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Surgical management of prostate cancer: Advances based on a rational approach to the data

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Abstract

The management of localised prostate cancer has undergone important changes in the past two decades, with major improvements in surgical technique, a greater emphasis on structured assessment of quality of life, and a greater attempt to tailor treatment to biological risk. Disease diagnosis is predicated on identification of demographic risk factors, serum levels of prostate-specific antigen and its derivatives, and extended biopsy techniques. Surgical removal of the prostate may be accomplished by open or minimally invasive techniques and in experienced hands results in good functional outcomes a high rate of cure for those with organ confined disease. Radical prostatectomy is also appropriate in selected patients with locally advanced disease and after failed radiation therapy.

Keywords: Prostate cancer; Radical prostatectomy; PSA; Prostate biopsy

1. Introduction

The management of localised prostate cancer has undergone important changes in the past two decades, with major improvements in surgical technique, a greater emphasis on structured assessment of quality of life, and a greater attempt to tailor treatment to biological risk. Many developments have had an impact on the outcomes of such treatment, including the evolution of stage migration (via the increased use of screening and of prostate-specific antigen (PSA) determinations in follow-up), changes in the demography of prostate cancer in different racial groups, improved precision in molecular prediction and prognostication, and a greater use of adjunctive systemic therapy to improve outcomes for patients with poor prognostic factors.

This paper reviews the changing demography of surgery for prostate cancer, and analyses critically the impact of emerging changes in science, diagnostics, prevention and therapeutics on results of surgery for localised prostate cancer.

2. Diagnosis

Histopathological examination of whole mount sections of radical prostatectomy (RP) specimens provided information about the zonal anatomy of the prostate and identified the peripheral zone as the most common site of origin for adenocarcinoma of the prostate [1]. Clinically, this information translated into development of a prostate biopsy regimen that sampled the lateral

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aspects of the peripheral zone for improved cancer detection [2–5]. PSA-induced stage migration, which resulted in majority of newly diagnosed cancers presenting in glands were palpably feel normal, made finger-guided techniques, which sampled only palpably abnormal areas outdated. With increased use of ultrasound-guided systematic sextant biopsies it became evident that this technique was associated with false-negative biopsy rates of 20% in certain PSA ranges [2,5]. Therefore, modifications of biopsy protocols and indications for re-biopsy of men with persistent suspicion of prostate cancer have been defined. Current biopsy regimens also help to define both prognosis and the need for, and aggressiveness of, therapy for individual patients.

2.1. Indication for prostate biopsies

The decision to perform a prostate biopsy should be taken only when a diagnostic or therapeutic consequence is foreseeable. It is important to be aware of the life expectancy of the individual and the cancer-specific mortality rate in cases of a positive result [6].

2.2. Prostate-specific antigen

Elevated serum PSA is the single most common indication for prostate biopsy. The likelihood that an individual has prostate cancer increases with increasing serum PSA-concentrations, even for PSA < 4 ng/ml, and there is no PSA level below which there is no risk of prostate cancer [7,8]. Retrospective studies suggest that PSA-elevations due to prostate cancer precede a palpable lesion by more than 6 years [9]. Other common disorders, such as benign prostatic hyperplasia (BPH) [10] and chronic prostatitis [11] may result in elevated concentrations of PSA. In men with BPH and clinically localised prostate cancer, PSA-levels overlap in a significant number of cases [12]. Moreover, BPH and prostate cancer frequently coexist in the same prostate [13]. In most practices a serum PSA > 4 ng/ml in a man with no special risk factors is considered an indication for biopsy; lower cut-offs may be used in those at higher risk by virtue of age, family history or race.

Men with PSA levels <4 ng/ml were initially considered low-risk for prostate cancer. However, cancer was detected in 15% of men with normal digital rectal examination and PSA < 4 ng/ml in the placebo arm of the Prostate Cancer Prevention Trial [8]. Fifteen percent of these cancers (or 2.25% of the total) were Gleason sum $\geqslant 7$ or greater. These data have been interpreted as support for lowering the cut-off for biopsy to 2.5 ng/ml in younger men. The PSA-range of 4–10 ng/ml, commonly referred to as the diagnostic grey zone, does not provide significant information as to whether PSA is elevated due to cancer or benign disease, and PSA in this range may be more reflective of prostate volume than the risk of cancer. Total PSA values >10 ng/ml have a positive predictive value (PPV) of about 50% and it is therefore common practice to perform biopsy in men with PSA values in this range even in the presence of a normal DRE [14].

2.3. Derivatives of total PSA

The arbitrary limit of 4 ng/ml PSA does not compensate for increasing prostate volume with age. This observation serves as the basis for defining age-specific PSA ranges, introduced to improve sensitivity of detection in younger patients and improve specificity by avoiding the detection of insignificant cancers in older patients [15]. In an evaluation of almost 4600 men using age-specific PSA ranges, detection of prostate cancer increased by 18% in younger men, but decreased by 22% in older men [16]. In men <60 years old, pathological findings were favourable (organ- or specimen-confined, Gleason score <7, no evidence of lymph node metastases or seminal vesicle invasion) in 80% of the cancers. The comparison of age-specific PSA-ranges with normal PSA cut-offs of 4 ng/ml in another screening population showed that the number of cancers detected increased by 8% using age-specific ranges in men under 59 years of age when digital rectal examination was unremarkable [17]. It was concluded that age-specific PSA-ranges improve sensitivity in younger populations. However, not all studies have replicated these findings and the standard PSA cut-off of 4 ng/ml may be the optimal and most cost-effective tool for all age groups [18]. Age-specific PSA ranges should be used with careful consideration, given the possibility of missing biologically significant and potentially curable cancers in the older population. Moreover, they are not approved by the US Food and Drug Administration (FDA) or the manufacturer, and a single cut-off may be easier to use in clinical practice.

The rationale for *PSA-density* (PSA-D) is based on the observation of a positive association of increasing prostate volume, and PSA levels secondary to benign hyperplasia [19]. PSA-D divides the serum PSA concentration by prostatic volume to adjust PSA concentration for prostate size. Since only prostatic epithelium produces PSA and the amount of stroma cannot be estimated from transrectal ultrasound (TRUS), this influences calculation of PSA-D to an unforeseeable extent, and results of biopsy schemes using PSA-D have not been uniform [12,13]. Using a PSA-D cut-off of 0.15 ng/ml, an initial report found that PSA-D enhanced prostate cancer detection when total PSA was below 10 ng/ml. Other studies reported that about 50% of all prostate cancers would have been missed using this cut-off or failed to find any statistically significant difference in men with positive or negative biopsy results when PSA-D was used [21,22]. Therefore, the role of

PSA-D in the early detection of prostate cancer has not yet been proven to be useful when PSA is 4–10 ng/ml and digital rectal examination is not suggestive of cancer.

A modification of PSA-D, transition zone density (PSA-TZD) normalises serum PSA to the transition zone volume [23]. It focuses on the assumption that, histologically, hyperplasia occurs almost exclusively in the transition zone. In an initial study with a cut-off of 0.35 ng/ml, the highest PPV for prostate cancer detection was found using PSA-TZD (74%). However, methodological problems of volume measurement and epithelial-to-stroma ratio affect PSA-TZD in the same way as simple PSA-D. For this reason PSA-TZD cannot be considered to be a routine tool for prostate cancer detection.

In contrast to the static analyses described above, *PSA velocity* (PSAV) describes dynamic PSA level changes over time. A PSAV of $\geqslant 0.75$ ng/ml/year results in detection of prostate cancer with 72% sensitivity and 95% specificity [25,26]. Significant differences in PSA velocity in BPH compared with prostate cancer were detectable up to 9 years before prostate cancer had been diagnosed. The clinical utility of PSAV is limited by the fact that PSA is not cancer-specific, and that there is significant intra-individual day-to-day-variation of PSA concentration in blood [27]. Moreover, short episodes of PSA elevation may interfere with the normal elevation of PSA over time.

