantages of using the robotic approach such as the loss of tactile feedback, the steep head-down body positioning, and the longer operating times. Although there is understandable enthusiasm for this technique, there remains considerable controversy concerning the relative surgical and oncological benefits.

A recent review of surgical series of robotic assisted radical prostatectomy summarized data from 16 studies published between 2006 and 2009.[51] The weighted mean operative duration was 117 minutes with a considerable range of means (105–236 min). The weighted mean estimated blood loss was 169 mL (103–609 mL) with a transfusion rate of 1.4%. The duration of hospitalization averaged 1.6 days. The complication rate was 10.5%, however, comparison between studies was difficult due to the varied definitions of complications. The rate of positive surgical margins is an important determinant of prostate surgery effectiveness and a mean overall estimate of 15% (range of means 9%–33%) was reported. The mean continence and potency rates at one year determined from 11 studies was 91% and 71%, the latter increasing to >94% at 18 months and beyond. Local hypothermia by cold intracorporeal irrigation and an endorectal cooling balloon, may reduce the incidence of incontinence during robotic radical prostatectomy, especially among the older patient.[52] Using standardized criteria for collecting and reporting postoperative complications following robotic-assisted radical prostatectomy, approximately 20% of men experience early complications, mostly mild, but grade 3 to 4 were seen in 3%.[53] There are few long-term outcomes available for robotic assisted radical prostatectomy, however, in a large series of 2,766 consecutive men, the 5-year biochemical-free survival was 84%.[54] Another recent, prospective series of 1,362 consecutive men, examined the trifecta outcomes after robotic assisted radical prostatectomy.[55] The trifecta rate of achieving continence, potency and being PSA recurrence-free was 74% at 2 years, using subjective definitions of continence and potency. These compare well with other surgical procedures for prostate cancer and provides evidence that robotic assisted radical prostatectomy is a feasible surgical option for men with this disease.

Open or laparoscopic radical prostatectomy?

The debate among surgeons as to which surgical option for radical prostatectomy is superior is currently vigorously debated. Urologists tend to advocate their own area of expertise. A meta-analysis of 19 observational studies published up to 2006 and including 3,893 patients compared retropubic prostatectomy with laparoscopic and/or robot-assisted prostatectomy.[56] The laparoscopic approaches were associated with a significant reduction in blood loss compared to open prostatectomy and were 17% less likely to require a blood transfusion. There was no significant difference in the overall rate of positive surgical margins. There was no significant difference in incontinence between groups at one year (relative risk 1.07, 95% confidence interval [CI]: 0.75–1.5; $P = 0.70$). There was a trend to increasing potency in the laparoscopic group but this was not statistically significant (relative risk 1.28, 95% CI: 0.96–1.5; $P = 0.09$). Although this meta-analysis provides useful information for discussion it should be noted that no randomized studies were available for analysis and that the definition of outcomes between studies were variable.

Recently a multinational, European group has published a systematic review citing 37 comparative studies of retropubic, laparoscopic and robot-assisted radical prostatectomy published up to January 2008.[57] Of these studies, 23 compared retroperitoneal with laparoscopic prostatectomy, 10 compared retroperitoneal with robotic laparoscopic prostatectomy and 4 compared robotic laparoscopic prostatectomy with laparoscopic prostatectomy. The perioperative parameters

of blood loss, transfusion rate, catheterization time, hospital stay and overall complication rate were significantly in favor of laparoscopic prostatectomy, whereas operative time was significantly shorter for retropubic prostatectomy. Analysis of four small, prospective studies demonstrated no significant difference in transfusion rates for retropubic versus robotic laparoscopic prostatectomy. A few studies compared the postoperative pain associated with retropubic and laparoscopic prostatectomy but the data were conflicting and inconclusive. The cumulative analysis for incontinence indicated that there was no significant difference between retropubic and laparoscopic prostatectomy (relative risk 0.87, 95% CI: 0.54–1.39; $P = 0.56$). Similarly, there was no evidence that one surgical approach was superior with regard to potency. Analysis of 16 studies reporting positive margin rates suggested that the rates were similar between retropubic and laparoscopic prostatectomy. Data from three Japanese studies failed to show any difference in quality of life following either surgical approach. The available data for this systematic review did not provide evidence of superiority of one surgical approach, however, the evidence base was of low quality with only one randomized study with data derived from one surgeons experience.

