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Evidence-Based Series 17-3 Version 2

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Guideline for Optimization of Surgical and Pathological Quality Performance for Radical Prostatectomy in Prostate Cancer Management

The Expert Panel on Prostate Cancer Surgery and Pathology

An assessment conducted in January 2024 deferred the review of Evidence-Based Series (EBS) 17-3 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 17-3 Version 2 is comprised of 4 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/556

Section 1: Surgical and Pathological Guidelines (ENDORSED)
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process
Section 4: Document Review Summary and Tool

October 13, 2017

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Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original version September 2008	1996-March 2007	Full Report	Can Urol Assoc J. 2010 Feb 1;4(1):13-25. Web publication	N.A.
Current Version 2 October 2017	March 2007 – May 2016	New data found in Section 4: Document Assessment and Review	Updated web publication	2008 recommendations ENDORSED Sections 2 and 3 are unchanged from the original 2008 guideline

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Evidence-Based Series #17-3 Version 2: Section 1

Guideline for Optimization of Surgical and Pathological Quality Performance for Radical Prostatectomy in Prostate Cancer Management: Surgical and Pathological Guidelines

The Expert Panel on Prostate Cancer Surgery and Pathology

A Quality Initiative of the Surgical Oncology Program, Cancer Care Ontario
and the Program in Evidence-based Care, Cancer Care Ontario
A Special Project of the Expert Panel on Prostate Cancer Surgery and Pathology

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Assessment and Review for a summary of updated evidence published between 2007 and 2016 and for details on how this Clinical Practice Guideline was ENDORSED

October 13, 2017

QUESTIONS

Surgical Questions

What are the recommended surgical procedures and outcomes for radical prostatectomy (RP), specifically:

1. What is the recommended extent of resection, and what is an acceptable positive margin rate?
2. What are the reported rates for surgical complications, specifically incontinence, erectile dysfunction, rectal injury, and blood transfusion, and does surgical technique (e.g., nerve sparing, bladder neck preservation) affect complication rates?
3. Under what circumstances should nerve-sparing techniques be used?
4. Which patients should receive pelvic lymph node dissection (PLND), and what is the recommended extent of PLND?

Pathological Questions

1. What are the recommended procedures for handling the RP specimen in the operating room and for handling and processing the RP specimen (with or without lymph nodes) in the pathology lab?
2. What diagnostic and prognostic elements should be included in the pathology report, what format should be used, and what reporting elements should be included?

Target Population

The target population is adult males with potentially curable prostate cancer for whom RP is the preferred treatment option.

- Risk Categories: Patients may be considered "low", "intermediate", or "high" risk for treatment failure (e.g., local recurrence, biochemical failure with prostate-specific antigen [PSA] relapse, emergence of metastatic disease) based on disease characteristics using the definitions proposed by D'Amico et al (1).

  Patient Risk:
  - Low Risk: PSA <10, Gleason ≤ 6, and clinical stage T1 or T2
  - Intermediate Risk: PSA 10-20, and/or Gleason 7
  - High Risk: PSA >20, Gleason ≥ 8, or clinical stage ≥T3

RECOMMENDATIONS

The following recommendations are based on the expert opinion consensus of members of the Prostate Cancer Surgery and Pathology Expert Panel (For membership, please see Section 2: Appendix 5.) and informed by evidence from case series studies located through a systematic review of the available clinical evidence. The pathological questions are largely addressed by the protocol for invasive carcinomas of the prostate gland developed by the College of American Pathologists (CAP). The 2006 version was endorsed by the CCO Expert Panel on Prostate Cancer Surgery and Pathology during preparation of the original 2008 guideline.

Qualifying Statement – Added to the 2017 Endorsement:

The recommendations for pathology were updated to align with the most recent CAP protocol released in February 2017 (2), based on the International Society of Urological Pathology (ISUP) consensus conferences in 2009 (3-8) and 2014 (9, 10), the (2016) WHO/IARC classification of urological tumours (11) and the seventh edition AJCC cancer staging manual. The eighth edition of the AJCC (12) will come into effect January 1, 2018 and a corresponding version of the CAP protocol was released June 2017 (13) in preparation for this change. The current documents may be obtained from the CAP website: http://www.cap.org/web/home/protocols-and-guidelines?_adf.ctrl-state=an0gly311_54&_afrLoop=482850301561693# See Section 4, for additional information.

SURGICAL RECOMMENDATIONS

The main goals of RP are (a) complete eradication of the cancer-containing organ with negative surgical margins, (b) preservation of urinary function, and (c) preservation of erectile function, where appropriate, but, in some cases, it is not possible to achieve all three. Positive surgical margins are associated with higher rates of cancer recurrence, but techniques for the preservation of urinary and erectile function may result in positive margins.

The consensus opinion of the expert panel is that the following techniques and objectives form the basis for good surgical management during RP. In Ontario currently, most RPs are performed via the open retropubic route, but other methods are acceptable.

Radical Prostatectomy

- RP should be offered to low-risk and intermediate-risk patients for whom surgery is the preferred option after full discussion with patient and taking into account patient preferences.
- The decision to offer surgery to high-risk patients should be made with careful consideration. High-risk patients should be offered a referral for radiation consultation or review at a Multidisciplinary Cancer Conference (MCC). The intent of the MCC is to ensure that all appropriate diagnostic tests, all suitable treatment options, and the most appropriate treatment recommendations are generated for each cancer patient and discussed prospectively with a multidisciplinary team with the knowledge and tools to provide a full array of surgical interventions, systemic and radiation treatments, and supportive and palliative care. The incidence of positive margins in this patient group is expected to be higher than in that for pT2 disease.
- Sparing of the neurovascular bundles should be considered the "standard approach" except for high-risk patients.
- In patients with otherwise low or intermediate risk, where there is an increased likelihood of positive margins, based on clinical evidence, or the likelihood of extracapsular tumour extension and risk categorization, wide excision of the neurovascular bundles would be warranted in order to avoid compromising cancer control.
- The panel consensus was that the goals are to achieve rates of <1% mortality, <1% for rectal injury and <10% for blood transfusion in non-anemic patients.
- Radical Prostatectomy should aim at achieving a negative margin, while ensuring a balance between margin rates and functional outcomes

Qualifying Statements – Added to the 2017 Endorsement:

The original 2008 recommendation on positive margin rates was modified in 2017 by the Expert Panel, removing the reference to a specific target and not limiting that patient population to pT2 cases. See Section 4 for additional information.

The original and the revision to the positive margin rate recommendations are based on the expert opinion of the guideline panels. In the updated literature review (to May 2016) no new data were identified to directly inform this recommendation.

Pelvic Lymph Node Dissection

- Standard PLND should be mandatory in high-risk patients and is recommended for the intermediate group. PLND is optional for low-risk patients. (Standard PLND should include all lymphatic tissue along the external iliac vein from the lymph node of Cloquet distally to the bifurcation of the common iliac vein proximally and includes all lymphatic tissue in the obturator fossa.)

- Evidence and opinions on the role of extended PLND in high-risk patients are divided. (An extended PLND entails the removal of lymph nodes medial and lateral to the internal iliac vessels up to and around the bifurcation of the common iliac artery, with the genitofemoral nerve as the lateral limit.)

Technical Considerations for Radical Prostatectomy

- For additional specific details concerning technical considerations for RP refer to Section 2: Appendix 4.a) of this document.

PATHOLOGICAL RECOMMENDATIONS

Handling of the Radical Prostatectomy Specimen in the Operating Room

- Frozen section analysis of the radical prostatectomy specimen (RPS) for margin status is not recommended.
- For routine handling, the RPS should be fixed in 10% neutral buffered formalin or other appropriate fixative. The specimen should be put in an appropriately sized container with a minimum formalin/tissue ratio of 10:1 (i.e., 500 cc formalin for a 50 cc prostate).

Pathology Requisition Information

- The surgical specimen should be accompanied by an appropriate pathology requisition that includes demographic and other identifying information, relevant clinical data (e.g., serum PSA, DRE findings [T1c versus T2], Gleason score on biopsy), and the history of neoadjuvant therapy (e.g., hormones)

Pathology Report

- The surgical pathology report should include the relevant diagnostic and prognostic information as outlined in the CAP Cancer Protocol for Carcinomas of the Prostate Gland (2, 13). CCO has recommended as a minimum standard that all required (core) elements on the CAP checklist be included in the RPS pathology report.