2.4. Free PSA

The majority of all PSA is found in stable complex with anti-proteases, mostly with alpha-1-antichymotrypsin, whereas $\leqslant 50\%$ of PSA occurs as free, uncomplexed forms [28]. A higher ratio of free PSA to total PSA occurs in patients without prostate cancer than in those with the disease, although the reasons are unknown [29]. Measuring both free and total PSA, and determining '% free PSA' results in improved prostate cancer detection [30–32]. The FDA has approved measurements of '% free PSA' for total PSA levels of 4–10 ng/ml. Longitudinal screening studies have demonstrated that '% free PSA' is useful to identify patients who will develop aggressive cancer. Within this study free and total PSA were measured in a group of patients for 10 years prior to diagnosing of prostate cancer with extra-prostatic extension, lymph node or bone metastases and this was compared with a group of patients who had prostate cancer with a more favourable pathology [33]. In comparing patients with BPH and prostate cancer, a statistically significant difference in % free PSA was detected in patients with small size prostates [34,35]. It can be concluded that '% free PSA' improves specificity while maintaining a high sensitivity for prostate cancer in men with total PSA levels of 2.6–10 ng/ml.

2.5. Atypical findings on biopsy

Certain histological lesions, including high-grade prostatic intra-epithelial neoplasia (PIN) and atypical small acinar proliferation (ASAP) are associated with a high likelihood of cancer and are absolute indications for repeat biopsy [36–38].

2.6. Digital rectal examination

While most men with prostate cancer have palpably normal prostates, a suspicious finding on digital rectal examination is an absolute indication to perform a biopsy irrespective of PSA. However, not all subjects with suspicious findings on digital rectal examination will have prostate cancer detected in a subsequent biopsy. In a multi-centre trial of more than 6000 men the PPV of a suspicious finding on DRE was 21.4% over the entire PSA range. For PSA levels below 4 ng/ml, 4–10 ng/ml or above 10 ng/ml, the PPVs were 10%, 40.8% and 69.1%, respectively. In comparison, the PPV was 24.4% when PSA was 4–10 ng/ml and digital rectal examination did not reveal suspicious findings [39]. Patients with suspicious findings on digital rectal examination have a higher percentage of clinically significant cancer, but a lower likelihood of a pathologically organ-confined disease compared with those detected by PSA elevation alone [41,42].

2.7. Transrectal ultrasonography

TRUS is the most common technique for imaging the prostate. Typically, cancerous nodules appear hypoechoic. Currently in the PSA era, most cancers appear isoechoic and thus the sensitivity of prostate cancer detection using TRUS alone is poor. The role of TRUS is now established to facilitate the performance of prostate biopsies from all locations relevant for prostate cancer by using systematic biopsies of isoechoic areas and additionally to obtain targeted biopsies of any hypoechoic lesions.

2.8. Biopsy protocols and techniques

2.8.1. Peripheral zone biopsies

In 1989 Hodge and colleagues presented a sextant biopsy regimen which included three biopsies from each prostatic lobes obtained from at the apex, mid and base [3]. They demonstrated that systematic TRUS-guided prostate biopsy has a higher detection rate of prostate cancer compared to targeted biopsies of suspicious regions. Terris and colleagues [43] demonstrated improved sensitivity by performing sextant biopsies from the lateral third of the peripheral zone. However, even laterally guided biopsy technique, were associated with a false negative rate of 20%, as

demonstrated by cancer detection on subsequent biopsies. To reduce this false negative rate, numbers of biopsy cores were obtained during each session and this was subsequently introduced into clinical practice. More extended biopsy protocols demonstrated a significantly improved detection rate without an increased detection of insignificant prostate cancers. Presti and colleagues performed standard sextant biopsies in 438 men with suspicious findings on digital rectal examination or elevated total PSA concentration. In addition they obtained four biopsy cores of the lateral aspects of the peripheral zone at the base and mid-prostate. Of 42% patients that had positive biopsies the 10-core biopsy regimen identified 96% of cancers. Gore and colleagues performed a study on 396 patients, expanding the standard sextant protocol with additional more laterally guided biopsies of the peripheral zone and in independent studies demonstrated that a significant proportion of all cancers of the peripheral zone were not detected in the standard protocol but only in the more laterally guided biopsies [45].

In addition to the number and location of biopsies, another confounding factor is the volume of the prostate, which has a significant impact on the detection rate. Uzzo and Karakiewicz in independent studies demonstrated that in prostates >50 ml the detection rate of a standard sextant biopsy is insufficient, and Karakiewicz suggested performing one biopsy per 5 ml of prostate volume [46,47]. A nomogram that incorporates age and prostatic volume has been reported by Djavan and colleagues and demonstrates that in younger patients with smaller prostates only 6–8 biopsies are required to detect 90% of cancers, whereas in patients aged 50–69 years with prostate size greater than 60 ml 14–16 biopsies are required to achieve the same detection rate [48].

The European multi-centre trial European Prostate Cancer Detection Study (EPCD) prospectively enrolled 1051 patients with total PSA levels 4–10 ng/ml for systematic prostate biopsies [49]. In case of a negative first biopsy, a subsequent sextant biopsy was performed. If the second biopsy was also negative, a third and, if again negative, fourth biopsy was performed. In each setting one sextant biopsy and two additional transition zone biopsies were obtained. In the first series 231/1051 patients were found to have prostate cancer, in the second series 83/820, in the third 36/737 and in the fourth series 4/94. If one were to assume that after four sets of biopsies no cancer remains undetected, it can be concluded that two biopsy series in succession detect 96% of all cancers. With regard to their pathological features, it was noteworthy that those cancers detected in the third and fourth biopsy series demonstrated significantly lower Gleason scores, lower total and Gleason grade 4/5 cancer volume, less multi-focality, and a higher rate of pathologically organ-confined prostate cancers.

A saturation biopsy was described by Stewart and colleagues [50]. In a series of 224 patients who underwent a repeat biopsy, on average 23 (range 14–45) samples were obtained under sedation and prostate cancer was found in 34% of all cases.

2.9. Complications of biopsy

Systematic prostate biopsy is safe, with low morbidity and acceptable discomfort when performed by experienced urologists under antibiotic protection, with the use of local anaesthesia. In a prospective evaluation of 1650 men who underwent TRUS guided biopsy in the Department of Urology, University Clinic Hamburg-Eppendorf the complications were recorded. Significant complications (bleeding that required intervention, acute prostatitis leading to hospitalisation) occured in 0.7%. A rise in temperature to 38 °C was seen in 2.1% of patients. Minute traces of blood in urine ejaculate or stool were seen in more than 50% of all patients. However, this resolved without need for further intervention. No differences in morbidity were observed between patients undergoing 6 core or 10 core biopsies.

2.10. Summary

TRUS-guided biopsy of the prostate is the standard tool used to detect prostate cancer. Suspicious findings on digital rectal examination, TRUS or PSA elevation are indications for biopsy. We recommend a minimum of 8–10 cores sampled from the peripheral zone in the first biopsy setting. A transition zone biopsy should not be undertaken in the course of the first biopsy. In case of a negative biopsy, a repeat biopsy should be performed within 3–6 months, based on PSA, percentage of free PSA and previous histological findings. In case of two negative sets of peripheral zone biopsies, a saturation biopsy performed under local anaesthesia or sedation may be considered.

3. Staging

3.1. TNM system – uses and limitations

The most widely used system for staging prostate cancer is the tumour-node-metastasis (TNM) system [51]. In the PSA era, most newly diagnosed tumours are non-palpable, defined as clinical stage T1c.