The comparative effectiveness of minimally invasive radical prostatectomy versus open radical prostatectomy has recently been reported by Hu and colleagues.[58] This observational study used data from the US Surveillance, Epidemiology, and End Reporting Medicare linked data on 1,938 men with prostate cancer undergoing minimally invasive radical prostatectomy and 6,899 undergoing open radical prostatectomy. They report that the use of minimally invasive radical prostatectomy increased from 9% in 2003 to 43% in 2006–2007 for all radical prostatectomies performed. There were significant demographic characteristics to those receiving minimally invasive radical prostatectomy; they were more likely to be caucasian, live in an area with >90% high school graduation rates, and a median income of at least US$60,000. Compared to open radical prostatectomy, men receiving minimally invasive radical prostatectomy had a shorter hospital stay, fewer respiratory and miscellaneous surgical complications and strictures, but experienced more incontinence and erectile dysfunction. However, there are a number of limitations to his study. The Medicare data was designed to facilitate billing information not detailed clinical information, and thus may have missed some important data. The short-term data follow-up may not be long enough to detect differences in cancer recurrence. In addition, the data could not distinguish whether nerve-sparing surgery was used, which may influence postoperative sexual function, or whether robotic surgery was used. Finally, there are questions about the generalizability of the data to younger men undergoing radical prostatectomy.

The largest series of 4,592 patients reporting on complications using standardized criteria (modified Clavien classification) following retropubic or laparoscopic prostatectomy found that medical and surgical complications were present in 8.8% and 18.7% of patients following retropubic prostatectomy and 14.5% and 24.5% of laparoscopic patients, respectively.[59]

There is little direct comparative data regarding early oncological outcomes for the different surgical approaches to radical prostatectomy. In one large series,[60] biochemical recurrence-free survival at 3 years was reported as 83.5% for retropubic prostatectomy and 84.0% for robotic laparoscopic prostatectomy ($P = 0.19$). In a matched comparison, the 3-year biochemical progression-free survival was similar for open retropubic and robotic laparoscopic techniques (92.2% and 92.4%, respectively, $P = 0.69$). At 5 years the PSA-free recurrence rates were 87.8%, 88.1% and 89.6% for open, laparoscopic, and robotic laparoscopic prostatectomy ($P = 0.93$). These studies indicate no significant difference in early oncological outcomes for the different surgical approaches to prostatectomy. However, two of the studies were retrospective, and until data from high quality randomized studies are available the contentious debate on prostatectomy methods will continue.

Prostatectomy outcomes compared to other treatment modalities

The debate of whether radical prostatectomy is the treatment of choice for clinically localized prostate cancer is long-standing. High quality evidence from contemporary clinical trials comparing radical prostatectomy with radiotherapy, surveillance, brachytherapy or minimally invasive techniques is either lacking or limited (Table 3).[61–69] Two early randomized studies compared prostatectomy against radiotherapy, using doses of 40–50 Gy to the whole pelvis with a 20 Gy prostatic boost.[61,62] A significant difference in disease progression was reported in favor of radical prostatectomy, although there was no significant difference in overall survival. However, the poorly reported randomization methods, the small sample populations and several design limitations in these studies, do not permit a definite conclusion to be made between surgery and radiotherapy.

Table 3 Clinical studies comparing radical prostatectomy with other primary treatments for localized prostate cancer