Added to the 2017 Endorsement:
See Section 4, Appendix 2 for the updated checklist.

- It is recommended that the diagnostic and prognostic factors be presented as a synopsis as opposed to a narrative or paragraph form. Data from CCO indicates that synopses are more likely to be complete.

Technical Considerations for Handling and Processing the Radical Prostatectomy Specimen in the Pathology Laboratory

- For additional specific details concerning technical considerations for handling and processing, refer to Section 2: Appendix 4.b) of this document.
- In the Pathology Laboratory, the RPS (with or without lymph nodes) is accessioned in the usual fashion.
- The RPS should be fixed in neutral buffered formalin (minimum 10:1 ratio) for a minimum of 18-24 hours prior to sectioning. A microwave-assisted technique may be used to reduce fixation time.
- The prostate gland should be weighed and measured in three dimensions; seminal vesicles should be measured; accompanying lymph node specimens should also be measured and a record made of the number and size of grossly identified nodes.
- The outer aspects of the RPS should be carefully inked to identify the surgical margins, prior to tissue banking.
- After appropriate fixation and inking, the distal apical segment is transected and then serially sectioned, perpendicular to the inked surface. An en face (shave) technique is to be discouraged at the apex, as this approach can result in false-positive margin interpretation.
- The basal (bladder neck) aspect is commonly doughnut shaped and irregular. It is transected from the main specimen and should also be submitted in a perpendicular fashion to minimize the possibility of a false-positive margin at this location.

- The intervening transverse sections can be either totally or subtotally submitted using regular-sized blocks. The submission protocol should be documented with an appropriate diagramatic or written block legend.
- For subtotal submissions, a systematic approach to include the posterolateral peripheral zone should be used.
- All lymph nodes accompanying the RPS should be submitted for histological analysis. It is not necessary to submit all perinodal fat, although it is often difficult to distinguish between adipose tissue and fatty lymph nodes.
- ***Updated in the 2017 Endorsement:***
  The full CAP checklist and protocol for RP are available from CAP at http://www.cap.org/web/oracle/webcenter/portalapp/pagehierarchy/cancer_protocol_templates.jspx?_adf.ctrl-state=i6f2zyq5p_9&_afrLoop=481147013012490#!

RELATED GUIDELINES

For a current listing of guidelines on prostate cancer, please visit the Cancer Care Ontario website at http://www.cancercare.on.ca:

- *Multidisciplinary Case Conference Standards*, June 2006
- Guideline 3-1-2016-1: *Brachytherapy for Patients with Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update*, March 2017
- Evidence-Based Series 3-15 Version 2: *Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer*, September 2014
- Evidence-Based Series 3-17 Version 3: *Adjuvant Radiotherapy Following Radical Prostatectomy for Pathologic T3 or Margin-Positive Prostate Cancer*, May 2014.

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The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:

Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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Evidence-Based Series #17-3 Version 2: Section 2

Guideline for Optimization of Surgical and Pathological Quality Performance for Radical Prostatectomy in Prostate Cancer Management: Evidentiary Base

The 2008 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making. See Section 4 for updated references.
The content of Section 2 is the original evidentiary base from the 2008 guideline and is unchanged.

J. Chin, J. Srigley, L.A. Mayhew, R.B. Rumble, C. Crossley, A. Hunter, N. Fleshner, B. Bora, R. McLeod, S. McNair, B. Langer, A. Evans, and the Expert Panel on Prostate Cancer Surgery and Pathology

A Quality Initiative of the Surgical Oncology Program, Cancer Care Ontario
and the Program in Evidence-based Care, Cancer Care Ontario
A Special Project of the Expert Panel on Prostate Cancer Surgery and Pathology

Report Date: September 11, 2008

QUESTIONS

Surgical Questions

What are the recommended surgical procedures and outcomes for radical prostatectomy (RP), specifically:

1. What is the recommended extent of resection and what is an acceptable positive margin rate?

2. What are the reported rates for surgical complications, specifically incontinence, erectile dysfunction, rectal injury, and blood transfusion, and does surgical technique (e.g., nerve sparing, bladder neck preservation) affect complication rates?
3. Under what circumstances should nerve-sparing techniques be used?
4. Which patients should receive pelvic lymph node dissection (PLND), and what is the recommended extent of PLND?

Pathological Questions

What are the recommended procedures for handling the RP specimen in the operating room and for handling and processing the RP specimen (with or without lymph nodes) in the pathology lab?

1. What diagnostic and prognostic elements should be included in the pathology report, what format should be used, and what reporting elements should be included?

Target Population

The target population is adult males with potentially curable prostate cancer for whom RP is the preferred treatment option.

INTRODUCTION

The number of newly diagnosed cases of prostate cancer in Canada is increasing as a result of an aging population, increased public awareness, and the widespread use of prostate specific antigen (PSA) as a tool for prostate cancer screening and early detection (1,2). Recent projections from Cancer Care Ontario (CCO) administrative data show that the incidence of prostate cancer in Ontario will increase from 9,900 cases in 2005 to almost 13,500 cases in 2010. The proportion of early-staged cancers has also increased because of these factors. While RP is only one of the several management options for localized disease in Ontario, approximately 3,000 RPs are completed per year, and this number is expected to increase with the demand for early-stage treatment. The main goals of RP are (a) complete eradication of the cancer-containing organ with negative surgical margins, (b) preservation of urinary function, and (c) preservation of erectile function, where appropriate, but, in some cases, it is not possible to achieve all three.

The effectiveness of RP in the treatment of prostate cancer depends on good surgical and pathological management and on the effectiveness of communication between the surgical and pathological teams and other cancer care providers. Proper handling of the specimen in the operating room and complete and clear communication of information in the accompanying requisition form provide the starting point for high-quality pathological analysis and reporting of results to the surgeon and other care providers. The pathological assessment of prognostic factors (e.g., Gleason score, pathologic stage, margin status) is best accomplished through systematic handling of the surgical specimen (3). Clear and unambiguous communication of the results (particularly the prognostic factors) in the pathology report are essential for planning the subsequent treatment and care of the individual patient, for assessing the quality of surgical management (margin status), and for system planning purposes. Therefore, to attain the highest quality treatment and management for prostate cancer, both surgical and pathological procedures need to be well integrated.

The majority of RPs in Ontario are currently performed by the open retropubic route; however, robotic-assisted and laparoscopic prostatectomy (LP) is being performed in some centres. RP is a technically challenging oncologic procedure that requires adequate prior training and proper patient selection. The expectations and outcomes for surgery are the same, regardless of the approach.

PLND has been commonly used to determine stage in the TNM system, where N refers to the extent of regional lymph node involvement. Current practice in Ontario includes PLND for some but not all patients undergoing RP.

The objective of this document is to provide guidelines for surgical techniques for RP and concurrent PLND and for the handling of the surgical specimens in the operating room and laboratory, in order to achieve optimal benefit for the patient, with minimal risk of harm. This document does not deal with the choice of management options for prostatectomy. The assumption is that a detailed discussion with the patient regarding treatment options and various techniques for performing prostatectomy, appropriate to the given disease grade and stage, has already taken place. Neither salvage prostatectomy (following local radiotherapy failure) nor the role of neoadjuvant hormonal therapy in RP is addressed in this document.

Definitions Used in This Document

- Positive surgical margin: The microscopic presence of a tumour at the inked margin of the surgically excised specimen (4).
- Clinically localized disease: Defined by digital rectal examination findings and/or bone scan and abdominal and pelvic computerized tomography (CT), as confined to the prostate, and no clinical evidence of extraprostatic disease (5,6).
- Risk Categories: Patients may be considered "low," "intermediate," or "high" risk for treatment failure (e.g., local recurrence, biochemical failure with PSA relapse, emergence of metastatic disease) based on disease characteristics, using the definitions proposed by D'Amico et al (7).

  Patient Risk:
  - Low Risk: PSA <10, Gleason ≤ 6, and clinical stage T1 or T2
  - Intermediate Risk: PSA 10-20, and/or Gleason 7
  - High Risk: PSA >20, Gleason ≥ 8, or clinical stage ≥T3

METHODS

The evidence-based series (EBS) guidelines developed by CCOs Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (8). For this project, the core methodology used to develop the evidentiary base was the systematic review.

