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Invited review

Practical aspects of surgical treatment for prostate cancer

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This review summarizes the different surgical approaches for prostatectomy. Radical prostatectomy can be performed using a perineal or retropubic approach. Walsh's landmark studies on pelvic and prostatic anatomy and the resultant surgical implications have increased the popularity of radical retropubic prostatectomy. Nerve sparing prostatectomy was developed to improve post-operative potency rates. Response to post-operative sildenafil (Viagra) is also improved with this technique. A new device, the Cavermap, has been developed to permit intraoperative nerve stimulation and localization. Nowadays, laparoscopic prostatectomy is increasingly used. The factors used in determining patient eligibility for radical prostatectomy are PSA, stage of disease, age, and wishes of the patient. There still exist controversies for patient selection, partly due to different results on predictor variables for biochemical disease-free status. The management of D1 (pelvic nodal metastases) patients is another controversial issue. Nodal cancer volume was the most significant determinant of progression to distant metastasis in lymph node-positive prostate cancer patients. Messing found an improved survival and reduced risk of recurrence in node positive patients after radical prostatectomy and pelvic lymphadenectomy when hormonal therapy was started immediately. The role of radiotherapy and hormonal treatment in combination with surgery is the subject of continuous research. A number of studies have addressed the value of neoadjuvant hormonal treatment prior to prostatectomy. The majority employed 2-3 months of total androgen blockade and reported less positive surgical margin, less extracapsular extension, clinical and pathological downstaging, but no improvement in biochemical progression or survival. After prostatectomy, patients whose PSA begins to rise after an undetectable level should be referred for salvage treatment with radiotherapy when their PSA is still less than or equal to 1.0 ng/ml.

Rak prostaty

W pracy omówiono dostępy chirurgiczne stosowane podczas operacji gruczołu krokowego. Radykalna prostatektomia może być przeprowadzona zarówno z dostępu kroczowego, jak i załonowego. Kamieniem milowym w poznawaniu anatomii miednicy małej, a w szczególności gruczołu krokowego i jego bezpośredniego sąsiedztwa, stanowiły prace Walsha. Odcisnęły się one na postępowaniu klinicznym, przyczyniając się do spopularyzowania radykalnej prostatektomii załonowej. Celem ograniczenia pooperacyjnych zaburzeń potencji wprowadzono prostatektomię oszczędzającą pęczki naczyniowo-nerwowe; przy tej technice operowania poprawia się odpowiedź na leczenie sildenafilem (Viagra) w okresie pooperacyjnym. Śródoperacyjną stymulację/lokalizację nerwów ułatwia urządzenie zwane „Cavermap". Ostatnio coraz częściej wykonuje się prostatektomię laparoskopową. Podstawowe czynniki brane pod uwagę podczas kwalifikacji do radykalnej prostatektomii to poziom PSA, stopień zaawansowania choroby, wiek oraz zgoda chorego. Kwalifikacja chorych nadal budzi kontrowersje, głównie z powodu rozbieżnych wyników badań biochemicznych, uważanych za czynniki rokownicze przeżycia bez choroby. Postępowanie u chorych z cechą D1 (przerzuty do węzłów chłonnych w obrębie miednicy) jest kolejnym zagadnieniem dyskusyjnym. Objętość mas przerzutowych w węzłach jest najbardziej istotnym czynnikiem węzłowym, określającym możliwość progresji o charakterze odległych przerzutów. Messing opisuje wydłużenie przeżycia i zmniejszenie ryzyka wznowy u chorych z przerzutami do węzłów chłonnych, u których, bezpośrednio po radykalnej prostatektomii i usunięciu węzłów chłonnych z miednicy, rozpoczęto hormonoterapię adiuwantową. Znaczenie radioterapii i leczenia hormonalnego, w połączeniu z leczeniem chirurgicznym jest przedmiotem intensywnych badań. W kilku spośród nich koncentrowano się na hormonoterapii neoadiuwantowej (przed radykalną prostatektomią), stosując zazwyczaj przez 2-3 miesiące całkowitą blokadę androgenową. Uzyskiwano wówczas lepsze wyniki podczas badania marginesów chirurgicznych, rzadziej obserwowano przekraczanie torebki gruczołu przez nowotwór, częściej natomiast obserwowano „downstaging" – zarówno klinicznie, jak i histopatologicznie. Z drugiej strony nie

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obserwowano poprawy zarówno w zakresie biochemicznych wykładników progresji, jak i w zakresie długości przeżycia. Pacjenci u których, po radykalnej prostatektomii, poziom PSA zaczyna wzrastać powyżej wartości nieoznaczalnych, powinni być skierowani celem przeprowadzenia ratującej radioterapii, zanim poziom PSA osiągnie poziom powyżej 1 ng/ml.

Key words: prostate cancer, hormone, radiotherapy, surgery
Słowa kluczowe: rak prostaty, hormony, radioterapia, chirurgia

Introduction

Radical prostatectomy is an option for the curative treatment of organ-confined prostate cancer and continues to be the mainstay of therapy for localised prostate carcinoma in the United States [1] where caring for radical prostatectomy patients accounts for approximately half of the $1.7 billion annual cost of prostate carcinoma treatment.

The surgical management of prostate cancer is a vast topic and this chapter will only review the evolution of surgical technique, the factors used in patient selection, and the indications for neoadjuvant and adjuvant therapy.

The determination of lymph node metastases has important prognostic implications for patients with suspected organ-confined disease. To date no radiological investigation, including and bipedal lymphangiography [2], has been shown to be able to accurately identify metastatic lymph node involvement pre-operatively. Prediction of pathological stage, however, can be estimated using preoperative values of PSA, clinical stage, and Gleason score [3]. In patients at high risk of pelvic node involvement, staging may be performed by laparoscopic pelvic lymph node dissection which is a low morbidity procedure.

