Introduction

Prostate cancer is the most common cancer in Canadian men with an estimated 24,600 cases diagnosed in 2010. An increasing proportion of this prostate cancer is now localized because improved screening efforts are diagnosing cancer at an earlier stage.

Table 1a. Therapies for Prostate Cancer

Surgery
Conservative Management
External beam radiotherapy (EBRT)
Brachytherapy
Cryotherapy
High Frequency Ultrasound (HIFU)
Primary Androgen Deprivation

Abstract

Any discussion of the future of medicine should include a discussion of prostate cancer surgery, which is presently one of the most rapidly evolving and technologically advanced areas of medicine. Prostate cancer is the most common cancer in men for which the surgical treatment is radical prostatectomy (RP). RP affords a high chance of cure for localized prostate cancer and has a demonstrated survival benefit. RP has been around for more than a century and has undergone a dramatic evolution culminating in modern techniques that allow for excellent oncologic control and quality of life. A variety of surgical approaches exist for RP including open, laparoscopic, and laparoscopic with robotic assistance. Outcomes, cost, learning curves and usage trends for these approaches are discussed. Conservative options that may precede surgery are also discussed.

Therapies for prostate cancer are detailed in Table 1a. This wide range of choices results in a confusing landscape for both patients and physicians alike. Surgery and EBRT are considered equivalent for cancer control but newer modalities are lacking high quality evidence in this regard. Comparative evidence to determine the best modality is also of poor quality or does not exist.

Although prostate cancer therapy is usually a major intervention that has significant side effects, specific modalities differ in how they impact quality of life (QOL). This leads us to the current paradigm that there is no single best treatment for prostate cancer and patient choice must be incorporated in the choice of treatment modality to optimize their individual QOL. Details of how each intervention impacts QOL are discussed elsewhere. It is likely that non-clinical factors such as those detailed in Table 1b play a large part in ultimate treatment selection. In efforts to decrease these predispositions, physicians dealing with this common disease who fully understand the treatment options may aid patients in making a properly informed decision. To this end, this review includes discussion of the history, procedure, outcomes, cost, side effects and future of surgery for prostate cancer. Conservative treatment in the context of it preceding surgery is also discussed. A discussion of non-surgical therapies for prostate cancer is not included and may be found elsewhere.

Table 1b. Non-clinical Factors Determining Prostate Cancer Treatment Choice

Patient choice
Specialty of physicians visited
Sociodemographic data of the patient
Surgeon profits
Comorbidity
Marketing to patients

History

Surgical therapy for prostate cancer is radical prostatectomy (RP). There were three major 20th century landmarks in RP that gave rise to the modern procedure performed today. The first systematic technique for the surgical removal of the prostate was devised by Hugh Hampton Young who performed the radical perineal prostatectomy (RPP) at Johns Hopkins University in 1904 (Figure 1). This was the primary procedure performed until the introduction of the retropubic approach in 1945 by Terence Millin which had an easier learning curve and allowed for pelvic lymph node dissection. The final landmark was an improved understanding of the relevant anatomy which allowed for significant improvements in the morbidity of the procedure. This included accurate description of the
dorsal vein complex which decreased bleeding during the procedure. The striated urethral sphincter was also better described during this time allowing for better preservation of continence. The final anatomic refinement was that of Patrick Walsh in 1983 which improved the anatomic understanding of the procedure to allow for preservation of neurovascular bundles innervating the penis without compromising adequacy of surgical margins, thereby maintaining erectile function.17

More recent advances in the procedure involve the development of laparoscopic radical prostatectomy (LRP). Laparoscopic radical prostatectomy was first performed in 1992 by Schuessler and standardized later by Guillonneau and Vallancien and others. Robotic approaches also gained prominence this millennium after their first report by Bnder and Kramer in 2001 and subsequent technical refinement. Newer modifications to this technique include the Bocciardi approach which allows for an entirely intrafascial dissection, potentially avoiding the neurovascular bundles that are necessary for erection and continence. Huang et al. also describe a technique for dealing with prostates affected with benign prostatic hypertrophy, a frequent comorbidity of prostate cancer.17

