Evolution and oncological outcomes of a contemporary radical prostatectomy practice in a UK regional tertiary referral centre

VJ Gnanapragasam[1,2*#]& D Thurtle[1*], A Srinivasan[2], D Volanis[2], A George[1], A Lophatananon[3], S Stearn[1], AY Warren[4], AD Lamb[1,2], G Shaw[2], N Sharma[5], BC Thomas[2], MG Tran[2], DE Neal[1], NC Shah[2]

[1] Academic Urology Group, Department of Surgery, University of Cambridge, Cambridge, UK

[2] Department of Urology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[3] Division of Health Sciences, Warwick Medical School, University of Warwick

[4] Department of Pathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[5] Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK

* Equal contribution

[#]Corresponding Author:

Mr. Vincent J Gnanapragasam, Academic Urology Group, Department of Surgery and Oncology, University of Cambridge, Box 279 [S4], Cambridge Biomedical Campus, Cambridge CB2 0QQ

E-mail: vjg29@cam.ac.uk Phone: 44-1223-763363

Key words

Prostate cancer

Robotic-assisted laparoscopic prostatectomy

Radical Prostatectomy

High-risk

Abstract

Objective

To investigate the clinical and pathological trends over a ten-year period for robotic-assisted laparoscopic prostatectomy (RALP) in a UK regional tertiary referral centre.

Patients and Methods

1500 consecutive patients underwent RALP between October 2005 and January 2015. Prospective data was collected on clinic-pathological details at presentation as well as surgical outcomes and compared over time.

Results

The median(range) age of patients throughout the period was 62(35-78) years. The proportion of pre-operative high-grade cases (Gleason sum 8-10) rose from 4.6% in 2005-2008 to 18.2% in 2013-2015 ($p<0.0001$). In the same periods the proportion of clinical stage T3 cases operated on rose from 2.4% to 11.4% ($p<0.0001$). Median PSA at diagnosis did not alter significantly. Overall 11.6% of men in 2005-2008 were classified pre-operatively as high-risk by NICE criteria, compared to 33.6% in 2013-2015 ($p<0.0001$). The corresponding proportions for low-risk cases were 48.6% and 17.3% respectively. Final surgical pathology demonstrated an increase in tumour stage, Gleason grade and nodal status across time. The proportion of pT3 cases rose from 43.2% in 2005-2008 to 55.5% in 2013-15 ($p=0.0007$), Gleason grade 9-10 tumours increased from 1.8% to 9.1% ($p=0.0002$) and positive nodal status increased from 1.6% to 12.9% ($p<0.0001$) between the same periods. Despite this, positive surgical margin rates showed a downward trend in all pT groups across the different eras ($p=0.72$).

Conclusion

This study suggests that the patient profile for RALP in our unit is changing, with increasing proportions of higher-stage and more advanced disease being referred and operated on. Surgical margin outcomes however have remained good.

Introduction

Prostate cancer (PCa) is the most common malignancy in men and is a leading cause of cancer related morbidity [1, 2]. Since the introduction of prostate-specific antigen (PSA) testing in the late 1980s there has been a steady migration toward lower stage and grade disease[3]. However, the trade-off from this migration was substantial over-diagnosis and over-treatment of cancers that may not have caused harm. Appreciation of this potential downside has gradually led to a more conservative approach in the treatment of low-risk disease. As a result surgery, as well as other radical treatment options, is increasingly reserved for patients with intermediate and high-risk disease [4]. Over the past decade there has been a demonstrable shift in the management of PCa in the UK with increasing use of surgery for younger patients with high-risk disease [4, 5]. In the US literature, where the robotic approach is better-established, a 'reverse stage migration' has been demonstrated in prostatectomy cohorts with centres such as Memorial-Sloan Kettering Cancer Centre reporting the proportion of men undergoing radical prostatectomy for low-risk disease progressively decreasing between 2000 and 2010[6]. It is, however, not known whether there has been a similar migration towards operative intervention in those with higher-risk disease in UK surgical centres.