Another option is to assess the nodes at the time of prostatectomy with intraoperative frozen sections. Unfortunately though, frozen section diagnosis of metastatic carcinoma in pelvic lymph nodes has a high false negative rate and is also costly [4]. Pathological examination also helps to evaluate the completeness of lymphadenectomy but anatomical studies investigating the average number of pelvic lymph nodes are few.

An interesting study is that of standard pelvic lymphadenectomy performed on 30 human cadavers and 59 consecutive patients with clinically organ confined prostate cancer during radical retropubic prostatectomy [5]. The mean number of lymph nodes removed in autopsy specimens were 22.7 ± 10.2 with a range 8-56, was nearly identical to that from patients with prostate cancer, mean of 20.5 ± 6.6 with a range of 10-37, although striking inter-individual differences were observed. Patients with prostate cancer demonstrated enlarged nodes regardless of whether they did or did not contain tumour. Lymphadenopathy in prostate cancer patients is not always a result of metastases but can be due to benign, hyperplastic changes of the nodal tissue.

Surgical Approaches

Perineal versus Retropubic Approach

Radical prostatectomy can be performed using a perineal (RPP) or retropubic (RRP) approach [1]. Patients who underwent RRP had a slightly longer length of hospital stay, five days with a range of 3-16, *versus* the RPP patients, four days with a range of 1-19. Other factors associated with longer hospital stays were the use of intraoperative epidural anaesthesia and the increased use of post-operative narcotics regardless of the surgical approach. Time to both fluid intake and solid food intake were significantly longer for patients who underwent the retropubic approach. As regards prostate cancer cure rates, RRP and RPP are comparable [6]. The advantages of RPP in this study included lowered blood loss, easier post-operative nursing care, lower analgesic use and earlier discharge from hospital. Using RRP however affords the ability to perform pelvic node dissection, and provides better exposure for nerve sparing techniques.

A modified extrafascial RRP technique was introduced to decrease the frequency of positive surgical margins in low volume T2 cancers < 2 cm^3 [7]. The anatomical details have been described which are necessary for exposure of periprostatic fascias and extrafascial dissection at (1) the prostatourethral junction which ensures wide excision of the anterior and apical aspect of the prostate and (2) the posterior and apical area (development of the prerectal space), and the lateral and posterior areas at the base of the prostate which ensures wide excision of the rectoprostatic fascia (Denonvilliers's fascia) and lateral prostatic fascia [7].

Nerve Sparing Prostatectomy & Erectile Function

Because of the significant emotional and lifestyle changes of impotence, nerve sparing prostatectomy was developed to improve post-operative potency rates [8]. Erectile function can be preserved in up to 75% patients if both cavernous nerves can be spared. Response to post-operative sildenafil (Viagra) is also improved with this technique. The cavernous nerves are often difficult to visualise and may have a variable course but a tumescent response to nerve stimulation can be consistently demonstrated. A new device, the Cavermap, has been developed to permit intraoperative nerve stimulation and localisation. An initial phase 2 and subsequent phase 3 single blind, randomised, multicentre study that compared Cavermap assisted prostatectomy with

conventional nerve sparing has demonstrated a significant benefit in terms of the duration of nocturnal tumescence at one year [9, 10]. Other approaches are being explored to preserve potency, including sural nerve grafting, and direct corpus cavernosum pressure monitoring during nerve stimulation [9]. These nerve sparing techniques may be applied to other oncological surgery such as cystectomy or abdominal-perineal resection.

Urinary Incontinence Avoidance

Many modifications in surgical technique have been developed to avoid urinary incontinence. Initially, creation of a neobladder neck, bladder neck preservation, periurethral injection of bulking agents, and anterior urethropexy were attempted, but with little success. Other modifications, however, have been more promising.

A technique of nerve dissection used in the Montefiore/Albert Einstein College of Medicine [11] starts at the lateral aspect of the prostate with secondary urethral dissection and limits the dissection around the striated sphincter. A technique for radical retropubic prostatectomy that spares the puboprostatic ligaments and preserves the normal anterior support of the urethra, has also been described [12, 13]. Careful dissection of the prostate from the bladder can be performed in such a manner as to preserve most of the circular fibres of the bladder neck [14]. This bladder-neck preservation technique appears to reduce the risk of an anastomotic stricture and to accelerate the return of urinary continence. Although the risk of incomplete resection is a possibility, an analysis of 676 consecutive prostatectomies revealed that only 4.3% of the men had tumour touching the inked bladder neck margin. Furthermore, only 1% had this as the only positive margin [14].

In another series, bladder neck preservation was associated with an increased rate of positive surgical margins in cancers that had focally penetrated through the prostatic capsule, stage pT3a. This manifested as a trend towards decreased PSA-free survival in this group [15]. In another study, bladder neck preservation did not shorten the time to achieve urinary continence [8]. A retrospective study on radical retropubic prostatectomy examined the merits of bladder neck preservation (101 patients), *tennis racket* reconstruction (63 patients), and anterior bladder tube reconstruction (56 patients) [16]. The mean follow-ups were 19.7, 36.7 and 16.2 months for the three subgroups: overall, bladder neck contracture occurred in 22/220 cases, including 5% with bladder neck preservation, 11% with *tennis racket* reconstruction and 18% with anterior bladder tube reconstruction. This data approached but did not reach statistical significance, $P = 0.061$. Urinary continence was assessed by a third party telephone interview of 165 patients, continence rates at one year for the three subgroups were 93%, 96% and 97%: not statistically significant, $P = 0.68$. Positive margin rates were 27.4% with bladder neck preservation *versus* 30.5% with excision, which was also not significantly different [16].