Variations of Radical Prostatectomy

This historical perspective allows us to understand current variations in radical prostatectomy. Preservation of the neurovascular bundles which contain nerves innervating the penis as described by Walsh is an important consideration in the surgical procedure. The neurovascular bundles exist bilaterally and either one or both may be spared resulting in improvements in postoperative continence and sexual function. In a recent series of 250 patients undergoing bilateral nerve sparing and 207 patients undergoing unilateral nerve sparing laparoscopic radical prostatectomies (nsLRP), 69% in the bilateral nsLRP and 43% in the unilateral nsLRP groups had the ability to engage in sexual intercourse at 1 year. Additionally, complete continence was 97% in the bilateral nsLRP compared to 88% in the unilateral nsLRP. Nerve sparing has also been found to improve health related quality of life. The final decision regarding nerve sparing should be made intraoperatively based on perceived oncologic benefit to removal of the neurovascular bundle. It is very rare that both must be removed. Preoperative impotence, imaging demonstrating extraprostatic invasion and nomogram prediction based on PSA and prostate biopsy findings may also suggest against nerve sparing.

Radical prostatectomy can then be retropubic, perineal or transperitoneal (Figure 1). The approach used varies by whether the surgery is performed open, laparoscopically or robotically assisted.

The perineal approach was once the main approach to radical prostatectomy. Radical perineal prostatectomy that incorporates a modern anatomic understanding and nerve sparing allow for excellent outcomes similar to other approaches. However, because pelvic lymphadenectomy cannot be concurrently performed it is not generally learned by trainees at our institution and has become much less popular.

Radical perineal prostatectomy could be considered in patients that would have difficulty undergoing prostatectomy via other techniques including those with morbid obesity, prior aborted laparoscopic or retropubic prostatectomies, superior vena cava syndrome, prior renal transplantation and prior abdominal-perineal resections.32
peutic benefits in patients at high risk of nodal metastasis. The endopelvic fascia is incised and the dorsal vein complex is controlled and divided. The vas deferens are divided, and the prostate and seminal vesicles are mobilized and removed. Care is taken to preserve neurovascular bundles coursing posterolaterally between the rectum and prostate. The bladder neck is then reconstructed and an anastomosis to the urethra is performed.

LRP may either use the extraperitoneal retroperitoneal approach described above or more frequently a transperitoneal approach. In the transperitoneal approach, the prostatectomy and remnant anatomy are similar except the prostate is initially accessed through the peritoneal cavity. There is little difference in operative time or perioperative outcomes between these approaches and the choice of approach is usually based on surgeon preference. The transperitoneal approach may minimize the potential for bowel injury and for bowel to fall into the operative field. A urine leak from the vesicourethral anastomosis may also be contained within the extraperitoneal space. The transperitoneal approach offers a relatively larger working space, lower tension on the vesicourethral anastomosis and decreased CO₂ absorption from the insufflated space.

In addition to primary prostate cancer treatment, prostatectomy may also be performed as a salvage treatment after recurrence following therapy with another modality. Series reporting success with laparoscopic and open techniques have been described.

**Indications**

Localized prostate cancer is classically divided into three different risk categories as described by D'Amico et al. Low risk patients with <25% chance of PSA failure have clinical stages T1c or T2a, PSA level of 10 ng/mL or less and biopsy Gleason score of 6 or less. Intermediate risk patients with 25-50% chance of PSA progression 5 years post therapy have PSA levels of 10-20 ng/mL, biopsy Gleason score of 7 or clinical stage T2b. Patients with high risk disease have higher than 50% at 5 years PSA failure will have T2c disease, 20 ng/mL PSA or more or a biopsy Gleason score of 8 or more. Other risk groupings exist which include nonlocalized cancers.

Radical prostatectomy is an option in all risk groups of prostate cancer. It is best for localized disease where it may be curative and improve survival. In more advanced disease, RP is not often curative but remains an option as local control may improve symptoms and overall survival. RP may also be performed as a salvage operation after failed therapy with another modality. Indications would include patient choice based on consideration of risks and benefits, a patient medically fit enough for major surgery, and a life expectancy of 5-10 years or greater.