This report, produced by CCOs Surgical Oncology Program (SOP) and the PEBC, is a convenient and up-to-date source of the best available evidence on surgical and pathological standards for prostate cancer surgery, developed through a systematic review of the available evidence. Members of both the SOP and the PEBC disclosed any potential conflicts of interest. The SOP is editorially independent of CCO and the Ontario Ministry of Health and Long-term Care (MOHLTC).

CCO and the Expert Panel on Prostate Cancer Surgery and Pathology endorse the protocol for invasive carcinomas of the prostate gland developed by the College of American Pathologists (CAP) (3), with an effective date of April 2007 and relevant material for this review is reproduced in Section 1 and in the Discussion in Section 2 of this EBS. The full protocol and checklist are included in Appendix 1 (also see Appendix 2). Since the questions of interest for this guideline are addressed in the CAP protocol, a literature search was not conducted for the pathological questions.

The systematic review and companion guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

The MEDLINE and EMBASE databases were searched for evidence related to the surgical questions during the month of March 2007, using the following text, MeSH, and EMBASE subject headings: 'prostatic neoplasms', 'prostate cancer', and 'prostate tumo?r'. These results were combined with the term 'prostatectom:' to provide a base pool of literature on surgical treatment of prostate cancer. These aggregate results were then combined with the terms 'nerve sparing', 'neurovascular bundles', 'nerve bundle', 'continence', 'incontinence', 'incontinent', 'urinary incontinence', 'pelvis lymphadenectomy', 'lymph node metastas?s', 'pelvis lymph node', 'lymph node dissection', 'pelvic lymph node dissection', 'pelvis surgery', 'lymph node excision', 'pelvic lymph node resection', 'lymph node resection', 'sentinel lymph node biopsy', 'neoplasm invasiveness', 'neoplasm residual', 'surgical margin$', 'margin status', 'surgical resection margin', 'margin clearance', and 'positive margin', with the total results being limited to human studies in the English language published from 1996 through to March 2007. These searches produced 5,311 references.

In order to search for evidence-based reviews and clinical practice guidelines, the following text, MeSH, and EMBASE subject headings: 'prostatic neoplasms', 'prostate cancer', and 'prostate tumo?r' were used. These results were combined with the term 'prostatectom:' to provide a base pool of literature on surgical treatment of prostate cancer. These results were then limited to evidence-based reviews. A separate search of the Cochrane database was also conducted, using the term "prostatectomy."

Study Selection Criteria

Inclusion Criteria

Studies were considered eligible for inclusion if they were:

1. Randomized trials comparing RP with any other treatment
2. Prospective case series studies of RP
3. Retrospective review of RP patient reports
4. Studies with more than 100 subjects
5. Systematic reviews
6. Clinical practice guidelines
7. Studies concerning PLND regardless of primary treatment
8. Database reviews

Exclusion Criteria

The following publication types were not eligible for inclusion in this report:

1. Review papers that were not systematic reviews
2. Letters to the editor
3. Single-patient case reports
4. Studies in which prostatectomy was salvage treatment
5. Studies that reported on cadavers or human tissue samples only
6. Studies that combined prostatectomy with other procedures (e.g., cystoprostatectomy)
7. Studies with less than 100 subjects
8. Studies concerning robotic surgery and techniques

Synthesizing the Evidence

Due to the anticipated non-comparative sources of evidence in this report, no pooling was planned.

Consultation with Urologists and Pathologists

Formal consensus methods were not employed in the development of this guideline. Ontario urologists and pathologists were consulted in October 2007, prior to the completion of the draft document, in order to obtain feedback on the recommendations drafted by the working group. The consultation included a survey, conducted by email, and an in-person meeting to discuss the draft recommendations along with current data regarding RP performance in Ontario. All Ontario urologists listed in the Canadian Medical Directory were sent surveys, except for retired and pediatric urologists (N=106). Thirty-three returned the survey, and 26 attended the meeting. Pathologists from each Local Health Integrated Network (LHIN) were identified through the CCO Pathology and Laboratory Medicine Program. Fifty-five pathologists were sent questionnaires, 11 returned surveys, and six attended the meeting. The questionnaire was sent by email or fax. The survey results and the opinions expressed at the in-person meeting are summarized in the Results section following the review of the evidence from the literature for each question.

RESULTS

SURGICAL QUESTIONS

Literature Search Results

The following results (Table 1) were obtained from the systematic literature review:

Table 1. Literature search results (1996 to Mar 2007).

Topic	Number of MEDLINE hits	Number of EMBASE hits	Number ordered for full-publication review	Number of articles included in this report	Table # Appendix 3
Radical prostatectomy					
Margins	189	479	56	39	2
Complications	1997	2285	31	22	3
Guidelines/Systematic reviews	7	0	0	0	-
Cochrane Reviews	13	-	0	0	-
PLND					
PLND	327	34	101	23	4

Systematic Reviews and Guidelines

A total of 20 potentially relevant clinical practice guidelines and evidence-based reviews were found. None of the seven guidelines or systematic reviews identified in the MEDLINE or EMBASE literature search was considered relevant: all concerned aspects of androgen deprivation therapy. Thirteen Cochrane reviews were found, but all were considered to be outside the scope of this document. The topics included catheterization policies (eight); drug management of postoperative pain, hormone therapy, and management of postoperative urinary incontinence (two each); and benign prostatic hyperplasia, screening, physical therapy after surgery, and drug protocols for postoperative nausea (one each).

Primary Studies

For the surgical questions, owing to the large number of potentially relevant studies, an initial sort of the 5,311 citation and abstract results was performed by author LM, using the inclusion and exclusion criteria specified in the Methods section above. The remaining 904 references were then reviewed by author JC, and 188 potentially relevant studies were ordered for full-publication review. These 188 studies were reviewed for relevancy by two other authors (SM and LM), and 95 were retained for inclusion in this report. Studies were excluded if the articles were not directly on topic or if they did not report any of the following outcomes:

positive margin rate or information on surgical margins, rate of incontinence, rate of impotence, rate of rectal injury, blood loss, blood transfusion, biochemical failure rate (five year or ten year), time to biochemical failure, clinical recurrence rate (local or distant), time to recurrence, biochemical progression-free survival, cancer-specific death or survival, recurrence-free survival, or progression-free survival. Studies for the PLND section were excluded if they did not present data on PLND separately from other data. Some studies were relevant to more than one topic and therefore appear in more than one table.

Study Quality

No randomized controlled trials (RCTs) were located that were designed to specifically determine how the extent of tumour resection, resection margins, continence outcomes, management of neurovascular bundles, extent of lymphadenectomy, or similar techniques are related to survival or other outcomes, and owing to ethical considerations, it is unlikely that such studies will become available in the future. One RCT was found that compared limited to extended PLND. For this reason, most of the evidence reviewed for these recommendations is based on retrospective reviews, databases, case series, and non-randomized prospective studies, often without comparison groups. These study designs are inherently more biased than randomized studies, and may be difficult to interpret and compare. Confounding factors such as neoadjuvant or adjuvant therapy and patient baseline characteristics were not always reported, and the surgical techniques used often varied from study to study. The following evidence summaries highlight the best available evidence located in this review, with respect to the questions posed. The evidence provided context and some direction for the development of recommendations, based on the expert opinion of the panel.

Surgical Questions

1. ***What is the recommended extent for resection, and what is an acceptable positive margin rate?***

The goal of resection is a negative surgical margin (-SM). Seven studies with sample sizes of N=1,000, or greater reported higher recurrence rates for positive margins versus negative margins and/or multivariate analyses showing margin status to be a significant predictor of biochemical recurrence. No data are available for the impact of positive surgical margin status on metastasis-free, disease-specific, or overall survival. These studies are reported in Appendix 3, Table 1.