Laparoscopic Lymphadenectomy

Walsh's landmark studies in 1983-84 on pelvic and prostatic anatomy and the resultant surgical implications have increased the popularity of radical retropubic prostatectomy [17, 18]. The perineal approach fell from favour and few urologists had the opportunity to learn this operation. With the introduction of the laparoscopic lymphadenectomy there has been a renewed interest in the radical perineal prostatectomy [19]. Because of the improved visualisation, lowered blood loss, and diminished morbidity the perineal approach has regained some of its popularity.

Combined prostatectomy and pelvic lymph node dissection can only be performed using the retropubic approach. Assessment of nodal status in high-risk patients can be performed as a separate procedure using laparoscopic or open techniques. Although the *minilap* has been described as a reasonable alternative to laparoscopic node dissection [20], the minimally invasive aspect of the latter technique has made it the treatment of choice for most urologists.

Transperitoneal laparoscopic radical prostatectomy has recently been developed as a minimally invasive approach to surgical treatment of prostate cancer [21]. Using this technique, the posterior aspect of the prostate is initially mobilised away from the rectum. The retropubic space is then entered by incising the parietal peritoneum and the apical dissection is performed. Once the prostate is fully mobilised, it is separated from the bladder using a bladder neck preserving dissection. The vesicourethral anastomosis is performed and the prostate gland removed. The proposed benefits of this minimally invasive approach are better visualisation deep in the pelvis, shorter post-operative hospital stays, and less post-operative pain. Early studies failed to show a decrease in length of hospital stay (mean hospital stay was 7. 8 days [21]) but nowadays patients are routinely sent home on the third post-operative day. Early reports described rectal injuries as intraoperative complications but these occurred early in the learning curve of the procedure [21, 22]. The mean post-operative bladder catheterisation time was 6.6 ± 2.4 days [23]. The positive and questionable surgical margin rate was 15% which is comparable to open prostatectomy series. Pathological tumour stage of these margin-positive cases was pT2a in four specimens (11%), pT2b in 11 (16%), pT3a in 0 and pT3b in 3 (50%).

In summary, laparoscopic prostatectomy appears to be a viable surgical option in experienced hands. It is important to state, however that this technique is technically demanding and should only be attempted by those surgeons experienced in laparoscopic surgery. As long-term data is still lacking, the exact role of laparoscopic prostate surgery is as yet undefined. Whether the longer surgical times and surgical expertise demanded by laparoscopic surgery will be offset by the potential benefits will only be determined by further study.

Routine Pelvic Lymphadenectomy

The need for routine pelvic lymphadenectomy in all prostatectomy patients has been questioned. Results from the Mount Zion Cancer Centre, University of San Francisco, showed that lymph node dissection is unnecessary in the subset of patients in which the risk of lymph node involvement is less than 18% [24]. In another study, 575 prostatectomy patients with favourable tumour characteristics, that is, PSA ≤ 10 ng/ml, Gleason score ≤ 6 or and clinical stage T1 or T2 [25], were divided into two groups according to whether PLND was performed (PLND, 372 patients) or omitted (No PLND, 203 patients). Proportional hazards were used to analyze the effect of age, race, family history, stage, biopsy Gleason score, initial PSA, PLND, and pathological findings on the likelihood of biochemical failure. After a mean follow-up of 38 months, range 1-141, the actuarial four-year biochemical relapse-free rate for the PLND *versus* No PLND groups was 91% *versus* 97%, P = 0.16. Therefore, the omission of PLND in patients with favourable tumour characteristics does not adversely affect biochemical relapse rates [25].

Sentinel Lymph Node Biopsy

Finally, it is noted with regard to surgical approaches that although sentinel lymph node (SLN) biopsy has been increasingly used in other cancer sites, such as, breast cancer, penile cancer and melanoma, it has not been found to be a reliable staging procedure for prostate cancer [26].

Patient Selection & Predictor Variables for Biochemical Disease-Free Status

PSA, Stage, Age & Patient Preference

The factors used in determining patient eligibility for radical prostatectomy are PSA, stage of disease, age, and wishes of the patient. In general, radical prostatectomy is reserved for men with at least a 10 year life expectancy and therefore patient age and co-morbid disease play an important part in patient selection. An age of 70 is often used as the upper limit of surgical consideration but this should not be viewed as an absolute cut-off value and selection should be individualised for each patient. In fact, using Medicare claims data, 29% of the radical prostatectomies were performed in men ≥ 70 years in 10 hospitals in Kentucky and Indiana [27].

Serum PSA

Although serum PSA can be considered a surrogate for tumour burden, no threshold value for surgical case selection has been determined. A total of 7/210 patients with PSA < 20 ng/ml presented with bone metastases including 4/7 with a PSA < 10 ng/ml [28]. The highest preoperative serum PSA was 23 ng/ml among the 181 men biochemically free of disease after prostatectomy [29]. Only 9/57 (15.8%) men with PSA > 15 ng/ml remained biochemically free of disease with a greater than three year follow-up. This study also found that transition zone cancers had improved disease-free survival *versus* peripheral zone disease.

Gleason Score, Serum PSA, Cancer Volume & Prostate Weight

The most important variables found to predict biochemical disease-free status for peripheral zone cancers were Gleason scores 4 and 5, cancer volume, serum PSA and prostate weight. Because of poor cure rates, it has been recommended [30] that men with serum PSA > 15 and perhaps even > 10 ng/ml be considered for rebiopsy in order to prove a transition zone location or else therapy other than radical retropubic prostatectomy should be sought. D'Amico also found that a pre-operative PSA > 10 ng/ml or a pathological Gleason score ≥ 7 have significant decrements in short-term PSA failure-free survival [31]. Positive margin is significantly more common when PSA > 15 ng/ml (P=0.006), higher Gleason grade (P=0.01), higher proportion of stage T2b or T2c (P=0.003) and nodal involvement (P=0.001) [32].