There is ongoing debate as to whether patients with high risk locally advanced prostate cancer may benefit from adjuvant radiation therapy vs. salvage radiotherapy on recurrence. Adjuvant radiation therapy was found to improve biochemical progression free survival, metastasis-free survival, lengthened the time to hormone therapy use and perhaps improved overall survival in three randomized-phase III trials. This led to the 2008 consensus statement on the matter by the Genito-Urinary Radiation Oncologists of Canada recommending that adjuvant EBRT be offered within 6 months of surgery to patients with adverse pathological features at prostatectomy, defined as margin positive, seminal vesicle positive or T3a disease. Morgan et al. issued similar recommendations on behalf of Cancer Care Ontario but reiterated that risks of genitourinary and rectal toxicity as well as disease relapse should be understood by patients. Morgan et al. also noted three additional uncertainties not addressed by current medical evidence. These uncertainties include the question of adjuvant versus salvage radiation, the role of androgen ablation in conjunction with adjuvant radiotherapy, and technical details regarding the actual radiotherapy administered. New uses of radiation including preoperative and intraoperative radiation therapy are also being investigated.

Unlike in radiotherapy, neoadjuvant hormone therapy is probably not beneficial prior to RP. The decision for adjuvant hormone therapy could be beneficial, particularly in more advanced cases and should be made in consideration of side effects including metabolic syndrome, hot flushes, gynecomastia and erectile dysfunction.
Complications

Complications may be viewed as intraoperative, perioperative and postoperative. RP is generally a safe procedure with relatively low intraoperative and perioperative complications, particularly in experienced hands.

Most complications rank low on the Clavien scale. Intraoperative complications would include obturator nerve, ureteral or rectal injury. As with any major surgery, there is also a risk of bleeding, thromboembolism, and cardiopulmonary complication.

An extensive series of perioperative medical and surgical complications experienced in a series of RP has been published by Rabbani et al.\(^5\) Reoperation prior to discharge was most frequently performed for postoperative bleeding and a retained drain. Reoperation after discharge was most often performed for incisional hernia/dehiscence, bowel ischemia/injury, and anastomotic disruption. ER visits were most frequently for urinary retention, lower extremity swelling/dehiscence, and anastomotic disruption. ER visits were most frequently performed for urinary retention, lower extremity swelling/dehiscence, bowel ischemia/injury, and anastomotic disruption. ER visits were most frequently performed for incisional hernia/dehiscence, bowel ischemia/injury, and anastomotic disruption.

Longer-term postoperative complications include oncologic recurrence, impotence and incontinence. Rates of oncologic recurrence depend on the preoperative stage, grade and PSA and can be estimated with nomograms from Han et al.\(^5\) Positive surgical margins will also increase biochemical and local recurrence, but may not be associated with cancer specific death or overall mortality.\(^5\) Although greatly improved in recent decades, functional postoperative complications can significantly affect quality of life, particularly if nerve sparing was unilateral or could not be performed.\(^10\)

The exact percentage of men that will recover continence depends on the series and relies on factors such as patient choice, specialty of physicians visited, sociodemographic data of the patient, surgeon profits, comorbidity, and patient marketing.\(^5\) The exact percentage of men that will recover continence depends on the series but the vast majority of men will be continent after a year. Most men will also regain potency which may be aided by phosphodiesterase-5 inhibitors.

Usage Trends

Radical prostatectomy is a popular treatment for prostate cancer. The exact frequency of surgical therapy compared to prostatectomy techniques has been steadily increasing in the US since its introduction in 2001.\(^23\) Hu et al.\(^3\) demonstrate an increase from 9.2% in 2003 to 43.2% in 2006-2007 in the use of minimally invasive radical prostatectomy with and without robotic assistance. This is based on their cohort from the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database. This database includes about 10% of the US population\(^3\) but has slightly different demographics from the US population at large.\(^23\) Intuitive Surgical, manufacturer of the da Robotic Surgical System, estimates that 80% of prostatectomies in the US or 72,000 will be robotic assisted laparoscopic prostatectomies by 2008.\(^4\) Although lagging slightly behind that of the US, minimally invasive techniques are prevalent in some European countries\(^3\) and have also been rapidly increasing in other resource-rich regions such as England\(^5\) and East Asia.\(^8\)

Comprehensive Canadian data is not available but we can make two safe assumptions. Firstly, the use of minimally invasive prostatectomy techniques has been steadily increasing in Canada since their introduction a decade ago. A survey conducted in 2008 of 56 Canadian urology residents in their final year of training reveals that 68% of respondents participated in a LRP in the last year and 46% believed that LRP looked promising.\(^6\) At our center the majority of prostatectomies are performed laparoscopically and trainees have the option of learning this procedure for their future practice. Currently practicing urologists have also learned to perform LRP in association with our institution. This dissemination of technique can only result in increasing use in the future.