The extent of resection varies depending on the size, location, and risk of extraprostatic extension (EP) of the tumour at the time of surgery and the preoperative and perioperative assessment of disease stage (e.g., PSA levels, clinical staging, Gleason score, pathological staging). In total, 39 case-series studies that addressed the extent of resection and reported on positive surgical margins (+SM) were included in the evidence review for this question. Bias is inherent in case series but may be somewhat minimized by a larger sample size. Study size ranged from N=100 to N=7,268, and 10 studies included 1,000, or more subjects. In 36 studies, open RP was conducted, and in three, the surgery was performed laparoscopically. Thirty-six of the studies were retrospective, and three were identified as prospective. These studies are summarized in Appendix 3, Table 2, which reports overall +SM rates, +SM rates by stage (Gleason score and TNM staging) and +SM rates by location (e.g., apex, posterior) and the results are summarized briefly below.

Overall +SM Rates

Overall +SM rates varied from 4.0% (9,10) to 45.2% (10) for open surgery. The only laparoscopic study that reported an overall +SM reported a rate of 16.7% (11).

Clinical Stage, Gleason Score, and +SM

Information concerning +SM by clinical stage can help inform decisions, because the surgeon often has only the clinical stage information available before and during surgery. Three studies reported +SM rate by clinical stage (12-14). The +SM rates reported were 0% (14) to 37% (13) for cT1 and 9.2% (14) to 44% (13) for cT2. Only one study (14) reported a rate for cT3, the rate being 22.4%. Nine studies reported +SM rate by Gleason score (12-20). In general, +SM rates for Gleason 2-6 ranged from 4.2% (17) to 31% (19), Gleason 7 ranged from 9.8% (17) to 41% (19), and Gleason 8-10 ranged from 17.7% (17) to 71.4% (20).

Pathological Stage and +SM

Rates for +SM by pathological cancer stage were compared in 12 studies (11-14,18,20-26). In general, the +SM increased with the pathological stage, with ranges from 0% (22) to 24% (13) for pT2 (with a rate of 3.3% (11) to 19.2% (23) for those receiving laparoscopic surgery), 24.2% (24) to 64.3% (13) for pT3a (30% (12) to 33% (11) for laparoscopic), 27.1% (24) to 80.0% (13) for pT3b (32% (12) to 47% (11) for laparoscopic), and 16.7% (22) to 40.0% (13) for pT3c. Three further studies (15,19,27) reported +SM by T stage, but as it was unclear as to whether these were clinical or pathological stage, these data are not included here.

Margin Site and +SM Rates

Ten studies (15,18,20,21,26,28-32) reported the location of positive margins. Reported apical +SM rates ranged from 8% (29) to 58% (28), posterior +SM ranged from 9% (21) to 40% (28), anterior +SM ranged from 1.2% (30) to 15% (15), base +SM ranged from 2% (18) to 19% (28), and bladder neck +SM rates ranged from 4% (29) to 20.9% (26). Five studies (13,25,26,33,34) reported the location of the positive margin by the stage of disease. Details are available in Appendix 3, Table 2.

One study of laparoscopic RP (12) reported that 50% of +SM were apical, 30% were posterolateral, and 20% occurred at the prostate base. A second laparoscopic study (23) found 40.3% of +SM were posterolateral, 26.1% were apical, 6.2% were anterior, and 6.2% were at the bladder neck.

Surgical Technique and +SM

Eight studies (13,23,25-27,29,31,32) compared +SM rates for nerve-sparing surgery versus non-nerve sparing, or nerve-sparing versus wide excision. This topic is discussed further in the section below under question #3 related to nerve sparing surgery.

Surgeon and +SM

While we did not locate many studies that specifically addressed differences in +SM by surgeon, Eastham et al (16) noted that the +SM rate ranged from 10% to 48%, depending on the surgeon.

Consultation with Urologists and Pathologists

Survey questions and response:

- The positive resection margin for pT2 ranges from 0 to 53% across Ontario. In your opinion, is this acceptable?
  Yes 5 (11.6%)
  No 38 (88.4%)

- The incidence of positive surgical margins should be <20% for pT2 disease.
  Agree 33 (75%)
  No 5 (11.4%)

- In high-risk patients, a positive surgical margin rate in the range of 35% should be achievable.
  Agree 43 (55.8%)
  Disagree 12 (27.9%)

Discussion:

A majority of participants agreed that the current provincial average should be improved and that an average of 25% is a reasonable target for pT2 patients. The issues raised included the fact that defining a benchmark rate is difficult because many factors affect +SM rates.

2. What are the reported rates for surgical complications, specifically incontinence, erectile dysfunction, rectal injury, and blood transfusion, and does surgical technique (e.g., nerve sparing, bladder neck preservation) affect complication rates?

A total of twenty-two studies were located, including one randomized trial that compared rectal injury rates and blood transfusion rates for radical retropubic prostatectomy (RRP) to rates for LP (35). Seventeen studies were retrospective case series, three were prospective case series, and two were cross-sectional surveys administered following surgical interventions. The results of these studies are reported in Appendix 3, Table 3; the studies are ordered in the table first by RP method (open, laparoscopic, and open and laparoscopic), then by study design, and then by sample size. Bias is inherent in these study designs but may be somewhat minimized by a larger sample size. Study size ranged from N=100 to N=10,737, and 10 studies had sample sizes of more than 500 subjects.

Perioperative mortality rates reported in eight studies ranged from 0% to 0.5%. Overall rates of postoperative complications were reported in five studies, ranging from 6.3% to 28.6%, but the complications included in these rates varied among studies and was unclear in some. The largest study (36) (N=10,737) reported statistically significant variation among 159 high-volume surgeons with respect to complication rates. Another study of 3,477 patients undergoing RP with one surgeon from 1983 to 2003 found that complications rates dropped over time from a high of 16.9% (1983-1991) to 7.4% (1992-2003) (37).

Urinary Function

Sixteen studies reported on incontinence. The results of these studies are difficult to interpret because incontinence was defined and assessed using different criteria, ranging from "any degree of loss" to the use of four or more pads daily. Some reported rates were related to the time post-surgery of 12 or 24 months and some to the age of the patients, while some reported daytime versus nighttime incontinence or combinations of these. In general, the reported incontinence rates ranged from 5% (38) to 67% (39), and those for more severe incontinence ranged from 0.8% to 20%. One study reported a decline in incontinence rates from 12 to 24 months post-surgery (38), and one reported a higher rate for men over 70 years of age (40).

Four studies compared continence rates for various surgical techniques. Incontinence rates were 1.3 % with bilateral nerve-sparing surgery (BNS), 3.4% with unilateral nerve-sparing surgery (UNS), and 13.7% with non-nerve-sparing surgery (41). Bladder neck preservation reduced incontinence rates at 12 months to 10.6% from 13.7% for bladder neck resection (42), and when both bladder neck-sparing and puboprostatic ligament-sparing techniques were employed, the incontinence rate at 12 months was 6% compared to 8% for either technique alone (29). Incontinence rates at 12 months were lower for laparoscopic surgery compared to

open RRP, with rates of 11.0 % versus 22.3% for diurnal incontinence and 4.0% versus 10.0% for nocturnal incontinence (43).

Erectile Function

This topic is covered in the section on neurovascular bundles below.

Rectal Injury

Seven studies (11,35,40,44-47) reported rates of rectal injury ranging from 0.3% to 1.45% for RRP and 1.7% for LP. One study found higher rates when a perineal approach was used, compared to a retropubic approach (p=0.03) (45).

Blood Transfusion

Seven studies (11,35,45-49) reported blood transfusion rates ranging from 1.4% (45) to 67% (47). One study reported a median value of three units of blood used (46); another reported an average of 2.13 with a range of one to seven units (48). Rates were lower for LP than for RRP for both homologous (0% versus [vs.] 9%) and autologous (13.3% vs. 45%) transfusion (35).

Consultation with Urologists and Pathologists

Survey questions and response:

- An acceptable rate for rectal injury should be <1%.
  Yes 42 (100%)
  No 0

- An acceptable rate for blood transfusion should be <10%
  Yes 38 (88.4%)
  No 4 (9.3%)

Discussion:

The blood transfusion rate should apply to non-anemic patients. The operation time frame and indications for transfusion should also be considered.

3. Under what circumstances should nerve-sparing techniques be used?

Various nerve-sparing techniques have been developed in an attempt to preserve potency in as many patients as possible. In the past, an assumption was made that using nerve-sparing techniques compromised cancer control, so their use has been controversial. There is also some controversy concerning whether preserving neurovascular bundles may also lead to increased continence rates.