Pelvic Lymph Node Dissection

Because of the accuracy in predicting organ confined disease based on pre-operative factors, pelvic lymph node dissection need not be performed in every patient. PSA level < 10 ng/ml and Gleason score < 7 are rarely associated with nodal involvement and therefore node dissection may be omitted [25, 33, 34].

Positive Prostate Needle Biopsy

The percentage of positive cores in prostate needle biopsy specimens is another pre-operative factor being studied [35]. It has been found to be a strong predictor of tumour stage and volume at radical prostatectomy. Multivariate analysis has showed that the percentage of positive cores (P=0.0003), initial serum PSA (P=0.005) and Gleason score in the needle biopsy (P=0.03) were the only parameters predictive of pathological stage: T2 *versus* T3.

Locally Advanced T3 Disease

The treatment of locally advanced stage T3 prostate carcinoma is a dilemma. The reliability of the clinical assessment of extracapsular extension by digital rectal examination (DRE) is crucial. Results from series of patients with T3 prostate cancer treated by radical prostatectomy indicate that DRE has shown a wide range of accuracy ranging from 44% to 82%. The assessment of capsule perforation on biopsy provides a 96% specificity rate and a positive predictive value of 60% [36]. Information regarding the correlation between T3 clinical

staging and conventional/endorectal coil MR imaging staging is still needed.

The accuracy rate of DRE for T3 staging increases to more than 90% if the PSA level is > 15 ng/ml: although 31% of T3 patients had node-positive disease, 25% were pathologically organ-confined tumours that had been clinically overstaged. Cancer-specific survival rates at five, 10, and 15 years were respectively 93%, 84%, and 74%, and operative morbidity paralleled that of patients with clinically localized disease [37].

In conclusion, preoperative factors including PSA should be carefully considered in clinically advanced disease. Surgical treatment of T3 disease still affords long-term survival with low treatment-related morbidity and can be supplemented with adjuvant therapy. Clinical T3 disease should thus not be considered an absolute contraindication to radical prostatectomy.

Pelvic Nodal Metastases, Stage D1

The management of D1 (pelvic nodal metastases) patients is another controversial issue. Nodal cancer volume was the most significant determinant of progression to distant metastasis in lymph node-positive prostate cancer patients [38]. Messing found an improved survival and reduced risk of recurrence in node positive patients after radical prostatectomy and pelvic lymphadenectomy when hormonal therapy was started immediately [39]. Progression-free survival was also found to be increased in D1 patients after radical prostatectomy *versus* those receiving radiotherapy or conservative therapy, P=0.055 [40].

Although pre-operative nodal involvement is considered an absolute contraindication to radical prostatectomy Frohmuller contested this idea [41]. His series of 139 patients with histologically proven stage D1 (T1-T3 pN1-2 M0) consisted of 87 patients followed by androgen deprivation alone (group 1) and 52 patients with additional radical prostatectomy (group 2). The actuarial 10-year non-progression rates were 14.6% in group 1 and 35.8% in group 2, P=0.0016. The overall and disease-specific 10-year survival rates were found to be 29.7% and 32.1% for group 1 and 50.8% and 70.7% for group 2. Local progression as the main parameter influencing quality of life occurred in 60/87 patients (69%) not subjected to radical prostatectomy. Transurethral resection of the prostate was required in 29 of these patients. In contrast, following radical prostatectomy, only 4 /52 patients (8%) had local progression and only one patient required a dilatation of the vesicourethral anastomosis for relief of infravesical obstruction.

Thus, radical prostatectomy plus androgen deprivation for patients with stage D1 prostate cancer appeared to be superior to androgen deprivation alone with respect to survival expectancy and quality of life [41]. Only high Gleason scores, 8 to 10, on the pre-operative biopsy was found to correlate with rapid progression to distant metastases ($P \leq 0.00001$) in a multivariate analysis [30]. If the Gleason score was < 8, the likelihood of distant metastases was only 18% and 41% at five and 10 years, whereas 85% of men with a Gleason score of 8, 9 or 10 had distant metastases by five years.

For urologists who believe that radical prostatectomy is useful in providing local control in men with positive lymph nodes, frozen section analysis of lymph nodes is probably not necessary in men who have pre-operative Gleason scores of < 8. Conversely, in patients with a Gleason score of 8 to 10 on needle biopsy, careful analysis of lymph nodes is necessary to avoid radical prostatectomy in those who will derive little benefit [30].

Patient's Viewpoint

Apart from the above objective selection considerations, the wishes of patient and family also need to be taken into account. Urinary incontinence following radical prostatectomy has a significant deleterious effect on quality of life and, unfortunately, is much more prevalent following surgery compared with other treatment modalities, such as radiation therapy. Alternative modalities of treatment should be carefully discussed with the patient and family so as to allow them to make an informed decision suited to their expectations.

Assessment of Prognostic Indicators

Host & Tumour Factors

Prognostic indicators can be divided into host (for example, age & race) and tumour factors (for example, Gleason grade & clinical stage) but sometimes they are to a certain extent inter-related. For instance, African Americans are less likely than Caucasians to receive PSA screening and may present at a later stage. However, given the same stage, preoperative PSA, Gleason score, in an equal access medical care facility, race was not an independent factor of biochemical recurrence in post-prostatectomy patients [42,43]. Similarly, other studies also reported that race does not appear to adversely affect biochemical disease-free survival in males treated for early stage prostate cancer. African-American males with early stage prostate cancer should expect similar biochemical disease-free survival rates to those seen in Caucasian males [44].