Clinical stage is principally defined by digital rectal examination, and therefore remains a subjective estimation of tumour extent. In the current TNM system, a non-palpable lesion visible on TRUS is classified as cT2. However, Ohori and colleagues and Augustin and colleagues reported no difference in recurrence-free survival for men with non-palpable cancers whether or not they

were visible on TRUS [52,53]. Therefore, many centres reserve the clinical stage T2 for palpable tumours only.

Smith and Catalona [54] showed significant inter-examiner variability of digital rectal examination in detecting prostate cancer. In a multivariate model by Graefen and colleagues [55] the *clinical* stage was not an independent predictor of organ-confinement on final pathology. Cagiannos and colleagues [56] could demonstrate that the current T2 substaging adds prognostic information to a predictive model containing pre-treatment PSA and Gleason sum. Thus, the TNM system is useful for rapid, albeit crude, characterisation of cancer spread and prognosis.

3.2. Nomograms and risk stratification

More than any other definitive therapy for localised prostate cancer, RP can be tailored to the individual tumour stage of the patient. Pelvic lymphadenectomy may be indicated depending on the risk of lymph-node metastases. In case of bilateral capsular penetration is likely, a non-nerve-sparing approach may be appropriate. Therefore, precise pre-operative estimation of the risk of lymph node involvement and final pathological stage are crucial for the planning surgical approach. Furthermore, patient counselling includes the efficacy of therapy assessed by the recurrence-free survival. Numerous statistical tools have been published to estimate these endpoints.

Statistical tools have been created to identify those men at low risk for lymph-node metastases to avoid an unnecessary node dissection. The most popular tool to estimate the risk of lymph-node metastases in prostate cancer are the 'Partin tables' [57,58]. Pre-operative PSA, clinical stage, and biopsy Gleason score are input variables for the prediction of organ-confinement, capsular penetration, seminal vesicle involvement and lymph-node metastases. This tool has been extensively validated on both United States (US) and European academic and community-based patient cohorts. Prediction by the tables is limited to lymph-node metastases in the standard lymphadenectomy area (obturator fossa) and not for more extended dissections. Cagiannos and collegues reported a multi-institutional nomogram predicting lymph-node metastases based on 5150 patients [59]. The negative predictive value of the nomogram was 0.99, with a predicted $\leqslant$3% chance of positive nodes.

The Partin tables are also the best-investigated predictive tool to estimate the likelihood of pathologically organ-confined disease.

The Partin tables have limited use in planning a nerve-sparing RP, as they do not specify the side of a potential extra-capsular tumour extension. To decide whether or not, and to what extent, a nerve-sparing procedure should be performed (unilateral or bilateral) a classification and regression tree (CART) analysis was published calculating the likelihood of side-specific organ-confinement of the diagnosed cancer [55]. In low-risk patients characterised by not more than one positive biopsy with high-grade cancer and a PSA level below 10 ng/ml, the likelihood of organ-confinement is almost 90%.

To predict likelihood of cure following RP the pre-operative Kattan nomogram represents the best investigated statistical tool [60]. Using PSA, biopsy Gleason grade and clinical stage as input variables, the likelihood of freedom from biochemical recurrence 5 years after RP is estimated. The largest validation study on nomogram to date was published in 2002 applying the pre-operative Kattan nomogram to more than 6000 patients from three continents [61]. The area under the curve (AUC) for all institutions combined was 0.75, with individual institution AUCs ranging from 0.67 to 0.83.

3.3. Imaging modalities – TRUS, MR CT, bone scan

Today the majority of prostate cancers are detected by TRUS-guided biopsies. Onur and collegues compared the incidence of cancer from cores taken from hypoechoic areas compared with cores from isoechoic areas [62]. Cancer was detected in 675 (25.5%) and 323 (25.4%) patients with or without hypoechoic lesions ($P = 0.97$). The cancer detection rate per core was uniform and averaged 9.3% and 10.4% for hypoechoic and isoechoic areas, respectively. The authors concluded that for impalpable tumours TRUS findings are not contributory for staging. These findings are in line with the studies that could not demonstrate a difference in recurrence-free survival in patients with or without visible lesions on TRUS [52,53,55,63].

Cross-sectional imaging with magnetic resonance imaging (MRI) to reveal local tumour extent and/or lymph node spread is not recommended as a routine procedure because of low sensitivity [64]. Abuzallouf and colleagues [65] presented a literature review of papers investigating the role of bone scanning and computerised tomography (CT) in men with newly diagnosed prostate cancer. Among 23 studies examining the role of bone scan, metastases were detected in 2.3%, 5.3% and 16.2% of patients with PSA levels less than 10, 10.1–19.9 and 20–49.9 ng/ml, respectively. Scanning detected metastases in 6.4% of men with organ-confined cancer and 49.5% with locally advanced disease. Detection rates were 5.6% and 29.9% for Gleason scores of 7 or less and 8 or more, respectively. Among 25 studies CT documented lymphadenopathy in 0 and 1.1% of patients with PSA levels less than 20 ng/ml and 20 ng/ml or greater, respectively. These data demonstrate that patients with low-risk prostate cancer are unlikely to have metastatic disease documented by bone scan or CT. However, patients with a PSA level of 20 ng/ml or

greater, locally advanced disease, or grade $\geqslant 8$ are at higher risk for bone metastases and should be considered for bone scan. CT may be useful in patients with locally advanced disease or grade $\geqslant 8$ but appears not to be of benefit in patients with increased PSA alone.

Combining MRI and MRI spectroscopy (MRS) might lead to a more accurate staging. Wang and colleagues investigated 216 men who underwent MRS prior to RP. MR imaging was compared with PSA, Gleason score, T stage, percentage of cancer in core biopsies, percentage of cancer-positive core in all core biopsy specimens, and presence of perineural invasion. At receiver operating characteristic (ROC) univariate analysis, endorectal MRI/MRS had the largest area under the ROC curve. At multivariate analysis, PSA, percentage of cancer in all core biopsy specimens, and endorectal MRI/MRS findings were predictors of extra-capsular extension (ECE). More extensive cost-effectiveness analyses are needed to define appropriate guidelines for ordering imaging studies to optimise the positive yield among men with newly diagnosed prostate cancer.

4. Radical prostatectomy

Patients with clinically organ-confined prostate cancer, reasonable life expectancy and no or minor co-morbidities are candidates for RP.

4.1. Role of pelvic lymph node dissection

Currently there is no clear-cut consensus regarding precise criteria for patient selection for lymph node dissection during RP. Although some prefer to perform routine pelvic lymph node dissections (PLND) on all patients, the incidence of lymph node metastasis in patients with a PSA < 10 ng/ml and Gleason score $\leqslant 6$ is low (<5%). Even in patients undergoing extended lymphadenectomy including obturator, external and internal iliac node dissections, only a 2% incidence of nodal metastases was noted in patients with PSA < 10.5 and Gleason score <7, and there is controversy over whether extended lymphadenectomy confers a survival benefit [67].

PLND is most commonly performed concomitantly in patients undergoing retropubic or laparoscopic RP. Real-time frozen section analysis of the nodes may be performed depending upon the philosophy of the surgeon and wishes of the patient [68]. PLND typically involves dissection of the obturator group of lymph nodes, with anatomical limits of lateral border of the external iliac vein, the obturator nerve, the circumflex iliac vein and the bifurcation of the iliac arteries. A more extended dissection may include the external and common iliac nodes.

4.2. Open retropubic RP

Millin in 1947 [69] described simple prostatectomy utilising the retropubic approach. The technique for retropubic RP based on this approach was fraught with difficulty secondary to excessive bleeding and poor visualisation. Subsequently, anatomical studies by Walsh [70,71] provided for better understanding of the anatomy of the dorsal venous complex and cavernous nerves and laid the foundation for modern RP.

4.3. Anaesthesia

RP may be performed under general, spinal, or epidural anaesthesia. Regional anaesthetics are associated with less blood loss, lower transfusion requirements, less sedation, less nausea and lower narcotic requirements [72–74].