Nerve-sparing Surgery and Positive Margin Rate

Neurovascular bundles are excised more often in men with higher grade disease (15), and patients in the nerve-sparing groups are also often younger and have a lower PSA (31), making comparisons between the two patient groups difficult. Information concerning nerve-sparing surgery and positive margin rates is available in Appendix 3, Table 2.

Graefen et al (22) noted that there was a higher positive margin rate for non-nerve-sparing surgery, particularly in pT3c cancers, but that there were no statistically significant differences in the incidence of biochemical relapse, even when an "ultra-sensitive" PSA test was used. Palisaar er al (25) also found higher positive margin rates for those who received non-nerve-sparing surgery for pT3 grade cancer, and noted that the five-year biochemical recurrence-free survival was higher for those who received nerve-sparing surgery.

Rabbani et al (13) reported that there was no significant difference in positive apical margin rates for patients undergoing bilateral, unilateral, or non-nerve-sparing surgery, when the patients were stratified by clinical stage or the presence of perineural invasion. Cannon et al (50) found that, in 61 patients with nerve-sparing surgery on a single side, only one had a positive surgical margin. Of the 57 patients who had both nerve bundles spared, only four patients had positive margins, and only one of those margins occurred on the same side as the perineural invasion. Sofer et al (31) found that patients who received nerve-sparing surgery were not at an increased risk of recurrence compared with non-nerve-sparing patients (hazard ratio [HR] 0.96, 95% confidence interval [CI] 0.53-1.72) when adjustments were made for positive surgical margins, PSA, Gleason, seminal vesicle invasion, T stage, capsular involvement, extraprostatic extension, and age.

In a large retrospective study of 7268 men, Ward et al (32) controlled for age, clinical stage, biopsy grade, year of surgery, and PSA levels, and found that nerve-sparing surgery had no significant impact on biochemical progression rates (HR 0.98, 95% CI 0.88 to 1.08, p=0.64). The rate of positive surgical margins was actually lower (odds ratio [OR] 0.86, 95% CI 0.76 to 0.97, p=0.012) in those who received nerve-sparing surgery.

Erectile Function

Ten studies reported on erectile function, and the information concerning erectile function can be found in Appendix 3, Table 3. The reported potency rates ranged from 48% (51) to 91.8% (45) of patients. One large study (N=5,238) (52) reported a median time of 12 months to recover erectile function and an increase of 7% from 18 months to 24 months. Three studies found that BNS resulted in higher rates of erectile function than did UNS, with differences of 23%, 21%, and 7% (21,37,40), respectively. Men 59 years and younger benefited more (41%, 49%) than men over 60 years (10%, 8%) (40). One study of 300 patients reported higher rates of erectile function for LP compared to RRP (41% vs. 30%, respectively) whether one neurovascular bundle (46% vs. 27%) or two (53% vs. 44%) were preserved (43). Catalona et al (40) also found that the proportion of men with a return of erections increased with the number of prior prostatectomies performed by the surgeon (61% for less than 500, 68% for 500 to 1,000, and 70% for 1,000 to 1,500; Armitage chi-square 4.8, p=0.03) and that there was a significant interaction for age by type of surgery (Wald chi-square 6.9, p=0.009), with the effect of BNS versus UNS on the odds of regaining potency decreasing with increasing age.

Continence

The role of nerve-sparing surgery in the recovery of continence is controversial. Information concerning continence and nerve-sparing surgery can be found in Appendix 3, Table 3. Graefen et al, Kundu et al, and Catalona et al (22,37,40) reported that the recovery of urinary incontinence was not associated with nerve-sparing surgery. Burkhard et al (41), however, found that when age, PSA, pT stage, Gleason, and node-positive status were examined along with type of surgery, attempted nerve-sparing surgery was the only statistically significant factor influencing urinary incontinence (OR 4.77, 95% CI 2.18 to 10.44, p= 0.0001).

Consultation with Urologists and Pathologists

Survey questions and response:

- Sparing of the neurovascular bundles should be considered the "standard approach" unless it is contraindicated.
  Yes 33 (76.7%)
  No 8 (18.6%)

- In situations where there is a high risk of positive margins, based on clinical evidence, or the likelihood of extracapsular tumour extension and risk categorization (e.g., clinical

stage >T2, Gleason >7, high-volume disease, intraoperative finding of induration of lateral pelvic fascia), wide excision of the neurovascular bundles would be warranted in order to avoid compromise to cancer control.
Yes 39 (97.5%)
No 0

- Clips should be used for hemostasis, and the use of electrocautery near the neurovascular bundles should be avoided.
Yes 31 (81.6%)
No 3 (7.9%)

Discussion:

There was general agreement that nerve-sparing techniques are appropriate for low-risk patients but should not be performed in high-risk patients or patients who are not sexually active. The decision to use nerve-sparing techniques should be determined a priori, giving consideration to cancer control, risk, potency, and continence, with the caveat that the intraoperative finding of induration of the lateral pelvic fascia might alter the a priori decision. Contraindications include PSA level, amount of high-risk cancer, extracapsular extension, and pathological stage. There was general agreement that in practice, patient selection is based on anecdote and feel in many cases.

4. Which patients should receive pelvic lymph node dissection (PLND), and what is the recommended extent of PLND?

A total of 22 studies were located: 21 case series (15 retrospective, and six prospective) and one randomized trial (N=123) (53) in which patients were prospectively randomized to have extended PLND on one side and limited PLND on the other. The case series studies lack controls and are not randomized; they are therefore more susceptible to bias than more robust study designs such as RCTs However, a case series with a large sample size is more robust than one with a small sample size. In these studies, sample size ranged from N=123 to N=9,182, and six studies had sample sizes of more than 1,000 subjects. The results of these studies are reported in Appendix 3, Table 4. Studies are ordered in the table first by RP method (open, laparoscopic, and open and laparoscopic), and then by sample size.

Other factors affect the quality of the evidence found. In retrospective studies, there is no control over patient selection, and so patients who received PLND or extended PLND may have been those considered to be at higher risk. As mentioned by Briganti et al (54), many of the patients receiving an extended PLND had higher PSAs and higher Gleason scores, and Berglund et al (55) noted that the treatment and no-treatment groups were statistically significantly different in age and disease stage. In addition, little information is available as to how patients were picked for extended versus limited PLND, making comparisons between these groups difficult. The staging methods used in these studies is also inconsistent, as some used Gleason scores, some used PSA values, some used clinical TNM, some used pathological TNM, and some used various combinations of these. Further, PSA tests have also become more common and more sensitive over time, which may be leading to a stage migration in the diagnosis of prostate cancer.

Therapeutic Value

In some other forms of cancer, such as testicular nonseminoma, removal of the pelvic lymph nodes has proved beneficial to the patient; however, the therapeutic value of removing pelvic lymph nodes in prostate cancer is not well established. Seven studies in this review addressed the therapeutic role of PLND in treating prostate cancer patients: three supported a therapeutic

value for PLND, and four rejected a therapeutic value for PLND. All these studies were retrospective case series.

In one study of 9,182 patients who received PLND, patients who had more than four lymph nodes examined showed a significant decrease in HR for cancer-specific death, and for patients with negative nodes, the HR for cancer-specific death increased significantly when more than 10 nodes were removed (56). Removing a large number of lymph nodes in node-negative men improved neither the HR for death (56) nor the biochemical recurrence rate (57). In another study, patients with nodal involvement and less than 15% positive nodes who received an extended PLND had a significantly higher PSA progression-free survival rate at five years than those who did not receive PLND (58).

Three studies, however, did not find any evidence of a therapeutic value for PLND, as performance or omission of PLND was not an independent predictor of outcome (55,59,60). DiMarco et al (61) also found that the number of nodes excised in PLND was not significantly associated with PSA progression, systemic progression, or cause-specific survival.

Staging

Of twenty studies identified that addressed the benefit of using PLND for staging, eleven supported performing a PLND, eight rejected performing a PLND or an extended PLND, and one study provided information supporting both sides of the issue Six of these studies were prospective; five supported PLND, and one rejected PLND.

Four studies (62-65) found that patients would be understaged without a PLND, particularly low-risk patients (64). Pagliarulo et al (66) found the presence of occult lymph node metastases in 13.3% of patients. Rogers et al (67) found that other preoperative factors (such as Gleason and PSA) were not sufficiently sensitive to predict who would have nodal metastases, and Bader et al (62) found that CT imaging has low sensitivity and accuracy for lymph node metastases.