CaPSURE Study

A report from the University of California, for a series of 1383 patients enrolled in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), a longitudinal registry of patients with prostate cancer, who underwent radical prostatectomy, stated that more complete pathological analysis of the prostatectomy specimen predicts outcome more accurately [45]. Specimens were considered step-sectioned only if the entire specimen was submitted for analysis and if sections were taken at 5 mm intervals or less. Patients with negative margins in whom step-sectioning was performed

exhibited significantly lower secondary non-adjuvant treatment use and appeared to have a lower risk of PSA recurrence than similar patients in the non-step-sectioned group [45]. Early biochemical recurrence was associated with other prognostic indicators including pre-operative PSA, tumour volume, Gleason score, clinical stage, surgical margin positivity, periprostatic tissue involvement, capsular invasion and seminal vesicle invasion [46].

Seminal Vesicle Involvement

Involvement of seminal vesicle is generally believed to herald distant metastases. TRUS guided seminal vesicle biopsy is useful and reliable for pre-operative staging and helpful in correct decision making for prostatectomy [47]. The use of the endorectal coil MR imaging data provides a more accurate prediction of the pathological outcome of seminal vesicle invasion [48]. Epstein and Walsh reported a few patients with node-negative, seminal vesicle-positive tumours who had an excellent long-term prognosis. Most of these patients can be split into two groups, one experiencing rapid and the other slower progression [49].

Perineural Invasion

Perineural invasion on preoperative prostate needle biopsy is a strong independent predictor of PSA recurrence in patients in whom prostate cancer was treated with radical prostatectomy [50]. However, when perineural invasion was compared with other post-operative parameters, including disease stage, surgical margins and seminal vesicle invasion, it was not an independent predictor because it closely correlated with tumour stage.

New Prognostic Indicators

Newer prognostic indicators are being investigated, including. tumour angiogenesis, Ki 67 labelling index and reverse transcriptase-polymerase chain reaction (RT-PCR) [51, 52]. Tumour angiogenesis as measured by microvessel density is associated with a negative clinical prognosis after radical prostatectomy [52]. A tumour cell proliferation marker: Ki 67 labelling index, is an independent predictor of tumour progression [51].

The RT-PCR assay for PSA can detect circulating prostate cells. It is the best predictor of potential surgical failures; 70% of patients with positive surgical margins or invasion into the seminal vesicle were identified pre-operatively by a positive RT-PCR assay (odds ratio = 12.0, positive predictive value = 64%, negative predictive value = 87%) [53]. RT-PCR was able to pre-operatively identify patients with adverse pathology, despite low serum PSA values of < 4.0 ng/ml. In patients with high PSA level, of > 10 ng/ml, RT-PCR discriminated between potentially curable candidates and those with established extraprostatic disease. Despite these impressive results, the final role for the RT-PCR assay is as yet undefined partly due to the high cost and limited availability of this technique.

Ultrasensitive PSA Assay & MR Imaging

Recent developments to detect recurrence include ultrasensitive PSA assay and MR imaging. Although the definition of biochemical recurrence is not absolutely defined, traditionally a post-operative PSA level > 0.2 ng/ml has often been used. With the advent of the ultrasensitive PSA assay, biochemical recurrence can be detected earlier. In one study, the ultrasensitive assay was found to detect recurrence by an average of 18 months earlier than the conventional PSA method [46]. PSA by ultrasensitive assay > 0.1 ng/ml is generally indicative of post-operative failures. MR imaging findings of definite extracapsular spread of disease helped to predict prostate tumour recurrence with high specificity, although with low sensitivity [54].

Timing of Post-Prostatectomy Failure

The timing of failure after prostatectomy has been studied in detail. Of the peripheral zone failures, 60% occurred in the first year after radical retropubic prostatectomy and 95% had occurred by the end of the fourth year [29]. Annual hazard rates for progression were highest during the first two years after radical prostatectomy for the entire population [55]. Patients with adverse prognostic features (that is, pT3b, PSA ≥ 10 ng/ml, Gleason score 8-10 and nondiploid cancers) had high initial hazard rates that decreased with time to lower levels. Those with pathologically organ-confined cancer had low but constant hazard rates throughout follow-up. Progression after radical prostatectomy usually occurs early reflecting the impact of clinical understaging. However a significant number of men, including those with organ confined cancers, will continue to have disease progression after five years. Patients undergoing radical prostatectomy should be subjected to long-term follow-up to allow the option of early intervention should progression occur [55].

Outcome: Radical Prostatectomy versus Radiotherapy

Martinez has compared the results of radical prostatectomy with pelvic lymph node dissection to external radiotherapy. For patients with pretreatment PSA levels ≤ 10 ng/ml and Gleason scores ≤ 6, conventional doses of external beam radiotherapy (median 66.6 Gy, range 59.2-70.2 Gy) and radical retropubic prostatectomy achieved similar seven-year rates of biochemical control and cause-specific survival, which were unaffected by age at diagnosis [56]. However for organ-confined prostate cancer as a whole, Paulson reviewed the randomised and non-randomised studies, and concluded that radical prostatectomy provides a significantly better outcome than does external beam radiotherapy [2, 57, 58].

A quality of life comparison of radical prostatectomy and interstitial brachytherapy in the treatment of clinically localised prostate cancer was reported by Krupski [59]. The primary outcome measures were the Functional Assessment of Cancer Therapy scale (FACT-G), American Urological Association (AUA) International Prostate Symptom Score (IPSS), *Urinary Function Questionnaire for Men after Radical Prostatectomy and Brief Sexual Function Inventory* [59]. Data from 138 patients were included in the analysis; 27 had radical prostatectomy (RP), 70 had brachytherapy monotherapy (BTM) of 115 Gy or combined brachytherapy (90 Gy) and external beam radiation (40-45 Gy) (BTC).