Study/design	Patients	Outcome	Surgery	Radiotherapy	Brachy-therapy	Watchful waiting
Paulson 1988[61]	106 T1–2	Progression:	10%	30% ($P = 0.04$)	–	–
RCT	5 years FU	Metastases:	5%	25%	–	–
Akakura 1999[62]	95 T2b–T3,	5-year BFFS:	90%	81% ($P = 0.04$)	–	–
RCT	median FU	5-year DSS:	97%	85% ($P = 0.02$)	–	–
	58.5 months	5-year OS:	86%	76% (NS)		
D'Amico 2007[63]	948 T1c–T3b	PCSM:				
Cohort	median FU	1 risk factor	2%	4%	–	–
	5.4 years	2 risk factors	7%	4%	–	–
		3 risk factors	14%	23%	–	–
		4 risk factors	40%	40%	–	–
Aizer 2009[64]	556 T1–T3	5-year BDFS:		IMRT		
Cohort		Low risk	92%	85% ($P = 0.02$)	–	–
		Intermediate	87%	82% ($P = 0.46$)	–	–
		High risk	38%	62% ($P < 0.001$)	–	–
Takizawa 2009[65]	162 T1–T3	5-year BRFS:				
cohort		Low risk	75%	75% ($P = 0.93$)	–	–
		Intermediate	61%	71% ($P = 0.69$)	–	–
		High risk	45%	80% ($P = 0.002$)	–	–
Klein 2009[66]	861	8-year BRFS:	63%	75%	82% ($P = 0 .52$)	–
cohort study		8-year RFS:	98%	90%	81% ($P = 0.02$)	–
		8-year OS:	88%	82%	94% ($P = 0.05$)	–
Giberti 2009[67]	200 T1c or T2a	BDFS:	91%	–	92%	–
RCT	5-year FU					
Byar 1981[68]	142 T1–T2,	Progression:	11.5%	–	–	18% (NS)
RCT	FU 6.6–7.7 years	Metastases:	9.8%	–	–	6% (NS)
		OS:	Stage I 00%	–	–	Stage I 60%
			Stage II 76%	–	–	Stage II 84%
Bill-Axelson 2008[69]	695	OM:	33%	–	–	40% ($P = 0.09$)
RCT	median	DSM:	13%	–	–	18% ($P = 0.03$)
	10.8 years	Metastases:	19%	–	–	26% ($P = 0.06$)

Abbreviations: RCT, randomized controlled trial; FU, follow up; NS, not significant; PFS, progression-free survival; OS, overall survival; DSM, disease-specific mortality; BRFS, biochemical recurrence-free survival; RFS, recurrence-free survival; IMRT, intensity modulated radiotherapy; BDFS, biochemical disease-free survival; BFFS, biochemical failure-free survival; PCSM, prostate cancer specific mortality.

Several comparative, retrospective cohort studies have been published that report oncological outcomes for prostatectomy and radiotherapy. D'Amico and colleagues[63] estimated the prostate cancer-specific mortality following radical prostatectomy or radiotherapy and stratified patients according to the number of risk factors they presented with. As to be expected the mortality rate increased with the number of risk factors but the proportions in each risk group did not differ significantly between treatment modalities.

A retrospective cohort analysis suggested that 5-year biochemical disease-free survival for low and intermediate risk prostate cancer were similar for those men receiving surgery or intensity modulated radiotherapy, but was significantly better for those patients with poor prognosis following radiotherapy T dose of ≥72 Gy plus androgen deprivation therapy.[64] The benefit of radiotherapy for high risk patients was also demonstrated in a recent, small cohort study from Japan.[65]

Using the Localized Prostate Cancer Database at the Cleveland Clinic (OH, USA), outcomes for consecutive men with intermediate risk prostate cancer receiving radical prostatectomy, radiotherapy or brachytherapy between 1996 and 2004 were analyzed.[66] The data showed no significant difference in biochemical relapse-free survival between groups. A statistically significant improvement in the rate of clinical failures and overall survival was observed favoring surgery. However, the number of events influencing clinical failure (distant metastases) and overall survival (deaths) were less than 2% making interpretation of the data weak.

A prospective randomized study of low risk prostate cancer patients recently reported on the comparison of surgery versus brachytherapy.[67] This study demonstrated no difference in the 5-year biochemical-free survival between the two groups. Brachytherapy was associated with a higher rate of urinary irritative disorders, but better rates of potency.

At one year post-treatment, both groups reported a significant worsening of physical and emotional functions. The study requires longer follow up to determine overall survival differences.

The first randomized study comparing prostatectomy with watchful waiting was conducted by the Veterans Administration Cooperative Urological Research Group.[68] This study reported no significant difference in rates of progression, the development of distant metastases and overall survival. A 23-year follow up indicated the median unadjusted survival was 10 years and 6 years for the prostatectomy and watchful waiting groups, respectively. A major criticism of this study is that it predates the use of PSA and that the methods used may not be comparable to modern surgery and radiotherapy techniques. More recently a well conducted Scandinavian randomized study comparing surgery with watchful waiting has reported long-term mortality data.[69] These data suggest that the metastatic rate, overall mortality and disease-specific mortality are significantly better with radical prostatectomy compared with watchful waiting. These differences remained stable at 10 years post-treatment. This study provides high quality evidence that outcomes following surgery are excellent compared to watchful waiting and that large randomized trials in localized prostate cancer are possible. However, it should be noted that surgery was associated with greater erectile dysfunction and urinary leakage. In addition, the majority of prostate cancers were not detected by PSA testing, raising the debate of how generalizable the results of this study are.

