ROBOTIC ASSISTED RADICAL PROSTATECTOMY VERSUS OPEN RETROPUBIC RADICAL PROSTATECTOMY: WHERE DO WE STAND IN 2015?

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Abstract

Robotic assisted radical prostatectomy has emerged as the dominant surgical technique for the management of localised prostate cancer in many Western countries. Yet the evidence to support such a radical change in surgical technique has been limited and of poor quality, with the driver of the change initially being aggressive marketing, followed by hospital and urologist competition, and lastly by patients themselves who perceive robotic assisted radical prostatectomy to be the better technique. A critical review of the contemporary literature would suggest that robotic assisted radical prostatectomy may indeed have benefits over traditional open surgery in the areas of length of inpatient stay, perioperative complications and transfusion rates. However, the important parameters of cancer control, continence and potency outcomes appear largely equivalent between the techniques and more determined by surgeon and hospital experience, and patient characteristics, with the advantages of robotic surgery coming at increased cost. There is no question that robotic assisted radical prostatectomy is already widely disseminated and this trend is irreversible regardless of the outcomes of future studies. This however, does pose challenges regarding training in centres that do not have access to robotic technology, credentialing requirements for transitioning open surgeons and maintenance of open skills where robotic assisted radical prostatectomy cannot be performed.

Robotic assisted radical prostatectomy (RARP) has become the surgical method of choice of urologists in many developed nations, in preference to an open radical prostatectomy (ORP). Since the introduction of robotic surgery over a decade ago, the debate over which is the 'best' technique has waged and been the topic of debates in many urology conferences around the world. Yet the level of evidence to support superiority between techniques is poor, with no randomised controlled trials of note to date.[1,2] Most studies have been level 4 data, namely retrospective single centre case series, often comparing a contemporary series of RARP to historical ORP data. In fact, a systematic review of the literature in 2010 demonstrated that 12 authors contributed to writing 72% of published studies.[2] Population data and meta-analyses since then have been valuable, but again do not replace a well conducted randomised control trial as much of the data is incomplete, surgical skill and experience is unstated, surgeon and hospital volumes are often unknown and there is no standardised reporting of complications, nor analysis of pathological outcomes by central pathology review. All these highlight the poor quality of data we have to date and why we look forward with considerable interest to the results of the randomised control trials being performed in Brisbane, Australia, currently comparing the techniques, within the same time period, with the same care pathways, in the same institution, with central pathology review and with experienced urologists performing the surgery.[3] This together with another prospective contemporary but non-randomised trial happening in Melbourne, Australia, will add a lot of knowledge regarding the true benefits of one technique over the other.

Oncological outcomes

Given the fact that a radical prostatectomy is essentially the same operation regardless of technique used, it

seems that oncological outcomes should be similar or identical, and driven more by tumour and surgeon factors. Due to the long lead time to identify differences in cause specific survival or even prostate specific antigen (PSA) free survival, positive surgical margins have been used as a surrogate for surgical quality. Naturally, this is also affected by factors such as pre-operative PSA, tumour volume, surgeon skill and experience, pathological processing and techniques, hospital volume and experience. As such, unless these factors are standardised, the results of comparisons between techniques may be flawed.

A recent meta-analysis demonstrated non-significant differences on the pT2 (p=0.31) margin rates, or overall margin rate (p=0.19), between techniques and no differences in seven year biochemical free survival (p=0.56).[4] This was supported by a meta-analysis of 286,000 radical prostatectomy cases from over 400 published papers, which demonstrated that overall and pT2 positive surgical margin rates were lower in RARP vs ORP (overall 24.2 vs 16.2%; pT2 16.2 vs 10.7%), however following propensity adjustment these differences were not statistically different. A study from the Mayo Clinic controlling for factors such as hospital, pathology and surgeon skill and experience, found no difference in positive margin rate, with RARP having a 15.6% margin rate to 17% with ORP (p=0.608), with no difference in long-term disease biochemical progression rate.[5] This is supported by data from a single centre in Belgium, with RARP having a 30% positive margin rate compared to 21% with ORP (p=.204),[6] from the Health Professionals Follow-up Study (24.5% vs 23.1% p=0.51),[7] from Johns Hopkins (34.3% vs 29.4%, P=0.52),[8] and from Memorial Sloan Kettering (15% each), all comparisons quoted being non-significant.[9] In the latter two studies no difference was noted in biochemical free survival between techniques (p=0.6),[8,9] although at Memorial Sloan Kettering they importantly noted a greater difference of biochemical free survival between surgeons (2.3% crude difference over two years) using the same technique rather than between techniques (0.8% crude difference over two years).[9] They concluded that the surgical approach should be based on the skill and confidence of the surgeon rather than being focused on a specific technique. Case volume appears to be a major factor, with a recent series demonstrating a positive surgical margin rate of 36% in the first 50 case RARP experience to 7.5% in case numbers 251-450.[10] Another demonstrated it required a case experience of more than 1600 cases to obtain a margin rate <10%.[11] This fact would apply equally to both ORP and RARP.