Correlations were noted between total FACT-G and urinary symptom score, degree of sexual function, frequency of diarrhoea, and frequency of hot flashes. Problems of urinary function correlated with the degree of urinary control. The radical prostatectomy and BTM groups had improvement in quality of life, voiding, diarrhoea, and sexual function with time, whereas the BTC group experienced a decline.

The Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE), also examined potency. Patients undergoing external beam radiotherapy or radical prostatectomy with or without nerve sparing all showed comparable rates of improvement in sexual function during the first year after treatment for early-stage prostate cancer. However, in the second year after treatment, patients treated with radiotherapy began to show declining sexual function, whereas patients treated with radical prostatectomy did not [60].

Treatment Morbidity after Prostatectomy

Table I shows the acute and chronic complications which can occur following prostatectomy and their incidence. In a large review of surgical patients, post-operative complications occurred in 10% of patients overall and were associated with older age, $P < 0.002$. The incidence of complications however declined significantly with increasing experience of the surgeon, $P < 0.0001$ [61].

Table I. Incidence of acute and chronic post-prostatectomy complications [62, 63]

Acute complication	Incidence (%)
Intraoperative bleeding	3.5
Post-operative bleeding	2
Impotence	22-95
Incontinence	< 5 – 27
Ureteral injury	< 1
Urinary fistula	1-2
Perforation of rectum	< 1
Mortality	1
Chronic complication	**Incidence (%)**
Urinary incontinence	8
Impotence	13
Bladder neck contractures	1-2

Urinary Incontinence

The overall incidence of urinary incontinence is higher than 2% regardless whether the surgical approach is retropubic or perineal [64]. The median time to continence recovery, based on the patient self-reporting, was significantly shorter in the nerve sparing than in the non-nerve sparing group when continence was defined as no urinary leakage: 5.3 months *versus* 10.9 months, $P < 0.01$. The nerve sparing technique of radical prostatectomy was associated with improved recovery of urinary continence in an age dependent manner. Patient age and the definition of incontinence may partially explain the variation of continence rates in the literature [8]. Pelvic floor education was found in a randomised controlled trial to be very effective to shorten the duration and improve the degree of incontinence after radical prostatectomy [65,66].

The morbidity associated with prostatectomy is variable and is affected by surgeon experience. Complications from large centres specializing in surgical treatment are low but nationwide surveys have reported a much higher risk of complications. Walsh reported outcomes of 62 men who underwent radical retropubic prostatectomy at the Johns Hopkins Hospital [63, 67]. By 18 months 93% of the patients were dry, that is, wearing no pads, and 93-98% characterised urinary problems as either none or small.

Impotence

The other important morbidity of prostatectomy is impotence. Involuntary loss of urine at orgasm may be the sufficient reason to avoid any sexual contact with their partner [68]. Pre-operative potency is definitely known to be associated with a better response to post-operative medical treatments with oral, intraurethral, or intracorporally injected agents [69]. Early institution of medical therapy with intracorporal injections starting two months post-operatively has resulted in a higher incidence of spontaneous return of erections at one year.

Vacuum erection devices may be successful in restoring erections but extensive practice in their use is necessary, and they may be unappealing to many patients. A penile prosthesis will allow intercourse but is not commonly chosen in this older population. Prostheses are expensive and require invasive surgery, but satisfaction rates among patients and partners who have used them have been surprisingly high.

In the Johns Hopkins study [63, 67] it was reported that potency, defined as the ability to achieve unassisted intercourse with or without the use of sildenafil, improved gradually and that by 18 months 86% of the patients were potent and 84% considered their degree of sexual problems as either none or small.

Medicare & Other Population-Based Studies

In another study, patients who underwent RRP in the Medicare population [62] were identified by all inpatient, outpatient, and physician Medicare claims for these men. Procedures performed for complications resulting from RRP were recorded, as were the diagnostic codes that may have heralded a complication after RRP. In 1991 a total of 25,651 men in the Medicare population underwent RRP: their mean age was 70.5 years. Procedures for the relief of bladder outlet obstruction or urethral strictures after RRP occurred in 19.5% of these men. A penile prosthesis was implanted in 718 men (2.8%) after prostatectomy, and 593 men (2.3%) had an artificial urinary sphincter placed after prostatectomy. A diagnosis of urinary incontinence was reported in 5573 men (21.7%) after radical prostatectomy, but only 2025 of these men (7.9%) continued to carry this diagnosis more than one year after prostatectomy. A diagnosis of erectile dysfunction was reported in 5510 men (21.5%) after radical prostatectomy, but only 3276 of these men (12.8%) continued to carry this diagnosis at more than one year post-surgery [62].

In another population based longitudinal cohort study, involving a total of 1291 patients, analysis at ≥ 18 months following radical prostatectomy, 8.4% of men were incontinent and 59.9% were impotent [70]. Among men who were potent before surgery, the proportion of men reporting impotence at 18 or more months after surgery varied according to whether the procedure was nerve sparing: 65.6% of non-nerve-sparing, 58.6% of unilateral, and 56.0% of bilateral nerve-sparing.

Sexual performance was assessed as a moderate-to-large problem in 41.9% of patients. Both sexual and urinary function varied by age, 39.0% of men aged < 60 years *versus* 15.3%-21.7% of older men were potent at ≥ 18 months, $P < 0.001$; 13.8% of men aged 75-79 years *versus* 0.7%-3.6% of younger men experienced the highest level of incontinence at ≥ 18 months, $P = 0.03$. Sexual function also varied by race, 38.4% of black males reported firm erections at ≥ 18 months *versus* 25.9% of Hispanic males and 21.3% of white males, $P = 0.001$.