4.4. Blood conservation techniques

The reported blood transfusion rate associated with radical retropubic prostatectomy ranges from 5% to 100% [76,77,119,120,124]. Several factors influence blood loss during RP, including obesity, co-morbidities, larger prostates and experience of the surgeon [78]. Transfusion of allogeneic blood is associated with the risk of disease transmission [79]. In order to minimise the need for allogeneic blood most centres adopt one or more blood conservation techniques, including pre-operative autologous blood donations, pre-operative erythropoietin, intra-operative acute normovolemic haemodilution and cell saver retrieval. Pre-operative autologous blood donation is the most commonly practised method. The disadvantages of this approach are higher costs and potential wastage of unused units. Erythropoietin administration generally results in a 3–4% increase in pre-operative haematocrit [80,81]. In one prospective randomised trial, allogeneic transfusion rates and costs were lowest using acute normovolemic haemodilution [82].

4.5. Operative technique

The patient is placed in the supine position, but many variations including extension at the lumbar spine, use of reverse Trendelenberg position, full lithotomy position, or supine with abducted legs for access to the perineum have been described [83,84]. A lower mid-line or Pfannensteil incision with extraperitoneal pelvic access is typically used, with one of a variety of self-retaining retractors.

Many variations in the specific manner and order in which individual operative steps are performed have been described, and mainly reflect surgeon preference. The operative steps for open RP include:

1. Incision of the endopelvic and lateral pelvic fascia to expose the prostate, with or without preservation of the most caudad portion of the puboprostatic ligaments.
2. Division of the dorsal vein complex after proximal and distal ligation.
3. Division of the urethra with care to preserve its anatomical integrity, length and innervation of the striated urethral sphincter.
4. When indicated, atraumatic dissection of the neurovascular bundles away from the prostate for preservation of potency and continence.
5. Ligation of the posterolateral pedicles.
6. Division of the bladder neck to separate the prostate from the bladder.
7. Division of the vasa deferentia and dissection of the seminal vesicle attachments.
8. Completion of the vesicourethral anastomosis over a Foley catheter.
9. Closure of the incision.

Outcomes related to quality of life and cancer control may be related in part to surgical technique and surgical experience [85,86]. Various surgical modifications to RP have been described in the literature and include:

4.5.1. Antegrade approach

This technique involves initial dissection of the prostate at the bladder neck and proceeds toward the apex, leaving ligation and division of the dorsal vein until last, thus providing a less bloody operative field [87,88].

4.5.2. Seminal vesicle sparing

The cavernous nerves lie in close proximity to the tips of the seminal vesicles and may be damaged by inexact dissection in this area, and some have therefore advocated a seminal vesicle-sparing RP [89]. The incidence of seminal vesicle invasion by prostate cancer ranges from 6% to 26%, and patients with seminal vesicle invasion have a high risk of biochemical failure following RP [90,91]. Sparing the seminal vesicles should be reserved for those with favourable pre-treatment parameters who are at low risk for seminal vesicle involvement.

4.5.3. Techniques to improve continence

Modifications include minimisation of tissue dissection distal to the apex of the prostate, preservation of anterolateral fascial attachments of the sphincter, bladder neck preservation, and creation of a tubularised bladder-based neourethra in order to improve urinary continence [92–96]. In general, these modifications have been shown to promote earlier return of urinary control but do not affect the overall rate of continence.

4.5.4. Techniques to improve potency

4.5.4.1. Mapping of the neurovascular bundles. Cavernous nerve mapping has been described as an aid to facilitate identification and confirm preservation of the neurovascular bundles. The procedure involves electrical stimulation of the nerves and observation of erectile response. One device consists of a nerve-stimulating probe, a control unit and a tumescence/detumescence sensor. The tumescence/detumesence response is associated with significant variability, related to depth of anaesthesia, effect of individual anaesthetic agents, surgical manipulation, presence of blood over the area of interest, and operator variability. Some authors have demonstrated improved potency in patients in whom intra-operative mapping was utilised, while others have reported that a response to stimulation did not necessarily correlate with anatomical location of the neurovascular bundles [97,98]. A randomised trial of intra-operative mapping *versus none demonstrated no improvement in potency when the device was used [99].*

4.5.4.2. Sural nerve grafting. Resection of the cavernous nerves during RP results in Wallerian nerve degeneration. Unlike the central nervous system (CNS), peripheral nerves retain the capacity to regenerate, provided the cell body of the nerve is preserved. Distal axotomy typically results in death only of the distal nerve segment with loss of synaptic transmission. Following nerve transection, Schwann cell proliferation is observed at the transected nerve end. Nerve grafting is based on the need for scaffolding for the severed nerve end to regenerate in an organised fashion toward the distal end of the nerve.

Experimental studies on cavernous nerve grafting in the rat model were initially reported by Quinlan [100]. In this experiment rats were divided into three groups: cavernous nerve ablation; nerve ablation followed by nerve grafting; and a no intervention control. At 4 months, erections were elicited by electrical stimulation in 10%, 50% and 100% of rats within the three groups, respectively. Subsequently, Walsh performed grafting utilizing the genitofemoral nerve in patients undergoing unilateral nerve resection during RP. Over a follow-up period of 5 years no differences in recovery of potency were noted between grafted *versus* ungrafted patients [101]. Recovery of potency following bilateral sural nerve grafting was evaluated by Kim and colleagues [102]. The study included patients who underwent bilateral sural nerve grafting following non-nerve-sparing prostatectomy ($n = 12$). Complete recovery, defined as the ability to perform unassisted intercourse, was noted in 33% of patients. Canto compared potency in patients who underwent unilateral nerve resection only ($n = 42$), and patients who underwent unilateral nerve resection followed by sural nerve grafting ($n = 51$) [103]. Recovery of potency, as defined by an International Index of

Erectile Function (IIEF) score of 17/30, was noted in 62.7% patients following sural nerve grafting *versus* 16.7% for ungrafted patients. Time to recovery was shorter for patients who underwent grafting (13.7 months *versus* 65.9 months). However, patients who underwent grafting were younger (56 *versus* 64 years). Despite this, following adjustment for age, patients who underwent sural nerve grafting had a four-times higher probability of recovery of erectile function.

4.5.4.3. Resection of the neurovascular bundles. Resection of the neurovascular bundles has a profound effect on postoperative recovery of sexual function [104,105]. Although increasingly rare because of PSA-induced stage migration, ECE may involve the cavernous nerves and, in such instances, it is appropriate to partially or fully resect one or both bundles as indicated [101]. Such decisions are made on a case-by-case basis based on nomogram predictions on the likelihood of organ confinement and on intra-operative findings [106–108,55,101]. Lepor [109,110] has demonstrated that that using explicit criteria derived from pre-operative grade, stage, and PSA to decide on nerve sparing resulted in more nerves saved and *fewer positive margins.*

4.6. Perineal prostatectomy

Perineal prostatectomy was first described by Young in 1905 [111]. Young's initial experience with the perineal approach was for relief of bladder outlet obstruction secondary to BPH. However, he discovered incidental cancer in the resected specimens and thereafter performed the first radical perineal prostatectomy in 1904. Belt described a modified approach in 1939 [112].

Perineal prostatectomy is performed in an exaggerated dorsal lithotomy position. The skin incision is 1-cm anterior to the anal verge, and extends posterolaterally on either side of the midline toward the ischial tuberosities. With Belt's modification the incision extends through the superficial and deep parts of the external anal sphincter. The perineal fascia is incised, the ischiorectal fossa is bluntly dissected, and the levator ani muscles are exposed. Dissection is continued along the anterior rectal wall, until the rectourethralis muscle is identified and divided. A Lowsley retractor is placed in the bladder to facilitate manipulation of the prostate. Denonvillier's fascia is identified along the posterior surface of the prostate. The remainder of the procedure is similar to the open retropubic approach, with the exception that the dissection is done underneath the dorsal vein without the need to divide it. The perineal approach provides better visualisation of the urethra than the retropubic approach, but length of hospital stay, return to full activities and return of continence and potency are similar in experienced hands.