It is also safe to assume that Canada has been more conservative in adopting robotic technology and thus RALP than the US. Only 9 da Vinci surgical robot systems have been installed in Canada in comparison to 916 in the United States in 221 in Europe.\(^3\) In the aforementioned survey of Canadian urology residents, 35.7% of residents had access to a surgical robot and only 7% of residents considered themselves trained in robotic-assisted procedures. There is obviously large regional variation as to the use of RALP located in higher usage centres. For example, Estey details that 371 of 481 (77%) prostatectomies performed in the Capital Health Region (Edmonton, AB) between September 2007 and March 2009 were RALP.\(^5\)

Learning Curve

Radical prostatectomy is a challenging procedure to learn. Vickers et al.\(^4\) conducted a study of 72 surgeons at four US institutions that demonstrated biochemical recurrence only plateaus after a surgeon has performed 250 cases. Biochemical recurrence rates were found to be 7.2% less (95% CI 4.6%-10.1%) after surgeons completed 250 vs. 10 operations. Freedom from biochemical recurrence depended on whether the disease was organ confined or not, approaching 100% and 70% respectively with experience.\(^5\)

LRP is a technically challenging procedure to learn. A recent multi-center study by Secin et al.\(^56\) based on 51 surgeons demonstrated that positive margin rates plateau after 200 to 250 surgeries have been completed. The absolute risk difference for 10 vs. 250 prior surgeries completed was found to be 4.5% (95% CI 1.5%-8.5%). Interestingly, prior experience with open RRP were not associated with a faster learning curve suggesting LRP is as difficult for experienced surgeons to learn as new trainees. Research conducted by Stolzenburg et al. suggests that the procedure may be successfully taught in a modular pattern with increasing level of difficulty.\(^67\) Methods to simulate the procedure may also aid in the learning curve.\(^66\) Secin et al. demonstrated a quicker learning curve than a previous Vickers et al.\(^5\) study that demonstrated biochemical recurrence of 17%, 16% and 9% with 10, 250 and 750 LRP performed, respectively. Both Secin et al.\(^56\)
and Vickers et al.\textsuperscript{70} suggest that the learning curve for LRP is slower than open RRP based on previous Vickers et al.\textsuperscript{64} data.

RALP aims to reduce the learning curve of LRP. Current data on the learning curve of RALP is lacking and usually based on reports of single surgeons.\textsuperscript{71-74} These reports definitely suggest a significant learning curve similar to other approaches in oncologic,\textsuperscript{75} functional\textsuperscript{76} and intraoperative\textsuperscript{72} outcomes. There is not enough data to conclude that RALP has a shorter learning curve than RRP or LRP at present.\textsuperscript{76} This learning curve also applies to surgeons with significant prior experience with LRP.\textsuperscript{77}

**Comparative Outcomes of RRP, LRP and RARP**

A 2010 review by Kang et al. demonstrated that although there is ample literature on RALP, it is of poor methodologic quality.\textsuperscript{78} The quality of this evidence has also not improved over time. This is also true of LRP.\textsuperscript{79}

Given these caveats, Ficarra et al.\textsuperscript{79} reviewed the literature published before January 2008 and found 37 comparative studies of RP, LRP and RALP which include 1 randomized controlled trial. They found lower rates of blood loss, transfusion rates, catheterization time, hospitalization duration and complications when LRP was performed. There is likely no difference between LRP and RALP for these outcomes. More recent literature also supports the claims of Ficarra et al. regarding lower rates of blood loss and transfusion with LRP and RALP. Coelho et al.\textsuperscript{80} published a review of the literature in 2010 that only included series with greater than 250 patients. This review made similar conclusions that LRP and RARP were associated with decreased operative blood loss. The rates of transfusion were found to be 20.1% for RRP, 3.5% for LRP and 1.4% for RARP. An analysis by Hu et al.\textsuperscript{81} of the previously mentioned SEER-Medicare database also found lower rates of blood transfusion with minimally invasive radical prostatectomy (2.7%) compared to open (20.8%).