Since the cancer Improving Outcome Guidelines in 2002, the surgical management of prostate cancer in the UK has largely been centralised. As a result, referral and treatment patterns are commonly reflective of practice across a wider geographical region rather than just one hospital, particularly as cases are discussed in a regional multidisciplinary team. Here we present case mix and outcome trends over a 10-year period from one UK tertiary referral centre. Our primary interest was to evaluate the evolution of a prostatectomy service, focusing on stage migration and its impact on oncological outcomes.

Patients and Methods

Study cohort

From 2005 onwards patients who underwent robotic radical prostatectomy at our centre were recruited into an ethically approved prospective study (MREC 01/4/061). Our centre is one of two

providing a tertiary referral service to the Anglia Cancer Network covering a population of 2.63 million people and including 9 hospitals trusts.

All patients who underwent RALP surgery from October 2005 until January 2015 were included with the exception of men who underwent salvage RALP. Pre-operative demographic data, biopsy details, clinical stage and PSA level at diagnosis were recorded prospectively for each patient. Pathological results and subsequent outcome data was recorded for all cases. The operative technique applied has been described in detail previously.[7] All cases were operated on by a consultant urologist who had received structured modular training (DEN, NCS, VJG). During the series the technique has been modified slightly, with the addition of extended lymph node dissection (including external iliac, obturator and internal iliac lymph nodes) for intermediate to high-risk disease from case 450 onwards. Patients were stratified according to date of operation into four era groups: 2005-2008, 2009-2010, 2011-2012 and 2013-2015. Patients were also stratified according to 2014 NICE risk groups: low-risk (T1-T2a and GS ≤6 and PSA ≤10), intermediate-risk (T2b and/or GS =7 and/or PSA >10–20), or high-risk (≥T2c or PSA >20 or GS 8–10).[8]

Pre-operative core-biopsy specimens and RALP specimens were examined by histopathologists with a special interest in uropathology and were subsequently reviewed in the Uro-Oncology Specialist MDT. Pathological processing of the surgical specimens has not changed over the course of the study and included 4-5mm sectioning and processing of the entire surgical specimen according to standard methodology. The Seventh edition of the American Joint Committee on Cancer tumor-lymph node (LN)-metastasis classification was used to define stage. Histopathologic grading was performed according to the International Society of Urological Pathology 2005 modification of the Gleason system[9]. A positive surgical margin (PSM) is defined as malignant cells in direct contact with the inked surface as reported by the uro-pathologist and reviewed in the MDT[10]. Biochemical recurrence (BCR) was defined as a confirmed PSA value of >0.2ng/ml[11].

Statistical analysis

Data processing and descriptive statistical analysis was performed using MS Excel 2013 (Microsoft, Redmond, Washington, USA). Statistical analysis was performed in StatsDirect (StatsDirect Ltd,

England, UK). ANOVA was used to look at mean differences between four groups. Chi square analysis was used to assess difference of distributions in numbers or proportions between groups. In tables 1 and 2 probability values relate to chi square analysis between all 4 groups, in the text values refer to direct analysis between the earliest and latest era groups. p values are therefore 'chi square p values,' a p value <0.05 was considered statistically significant.

Results

1500 patients were included in the study. Over the course of the study the annual caseload increased from 51 in 2006 to over 200 cases annually from 2009 onwards. There were no conversions to open surgery however there were 3 cases where the robotic approach was not feasible due to adhesions, pubic symphysis exostosis and intolerance of Trendelenburg position and all patients were treated by radiotherapy.