The majority of the available evidence presented in Table 3 comparing prostatectomy with radiotherapy for localized or locally advanced prostate cancer is of poor quality and does not provide a basis for a firm conclusion to be made. The Scandinavian study,[69] however, is of high quality and provides strong evidence that prostatectomy is significantly better than watchful waiting, at least up to 12 years post-treatment.

Comparative health-related quality of life estimates following primary therapies

The lack of conclusive oncological outcome data between primary treatment options for localized and locally advanced prostate cancer emphasises the importance of quality of life (QOL) issues in patients' decision making. Many recent studies have examined quality of life following treatment and have shown that the choice of treatment has a considerable impact (Table 4).[70–75]

A controlled study examined the negative effects three years after treatment for localized prostate cancer and reported worse urinary function associated with surgery; whereas bowel function was poorest with radiotherapy.[70] Sexual dysfunction was similar between groups. One study examined the QOL after radical prostatectomy, radiotherapy or brachytherapy and demonstrated QOL varies as a function of treatment.[71] A general health-related QOL questionnaire was used (Medical Outcomes Study Short-Form 36 [SF-36]), composed of physical (PCS) and mental (MCS) component scores, and a specific health-related quality of life (HRQOL) questionnaire with domains of urinary, sexual and incontinence. At 2 years these three QOL measures were worse with prostatectomy. There were minimal differences between radiotherapy and brachytherapy, although the latter had slightly greater urinary irritation compared with the two treatments.

An American study examined the differences in QOL in men with localized prostate cancer receiving radical prostatectomy, intensity modulated radiotherapy (IMRT) plus high-dose rate brachytherapy or IMRT plus temporary seed implant brachytherapy.[73] They report that men receiving either of the radiotherapy regimes had significantly higher bowel and urinary QOL scores at 6 and 12 months post-treatment compared to those men receiving surgery. No difference in QOL outcomes associated with sexual function was observed.

Kobuke and colleagues[75] used a general (SF-36) and specific (PCI) HRQOL assessment for men undergoing prostatectomy or brachytherapy. Disease-specific quality of life following surgery scored low for both urinary and sexual function compared to brachytherapy. However, patients receiving brachytherapy had lower scores for general and mental health.

A recent systematic review compared QOL outcomes following prostatectomy, radiotherapy, brachytherapy, and cryotherapy.[76] It concluded that robotic and open radical prostatectomy had similar sexual and incontinence QOL outcomes and both surgical procedures were worse than the other treatment options. Bowel QOL was worse with radiotherapy, whereas brachytherapy was associated with the most irritative urinary symptoms. Sexual function was significantly impaired with cryotherapy.

It appears that each treatment modality for localized prostate cancer is associated with a specific QOL scenario, with variation in the extent of sexual, urinary and bowel QOL

Table 4 Contemporary studies comparing quality of life estimates following prostatectomy with other primary treatments