Oncologic, potency and continence outcomes from these three techniques are difficult to measure because they are dependent on the experience of the surgeon and hospital. A 2010 review by Barocas et al.\textsuperscript{82} of 13 original studies and a meta-analysis finds this to be a consistent trend with regards to radical prostatectomy. High hospital and surgeon volume was associated with lower perioperative mortality, perioperative complications, length of stay, long-term continence and urinary complications, positive margin rates and recurrence rates. Although these conclusions were based on observational studies of RRP, consistency amongst studies, high volume of effect and attempts to address confounders add to the legitimacy of these conclusions.\textsuperscript{83}

Nonetheless, the aforementioned review by Ficarra et al.\textsuperscript{79} does not demonstrate significant absolute differences in oncologic, potency, and continence outcomes between RRP, LRP and RARP. Additionally, a 2010 study of 522 patients RARP matched with the same number undergoing LRP and RRP by Magheli et al. also found similar rates of biochemical recurrence between LRP, RRRP and RALP, although a slightly higher positive surgical margin rate in the RARP group was found (19.5% vs. 14.4% for RRP and 13.0% for LRP).\textsuperscript{84} Positive margin rates were not significantly different for pT2 disease. This study used propensity scoring to control for patient age, race, preoperative prostate-specific antigen, biopsy Gleason score and clinical stage.

The bottom line is that three reasonable conclusions may be made regarding the outcomes of LRP, RARP and RPP. Firstly, RRP, LRP and RARP are safe operations in wide use that offer good outcomes. Secondly, it is likely that minimally invasive techniques reduce operative blood loss and transfusion rates. Finally, surgeon and center experience are more important than operative technique in determining oncologic, continence and potency outcomes.

**Cost**

A retrospective comparison of 70 consecutive cases of retropubic radical prostatectomy (RRP) and laparoscopic radical prostatectomy (LRP) at our institution found an insignificant difference in cost.\textsuperscript{85} Higher operating room and disposable instrument costs in LRP were offset by decreased cost of blood transfusion, hospital stay and analgesia.

An analysis by of 643 consecutive patients Bolenz et al.\textsuperscript{86} in Texas found a median cost of $6,752 for RALP, $5,687 for LRP and $4,437 for RRP. Purchase and maintenance costs for the robot add $2,698 per patient given an average of 126 cases per year. An analysis at this same institution also found that surgeon profits were the highest with RALP although the hospital lost a large amount of money on LRP and RALP.\textsuperscript{7} Additional studies based in the United States have been published and this pattern generally holds true.\textsuperscript{87,88} LRP was found to be $1,237 cheaper than RRP in a French institution\textsuperscript{89} but this likely reflects different patterns in hospital stay (6 days for LRP vs. 8.1 days for RRP) not directly relevant to the Canadian context.

In summary, RALP is significantly more expensive than LRP and RRP. LRP and RRP are likely similar in cost but this will be context dependant.

**Initial Conservative Management**

Surgery may not be immediately performed on the diagnosis of prostate cancer. Conservative management may precede surgery. Conservative management for prostate cancer may take two very distinct forms — watchful waiting and active surveillance (AS).

Watchful waiting involves not treating prostate cancer until the disease manifests with symptoms of local or metastatic advancement, which are then treated in a palliative manner. A recent systematic review of the effectiveness of RP relative to watchful waiting found only one relevant well designed randomized control trial.\textsuperscript{88} This Scandinavian trial demonstrated a benefit in overall and disease specific survival as well as distant metastasis with radical prostatectomy versus watchful waiting after 12 years follow-up.\textsuperscript{84} Wide confidence intervals at 12 years in this trial do not allow a good answer to the absolute reduction in mortality but RP especially benefited men under the age of 65. In a 10 year report of this trial, relative risk of death from prostate cancer with RP relative to watchful waiting was 0.56 (95% C.I. 0.36-0.88).\textsuperscript{90} This trial commenced before the widespread introduction of PSA screening and thus results may be different in the PSA era where cancers are
detected at an earlier stage. Nonetheless, watchful waiting should be limited to those with limited life expectancy based on current evidence.

