

MAJOR ADVANCES IN SURGICAL TECHNIQUE FOR THE TREATMENT OF GENITOURINARY CANCERS

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Abstract

There have been numerous recent advances in surgical techniques for the treatment of genitourinary cancer. The advent of robotic-assisted laparoscopic radical prostatectomy is certainly a major technical development, however its superiority over the open technique has not yet been proven. Clinical trials of focal prostate therapy have begun, utilising the latest generation of ablative technologies such as cryotherapy and high intensity focused ultrasound. Small renal masses are now managed by active surveillance, nephron sparing surgery and ablative techniques with good success. Finally, extended lymphadenectomy for bladder cancer and high risk prostate cancer not only allows better pathological staging but also improved survival.

Significant advances in the surgery of genitourinary cancers have been made in the last five years. A comprehensive evaluation of all the major changes is beyond the scope of this article. However, we have selected the changes that we consider the most significant in terms of treatment outcomes and future trends.

Prostate: is robotic assisted laparoscopic prostatectomy better?

The development of the robotic-assisted laparoscopic retropubic prostatectomy (RALRP) in 2000 has been a major development in the technique of radical prostatectomy. In the US, this is now the most common approach for surgical removal of the malignant prostate and is gaining popularity in other parts of the world as well.

The proponents for this approach claim that it is associated with shorter hospitalisation, less pain, better cosmesis, shorter catheter time, lower transfusion rates and improved continence and potency rates. Open radical retropubic prostatectomy (ORRP) has also made significant improvements over the last decade and has become less invasive with significantly smaller incisions (8-10cm), quicker discharge from hospital and return to work, lower transfusion rates and much improved continence and potency outcomes (www.intuitivesurgical.com/patientresources/conditions/urologic/dvp.aspx).

In terms of the most important clinical outcomes following radical prostatectomy, there is a lack of high level evidence supporting superiority of RALRP over modern ORRP. A report based on the Medicare database in the US between 2003 and 2005 shows that following RALRP, 28% of men required salvage cancer treatments compared to 9% following ORRP, suggesting that laparoscopic techniques are failing to achieve the most important objective of treatment.¹ This study also showed that urethral stricture rates were 40% higher with RALRP. RALRP is however, clearly associated with lower blood loss but not lower transfusion rates.²

In relation to sexual functioning, the study with the highest level of evidence comparing the various methods of radical prostatectomy did not show any difference between ORRP and RALRP,³ and this result has been replicated in a number of other studies. Claims on websites dedicated to robotic surgery that the RALRP method results in better sexual functioning have not been substantiated by scientific evidence. Continence rates also appear similar to conventional open surgery.

The modern ORRP is usually performed with a small incision and extraperitoneal approach, which minimises bowel disturbance. The operation takes approximately two hours and men are ambulatory and eating normally the next day and discharged two to three days post operatively. RALRP is very similar and the sum of all the multiple incisions is the same as the total length of an ORRP incision. In Australia, hospital stays have also been approximately two to three days. There are numerous conflicting studies showing that both RALRP and ORRP result in quicker return to normal activities. Unfortunately, there have been no large, prospective, well selected longitudinal studies ascertaining when men return to work or unrestricted activities following RALRP.

Satisfaction and regret rates differed substantially between men having RALRP versus ORRP in a Duke Medical Center study. After adjusting for baseline factors, the odds of being satisfied with treatment were four times higher in men who underwent ORRP rather than RALRP; and, the odds of regretting their treatment was three times higher in men who had RALRP rather than ORRP.⁴ These counterintuitive findings are most likely due to unrealistic expectations rather than major differences in outcome between the two techniques. Further studies show that long-term satisfaction is independently associated with disease control, continence and potency and not by factors such as return to work time, length of stay and incision length.

In summary, the major technological advance of RALRP has not resulted in any significant improvement in continence or potency. The new procedure may however, be associated with poorer cancer control and higher levels of dissatisfaction and regret. The outcomes of earlier return to normal activities are still controversial.

Prostate: focal therapy is possible

With increasing screening, the burden of prostate cancer disease which may not pose a significant risk to life expectancy is increasing.⁵ The therapeutic dilemma for a man diagnosed with low risk prostate cancer lies between the extremes of radical therapy on the one hand and active surveillance on the other. The former maximises the chances of cure at the expense of urinary and sexual morbidity. The latter preserves genitourinary function at the expense of psychological burden, potential for disease progression and economic burden of intensive surveillance.

Traditionally, treatment of the whole gland has been the standard of care as there is no natural surgical plane to allow partial treatment. Prostate cancer has also been regarded as a multifocal disease requiring treatment of the whole gland. Recent studies show that between 10% and 40% of men who undergo ORRP have unilateral disease.⁶ This raises the concept of focal ablation of the tumour focus. It has also been shown that in men with multifocal disease, approximately 80% of tumour foci have a volume of less than 0.5cm,³ which may represent clinically insignificant disease.⁷

Active surveillance appears to be a very suitable therapy for men with low risk disease, however, the major limitation is the ability to accurately identify men with significant disease that is going to progress clinically. As a result, the failure rate or intervention rate is approximately 20% in active surveillance series.^{8,9} The oncological safety of active surveillance is also not well established, as the follow-up in cohort studies is still relatively short, although recent publications suggest that of those who come to definitive treatment, 50% may subsequently develop biochemical failure. In addition to this, the potential psychological burden and increased cost of close surveillance may make it less desirable than whole gland treatment by surgery or radiotherapy.