Pre-operative clinico-pathological characteristics

Baseline patient characteristics according to time period are listed in Table 1. The mean age across the entire cohort was 61.5 (range 35-78) years; there was no statistically significant difference in age between the populations in the four era (p=0.91). Overall, the mean pre-operative PSA was 8.5 (range 0.5-89) ng/mL; there were no statistically significant differences in the PSA levels between eras (p=0.10). With regards to the pre-treatment clinical stage, there were statistically significant differences over time, with the proportion of cT1 tumours declining from 64.4% in 2005-8 to 45.9% in the most recent era (p<0.0001). In parallel, there was a significant increase in the proportion of higher clinical stage tumours, with cT3 representing 2.4% of pre-operative cases in 2005-8 as compared to 11.4% in 2013-5 (p<0.0001). An upward trend was also noted in the pre-operative Gleason score over time (Table 1). More specifically, the proportion of Gleason sum ≥8 increased from 4.6% to 18.2% between the periods of 2005-8 and 2013-15. Similarly, pre-operative NICE Risk Group also changed over the series with the proportion of patients pre-operatively defined as high-risk disease increasing from 11.6% to 33.6% between the periods of 2005-8 and 2013-15 (p <0.0001).

Surgical pathology outcomes

Table 2 demonstrates the final pathological characteristics of the resected prostates including the PSM rates for each era. In 3 cases, no tumour was found on the final pathological analysis (pT0), although 1 case demonstrated HGPIN. The pre-operative biopsies were re-reviewed in each case, to confirm presence of carcinoma. The proportion of final Gleason 3+3=6 tumours decreased from 38.6% in 2005-8 to 11.1% in 2013-15 (p<0.0001) whereas the proportion of Gleason 9-10 tumours increased, from 1.8% to 9.1% (p<0.0001) between the same periods. Across all eras, the final pathology in the majority of cases revealed Gleason 7 disease. With regards to the pathological stage there was a reduction in the proportion of pT2a tumours over time from 36.8% in 2005-8 to

5.5% in 2013-15 but a concomitant increase in pT2c cases from 16.1% to 37.1% (p<0.0001) (Table 2). The overall proportion of pT3a cases was stable (38.0% 2005-2008 and 43.9% in 2013-2015) (p=0.102) however the proportion of pT3b tumours increased from 5.2% to 11.6% between the same dates (p<0.0001). No significant change in overall PSM rates was observed across the series over time (p=0.72). When analysed by individual tumour stage, PSM rates were reduced for each category but did not reach statistical significance. In pT2 disease PSM rates differed from 11.96% in 2005-8 to 6.28% in 2013-15 (P=0.06). In the same 2 periods, PSM rates in pT3a disease were 31.2% and 25.9% respectively (p=0.91) and in pT3b disease 64.7% and 43.1% (p= 0.60). Overall pT3 PSM rates were 35.2% in 2005-8 and 29.5% in 2013-15 (p=0.24). Finally, we did also analyse lymph node involvement in our study. Of the total number of patients, 1033 (68.9%) underwent lymph node dissection (LND). Pathological evidence of LN involvement increased by era (Table 2). There were significant differences in the incidence of metastasis in the LN. With only 1.6% of those who underwent LND in 2005-8 found to have metastasis compared to 12.9% in 2013-5 (P<0.0001). However we interpret this with caution given the changes in lymph node dissection usage and extent across the series.

Surgical outcomes

There were two peri-operative mortalities in this series, one man of myocardial infarction in theatre recovery, and a second dying at home on day 13 post-operation from a presumed pulmonary embolism. Follow-up and BCR data was available for 1358 (90.5%) men, with a mean(range) follow up of 36.1(0-97) months. 92 men were excluded as they underwent immediate adjuvant radiation therapy. Overall 114 patients (8.4%) developed BCR during the follow-up period, this was associated with pathological tumour stage, with 5.98% of pT2 and 22.1% of pT3b patients experiencing BCR (p<0.0001). The follow-up is insufficient to draw conclusions on long-term outcomes but initial 1-year BCR rates are encouraging at 3.9%, 2.4% and 3.4% for the first 3 eras.