Patient Self-Reporting of Complications

The patient self-reported incidence of any degree of post-prostatectomy incontinence, impotence and bladder neck contracture or urethral stricture is generally higher than surgeons' reported rates. In a multicentre patient self-reported questionnaire on incontinence, impotence and bladder neck contracture or urethral stricture, the rates were respectively 65.6%, 88.4% and 20.5% [36]. The incidence of incontinence requiring protection was 33% and only 2.8% of respondents had persistent bladder neck contracture or urethral stricture.

Although incontinence and impotence significantly affected self-reported sexual function satisfaction, and quality of life, $P = 0.001$, 77.5% of patients responded that they would elect surgery again. This finding remained true even after adjusting by multiple logistic regression for demographic variables, and the time between surgery and the survey.

Treatment Costs

Radical prostatectomy accounts for approximately half of the $1.7 billion annual cost of prostate carcinoma treatment in the United States [1]. The total relative perioperative cost for transperineal brachytherapy with ^{125}I seeds exceeded that for RRP by 85-105% [71]. The technical costs included those incurred for anaesthesiology, laboratory medicine, medicine, pharmacy, nursing, radiology, ^{125}I seeds and brachytherapy. Professional costs included fees from anaesthesiology, laboratory medicine, medicine, urology, radiation oncology and physics. Technical cost, exclusive of ^{125}I seeds, was substantially lower for transperineal brachytherapy (relative to prostatectomy cost 0.36-0.42) but was more than offset by the cost of the ^{125}I seeds when comparing total cost with radical prostatectomy using a perineal approach (RRP). Not much work has been undertaken in the cost-effectiveness of ^{103}Pd seeds, but we know that they are more expensive than ^{125}I seeds.

Role of Neoadjuvant & Adjuvant Hormonal Treatment

A number of studies have addressed the value of neoadjuvant hormonal treatment prior to prostatectomy [72]. The majority employed 2-3 months of total androgen blockade and reported less positive surgical margin, less extracapsular extension, clinical and pathological downstaging, but no improvement in biochemical progression or survival [73-78]. Surgical margins were less often positive in the hormonal therapy (25%) than the prostatectomy alone (47%) group, $P = 0.0001$ [76]. The downstaging suggests the possibility of an improvement in the morbidity from prostate cancer if post-operative radiotherapy is not required. No difference in risk of PSA failure was observed overall between the hormonal therapy and prostatectomy only groups: hazards ratio 0.94, 95% CI 0.68-1.30.

Treatments with antiandrogen alone for any duration, and those combining antiandrogen and luteinising hormone-releasing hormone analogue for (3 months were not associated with improved survival. However, patients receiving combined therapy for ≤ 3 months had a significantly lower risk of PSA failure than those treated with radical prostatectomy alone: hazards ratio 0.52, 95% CI 0.29-0.93. Prolonged neoadjuvant hormonal therapy combining antiandrogen and luteinizing hormone-releasing hormone analogue may improve disease-free survival after radical prostatectomy [76].

In a study from Vancouver, neoadjuvant hormone therapy prior to radical prostatectomy was given for eight months to 156 patients [79] and it was found that the risk of PSA is low after five years of follow-up. The duration

of neoadjuvant hormonal therapy needed for beneficial effect has not yet been determined. More supporting evidence for a longer duration of hormonal therapy comes from Norway, CT and MR serial examinations suggest that neoadjuvant androgen deprivation before local treatment should last at least six months in order to achieve a maximal effect in the majority of the patients [80]. The Canadian Urologic Oncology Group (CUOG) is presently performing a randomised trial of 3 months *versus* 8 months of neoadjuvant androgen deprivation.

The possible theories which might explain the lack of survival benefit from neoadjuvant hormonal therapy include the emergence of a hormone resistant tumour clone, development of a tumour clone that more readily metastasises, the difficulty of the pathologists to identify minimal residual disease at the margin after cytoreductive hormonal treatment, and a rebound phenomenon of testosterone after cessation of hormonal therapy. The latter has not been observed in studies of intermittent hormonal therapy [81].

Based on the data available, neoadjuvant hormonal treatment prior to surgery would appear appropriate for those patients at high risk of having a positive surgical margin [82]. Currently, the LH-RH agonists are the drugs of choice for adjuvant therapy, whereas combined androgen blockade has generally been used as neoadjuvant therapy [77].

When to Prescribe Adjuvant Radiotherapy

Many authors, particularly in Europe, consider that only clinical recurrences warrant additional treatment, usually in the form of radiation therapy [83]. At the time of clinical recurrence, imaging studies should be performed to confirm the absence of metastases. Another valuable tool in determining tumour burden (and indirectly metastatic disease) is the evaluation of PSA kinetics (PSA velocity or post-operative doubling time). If the recurrence seems local, radiation therapy alone is the best initial option, since concomitant hormone therapy leads to a decrease in PSA levels even in the presence of metastatic disease, thus depriving the patient and physician of a valuable test for monitoring treatment response.

Increasing evidence points to the advisability of early radiotherapy for patients with high risk of recurrence after prostatectomy [84]. Widely quoted studies include review of 368 total patients, (the numbers of patients in the various studies are as follows: Forman, 47; Vincini, 68; Morris, 88; Peschel, 52; Schild, 46; Wu, 53; and Wilder, 14) and all point towards the value of early adjuvant radiotherapy [85-91].