4.7. Laparoscopic RP

Guillonneau and Vallencien described the initial technique for laparoscopic RP [115]. This technique may be performed utilising a transperitoneal or extraperitoneal approach. Contraindications include obesity, a large prostate, presence of a prominent median lobe, a prior history of pelvic surgery, or the presence of adhesions secondary to prior abdominal explorations [113].

Patients are placed in a lithotomy position for this procedure. The arms are adducted, and pressure points are padded. During the procedure the patient may need to be placed in the Trendelenberg position in order to facilitate displacement of bowel loops from the pelvic cavity, and hence the patient is secured to the operating table. Two monitors, placed at the foot of the table, are utilised for the procedure. The surgeon stands to the left and utilises the monitor placed beyond the right foot of the patient. The assistant, who controls the laparoscope, is positioned to the right and utilises the left monitor. Laparoscopic equipment required includes: two 10-mm ports, 3–4 5-mm ports, a 10-mm zero-degree laparoscope, a suction irrigation device, an insufflator, a light source and image processor, a range of atraumatic graspers, clip applicator, scissors with monopolar electrocautery, haemostatic devices, such as harmonic scalpel and a bipolar electrocautery device, and laparoscopic needle drivers.

4.7.1. Operative technique

4.7.1.1. Transperitoneal anterior approach [113,114]. A 5- to 6-port transperitoneal laparoscopic technique is employed, with the primary port placed in the inferior umbilical crease. 10-mm ports are placed along the lateral border of the right and left rectus belly, 1–2 finger-breadths inferior to the primary port. A 5-mm port is placed 2 finger-breadths lateral to the anterior superior iliac spine, bilaterally. An additional 5-mm port may be placed in the midline 2–3 finger-breadths superior to the pubic symphysis to facilitate tissue retraction during dissection, and also for following sutures during the urethrovesical anastomosis. The space of Retzius is entered by dissecting the bladder off the pelvic side-wall, and off the anterior abdominal wall. To facilitate this manoeuvre the bladder may be inflated with 150–200 ml of water or saline. The peritoneum is incised in an inverted U pattern, beginning lateral to the median umbilical ligaments. The peritoneal incision is created medial to the external iliac artery pulsations. The incision is then extended across the midline to include the urachus, and is then continued lateral to the contralateral medial umbilical ligament. The remainder of the procedure is performed in a manner similar to that described for open retropubic RP, using instruments adapted for laparoscopy.

4.7.1.2. Transperitoneal posterior approach [115]. The posterior laparoscopic approach involves initial

dissection of the seminal vesicles and vasa. The peritoneum is incised posterior to the bladder and the pouch of Douglas is entered. The seminal vesicles and vasa are identified and dissected. Following this the space of Retzius is entered and subsequent steps of the procedure are similar to the procedure described above.

4.7.1.3. Extraperitoneal approach [116]. The extraperitoneal approach involves balloon dissection of the pelvic extraperitoneal space. The benefit of this technique is that the peritoneal cavity is not entered, which reduces the incidence of bowel-related complications. A limitation of this technique is that only limited operating space is available in the narrow confines of the extraperitoneal pelvic space. This makes dissection and laparoscopic suturing technically difficult.

4.8. Robotic RP

With regard to surgical technique, robotic RP is inherently similar to laparoscopic RP. However, the key difference is the use of a unique interface designed to overcome technical challenges associated with conventional laparoscopy. Conventional laparoscopic surgery is associated with several limitations, including restricted range of instrument motion, lack of depth of perception, lack of haptic feedback, and exaggeration of amplitude of motion and tremor. Also, laparoscopic surgery is associated with a steep learning curve. Robotic technology is directed toward overcoming these shortcomings associated with laparoscopy [117].

The robotic system consists of three robotic operating arms, controlled by a surgeon seated at a remote console. Of the three arms, one is designed to control the laparoscope and the other two are designed to facilitate instrument control. Each arm of the robot has several joints and links to optimise dexterity. Compared with conventional laparoscopy, robotic arms are capable of superior freedom of motion. This translates into improved dissection and reconstructive skills for the operating surgeon. The robotic system incorporates motion-scaling technology to reduce exaggerated instrument motion and hand tremor. Furthermore, robotic technology incorporates improved stereoscopic optics, and haptic feedback. Also, compared with laparoscopy, the robotic system provides an environment that is ergonomically superior. As a result of these features, improved surgical precision and a decrease in the learning curve are anticipated [118]. Robotic systems incorporate safety features to minimise the risk of inadvertent injury. The robot is operated by a single surgeon, who activates the system by pressing down a foot pedal. The robotic system incorporates a safety clutch in each of its arms. This prevents unabated forceful motion of the arms against tissue resistance. Costs for robotic systems range are on the order of $1,000,000, exclusive of instruments and maintenance fees.

4.9. Postoperative routine

Recovery of patients undergoing retropubic, perineal and laparoscopic RP follows a similar course. In general, patients are maintained on intravenous fluids for approximately 24 h, until they can resume oral intake. Drains are removed prior to discharge unless a urine leak occurs. Analgesia is provided by a patient-controlled analgesia (PCA) pump via the epidural or intravenous routes, followed by oral ketorolac on the second post operative day. Length of stay, duration of catheterisation, and return to regular activities are similar for all of the techniques described and dependent upon surgeon and patient preference.

4.10. Complications

Perioperative mortality following RP is <0.4%, regardless of surgical technique utilised. Complications associated with various techniques are summarised in Tables 1–5. In general, the incidence of surgical complications and outcomes are related to surgical experience and the performance status of the patients. Compared with the perineal and laparoscopic approaches, retropubic RP is associated with higher blood loss. The data also indicates that the perineal approach is associated more frequently with bowel-related complications, including rectal injury, recto-urethral fistulas, recto-cutaneous fistulas, and faecal incontinence, ranging from 1% to 6%. The laparoscopic approach is specifically associated with complications such as inadvertent vascular, bowel and bladder injury, open conversion, and those related to CO_2 insufflation.

4.11. Benefits and limitations

4.11.1. Retropubic RP

Compared with some of the more recent techniques, such as laparoscopic and robotic prostatectomy, open retropubic RP is a time-tested approach. The availability of long-term results demonstrates the durability of the procedure from a functional and oncological standpoint, with the best cancer control, potency and continence data reported for this approach. A disadvantage of this approach is the potential for blood loss. However, blood loss decreases with increased surgical experience, and in most series the need for non-autologous blood is <5%, comparable to the perineal and laparoscopic techniques.

4.11.2. Perineal prostatectomy

Although functional and oncological outcomes with this approach are similar to retropubic RP, a major

Table 1
Perioperative complications: retropubic radical prostatectomy

Reference	Number of patients	Rate of re-operation (%)	Bowel injury (%)	Lymphatic[a] (%)	Urine leak/urinoma/ ureteral injury (%)	Anastomotic stricture (%)	Nerve injury	DVT (%)	PE (%)	EBL (ml)	Transfusion rate (%)	Wound infections (%)	MI (%)	Mortality (%)
Zincke [162]	3170	NA	1	NA	NA	NA	NA	1.1	0.8	NA	NA	NA	0.4	0.3
Catalona [163]	1870	NA	0.1	0.4	0.1	4	0.3	2	NA	NA	NA	NA	0.1	0
Lepor [75]	1000	0.5	0.5	0.1	0.1	1	0.1	0.3	0.3	818.6	9.7	NA	0.3	0.1
Dillioglugil [76]	472	1.7	0.4	2.5	0.2	NA	1.5	1.1	1.3	NA	28.6	0.2	1.7	NA
Leandri [77]	620	NA	0.5	2.6	0.3	0.5	NA	2.6	0.5	NA	NA	1.0	0.2	0.2

MI, myocardial infarction; PE, pulmonary embolus; DVT, deep vein thrombosis; EBL, estimated blood loss; NA, data not available/not specified/not specified for the entire study population/not applicable.
[a] Lymphorrhoea or lymphocele.