Discussion

In the UK there has been a significant increase in the use of surgery for intermediate and high risk PCa since the 1990s despite a lack of randomised evidence to suggest efficacy when compared to other forms of treatment [4, 5, 12, 13]. Data from large observational cohort studies have suggested that surgery may improve outcomes in men with localised disease but this is most evident in younger patients with higher risk disease [14, 15]. Work from our own centre also suggests that this may be true in a UK population [4]. In a study of over 4700 men, surgery appeared to provide superior cancer specific mortality outcomes but specifically in younger men and with high-risk disease. These data are also supported by national opinions on radical therapy usage from UK urologists and oncologists [16]. As our unit's practice is based on a regional referral structure, it is likely to be indicative of the preferences and opinions of prostate cancer specialists from a number of different hospital. Our results have suggested evidence for an increase in the proportion of preoperative high-risk patients undergoing surgery and a concomitant fall in number of cases referred with low-risk disease. Although we did not observe any change in presenting age, the median age in our study was already low at 61 years. This is also reflected in an increase in the final pathologic staging characteristics across the series. In the most recent era, the proportion of pT3 disease was in excess of 50% which is considerably higher than other contemporary international series[17, 18]. Encouragingly, this change has not affected surgical margin rates. In fact we observed modest trends towards improved margin free rates in both pT2 and pT3 cases. The explanation for this shift in tumour characteristics is likely to be multi-factorial, including an increasing appreciation of overtreatment and the use of active surveillance as a valid treatment option. Another contributing factor is the maturation of our robotic prostatectomy service and increased experience of our surgeons.

This is the first report demonstrating this shift in population in a UK RRP series. Our findings however are consistent with reports from other high-volume centres. Bernie *et al* in 2014 reviewed their RALP series of 3451 men in Houston, USA, and demonstrated an increase in the rate of high-risk preoperative and final pathologic disease[19]. The surgical margin status also remained stable in their series despite the increasing proportion of men with pT3 disease. According to the authors this possibly reflected the changing dynamics of the population opting for surgery and the learning curve of the surgeons. In an older study published in 2011, Silberstein *et al* from Memorial Sloan-Kettering Cancer Centre evaluated changes in clinical and pathological

characteristics of patients treated surgically for localized PCa[6]. The authors performed a retrospective review of 6,624 consecutive patients who underwent surgery from 2000 to 2010. The patients were stratified according to the surgical approach (open, laparoscopic and RALP) as well as according to the National Comprehensive Cancer Network (NCCN) guidelines risk categories. Overall, they found evidence that the proportion of patients who fell into the intermediate and high-risk categories increased during the course of the series, while the proportion of patients in the low-risk category decreased. More recently Huland and Graefen in 2015 reported changing trends in the surgical management of prostate cancer from a high volume European centre over the past 15 years[18]. According to the reported data, the rate of low-risk patients treated surgically declined from 60% in 2004 to 27% in 2011–2013. Similarly, the rate of organ-confined disease dropped from 80% to 62% in the same time period. The authors suggested that their findings reflect the better selection of patients undergoing surgery in contemporary clinical practice, which minimizes the risk of over treatment.

There are of course inherent limitations in our study. This study has focused on those PCa patients managed surgically and we have not sought to quantify any changing enrollment to active surveillance or radiotherapy which would predominantly occur at patients' local hospitals, prior to referral for surgery. We have however previously reported regional changes in trends for non-surgical management of prostate cancer,[4] and expect our results reflect this increasing confidence and use of conservative management. We have also not sought to study continence or potency outcomes in this study. Results from an earlier paper in this cohort have already been published and we do not yet have complete outcome data for the most recent men in this series[7]. Our findings may also not be representative of national trends, although there is no reason to expect significant differences in uptake of national guidelines. Margin status is associated with surgical experience and therefore we might expect a relatively higher incidence among individual surgeons. However in a recent report, we observed no difference in the SM rates in consultants starting their series at different time points in our cohort[20]. Lastly, longer term outcomes are required to fully assess the changing use of RALP in high-risk patients and forms part of our ongoing data collection. Encouragingly, the number of men experiencing BCR in our cohort was low, although we have insufficient follow up to draw conclusions on long-term outcomes. Few comparable series have published BCR rates, the aforementioned Canadian series report 4.9% BCR rate over a median follow-up of 18 months [17], whilst an American series in 2005 published a 5% 1-year BCR rate amongst a lower-risk group [21].