Other studies have not found PLND to be an important part of staging. Three studies (55,68,69) found that other clinicobiological factors could identify patients with an increased risk of positive lymph nodes. Further, Briganti et al (54) stated that the staging benefit of PLND should be juxtaposed with the higher complication rates and longer hospital stay, especially with extended PLND.

Extent

In the literature reviewed, there was considerable variation in the reported extent of PLND and the definition of the terms used to describe the extent of surgical removal of tissue. In some studies, standard or limited PLND was compared to extended or meticulous PLND or to no PLND, but the descriptions of these terms differed among studies (see definitions from four of the larger studies in Table 2 below).

Table 2. Definitions of pelvic lymph node dissection extent reported in the largest studies included in this review.

Study	N	PLND	Definition
Masterson 2006 (57)	4,611,	Extended	Included the lymphatic tissues bordered proximally by the bifurcation of the common iliac arteries and caudally by the femoral canal and the deep circumflex vessels, along the external iliac vein, and limited laterally by the pelvic side wall. Lymphatics at the confluence of the internal and external iliac veins, and the obturator fossa were removed, sparing only the obturator vessels and nerve.

Berglund 2007 (55)	4,693,	Limited	Nine lymph nodes removed
Allaf 2004 (58)	4,000,	Extended	Excision of the fibrofatty and lymphatic tissues in an area bordered superiorly by the bifurcation of the common iliac artery. The inferior margin was the femoral canal, while the dissection was carried laterally to the pelvic sidewall.
	4,000,	Limited	Limited pelvic lymph node dissection differed in that the posterior extent of the dissection terminated with the fibrofatty tissue along the obturator nerve.

Eight studies found positive lymph nodes outside the area of a standard PLND and were in support of performing an extended PLND (44,58,62,63,69-72). Three studies, found that an extended PLND was unnecessary (57). In the randomized trial by Clark (53), where patients had a limited PLND on one side and an extended PLND on the other side, there was no difference found in the number of positive nodes between the limited and the extended PLND.

Complications in PLND

Balanced against the potential value of PLND as a staging tool or for therapeutic value is the potential for complications from the surgery. Bhatta-Dhar et al (59) noted that the complication rate for PLND is about 1% and that there is a greater likelihood of a complication resulting from PLND (1%) than of finding positive lymph nodes (0.7%). Briganti et al (54) found that the complication rate for extended PLND (19.8%) was significantly higher than the complication rate for the limited PLND (8.2%, OR 2.7, $p<0.001$), that the rate of lymphoceles was higher in the extended PLND group, and that extended PLND also resulted in a significantly longer hospital stay. In the randomized trial by Clark (53), nearly 77% of complications were on the side of the extended PLND, while there was no difference in the rate of detection of metastases.

Consultation with Urologists and Pathologists

Survey questions and response:

- PLND should be mandatory in high-risk patients.
  Yes 41 (97.6%)
  No 1 (2.4%)

- PLND should be recommended for the intermediate group.
  Yes 41 (97.6%)
  No 2 (4.8%)

- Standard PLND should include all lymphatic tissue along the external iliac vein from the lymph node of Cloquet distally to the bifurcation of the common iliac vein proximally, and includes all lymphatic tissue in the obturator fossa.
  Yes 32 (80%)
  No 8 (20%)

- Evidence and opinions on the role of extended PLND in high-risk patients are divided.
  Yes 36 (90%)
  No 3 (7.5%)

- An extended PLND entails removal of lymph nodes medial and lateral to the internal iliac vessels up to and around the bifurcation of the common iliac artery, with the genitofemoral nerve as the lateral limit.
  Yes 34 (85%)
  No 2 (4%)

Discussion:
There was general agreement with the recommendations.

PATHOLOGICAL QUESTIONS

The Expert Panel on Prostate Cancer Surgery and Pathology endorses the CAP protocol for invasive carcinomas of the prostate gland, and a literature search was not conducted for the pathological questions. The results of the consultation with urologists and pathologists with respect to the pathological questions are presented for each of the recommendations below. (Note: total responses do not sum to 100% because some respondents did not answer yes or no but provided a comment.)

Pathological Questions

1. ***What are the recommended procedures for handling the RP specimen in the operating room, and for handling and processing the RP specimen (with or without lymph nodes) in the pathology lab?***

Consultation with Urologists and Pathologists

Survey questions and response:

- Frozen section analysis of the radical prostatectomy specimen (RPS) for margin status is not recommended.
  Yes 42 (93%)
  No 0

- For routine handling, the RPS should be fixed in 10% neutral buffered formalin or other appropriate fixative. The specimen should be put in an appropriately sized container with a minimum formalin/tissue ratio of 10:1 (i.e., 500cc formalin for a 50cc prostate).
  Yes 42 (93%)
  No 0

- The surgical specimen should be accompanied by an appropriate pathology requisition that includes demographic and other identifying information, relevant clinical data (serum PSA, DRE findings [T1c versus T2], and Gleason score on biopsy), and a history of neoadjuvant therapy (e.g., hormones).
  Yes 42 (91.3%)
  No 4 (8.7%)

- The prostate gland should be weighed and measured in three dimensions.
  Yes 41 (93.2%)
  No 2 (4.6%)

- Seminal vesicles should be measured.
  Yes 28 (62.2%)
  No 13 (33.33%)

- Accompanying lymph node specimens should also be measured and a record made of the number and size of grossly identified nodes.
  Yes 38 (82.6%)
  No 6 (13%)

- The outer aspects of the RPS should be carefully inked to identify the surgical margins. A variety of techniques are suitable, including India ink and multi-coloured dyes.
  Yes 43 (97.7%)
  No 1 (2.3%)

- After appropriate fixation and inking, the distal apical segment should be transected and then serially sectioned, perpendicular to the inked surface. An en face (shave) technique is not recommended at the apex.
  Yes 37 (86.1%)
  No 0

Discussion:

There was general agreement with the recommendations.

2. What diagnostic and prognostic elements should be included in the pathology report, what format should be used, and what reporting elements should be included?

All the respondents agreed that the following items from the CAP RPS checklist should be included in the pathology report: histological tumour type, Gleason grading, presence/absence of seminal vesicle invasion, presence of extraprostatic extension, pT and pN designation, and margin status.

Other desirable, although not required (core), elements:

- Presence of tertiary Gleason patterns. Agree 86.7%
- Tumour quantification. Agree 93.3%
- Extent of extraprostatic extension. Agree 91.1%
- Presence/absence of lymphatic (small vessel) invasion. Agree 84.4%
- Presence/absence of venous (large vessel) invasion. Agree 82.2%

DISCUSSION

The main goals of RP include the (a) complete eradication of the cancer-containing organ with negative surgical margins, (b) preservation of urinary function, and (c) preservation of erectile function where appropriate. The impact of a positive surgical margin is significant since it is an independent prognostic factor for disease recurrence and an indicator for consideration of secondary therapy. Margins are more likely to be reported as positive in more advanced disease but may also be positive because of variation in surgical or pathologic technique. The rate of positive surgical margins for RP has declined over the last ten years, from upwards of 50% in the past to a low of 4% in some contemporary series. This may be partially owing to "stage migration," with more cases of organ-confined cancer being treated with surgery, and to improved surgical techniques. The incidence of positive surgical margins also varies considerably among individual surgeons and individual institutions, with an association between higher volumes and lower rates of margin positivity. In Ontario, the CCO 2005 data indicated that, among the various LHINs, positive resection margin rates ranged from 16% to 42% for pT2 disease and 42% to 83% for pT3 disease. In the 2005/2006 CCO Pathology Audit, the average positive margin rates were 32% for pT2 Gleason ≤7 and 59.0% for pT2 Gleason >8 or pT3. The incidence of postoperative incontinence and erectile dysfunction is more

difficult to document, but, as in the case of margins, both tumour stage and surgical technique may play an important role.

Surgical Management

The currently available evidence from the literature on surgical quality performance for RP was limited to case series reports and retrospective reviews without randomization or control groups. In general, the evidence from the published literature alone does not provide a strong basis for recommendations, and, therefore, the expert panel developed recommendations and guidance on technical considerations on the basis of a consensus of the expert opinion of the working group and through a consultation with a group of 44 urologists and pathologists in October 2007.