Major technological advances allowing focal treatment of affected parts of the prostate include cryotherapy, high intensity focused ultrasound (HIFU) and photodynamic therapy. This addresses the dilemmas of the untreated prostate in active surveillance, and does so with minimal side-effects, which is the major disadvantage of whole gland therapy. To date only early results of small series from single institutions have been reported. Most series used extended or saturation TRUS biopsy to accurately localise the lesion(s) and exclude contralateral disease (although even with these techniques understaging and undergrading can occur in 20-25% of patients). In a report of hemi-ablation using cryotherapy in 55 men with at least one year follow-up, 95% had stable PSAs and 86% remained potent,¹⁰ however seven men had to be retreated due to cancer in the contralateral half of the prostate.

Another series of hemi-ablation with cryotherapy, with a mean follow-up of 70 months, reported 93% disease-free survival and 48% potency rate.¹¹ A report on hemi-ablation by Muto, using the Sonoblate 500 HIFU® device in 29 men with unilateral disease, demonstrated that at six months, 10% had positive biopsies, however a further 23% had positive biopsies at 12 months.¹² There was no significant change in urinary symptom scores measured with the validated International Prostate Symptom Score questionnaire. Erectile function was not measured in this cohort.

Photodynamic therapy involves administration of a photosensitising drug followed by delivery of a specific wavelength of light into the appropriate region of the prostate by transperineal needle, resulting in ablation similar to cryotherapy. It is currently in its infancy, however multicentre trials of focal ablation are being planned. Radiofrequency ablation is also a technology which has been used in ablation of solid organs such as kidney and liver. It is currently in early studies for prostate but will soon be studied for focal ablation.

In summary, focal ablation appears to be the middle ground between the untreated tumour of active surveillance and excessive side-effects of whole gland treatment. Cryotherapy and HIFU in very small series, with limited follow-up, do demonstrate some promise, however further studies of all ablation methods are required to determine their real place in prostate cancer treatment. The main barrier preventing adoption of these techniques is effective cancer localisation at the time of biopsy, to ensure that the focal therapy is indeed treating all the cancer present in the gland.

Prostate: lymphadenectomy is therapeutic

The decision of whether to perform a pelvic lymph node dissection (PLND) at all in combination with radical retropubic prostatectomy (RRP), and if so the extent of the dissection, depends on many factors. The likelihood of lymph node disease can be estimated from the Partin tables¹³ or Memorial Sloan Kettering Cancer Center nomograms.¹⁴ Most surgeons will perform a limited PLND, or none at all, for men with low risk prostate cancer; however evidence is emerging that men with higher risk prostate cancer should have an extended lymph node dissection.

The first reason for an extended dissection is the higher incidence of lymph node metastases in regions beyond the standard PLND obturator region of dissection. Better staging of disease allows better counselling and implementation of adjuvant therapies such as immediate androgen deprivation therapy. One study showed that an extended PLND (ePLND) including obturator, internal iliac and external and common iliac arteries, resulted in much higher numbers of positive lymph nodes being identified than a standard lymph node dissection (eg. 26% v 12%), with 42% of all positive lymph nodes detected outside the standard template.¹⁵ Similar results in another study suggested approximately 60% of positive lymph nodes would have been missed if only a standard PLND was performed.

There is accumulating evidence that PLND may also be therapeutic. A study of 13,020 patients from the surveillance epidemiology and end results (SEER) database showed that men who had more than four lymph nodes removed at ORRP had a 23% relative reduction in the risk of prostate cancer death.¹⁶ Another finding was that men who had a more extensive PLND (10+ nodes removed) had a 15% relative reduction in the risk of prostate cancer death, even when the analysis was restricted to men with uninvolved nodes. A further study by Heidenreich has also shown that men with no histopathologic evidence of lymph node involvement after ORRP had a 23% risk of relapse if they had sPLND compared with an 8% risk if they had ePLND.¹⁵ There are also a number of reports of men with ePLND who had small volume microscopically involved lymph nodes, but achieved 40% long-term disease free survival.¹⁷

In summary, ePLND dissection is recommended for men who have high risk prostate cancer because it enables better staging and hence further therapies, however emerging evidence also suggests improvement in disease free survival and overall survival, possibly due to the presence of micrometastases that may only be detected using molecular techniques.

Kidney: management of small renal masses

Due to the increased use of diagnostic imaging for evaluating patients with abdominal complaints, incidentally diagnosed small renal masses (SRMs) are being diagnosed with increased frequency and account for between 48% and 66% of renal cell carcinoma diagnoses, resulting in greater surgical intervention over the last three years.¹⁸ Over the last decade there has been growing awareness that these SRMs, typically described as solid renal masses less than 4cm, can be managed in a variety of ways.