Some multi-institutional studies however, have shown some benefit for RARP over ORP with regards to margins (22.8% vs 13.8%).[12] However, ORP patients had higher risk prostate cancer at the time of this surgical series and were operated on earlier in the study time period, introducing some selection bias. Logistic regression to attempt to correct for these factors demonstrated an odds ratio of 0.76 in favour of robotic surgery (p<0.001). Surgical and hospital case volume and experience were uncertain, and pathological processes likely to be vastly different between centres with no central review. Similar concerns can be raised regarding a recent analysis of the SEER data, comprising 5556 RARP cases, 7878 ORP cases, but critically with nearly 9000 cases excluded from the analysis.[13] ORP once again had higher pre-operative PSA levels and higher clinical stages, and there was no standardisation of pathology processes. RARP was associated with fewer positive margins (13.6% vs 18.3%), mostly in the intermediate and high risk cases. RARP was also associated with less use of additional cancer therapies within six months of surgery (4.5% vs 6.2%), but there was no information about PSA relapse rates, nor cause specific survivals, and hence uncertainty about why these secondary therapies were introduced.

A well-designed prospective, controlled, non-randomised trial (LAPPRO) from Sweden, established that the incidence of positive surgical margins did not differ significantly between groups (21.8% vs 20.9%).[14] However, the population-based Prostate Cancer Registry in Victoria, Australia, in an analysis of 2385 radical prostatectomies over a five-year period, reported a 31% lower PSM rate (p=0.002) in a multivariable analysis comparing RARP with ORP. Patients experiencing a PSM in this series had a greater than five times risk of receiving additional cancer therapy over the following 12 month period. However, this series could not control for patient factors such as clinical stage and surgeon factors such as experience. Training biases may also have contributed to these results, with the bulk of the RARP cases being performed by expert surgeons in the private sector, compared to most ORP being performed by training surgeons under supervision in public hospitals.[15]

The bulk of the literature would suggest that oncological outcomes with regards to surgical margins, biochemical evidence of recurrence and additional therapies are equivalent, with any differences likely to be attributable to factors such as tumour volume, pathology and surgical case volume and experience.

Incontinence

Stress urinary incontinence is one of the more feared complications from radical prostatectomy. Studies are hampered by lack of consistent definitions of incontinence, and the failure to use patient reported outcomes and validated instruments in describing incidence and severity of this complication. Once again, the lack of consistency in regards to matching surgeon skill and experience also makes the interpretation of the data that exist problematic. Most studies appear to demonstrate equivalence when the surgery is performed by skilled surgeons. At the Mayo Clinic, using a

definition of no pads at all as continent, RARP achieved 81.6% continence vs 88% with retropubic radical prostatectomy, which was not statistically significant. Defined as no pads or one security pad only, it was 91.8% versus 93.7%.[5] Further studies using the EPIC-26 questionnaire demonstrated identical scores for RARP and ORP for urinary incontinence (p=0.93).[7] The LAPPRO study also failed to show significant difference between techniques, with 21.3% of men undergoing RARP incontinent versus 20.2% after ORP.[14]

A recent meta-analysis however, was based on nine studies comparing RARP with ORP (mostly historical controls), and demonstrated a mean no pad incontinence rate of 16%.[16] The authors did conclude that RARP achieved better continence rates compared to ORP (92.5% vs 88.7%), with some studies in the analysis demonstrating a faster return to continence with the robotic approach. However, they concluded that age, body mass index, comorbidity index, prior lower urinary tract symptoms and prostate volume were significant pre-operative predictors of urinary incontinence, which naturally were not controlled in any of these comparative studies, let alone with reference to surgeon experience. The authors concluded that multiple design and methodological factors needed to be considered when interpreting these outcomes.