When surgery has been determined to be the best treatment option for the management of prostate cancer, RP is recommended. In Ontario currently, most are performed via the open retropubic route, but other methods are acceptable. The goals for good surgical management are negative surgical margins, no adverse effects or complications resulting from surgery, and maintenance of continence and erectile function. The decision to offer surgery to high-risk patients should be made with careful consideration. High-risk patients should be offered a referral for radiation consultation or review at a Multidisciplinary Cancer Conference (MCC).

Surgical Margins and Extent of Radical Prostatectomy

There is a demonstrated association between positive surgical margins and higher rates of biochemical failure and clinical recurrence. The rate of positive surgical resection margins is dependent on the tumour risk category (e.g., preoperative PSA level, Biopsy Gleason score, clinical T staging, the number of positive biopsy cores, the percentage of involvement of the biopsy cores), extent of surgical dissection and surgical technique, and also the pathologist's handling and reporting with respect to the surgical specimen. It was the consensus of the expert panel that attaining a positive margin rate of <25% for pT2 disease, without compromising disease control, is an achievable goal. Many factors influence the suitability of patients in the high-risk group for RP, and important factors (such as the tumour risk category mentioned above) should be considered in the context of an MCC. Higher +SM rates are expected for high-risk patients. Positive margins occur at a higher rate at the prostatic apex than at the posterior, base, or anterior of the prostate, and positive margin rates are lower in early-stage cancer than in late-stage cancer.

Surgical Complications

The reported rates of perioperative mortality in RP are consistently <0.5%. Incontinence and loss of erectile function are potential negative outcomes of RP that have a serious impact on the long-term quality of life for patients, although initial post-surgery rates appear to decline over time from 12 to 24 months. There is limited evidence that nerve-sparing surgery, bladder neck preservation, and laparoscopic surgery result in lower incontinence rates, but the evidence is difficult to interpret due to the variation in assessment and reporting of continence outcomes. There is some evidence that BNS results in higher rates of erectile function than does UNS and that the benefit was more pronounced in younger men. Based on a consensus of expert opinion, the recommendations of the panel are that:

- Radical prostatectomy should be offered to low-risk and intermediate-risk patients for whom surgery is considered the preferred option.
- The decision to offer surgery to high-risk patients should be made with careful consideration. High-risk patients should be offered a referral for radiation consultation or review at a Multidisciplinary Cancer Conference (MCC). The intent of the MCC is to

ensure that all appropriate diagnostic tests, all suitable treatment options, and the most appropriate treatment recommendations are generated for each cancer patient and discussed prospectively with a multidisciplinary team with the knowledge and tools to provide a full array of surgical interventions, systemic and radiation treatments, and supportive and palliative care. The incidence of positive margins in this patient group is expected to be higher than that for pT2 disease.

- Sparing of the neurovascular bundles should be considered the "standard approach" except for high-risk patients.
- In situations where there is a high risk of positive margins based on clinical evidence, or the likelihood of extracapsular tumour extension and risk categorization (clinical stage > T2, Gleason >7, high-volume disease, intraoperative finding of induration of lateral pelvic fascia), wide excision of the neurovascular bundles would be warranted, in order to avoid the compromise of cancer control.
- Attaining a positive margin rate of <25% for pT2 disease should be an achievable goal.
- Achieving rates of <1% for rectal injury and <10% for blood transfusion in non-anemic patients are the goals.

PLND

PLND has been used as both a staging tool to determine if there were lymph node metastases and as a treatment for reducing the disease burden in patients. PLND is an invasive procedure with significant risk of complications (44,54), and the available evidence is inconclusive on whether the benefits of performing PLND outweigh the harms. Six studies provided evidence to suggest a survival benefit with more extensive PLND (i.e., more nodes removed) for both node-positive and node-negative patients (56,57,62,63,65,71). Three other studies showed no benefit (55,59,61). Lymph node metastases may be predicted by the use of predictive nomograms, using variables such as pretreatment PSA, Gleason sum and clinical stage (73), but other studies conclude that PLND is the definitive method (67). Survival and recurrence may be predicted by Gleason scores alone (74).

The following recommendations are based on the expert opinion and consensus of the panel. The recommendations are based on the D'Amico low-, intermediate-, and high-risk groups. The panel noted that extended PLND might not always be possible, owing to complications from surgery.

- Standard PLND should be mandatory in high-risk patients and is recommended for the intermediate group. PLND is optional for low-risk patients. (Standard PLND should include all lymphatic tissue along the external iliac vein from the lymph node of Cloquet distally to the bifurcation of the common iliac vein proximally, and includes all lymphatic tissue in the obturator fossa.)

- Evidence and opinions on the role of extended PLND in high-risk patients are divided. (An extended PLND entails the removal of lymph nodes medial and lateral to the internal iliac vessels, up to and around the bifurcation of the common iliac artery, with the genitofemoral nerve as the lateral limit.)

The panel drafted additional surgical recommendations of a technical nature, and these are compiled in Appendix 4.a) of this document, "Technical Considerations for Radical Prostatectomy."

Pathological Management

Clear and effective communication of information among surgeons, pathologists, and other caregivers is necessary in order to achieve optimal results for the patient. The expert panel recommendations are based on the CAP recommendations and protocols for reporting and handling of radical prostatectomy specimens in the operating room and the pathology lab as endorsed by CCO (see Appendix 1 and Appendix 2 for details).

The CAP protocol provides a comprehensive standardized method for reporting and handling that can be used to ensure the consistent and reproducible transfer and processing of specimens and the accurate reporting of essential information among surgeons, pathologists, and other health care providers.

Some additional technical recommendations related to the handling and processing of the specimen were not addressed in the CAP protocol but were agreed to by the panel. These are listed below (see also Appendix 4.b).

In the Operating Room

- Frozen section analysis of the radical prostatectomy specimen (RPS) for margin status is not recommended. The handling and sectioning of the fresh specimen may significantly distort tissue and impair the final analysis.
- It must be decided whether the RPS is being submitted for research studies/tumour banking or for routine handling.
- For research purposes or fresh tumour banking, the RPS should be immediately transported to the pathology laboratory for appropriate handling as per relevant protocols. As there is a rapid degradation of some macromolecules (especially RNA) after devitalization, it is important that this be handled as quickly as possible. An appropriate transportation system is required to ensure rapid delivery to the laboratory.
- For routine handling, the RPS should be fixed in 10% neutral buffered formalin or other appropriate fixative. The specimen should be put in an appropriately sized container with a minimum formalin/tissue ratio of 10:1 (i.e., 500 cc formalin for a 50 cc prostate).

In the Pathology Laboratory:

- The RPS specimen (with or without lymph nodes) is accessioned in the usual fashion.
- The RPS should be fixed (if not done so already) in an appropriate volume of neutral buffered formalin (minimum 10:1 ratio). In general, the specimen should be fixed for a minimum of 18-24 hours prior to sectioning. A microwave-assisted technique may be used to reduce fixation time.
- The prostate gland should be weighed and measured in three dimensions, seminal vesicles should be measured, and accompanying lymph node specimens should also be measured and a record made of the number and size of grossly identified nodes.
- The outer aspects of the RPS should be carefully inked to identify the surgical margins. Various techniques are suitable. Some pathologists prefer India ink, while others use multi-coloured dyes.
- After appropriate fixation and inking, the distal apical segment is transected and then serially sectioned, perpendicular to the inked surface. An en face (shave) technique is to be discouraged at the apex as this approach can result in false-positive margin interpretation.
- The basal (bladder neck) aspect is commonly doughnut shaped and irregular. It is transected from the main specimen and should also be submitted in a perpendicular fashion to minimize the possibility of a false-positive margin at this location.
- Seminal vesicles may be sectioned in transverse or longitudinal fashion. It is not necessary to block the whole seminal vesicle, although the junction between the seminal vesicle and prostate should be entirely blocked.