Acute toxicity from Wilder's study [90] was mild and did not require medication: Radiation Therapy Oncology Group grade I. A total of 4/14 patients experienced genitourinary morbidity and 3/14 experienced gastrointestinal morbidity [90]. With regard to late toxicity, 1/14 developed a urethral stricture requiring dilatation: Radiation Therapy Oncology Group grade III. All 5/14 patients who were potent at the start of radiotherapy remained potent. Forman's study from the Detroit Medical Centre reported a chronic complication rate of 17% [85]. In terms of cost, Medicare's median reimbursement for salvage 3D conformal radiotherapy in Wilder's study ($7,512 in 1999 U.S. dollars) is equivalent to its reimbursement for a 17-month course of goserelin hormonal therapy [90].

In conclusion, current evidence suggests that post-prostatectomy patients whose PSA begins to rise after an undetectable level should be referred for salvage treatment with radiotherapy when their PSA is still less than or equal to 1.0 ng/ml. It is also noted that Peschel reported that the three-year biochemical no evidence of disease (bNED) survival rate for the adjuvant radiation group was 85% compared with 27% for salvage radiation and 43% for the observation group [87]. These results are statistically significant. Factors that predict biochemical failure following post-operative radiation therapy include pre-operative PSA level, pre-radiation therapy PSA level, and seminal vesicle involvement.

Summarising the results in the literature, Grossfeld constructed a decision tree model of the management of a positive surgical margin after radical prostatectomy [92]. The conclusion was that immediate radiation may be appropriate for patients with positive surgical margins and a high likelihood of recurrent local rather than distant disease [31, 92, 93].

Not all reports in the literature are specific concerning the percentage of cases with single or multiple positive margins. The Mayo clinic performed a retrospective case-matched study of 152 patients to assess the benefit of adjuvant radiation therapy for localised prostate cancer with a single positive surgical margin [94]. They studied the records of a nested matched cohort of 76 patients with pathological stage T2N0 prostate cancer and a single positive margin who underwent adjuvant radiation therapy within three months of radical prostatectomy. These patients were matched 1:1 with 76 controls who did not receive adjuvant radiation therapy. Neither group received androgen deprivation therapy. Patients and controls were matched exactly for the margin positive site, age at surgery, preoperative serum prostate specific antigen, Gleason score and DNA ploidy. Biochemical relapse was defined as post-treatment PSA > 0.2 ng/ml. No patient who received radiation therapy had local or distant recurrence, while 16% of controls had recurrence, $P = 0.015$. The estimated improvement in five-year clinical and biochemical progression-free survival was significant with $88\% \pm 5\%$ *versus* $59\% \pm 11\%$ of patients treated with adjuvant radiation therapy *versus* no radiation therapy, $P = 0.005$.

The treatment outcome of radiotherapy after radical prostatectomy is encouraging [95]. Patients who received radiotherapy (RT) with a pre-RT PSA < 1.0 ng/ml demonstrated a progression-free outcome equivalent to those who received adjuvant RT. Two distinct patterns of PSA failure were observed on the basis of PSA nadir after RT. Patients whose PSA failed to reach

a nadir < 0.2 ng/ml after RT had progression with a high PSA velocity (1.5 ng/ml/yr). Patients whose PSA reached a nadir < 0.2 ng/mL but who subsequently had treatment failure progressed later with a lower PSA velocity (0.36 ng/ml/yr) [95].

Currently the Radiation Therapy Oncology Group is enrolling high risk pT3N0 patients after prostatectomy for adjuvant therapy: RTOG P-0011. The three arms are: (1) LH-RH agonist for 2 years plus radiation therapy to 63-66.6 Gy; (2) radiation therapy to 63-66.6 Gy; (3) LH-RH agonist for 2 years. Results from this trial would be very useful. Arm 3 was closed due to poor accrual recently.

Role of Surgery after Radiation for Residual or Recurrent Disease

The role of salvage prostatectomy in this situation remains unclear. Recurrent prostate cancer after radiation therapy is in many cases biologically aggressive. It is unclear whether the biological aggressiveness of radio-recurrent prostate cancer is due to time-dependent cancer clonal evolution, potentially induced by radiation damage, or is due to an innately aggressive tumour secondary to overexpression or mutation of apoptotic inhibitors that render these tumours resistant to radiation [96].

Surgery is not often used for salvage of residual or recurrent disease after radiation due to unacceptable morbidity. In an effort to decrease morbidity, the M.D. Anderson Cancer Centre reported on 13 patients with biopsy proven, locally recurrent prostate cancer after radiation therapy, who underwent salvage prostatectomy with complete bladder neck closure and reconstruction with an appendicovesicostomy to the native bladder in 9/14 and ileovesicostomy in 4/14 [97]. There were no intraoperative complications. Four patients had serious complications necessitating reoperation, including a vesicourethral fistula requiring delayed cystectomy, wound dehiscence with disruption of the appendicovesical anastomosis, leakage from the small bowel anastomosis that resulted in sepsis and death, and stomal stenosis requiring delayed stomal revision. Of 12 patients two used pads for incontinence, while 10/12 were dry during the day and night with a catheterisation interval of 2-6 hours. The post-operative continence rate is excellent and appears superior to those in the literature for salvage prostatectomy and vesicourethral anastomosis.

Cryotherapy

Cryotherapy is another treatment option for primary disease, local residual or recurrent prostate cancer after radiotherapy, although experience is still limited. Future efforts designed to improve the current technique should be encouraged. Longer follow-up results will be available in the future [98].

Conclusions

Radical prostatectomy is a valid treatment option for localised prostate cancer and results in excellent long-term survival. With the evolution of surgical techniques, morbidity has decreased to acceptable levels. Research on pre-operative staging tests, newer minimally invasive techniques, and neoadjuvant/adjuvant therapy will likely improve on current biochemical recurrence free survival rates in the future.

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