Erectile dysfunction

Erectile dysfunction is another common complication after radical prostatectomy, but studies are again hampered by lack of standard definitions and the lack of use of patient reported outcomes via validated instruments. It has been well shown that erectile dysfunction can also be effected by the ability to nerve spare at radical prostatectomy, age, pre-existing erectile function and co-morbidities. Very few studies have adequately controlled for these factors, nor do they take into account surgeon experience or skill. Data from the Mayo Clinic demonstrated no significant difference between techniques (70% RARP vs 62.8% ORP p=0.08),[5] with results from the Health Professionals Follow Up Study showing no difference in EPIC-26 scores (p=0.66).[7] In the LAPPRO study, erectile dysfunction was found in 70.5% after RARP, and 74.7% after ORP, which was modestly beneficial for RARP with an adjusted OR of 0.81 (95% CI 0.66-0.98),[14] even taking into account factors as mentioned above. Importantly, 40% of patients were not potent pre-operatively, were not interested in sexual activities or did not have nerve sparing for oncological reasons. Of the remaining patients, the three, six and 12 month potency recovery rates were 10%, 53% and 82% respectively, with median time to potency of six months.

A recent systematic review looked at six studies comparing RARP to ORP.[17] Age, baseline potency status, co-morbidities index, and extent of nerve sparing were the most important predictive factors, however an advantage was found in favour of RARP based on seven studies all of level three or four evidence. The authors concluded that 47.8% after ORP had erectile dysfunction compared to 24.2% after RARP, however other factors might have contributed to these discrepancies. Overall, most studies demonstrate modest improvement in potency rates with RARP, although other factors may have played a role when interpreting these results.

Blood loss and transfusion rates

RARP has an advantage in relation to blood loss and transfusion requirements due to the higher intraperitoneal pressure and steep head down position of the patient, thus reducing venous blood loss intra-operatively. Accurate measurements of blood loss, and non-standardised protocols regarding indicators for transfusion, hamper these analyses, however the results consistently demonstrate an advantage of RARP over ORP. Mayo data demonstrated a 13.1% transfusion rate in ORP vs 5.1% in RARP group (p<0.001),[5] and the Health Professionals Follow Up Study with ORP 30.3% vs RARP 4.3% (p<0.001).[7] The investigators estimated on average, 495mL less blood loss with RARP, however they noted that the ORP group was demonstrating a 66 mL/year reduced estimated blood loss, while the RARP cohort was not, indicating that one can no longer compare RARP to historical ORP controls. A systematic review also indicated a 580mL reduced estimated blood loss with RARP, but analysis of the trials included showed huge variability in transfusion rates with ORP, with some series as low as 2-3% of cases, suggesting that case selection, as well as surgeon and hospital experience, may be factors.[4] Another recent systematic review comparing RARP to historical ORP controls demonstrated an advantage to RARP (12.5% vs 1.8%),[18] as well as an analysis of the Nationwide Inpatient Sample (7.7% vs 2.4%).[19] The difficulty in interpreting these data is that the RARP patients had fewer co-morbidities and were more likely to have surgery performed in urban high-volume academic institutions, which may have introduced selection bias. Overall the weight of evidence would suggest a reduced blood loss and transfusion rate with RARP, however the extent of this remains unclear given methodological issues with the studies performed. Contemporary transfusion rates are now low regardless of technique with the gap between techniques appearing to narrow.

Pain/length of stay/peri-operative complications

The suggestion has been made that as RARP offers smaller incisions, this should result in less postoperative pain, and a more rapid return to normal activities. This scenario needs to be compared to a single lower abdominal muscle splitting incision, which traditionally has been a procedure with relatively low pain levels. However, formal studies on analgesic requirements and return to full activities remain sparse in the literature.

Webster et al found that beyond day one, there were no significant differences in pain levels,[20] findings substantiated by Wood et al.[21] A further study did demonstrate minor reductions in morphine sulphate equivalents, with less post-operative analgesic use with RARP, with 28.9% of ORP requiring a single post-operative analgesic refill vs 20.2% of RARP patients.[22] With regard to return to activities, there are no good quality studies comparing RARP and ORP. A study comparing pure laparoscopic RP to ORP, examining quality of life at six weeks, demonstrated a one week advantage in quality of life and return to activities of RARP over ORP, but failed to take into account crucial factors such as activity levels and co-morbidities pre-operatively, nor type of work engaged in by the patient, all of which could have affected the outcomes.[23]

Meta-analyses have consistently confirmed reduced peri-operative complications in patients undergoing RARP owing to the laparoscopic approach, but again uncontrolled for surgical and institutional experience. These include readmission, re-operation, pneumonia, deep vein thrombosis, wound complications and anastomotic leak.[18,19] Furthermore, the urethro-vesical anastomotic stricture rate is significantly reduced with this, sometimes troubling complication, almost eliminated in robotic series where the suturing is completed under direct vision.