Table 2
Perioperative complications: perineal radical prostatectomy

Reference	Number of patients	Rate of re-operation (%)	Bowel injury[a] (%)	Urine leak/urinoma/ ureteral injury (%)	Transient urinary retention (%)	Anastomotic stricture (%)	De novo changes in bowel habits[b] (%)	Nerve injury (%)	DVT (%)	EBL (ml)	Transfusion rate (%)	Wound infections (%)	Others (%)
Gillitzer [164]	630	2.4	5.9	4.3	5.6	2.7	9	0.7	NA	NA	5.9	0.3	Epi 2.2
Weldon [122]	220	NA	1	2	0.5	1		2	0.5	645	5	1	PE 1
Ruiz-Deya [123]	250	NA	1.6	0.8	NA	3	7	0.8	NA	NA	11	0.4	–
Gibbons [165]	207	NA	5	NA	NA	18	NA	NA	NA	NA	NA	1	Rectal abscess 1
Frazier [166]	122	NA	NA	0.8%	NA	7	NA	NA	NA	NA	0	0.8	Epi 0.8
Haab [167]	35	NA	2.9	2.9	NA		NA	NA	NA	NA	54	5.7	–
Lance [168]	190	NA	4.9	NA	NA	3.5	NA	NA	NA	NA	NA	0.8	Wound dehiscence 1.6

Epi, epididimytis; PE, pulmonary embolism; NA, data not available/not specified/not specified for the entire study population/not applicable. Mortality: for all the studies listed above, there was either no mortality or mortality was not reported.
[a] Includes intra-operative rectal injury and postoperatively detected faecal fistula.
[b] Includes faecal incontinence, diarrhoea.

Table 3
Perioperative complications: laparoscopic radical prostatectomy

Reference	Number of patients	Rate of re-operation (%)	Ureteral injury (%)	Bowel injury (%)	Vascular injury (%)	Urine leak/ urinoma/ ureteral injury (%)	Lymph-related[a] (%)	Anastomotic stricture (%)	Nerve injury (%)	DVT (%)	EBL (ml)	Transfusion rate (%)	Post-operative bowel-related[b] (%)	Conversion to open (%)	Mortality (%)
Guillonneau [169]	567	3.7	0.7	1.9	0.5	10	0.2	NA	0.5	0.3	380	4.9	1.0	1.2	0
Hoznek [170]	200	NA	NA	1.0	NA	2.5	2.0	NA	NA	0.5	NA	3.0	NA	0	NA
Rassweiler [128]	180	4.4	NA	1.7	NA	2.2	NA	3.3	NA	NA	1230	31.0	2.8	4.4	NA
Turk [127]	125	NA	0.8	3.2	0.8	NA	NA	1.6	NA	2.4	185	2.0	3.2	0	NA

Wound dehiscence and wound infection. NA, data not available/not specified/not specified for the entire study population/not applicable.
[a] Lymphorrhoea and lymphocele.
[b] Includes ileus and bowel obstruction.

Table 4
Complications: perineal *versus* retropubic radical prostatectomy

Reference	Procedure	Number of patients	Intra-operative complications		Transfusions (%)	Anastomotic stricture (%)	Urine leak, wound-related (%)	Mortality (%)
			EBL (ml)	Rectal injury (%)				
Haab [167]	P	35	NA	2.8	54	0	2.8	0
	R	36	NA	2.7	100	5.6	NA	0
Frazier [124]	P	122	565	NA	0	6.6	NA	0.8
	R	51	2000	NA	5.9	7.8	NA	0
Lance [168]	P	190	NA	4.9	0.3 units per patient	3.5	NA	0
	R	190	NA	NA	1.7 units per patient	9.3	NA	0

P, perineal radical prostatectomy; R, retropubic radical prostatectomy; EBL, estimated blood loss; NA, not available/not specified.

Table 5
Complications: laparoscopic *versus* retropubic radical prostatectomy

Reference	Procedure	Number of patients	Intra-operative complications					Re-exploration	Anastomotic stricture	PE	Neurological	Urine leak	Lymporrhoea/ lymphocele	Ileus	others
			EBL (ml)	Vascular injury	Bowel injury	Ureteral injury	Conversion to open								
Bhayani [171]	L	36	533	1	0	1	3	NA	NA	NA	1	NA	NA	NA	Myositis ($n = 1$)
	R	24	1473	0	0	0	NA	NA	3	NA	NA	NA	NA	NA	–
Roumegure [172]	L	85	522	0	1	0	2	2		NA	NA	NA	NA	NA	ARF ($n = 1$)
	R	77	1514	0	0	0	NA	2	NA	NA	NA	NA	NA	NA	–
Rassweiler [173]	L	438	NA	0	3	0	NA	26	21	2	2	7	NA	8	Wound infection ($n = 1$)
	R	219	1550	0	3	0	NA	38	35	5	3	1	15	1	Wound infection ($n = 5$), sepsis ($n = 1$)

L, laparoscopic radical prostatectomy; R, retropubic radical prostatectomy; ARF, acute renal failure; NA, not available/not applicable.

disadvantage is the inability to perform concomitant pelvic lymphadenectomy. The exaggerated lithotomy position may lead to ventilatory problems in obese patients and may be an issue in patients with orthopaedic problems. The incidence of bowel-related complications are higher with this approach (Table 2), where damage to the anal sphincter seems to make patients more prone to postoperative faecal incontinence. In studies comparing retropubic and perineal RP, blood loss is lower with the perineal approach.

4.11.3. Laparoscopic and robotic RP

Laparoscopic and robotic RP are relatively new techniques. As result, long-term oncological data are lacking. However, surrogate indicators of oncological efficacy, such as reported surgical margin rates, are higher than other approaches (especially early in the learning curve) and functional outcomes have not achieved the best reported outcomes in the most experienced hands for open prostatectomy, although some surgeons using laparoscopic and robotic techniques achieve better results than they did with the open approach. Advantages associated with the laparoscopic technique include less intra-operative blood loss and magnified visualisation in the depths of the pelvis. Disadvantages include a steep learning curve, lack of tactile feedback, and complications associated with the use of CO_2 pneumoperitoneum, such as hypercarbia and subcutaneous emphysema.

4.11.4. Potency, continence and health-related quality of life

Reported ranges of recovery of potency following open RP, perineal prostatectomy and laparoscopic RP are 44–85% [119–121,77], 22–77% [122–125] and 5–59% [126–129], respectively (Tables 6–8). Recovery of potency is associated with age, absence of cardiovascular co-morbidities, and the experience of the surgeon [104,105,121]. Ranges of recovery of continence following open RP, perineal prostatectomy, and laparoscopic RP are 31.9–95% (Table 6), 64.8–96% (Table 7) and 73.3–97% (Table 8), respectively. Recovery of urinary continence is also dependent on patient age and surgical experience, and perhaps on the number or neurovascular bundles spared [105,121].