In summary this paper demonstrates first evidence of reverse stage migration and a shift toward operating on higher-risk PCa in a UK tertiary referral centre. Despite this change, PSM rates have remained unchanged and short term BCR rates are encouraging. Our data reflect an emerging selection preference for performing surgery in men with higher-risk disease which is consistent with evidence of the oncological efficacy of this approach. This further suggests that surgical over-treatment may be gradually becoming less of a problem in our Institution and very likely in the rest of the UK. Further work should seek to confirm these findings in other UK Institutions and further investigation is required to evaluate the impact of this change on long-term oncologic outcomes.

References

[1] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013 Apr: 49:1374-403
[2]Cancer Research UK. http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/. [cited; Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/
[3] Loeb S, Bjurlin MA, Nicholson J, et al. Overdiagnosis and overtreatment of prostate cancer. Eur Urol. 2014 Jun: 65:1046-55
[4] Greenberg DC, Lophatananon A, Wright KA, Muir KR, Gnanapragasam VJ. Trends and outcome from radical therapy for primary non-metastatic prostate cancer in a UK population. PLoS One. 2015: 10:e0119494
[5] Fairley L, Baker M, Whiteway J, Cross W, Forman D. Trends in non-metastatic prostate cancer management in the Northern and Yorkshire region of England, 2000-2006. Br J Cancer. 2009 Dec: 101:1839-45
[6] Silberstein JL, Vickers AJ, Power NE, et al. Reverse stage shift at a tertiary care center: escalating risk in men undergoing radical prostatectomy. Cancer. 2011 Nov: 117:4855-60
[7] Sharma NL, Papadopoulos A, Lee D, et al. First 500 cases of robotic-assisted laparoscopic radical prostatectomy from a single UK centre: learning curves of two surgeons. BJU Int. 2011 Sep: 108:739-47
[8] National Institute for Health and Clinical Excellence. NICE Guidelines [CG175] Prostate cancer: diagnosis and treatment. January 2014
[9] Epstein JI, Allsbrook WC, Amin MB, Egevad LL, Committee IG. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol. 2005 Sep: 29:1228-42
[10] Tan PH, Cheng L, Srigley JR, et al. International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 5: surgical margins. Mod Pathol. 2011 Jan: 24:48-57
[11] Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014 Feb: 65:467-79
[12] Oliver SE, Donovan JL, Peters TJ, Frankel S, Hamdy FC, Neal DE. Recent trends in the use of radical prostatectomy in England: the epidemiology of diffusion. BJU Int. 2003 Mar: 91:331-6; discussion 6
[13] Gnanapragasam VJ, Mason MD, Shaw GL, Neal DE. The role of surgery in high-risk localised prostate cancer. BJU Int. 2012 Mar: 109:648-58
[14] Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012 Jul: 367:203-13
[15] Sooriakumaran P, Nyberg T, Akre O, et al. Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes. BMJ. 2014: 348:g1502
[16] Gnanapragasam VJ, Persad R, Payne HA. Radiotherapy and surgery for high-risk localized prostate cancer: a UK questionnaire survey of urologists and clinical oncologists. BJU Int. 2012 Sep: 110:608-12
[17] Tholomier C, Bienz M, Hueber PA, et al. Oncological and functional outcomes of 722 robot-assisted radical prostatectomy (RARP) cases: The largest Canadian 5-year experience. Can Urol Assoc J. 2014 May: 8:195-201
[18] Huland H, Graefen M. Changing Trends in Surgical Management of Prostate Cancer: The End of Overtreatment? Eur Urol. 2015 Feb:

[19] Bernie A, Ramasamy R, Ali A, Tewari AK. Changes in pathologic outcomes and operative trends with robot-assisted laparoscopic radical prostatectomy. Indian J Urol. 2014 Oct: 30:378-82
[20] Srinivasan A, Shah NC, Neal DE, Gnanapragasam VJ. A comparison of learning curves in robotic prostatectomy within a changing referral practice. International Journal of Surgery, 2015 Nov 30;23:S121.
[21] Patel VR, Tully AS, Holmes R, Lindsay J. Robotic radical prostatectomy in the community setting--the learning curve and beyond: initial 200 cases. J Urol. 2005 Jul: 174:269-72

Conflict of Interest Statement

We have read and understood BJUI policy on declaration of interests and in concordance with the ICMJE conflict of interest disclosure forms I can confirm we have no conflicts of interest to declare.