Length of stay (LOS) was consistently shorter in the RARP group compared to ORP by approximately one day in most series. In the European series, a reduction from 4.1 to 3.3 days was seen (P<0.001), while in the US Nationwide Inpatient Sample, a prolonged LOS greater than two days was seen in only 14.5% of RARP patients compared to 39.6% of ORP patients (p<0.001).[19] In an academic setting however, a prolonged LOS greater than two days was found in 10.8% of RARP patients compared to 12.6% of ORP, demonstrating that surgical and centre caseload is likely to have an effect in mitigating some of this observed LOS discrepancy.[5] In Australia, the data are more pronounced where LOS with open surgery still remains at greater levels (at least two days), but may reflect lack of adoption of protocols, anaesthetic and pain pathways that are dated and, preoperative counselling.

Cost

All series demonstrate higher costs associated with RARP. A study from the US calculated that RARP was associated with a higher median direct cost of $2315 over ORP, mostly due to surgical supply costs and time in the operating room. If one considered the purchase and maintenance costs, the burden would increase by a further $2698 per patient to an overall increased cost of just over $5000 per patient, based on a centre that performs 126 cases per year.[25] These figures are supported by data from the National Inpatient Sample that demonstrated $2542 higher direct costs with RARP, not including purchase or maintenance costs.[26]

Training in radical prostatectomy

Surgical training in Australia has traditionally followed a master-apprentice relationship, whereby the trainee is given greater responsibility in surgical cases as they gain experience under the watchful eye of the more experienced surgeon. In Australia, data has emerged from Victoria for ORP, where it was concluded that the value of high-volume and fellowship-trained urologists in performing and teaching ORP was a key factor in patient outcomes.[27] There is no such data for RARP, and indeed with only a select few public institutions offering RARP, the role of long-term fellowships cannot be underscored. At present, trainees must assist surgeons in the private sector, which is helpful but does not allow the graduation to an independent surgeon easily. Mini-fellowships and mentoring help in some respects, but a drop in key indicators by surgeons switching to RARP from open, or whom have had little training, is generally accepted as part of a long 'learning curve' of any new technique. In the future, as outcomes are increasingly scrutinised with audits, the best strategy for clinicians to maintain standards and optimal patient outcomes is to understand these elements and direct trainees to appropriate centres for training and fellowships.

Conclusion

While we await the results of the only randomised control trials to have been performed comparing RARP and ORP, we can conclude that RARP is a well-established operation, which gives excellent results in experienced hands, as does ORP. While the important long-term oncologic and functional results appear to remain largely surgeon dependent, for a given surgeon RARP will offer at least equivalent results, with a reduction in peri-operative complications and bladder neck stricture rates. RARP does appear to carry a small (and possibly narrowing) advantage with regards to LOS and transfusion rates, but at an increased cost. Trials to date are often subject to substantial selection bias influencing outcomes, and making conclusions hard to interpret. Nonetheless, an entire generation of trainees in the US have now been trained in RARP, with subsequent de-skilling in ORP. This raises some serious issues for future surgical planning, namely how to train when institutions do not have access to a robot, how does one credential an existing open surgeon transitioning to robotics and how does one maintain open skills in this procedure for those rare occasions where RARP may not be possible for anatomical or mechanical reasons.

It is perhaps time to put this debate to rest and accept that each surgeon should choose their preferred method of performing radical prostatectomy, without the claims from companies, hospitals and urologists that one technique is vastly superior to the other. As demonstrated by the team at Memorial Sloan Kettering,

there was more variability between surgeons using the same technique then between techniques themselves.

While it is entirely appropriate to train new surgeons in robotic technology, it is important that benefits of RARP over ORP are not over-stated and that experienced surgeons in ORP should feel comfortable continuing to offer their preferred operation. A recent study of this transitioning process in an experienced open surgeon demonstrated that it required 99 RARP cases to reach previous ORP levels in regards to sexual function, 182 cases for incontinence and 200 cases with regards to margins, with up to 700 cases to plateau outcomes.[28] This then translates to several, and in some circumstances many years of patients being subjected to a worse functional and oncological outcome should these open surgeons transition. Indeed, some experienced open surgeons may never reach what they were achieving with ORP previously, and therefore this issue remains a potential major ethical dilemma as long as this debate continues.

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