Meta-analyses of active surveillance studies have shown that SRMs with a median size of 3.04cm had a median growth rate of only 0.28cm per year.¹⁹ Moreover, 26% to 33% of SRMs demonstrate zero net growth rate when observed for a median of 29 months.²⁰ While there can be considerable growth rate variability between tumours, only 1% of observed lesions in the meta-analysis progressed to metastatic disease with a median three years follow-up.¹⁹

Alternative treatments for SRMs which demonstrate significant growth, adverse pathology on biopsy or cause significant psychological distress to the patients, include nephron sparing surgery and various ablative techniques such as radiofrequency ablation and cryotherapy.

Meta-analysis of nephron sparing surgery (NSS) for SRMs with a median size of 3.26cm, have shown a local recurrence rate of 2.6% after a mean follow-up of 54 months.²¹ Progression to metastatic disease was observed in 5.6% of these patients. Compared to active surveillance and NSS, the newer ablative techniques have smaller median tumour sizes (2.56cm and 2.69cm) and shorter follow-up times (18 months and 16 months) for cryotherapy and radiofrequency ablation respectively. Following treatment, the local recurrence rate is higher than NSS at 4.6% and 11.7%, however metastatic progression was not different at 1.2% and 2.3% respectively.²¹ It is

important to note that although local recurrence rates may be higher for the new ablative therapies, it is often possible to repeat the therapy. A particular difficulty arises in determining local recurrence, as contrast enhancement does underestimate the presence of actual residual disease in the treated region,²² suggesting that biopsy should be used to determine efficacy of treatment.

In summary, the treatment of SRM is still controversial. Accumulating evidence suggests that active surveillance is safe, but for patients in whom this is deemed inappropriate, NSS delivers the optimal oncological outcomes. The new ablative therapies are promising and can be considered alternatives in special circumstances, however local recurrence rates are higher and longer term data are required for better evaluation.

Bladder: the importance of extended lymph node dissection

While it has been long established that regional lymphadenectomy with radical cystectomy for muscle invasive bladder cancer is very important in staging of the patient, and the presence of lymph node metastases is one of the strongest predictors of prognosis, there has been growing evidence that lymphadenectomy has a significant therapeutic role as well. This is not only because it instigates the use of adjuvant therapy in many cases of node-positive disease, but the surgery itself may be therapeutic.

It has been established for over a decade that following surgery alone, five year survival rates may be as high as 14% for patients with macroscopically involved lymph nodes,²³ and up to 50% for patients with only microscopically involved nodes.²⁴

The extent of lymph node dissection traditionally involved the internal and external iliac arteries from the obturator fossa to the common iliac bifurcation. More recently an ePLND dissection which includes the common iliac arteries to the aortic bifurcation, and in some series even the distal aorta, has been proposed. The use of a standard template instead of an extended template misses over 34% of positive lymph nodes²⁴ and ePLND yields a median 22 nodes compared with eight nodes from a standard dissection.²⁵

There is now significant data that shows that the number of lymph nodes removed correlates with oncological outcome. Patients with higher lymph node yields have lower loco-regional recurrence,²⁶ and also risk of developing distant metastasis,²⁷ irrespective of whether the nodes are positive or negative. A number of studies have also shown that larger numbers of nodes removed are associated with a longer disease free interval and higher disease specific survival. For example, Herr et al reported five year survival rates with 0-5, 6-10, 11-14 and 14+ nodes removed were 33%, 44%, 73% and 79% respectively.²⁸ In patients with positive nodes, the lymph node density (positive nodes/total nodes) has been shown to also predict survival.²⁹

While it has been clearly shown that extended lymph node dissection and the removal of more nodes is associated with better disease control and survival, there are a number of possible theories why. The most likely is that the removal of macroscopic and occult microscopic disease truly improves survival. However, it may be that lymph node count may merely be a confounder for patient health, surgeon or institution factors. For example, a sicker patient with more comorbidities or more extensive cancer may have fewer nodes removed and also have a higher mortality. Another explanation is the "Will Rogers" phenomenon, where better staging results in better prognosis for all stage categories. This occurs when better detection of positive nodes leads to movement of people from previously node negative to node positive. Because of this, removing them from the previously node negative group increases the outcomes of the node negative group. Likewise, the migrated node positive patients have lower volume disease than the already node positive group, so adding them raises the average outcome that group as well. Irrespective of the cause, current treatment of muscle invasive bladder cancer in Australia should include extended lymph node dissection.

There continue to be major and minor modifications to the surgical treatment of urological cancers. The future is most likely a combination of technological advances allowing surgical removal or ablation with minimisation of morbidity. In addition the rapid development of biological treatments such as tyrosine kinase inhibitors for renal cell carcinomas will possibly allow more patients to become operable by the downsizing of tumours.

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