Health-related quality of life (HRQOL) after RP was evaluated by Hu in the CapSure database using validated instruments [130]. One year after surgery, return to baseline urinary and sexual function and mental and physical health was seen in 63%, 20%, 86% and 80% of patients, respectively. Patients <65 years of age, without the presence of co-morbidities, and high health self-ratings were more likely to return to baseline. In addition to surgical morbidity, HRQOL may also be affected by cancer recurrence. Pietrow demonstrated a significant decrease in one category of the RAND 36-Item Health Survey pertaining to mental health in

Table 6
Radical retropubic prostatectomy: functional outcome

Reference	Number of patients	Follow-up period of study	Continence rate	Definition of continence	Potency following UNS (%)	Potency following BNS (%)	Overall potency rate	Definition of potency
Catalona [163]	1870	50 months	92% at 18 months	Completely dry	47 ($n = 60$)	68 ($n = 798$)	NA	Erection sufficient for penetration/intercourse
Zincke [162]	3170	5 years	95%	<3 pads per day	NA	NA	NA	NA
Eastham [174]	581	NA	91% at 24 months	No pads, occasional pad but dry with moderate exercise	NA	NA	NA	NA
Walsh [175]	NA	NA	92% ($n = 593$)	Complete urinary control	NA	NA	68% ($n = 503$)	Erections sufficient for intercourse
Stanford [176]	1291	24 months	31.9% at 24 months	VQ (total control)	41.4	44	NA	VQ
Leandri [177]	620	NA	95% at 12 months ($n = 377$)	Complete return of urinary control	NA	NA	56% at 12 months ($n = 106$)	Completely potent

VQ, self-administered validated questionnaire; NA, data not available/or non-nerve-sparing.

Table 7
Radical perineal prostatectomy: functional outcome

Reference	Number of patients	Follow-up period of study	Continence rate	Definition of continence	Potency following UNS	Potency following BNS	Overall potency rate	Definition of potency
Bishoff [178]	123	Minimum 12 months	70% at 12 months	Full continence	NA	NA	NA	NA
Weldon [122]	220	Minimum 18 months	95% at 10 months	Not requiring daily use of pads	$n = 28$	$n = 22$	70% at 2 years ($n = 50$)	Prolonged/repeated vaginal penetration without assistance
Young [179]	92	3 months	65.2% at 6 months	Slight problem only	NA	NA	NA	NA
Ruiz-Deya [123]	124	30 months	93% at 12 months	Incontinence defined as significant urinary incontinence limiting daily activity	NA	NA	41%	Sufficient for vaginal penetration and satisfaction
Gibbons [165]	207		92% at 6 months	Normal urinary control	NA	NA	NA	NA
Frazier [166]	122		96%	<1 pad per day	NA	NA	77.3% ($n = 22$)	Not specified
Haab [167]	35		88% at 6 months	No pads	NA	NA	NA	NA
Lance [168]	190		64.8%	Incontinence defined as involuntary loss of urine			NA	NA
Lerner [125]	49	23 months	84%	Completely continent	NA	NA	22% ($n = 27$)	Sexually active with erections sufficient for vaginal penetration

NA, data not available or non-nerve-sparing.

Table 8
Laparoscopic radical prostatectomy: functional outcome

Reference	Number of patients	Follow-up period of study	Continence rate	Definition of continence	Potency following UNS	Potency following BNS	Overall potency rate	Definition of potency
Hasan [114]	150	6 months	94% at 6 months	NA	NA	NA	NA	NA
Salomon [126]	235	12 months	90% at 12 months ($n = 100$)	No leak and no pad	53.8% with sildenafil	58.8% with sildenafil	49.3% with no adjuvant treatment ($n = 77$)	Erections sufficient for intercourse
Turk [127]	125	6 months	86% at 6 months	< 1 pad per day	$n = 39$	$n = 5$	59% ($n = 44$) 30.8% of these patients were on sildenafil	NA
Rassweiler [128]	180	12 months	97% at 12 months	NA	$n = 8$	$n = 2$	40% ($n = 10$) with sildenafil	Sufficient erections
Guillonneau [129]	120	6 months	73.3% at 6 months ($n = 60$)	VQ	NA	NA	(45% at 6 months) 5% had rigidity sufficient for intercourse	Rigidity sufficient for intercourse VQ

VQ, self-administered validated questionnaire; NA, data not available/or non-nerve-sparing.

patients with biochemical recurrence compared with those without recurrence [131].

HRQOL was assessed in 109 patients who underwent perineal prostatectomy utilising the Expanded Prostate Cancer Index Composite (EPIC). Recovery of sexual function to baseline was noted in 25% of men at 18 months. At 6 months, 65.1% of patients recovered urinary domain scores and 93.6% recovered bowel domain scores. Younger patients did significantly better in all domains, while recovery of bowel domain scores was noted to be dependent on individual surgeons [132]. In another study using the European Organisation for Research and Treatment of Cancer (EORTC) instrument, no difference in overall HRQOL was noted at 6 months after open and laparoscopic RP [133].

4.12. Oncological outcomes

Biochemical recurrence after RP is generally defined as recurrence detection of 2 or more PSA values $\geqslant$0.2 ng/dl [134]. Risk of progression following RP can be assessed based on several factors, including pre-operative serum PSA, clinical stage, pathological stage, margin status and Gleason score, where higher pre-treatment PSA, more advanced local stage and higher tumour grade are associated with a higher risk of recurrence. In one study, recurrence-free rates at 5, 10 and 15 years for patients with baseline PSA values between 0 and 4, 4.1–10.0, 10.1–20.0, and >20.0 ng/ml were: 94%, 91% and 67%; 89%, 79% and 75%; 73%, 57%, and 54%; and 60%, 48% and 48%, respectively [135]. Similarly, Catalona reported 7-year progression-free rates of 93%, 88%, 76% and 49% in patients with PSA $\leqslant$2.5, 2.6–4.0, 4.1–9.9 and $\geqslant$10 ng/ml, respectively [105]. At the Cleveland Clinic, Cleveland, Ohio, USA, after open RP, patients with pathologically organ-confined disease have cure rates of 90% at 13 years, with decrements seen for positive margins, ECE, seminal vesicle invasion, lymph node involvement and higher grades (Fig. 1). Of interest is that 35% of those with seminal vesicle invasion and 20% with positive lymph nodes were disease-free without adjuvant therapy at 13 years. Randomised controlled trials comparing different surgical techniques for long-term progression and survival are lacking, but it is likely that the results will be dictated by the rates of positive margins, tumour grade and presence or absence of ECE rather than by the technique used.

5. RP for locally advanced prostate cancer

5.1. Definition of locally advanced disease

Tumours that extend beyond the confines of the prostate gland or invade the seminal vesicles without evidence of metastatic spread may be deemed 'locally advanced'. Margin status of the resected specimen and the extent of tumour invasion into the prostate capsule have been shown independently to alter disease control after RP and are additional risk factors [136].

Overall, 10-year cancer-specific survival rates from large RP series of locally advanced disease concurrently range from 70% to 80% [137,138]. Considering PSA as

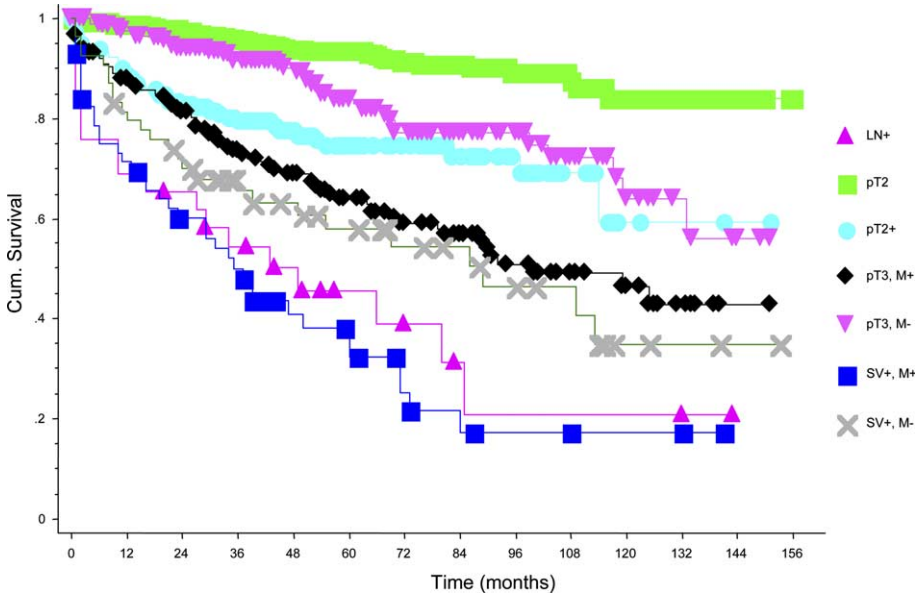

Fig. 1. Kaplan–Meier estimates of biochemical relapse-free survival by pathological stage in 2263 patients treated by open radical prostatectomy (RP) between 1987 and 2000. pT2, organ-confined; pT2+, organ-confined with positive margin; pT3, M−, extracapsular extension, margin negative; pT3, M+, extracapsular extension, margin positive; SV+, M−, seminal vesicle invasion, margin negative; SV+, M+, seminal vesicle invasion, margin positive; LN+, lymph node-positive.