Table 1 -Pre-operative characteristics of the cohort. (IQR- interquartile range, p values refer to comparisons between the first and last periods)

Characteristic	**2005-2008**		**2009-2010**		**2011-2012**	
	n	**%/IQR**	**n**	**%/IQR**	**n**	**%/IQR**
Number of patients	329		367		364	
Age Median (IQR) [years]	62	(58, 66)	63	(58, 66)	62	(57, 66)
Pre-op PSA Median [ng/ml]	7.3	(5.3, 10.0)	7.3	(5.6, 9.5)	7.3	(5.7, 10.1)
Clinical stage						
T1	212	64.4	226	61.6	193	53
T2a	92	28	74	20.2	71	19.5
T2b	15	4.6	29	7.9	47	12.9
T2c	2	0.6	20	5.4	38	10.4
T3a/T3b	8	2.4	18	4.9	15	4.1
Pre-op Gleason sum						
≤6	184	55.9	161	43.9	130	35.7
7	130	39.5	177	48.2	197	54.1
≥8	15	4.6	29	7.9	37	10.2
NICE Risk Category						
Low	160	48.6	136	27.2	114	31.3
Intermediate	131	39.8	163	44.4	176	48.4
High	38	11.6	68	18.5	74	20.3

Table 2 - Final post-operative pathological characteristics.

Characteristic	2005-2008		2009-2010		2011-2012		2013-2015		Total		p value
Final Pathology Gleason	n	%	n	%	n	%	n	%	n	%	
≤6	127	38.60	113	30.79	86	23.63	49	11.14	375	25.00	<0.0001
7	184	55.93	222	60.49	244	67.03	330	75.00	980	65.33	<0.0001
3+4	158	48.02	189	51.50	188	51.65	262	59.55	797	53.13	0.0096
4+3	26	7.90	33	8.99	56	15.38	68	15.45	183	12.20	0.0007
8	12	3.65	15	4.09	12	3.30	21	4.77	60	4.00	0.61
9 or 10	6	1.82	17	4.63	22	6.04	40	9.09	85	5.67	0.0002
Pathological stage											
No tumour found	1	0.30	0	0.00	0	0.00	2	0.45	3	0.20	NA
pT2a	121	36.78	55	14.99	38	10.44	24	5.45	238	15.87	<0.0001
pT2b	10	3.04	2	0.54	7	1.92	4	0.91	23	1.53	NA
pT2c	53	16.11	136	37.06	138	37.91	163	37.05	490	32.67	<0.0001
pT3a	125	37.99	147	40.05	150	41.21	193	43.86	615	41.00	0.41
pT3b	17	5.17	26	7.08	31	8.52	51	11.59	125	8.33	<0.0001
pT4	2	0.61	1	0.27	0	0.00	3	0.68	6	0.40	NA
Nodal Mets, n (%)											
pNx	139	42.25	74	20.16	124	34.07	130	29.55	467	31.13	NA
pN0	187	98.42	281	95.90	219	91.25	270	87.10	957	92.64	<0.0001
pN1	3	1.58	12	4.10	21	8.75	40	12.90	76	7.36	<0.0001
Surgical margin status											
Overall -ve	255	77.51	288	78.47	281	77.20	353	80.23	1177	78.47	0.72
Overall +ve	74	22.49	79	21.53	83	22.80	87	19.77	323	21.53	0.72
pT2 PSM	22	11.96	17	8.81	17	9.29	12	6.28	68	9.05	0.076
pT3a PSM	39	31.20	46	31.29	47	31.33	50	25.91	182	29.59	0.91
pT3b PSM	11	64.71	15	57.69	19	61.29	22	43.14	67	53.60	0.60