On the other hand, AS is very different from watchful waiting. AS is based on the premise that screening has resulted in a diagnosis of some indolent forms of prostate cancer that will not significantly increase morbidity or mortality. AS is based on differentiating between those that fall into this category and those that have disease which will cause morbidity and mortality.

Klotz describes four elements to active surveillance detailed in Table 2. The primary goal of AS would be to allow patients with indolent disease to avoid the side effects of curative treatment such as urinary incontinence and impotence while providing those who need it appropriate treatment. A recent decision analysis demonstrates that active surveillance may have the greatest quality adjusted life expectancy for a man with very low risk prostate cancer.

<table>
<thead>
<tr>
<th>Table 2. Four Elements of Active Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Identification of favorable-risk patients</td>
</tr>
<tr>
<td>2. Countering cancer hysteria with education and reassurance</td>
</tr>
<tr>
<td>3. Close monitoring over time with serial PSA and periodic biopsy</td>
</tr>
<tr>
<td>4. Providing definitive therapy to those whose disease is classified as higher risk</td>
</tr>
</tbody>
</table>

The evidence behind adopting a policy of active surveillance is currently based on 7 cohort studies with 2,365 patients enrolled demonstrating exceptionally low prostate cancer specific mortality and about one third of prostate cancer patients on AS being reclassified to require curative treatment. There is also evidence to suggest that AS may cost less than surgery. Additionally there is evidence that delaying treatment slightly for those initially put on surveillance and reclassified may not have impact on mortality.

Challenges involved in active surveillance include defining who should be included in a surveillance protocol as opposed to definitive treatment initially, how to screen those under surveillance for more aggressive disease, and what screening results should prompt offering of definitive treatment. Enrollment criteria involves biopsy and PSA criteria that vary based on age and a strong emphasis on patient choice. Current cohorts use a variation of PSA kinetics and serial biopsies to monitor patients with various indications for interventions. There has been no conclusive validation of criteria of inclusion and thus there is always a very small risk that young patients who might have been cured with earlier surgery will go on to develop metastatic disease. Some patients may also experience anxiety and distress while on AS but on average anxiety and distress remain low.

Advances in surveillance methods will improve the effectiveness of AS. It is also likely that cancer biomarkers such as PCA3 will be incorporated in AS criteria. Improved understanding of the genetics of prostate cancer will further help to stratify risk.

In summary, AS is a viable choice patients can make instead of RP, particularly for older men with low risk disease.

Conclusions and Future Outlook

Radical prostatectomy (RP) is the surgical therapy for prostate cancer performed with curative or palliative intent in localized and advanced disease respectively. Modern RP is the product of a century of innovation culminating in a safe therapy for prostate cancer with excellent postoperative rates of freedom from oncologic progression, potency and continence. It also has a demonstrated survival benefit.

RP may be performed with open, laparoscopic or robotically assisted laparoscopic approaches. These approaches are similar at present but technical refinements in the future as well as good quality evidence will likely demonstrate a superior technique. Naturally, functional and oncologic outcomes of treatments will be improved through innovation over time. There is already evidence that single port LRP is possible which may herald a new era of even more minimally invasive surgery.

Viable alternatives to RP include active surveillance and external beam radiotherapy. Future research will bring into focus when each of these therapies is best. When appropriate active surveillance criteria and monitoring protocols are well validated, possibly including new biomarkers, imaging, or genetic markers, this will certainly represent a viable option for indolent disease. It is also likely that optimum combinations of neoadjuvant, adjuvant and primary therapies will be developed based on randomized controlled trials specific to a patients disease characteristics. Evidence validating focal therapies like cryotherapy and HIFU as well as brachytherapy may accumulate thereby increasing patient choice and quality of life.

References


53. Xylinas E, d’Ache, Roupert M. Is radical prostatectomy a viable therapeu tic option in clinically locally advanced (cT3) prostate cancer? BJU Int. 2010; 106(11):1596-600.