the end-point, 58–63% have biochemical failure at 10 years, suggesting some overstaging error at the time of diagnosis. Risk assessment against the background of morbidity and age represents the essential ingredient for selection of optimal, potentially curable candidates who may benefit from surgical treatment. In those patients, assigned to be at high risk for disease progression, adjunctive treatment modalities need to be considered. Prevention of morbidity caused by local cancer progression is also an important goal for surgical treatment of locally advanced disease.

5.2. RP and adjuvant therapy for locally advanced prostate cancer

5.2.1. RP and hormonal therapy

The EORTC and Eastern Cooperative Oncology Group (ECOG) studied the impact on immediate *versus* late hormonal therapy among patients who were lymph node-positive (LN+) [139,140]. Both showed a significantly longer time to progression in the immediately-treated than in the delayed-treated group. An updated analysis (median follow-up 5.3 years) of the bicalutamide adjuvant trial showed that, compared with placebo, bicalutamide significantly delayed clinical progression but did not affect overall survival [141]. The observed benefits in delaying clinical progression were greatest in patients with locally advanced disease.

5.2.2. RP and adjuvant radiotherapy

The rational basis of adjuvant radiation following RP is the ability to treat residual disease when the tumour has the smallest possible volume [142]. Locally advanced prostate cancers typically recur with systemic rather than local progression and those patients may not benefit from early adjuvant radiation. Thus, radiotherapy adjuvant to RP has been suggested to be more appropriate for subjects with a positive surgical margin in the absence of seminal vesicle or lymph-node involvement. However, since a positive margin does not necessarily mean that local tumour has been left behind, adjuvant radiation of all positive margins would result in a large number of overtreated patients. In fact, only 40–50% of patients with a positive surgical margin without adjunctive treatment develop biochemical failure within 5 years [143].

The majority of published reports suggest that adjuvant radiation therapy reduces the rates of local recurrence and biochemical failure, but evidence demonstrating a disease-specific survival has not been established [144]. The Radiation Therapy Oncology Group (RTOG) is accruing patients with pathological stage 2 and 3 disease at high risk for biochemical failure to a three-arm randomised trial that will test the efficacy of radiotherapy and hormonal deprivation, both alone and in combination. The EORTC trial of adjuvant radiation *versus* observation for pT3 disease reported improved biochemical and clinical progression-free survival for adjuvant radiotherapy, but longer follow-up is needed to analyse survival [145]. The early use of adjuvant radiation in patients with adverse pathological features but undetectable PSA remains open to the philosophy of the treating physician.

5.2.3. Neoadjuvant therapy and RP for locally advanced prostate cancer

The rational basis of neoadjuvant treatment modalities for locally advanced prostate cancer is the reduction of tumour clones to improve local cancer control and the elimination of potentially circulating cancer cells to prevent the establishment of micrometastases.

5.2.4. Neoadjuvant hormonal therapy

Neoadjuvant hormonal therapy prior to RP has been advocated on clinical observations of good local response as assessed by digital rectal examination, theoretical grounds that androgen deprivation will eliminate the part of the tumour that is androgen-dependent or sensitive, animal models demonstrating longer survival, phase II trials suggesting lower rates of positive margins in pre-treated patients, and apparent benefit of early hormonal therapy in patients with metastatic disease. All of the seven published randomised, placebo-controlled trials totalling more than 1400 patients comparing neoadjuvant hormonal deprivation plus RP with RP alone have shown a reduced incidence of positive margins with the use of neoadjuvant hormones, but none have demonstrated any improvement in biochemical relapse-free survival (bRFS) with follow-up as long as 6 years [146,147]. Similarly, the recently reported Canadian trial comparing 3 *versus* 8 months of hormone therapy demonstrated no advantage of longer-term hormone therapy prior to RP. Weighing the toxicity of hormonal therapy against the lack of demonstrable benefit in randomised trials strongly argues against the utility of this approach.

5.2.5. Neoadjuvant chemo-hormonal therapy

Neoadjuvant combinations of androgen ablation and chemotherapy are currently evolving at the level of experimental treatment modalities. Since some chemotherapeutic drugs have shown favourable impact on disease progression of hormone-refractory prostate cancer, they are hypothesised to have potential inverse influence on proliferation of androgen-resistant cell clones and thus may have an additive cytotoxic effect to anti-hormonal treatment [148]. Currently, five publications have reported preliminary experience with neoadjuvant chemotherapy with a variety of treatment regimens [149–153]. Lowest toxicity was reported for a combination of androgen ablation and doxetacel monotherapy [43]. All studies demonstrated that chemotherapy

neoadjuvant to RP is associated with an acceptable morbidity. Prospective randomised trials are planed to objectify the impact on progression and survival.

6. Salvage prostatectomy

Salvage RP has been utilised to treat patients with isolated local recurrence following external beam radiation or brachytherapy. Such an undertaking would be futile in the presence of distant spread, unless the procedure is being performed purely for symptomatic relief. This includes the occasional patient with troublesome radiation cystitis who is being considered for bladder removal. Prior to considering salvage surgery, every effort needs to be made toward ruling out distant metastases, including all available imaging modalities.

Candidates for salvage prostatectomy should be in good health, have normal bladder function and a minimum 10-year life expectancy. Patients with PSA < 10 ng/ml, non-palpable disease and moderately differentiated tumours at the time of salvage have the best chance of having organ-confined disease and cure [154–156].

Operating in a previously radiated pelvis can be technically challenging. Dense fibrosis obliterates tissue planes making for difficult tissue dissection. This problem may be compounded following initiation of hormonal treatment. Patients should be counselled for the increased incidence of complications associated with this procedure. Conversion of salvage prostatectomy to a cystoprostatectomy secondary to technical difficulties is occasionally necessary. Utilisation of combined abdominal and perineal approaches may facilitate dissection. Salvage prostatectomy is associated with an increased incidence of complications. The incidence of rectal and ureteral injuries may be as high as 19% and 12%, respectively [157–161]. The incidence of bladder neck contracture in these patients ranges from 11% to 27% and urinary incontinence occurs in 27–67% of patients.

Cancer-specific survival rates of 89–95% at 5 years and 72% at 10 years have been reported [155]. Progression-free rates of 100% at 5 years have been noted in patients who had organ-confined disease.

7. Conclusion

Although it is clear that many factors have contributed to improved surgical outcomes for prostate cancer in the modern era, with increased cure rates, more precisely defined improvements in quality of life, altered case selection and more aggressive use of systemic therapy as tailored treatment for poor-prognosis localised prostate cancer, it is also easy to show that the surgical techniques themselves, with improved mortality and morbidity and reduced length of hospitalisation, have improved substantially. It is no longer appropriate to consider any treatment modality in isolation, and thus our philosophy is one of multi-disciplinary care, in which scientists and clinicians from several disciplines constitute a team that can attribute risk rationally and define the optimal strategies of treatment.

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