Study/design	Patients	Outcome	Surgery	Radiotherapy	Brachytherapy	Watchful waiting
Smith 2009[70]	1,642 patients	3-year domain score:			(high-dose rate)	
	495 controls	Physical	50	47	49	47
		Mental	53	53	52	53
		Urinary	86	93	90	92
		Bowel	89	86	88	87
		Sexual	72	32	66	44
Gueda 2009[71]	304 T1–T2 (QOL at 2 years)	Mean change from baseline:				
		General				
		PCS	–4	–3	–3 ($P = 0.8$)	–
		MCS	1.1	1.4	0.1 ($P = 0.6$)	–
		Specific				
		Incontinence	–27	–4	–12 ($P < 0.001$)	–
		Sexual	–27	–7	–6 ($P < 0.001$)	–
		Bowel	0.03	–2.3	–0.4 ($P = 0.2$)	–
Wyler 2009[72]	212	Mean global health score	78	83	–	–
	Mean FU 2 years	(higher = better)	(range 1–100)	(range 33–100)		
Lev 2009[73]	159 T1–T2	QOL score at 12 months relative to baseline:		IMRT + HDR	IMRT + seed*	
		Sexual -				
		Urinary -	+13	+10	+10	–
		Bowel -	–4	+2	+8	–
			–0.3	+5	+4	–
Hashine 2008[74]	122 T1c–T2	General HRQOL	PF: 89	–	87	–
		scores at 12 months	RP: 86	–	83	–
			BP: 86	–	86	–
			GH: 63	–	65	–
			VT: 71	–	69	–
			RE: 89	–	91	–
			RE: 89	–	84	–
			MH: 76	–	77	–
Kobuke 2009[75]	73 T1–T2	General (1 year)				
		scores				
		PCS	94	–	88	–
		MCS	82	–	76	–
		Specific				
		Incontinence	62	–	82	–
		Sexual	10	–	39	–
		Bowel	92	–	86	–

Note: *Temporary seed implant brachytherapy.

Abbreviations: HRQOL, health-related quality of life; PF, physical functioning; RP, role physical; BP, body pain; FU, follow-up; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; PCS, physical component score; MCS, mental component score; IMRT, intensity modulated radiotherapy; HDR, high-dose rate brachytherapy.

issues. Often data from different studies are inconsistent and may reflect the method of assessment and also the varying time-points following treatment. It should be noted that irrespective of the treatment, the patients' quality of life concerning sexual function may significantly effect the satisfaction of treatment outcome in spouses or partners.[77] However, the available QOL evidence suggest that patients undergoing surgery are more likely to suffer QOL issues related to incontinence, those receiving radiotherapy have worse bowel QOL problems and those receiving brachytherapy tend to have decreased QOL related to greater irritative urinary and obstructive symptoms. It is clear that QOL can be adversely affected by all forms of local therapy for prostate cancer with none providing a significantly superior outcome.

Conclusions

For men with localized prostate cancer there remains uncertainty concerning the relative effectiveness of primary treatments for their disease. Data from clinical studies have shown that radical prostatectomy is an effective treatment option. However, due to the paucity of comparative data, the question of whether it is the treatment of choice cannot

be answered definitively at present. There are no published data from randomized controlled trials directly comparing the commonly used primary treatment modalities. At present, there is only one randomized trial that provides convincing evidence that radical prostatectomy affords better cause-specific and overall survival compared to watchful waiting.[69] Whether this benefit is generalizable to active monitoring and remains beyond 12 years remains to be established.

There are a number of ongoing randomized trials that will contribute useful comparative data on the treatment options for localized prostate cancer. The PROTECT study (Prostate Testing for Cancer Treatment) is a randomized trial recruiting from nine cancer centers in the UK and is directly comparing radical prostatectomy, radiotherapy and active monitoring. The study was open to treatment from 2001–2008 and aims to provide outcome data at 5 and 10 years. The trial will investigate general health, QOL, prostate cancer development, treatment outcomes and cost implications.

The PIVOT study (Prostate Cancer Intervention versus Observational Trial) started in 1992 and is based in the USA. This study is comparing radical prostatectomy with watchful waiting in 731 men with T1 or T2 tumors detected by PSA measurement. The primary outcome of interest is overall mortality with secondary outcomes of QOL and treatment related adverse effects. This study is now approaching completion and should report in the near future.

The third study is the START (Standard Treatment Against Restricted Treatments) multinational randomized trial involving centers in Canada, USA and UK. This trial is comparing active surveillance versus radical prostatectomy, radiotherapy and brachytherapy and aims to recruit 2130 men with low-risk prostate cancer. The main outcome is disease-specific survival, but the trial is at an early stage of development.

The publication of results from these three randomized trials are eagerly awaited by clinicians and patients. The data will strengthen the evidence base for making informed decisions on treatment options for localized prostate cancer. The Agency for Healthcare Research and Quality has recently undertaken a comprehensive review comparing outcomes of primary therapy for localized prostate cancer.[78] They conclude that due to the limitations of evidence, no one therapy can be considered the preferred treatment option. The data presented in this present review supports these findings. Therefore, until new data are available from randomized studies on the treatment outcomes and QOL, the man with localized prostate cancer remains in a quandary.

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