- The portion of the RPS between apical and basal aspects should be serially sectioned at 3-5 mm intervals perpendicular to the rectal surface. These sections are carefully examined to identify gross tumour (often not visible in T1c disease). Macroscopic features should be discussed in the pathology report.
- For purposes of tissue submission, the entire apical and basal portions are submitted. The intervening transverse sections can be either totally or subtotally submitted using regular-sized blocks. The submission protocol should be a documented with an appropriate diagramatic or written block legend.
- For subtotal submissions, a systematic approach to include the posterolateral peripheral zone should be used.
- A whole organ sectioning technique is a reasonable alternative to the above-described process.
- All lymph nodes accompanying the RPS should be submitted for histological analysis. It is not necessary to submit all perinodal fat, although it is often difficult to distinguish between adipose tissue and fatty lymph nodes.

CONCLUSIONS

The members of the Expert Panel on Prostate Cancer Surgery and Pathology conclude that RP is recommended for the surgical treatment of prostate cancer, depending on a patient-risk profile preoperatively. The quality and effectiveness of this treatment and of subsequent patient care depend on good surgical and pathological management and on the effectiveness of the communication and reporting between surgeons and pathologists working together as part of a multidisciplinary team. The primary goal of RP is the complete eradication of the cancer-containing organ, with negative surgical margins, with preservation of urinary function and preservation of erectile function where appropriate.

CONFLICT OF INTEREST

Members of the Expert Panel on Prostate Cancer Surgery and Pathology who were involved in the writing of this document were polled for potential conflicts of interest. No conflicts were declared.

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Appendix 1. College of American Pathologists surgical pathology case summary checklist

Note: This checklist has been replaced by an updated protocol released in 2017. See Section 4 for details.

Appendix 2. College of American Pathologists Checklist elements to include in radical prostatectomy report.

Note: This checklist has been replaced by an updated protocol released in 2017. See Section 4, Appendix 2 for details.

Appendix 3. Table 1. Studies (N ≥ 1,000) reporting recurrence rates by margin status and/or multivariate analyses of the effect of margin status and other risk factors. Studies are ordered by open vs. laparoscopic radical prostatectomy, then sample size.

Study	N	Study Design	Positive Margin (%)	Biochemical Recurrence (%)	Other
OPEN SURGERY					
Ward (2004) (32)	7268	Retro CS No adjuvant hormonal or radiation therapy	38%	Progression free survival: 5 year: 76% (SE: ± 1) 10 year: 63% (SE: ± 1)	Multivariate Cox proportional hazards regression: (adjusted for organ confinement, pathological grade, SM, SVI, preoperative PSA, year of surgery) +SM vs –SM HR 1.56 (CI: 1.40 – 1.74) p<0.001
Karakiewicz (2005) (75)	5831	Pro CS No adjuvant hormonal or radiation therapy	Overall: 26.7%	Recurrence-free survival: 5 yr: (95% CI) Overall: 0.75 (0.74-0.77) -SM: 0.83 (0.82-0.85); +SM: 0.53 (0.49-0.57) 10 yr: (95% CI) Overall: 0.61 (0.57 to 0.65) -SM: 0.70 (0.66-0.74); +SM: 0.36 (0.28-0.45)	Multivariate Cox proportional hazards regression: (adjusted for pretreatment PSA, pathologic Gleason sum, SM, ECE, SVI, LNI) +SM vs –SM HR 2.18 (CI: 1.907-2.494) p<0.001
Blute (1997) (28)	2334	Retro CS Stage: All pT2NO, No prior adjuvant therapy	Overall : 26%	5 yr. survival free of clinical or PSA failure: -SM: 86% (SE: ± 1%) +SM: 75% (SE: ± 3%) p< 0.001	Relative Risk (Cox model, adjusted for PSA, Gleason, DNA ploidy) associated with +SM: Overall death: (N=69) 0.85 (0.41-1.72) p=0.64 Clinical recurrence: (N=68) 0.91 (0.47-1.77) p=0.78 Clinical/PSA Failure: (N=249) 1.68 (1.24-2.18) p=0.0006
Bianco (2005) (Urology) (52)	1746	Retro CS No prior adjuvant hormonal or radiation therapy	Overall: 12%	Freedom from PSA recurrence: 5 year: (95% CI) -SM: 86% (84-88); +SM: 51% (44-59) 10 year: (95% CI) -SM: 82% (79-85); +SM: 42% (34-51) 15 year: (95% CI) -SM: 81% (77-84); +SM: 42% (34-51)	
Swindle (2005) (14)	1389	Retro CS Excluded pts. With adjuvant therapy	Overall: 12.9 pT2: 6.8% pT3: 23%	Probability at 10yr Progression-free: -SM: 81% ± 3% +SM: 58% ± 12%	Multivariate Cox proportional hazards regression: (adjusted for ECE, LNI, SVI, SM, NS, Gleason score, preoperative PSA) HR for +SM: 1.66 (1.17-2.38) p=0.005)
Palisaar (2005) (25)	1343	Retro CS Excluded neo-adjuvant hormonal treatment	Overall: 19.6% pT2: 10.6% pT3a: 26.7% pT3b: 36.7% pT4: 44.4%	Recurrence-free survival 3 year: pT2: -SM: 96.3; +SM: 93.2 pT3a: -SM: 78; +SM: 59 pT3b: -SM: 41.9; +SM: 30.8 5 year: pT2: -SM: 93.2; +SM: 88.9 pT3a: -SM: 67; +SM: 39 pT3b: -SM: 39; +SM: 16.2	Multivariate Cox proportional hazards regression: (adjusted for SM, Gleason sum, ECE, SVI, LNI, PSA) HR for +SM: 1.4 (1.07-1.82) p=0.013
LAPAROSCOPIC SURGERY					
Guillonneau (2003) (12)	1000	Retro CS	pT1c: 16% pT2a: 14% pT2b: 41%	Median followup: 12 months (1 to 48) Progression-free survival: 3 year: -SM: 90%; +SM: 67%; p<0.001	Multivariate Cox proportional hazards regression: (adjusted for preoperative PSA, pathological stage, margin status, postoperative Gleason score) HR for +SM: 2.57 (1.68-3.95) p<0.001

Notes: SM = surgical margin status; SVI = seminal vesicle invasion; ECE = extracapsular extension; LNI = lymph node involvement; NS = nerve-sparing surgery; HR = hazard ratio

Appendix 3. Table 2. Studies reporting overall +SM rates and +SM rates by margin site, pathological stage, and surgical technique. Studies are ordered in the table by radical prostatectomy method (open vs. laparoscopic) and sample size.

<table>
<tr><th rowspan="2">Study</th><th rowspan="2">Surgical Type Stage</th><th rowspan="2">Study Design</th><th colspan="3">Positive Margin (%)</th><th rowspan="2">Other</th></tr>
<tr><th>Overall</th><th>By Stage</th><th>By Location</th></tr>
<tr><td colspan="7">OPEN SURGERY</td></tr>
<tr><td>Ward (2004) (32)
N=7268</td><td>RP
cT1a-T3</td><td>Retro CS</td><td>38%
72% focally positive;
28% multiple margins</td><td></td><td>Positive surgical margin by location
<table><tr><th>Location</th><th>NS %</th><th>NNS %</th><th>Overall %</th></tr><tr><td>Apex</td><td>18</td><td>25</td><td>21</td></tr><tr><td>Posterior</td><td>16</td><td>19</td><td>18</td></tr><tr><td>Base</td><td>5</td><td>11</td><td>8</td></tr><tr><td>Urethra</td><td>2</td><td>5</td><td>4</td></tr><tr><td>Anterior</td><td>2</td><td>2</td><td>2</td></tr></table></td><td>OR for +SM in NS-RP: 0.86 (95% CI 0.76-0.97, p=0.012).</td></tr>
<tr><td>Karakiewicz (2005) (75)
N=5831</td><td>RRP
Gleason 2-10</td><td>Pro CS</td><td>26.7%</td><td></td><td></td><td>Higher progression rate with +SM (log-rank p=0.0001)</td></tr>
<tr><td>Eastham (2003) (16)
N=4629</td><td>RP
Stage: cT1-T3NxMO</td><td>Retro CS</td><td>20%
10%-48% by surgeon</td><td>Positive margins by Gleason score
<table><tr><th>Score</th><th># pts.</th><th>% of pts.</th><th>% +SM</th></tr><tr><td>2</td><td>1</td><td>0.0</td><td>100</td></tr><tr><td>3</td><td>3</td><td>0.0</td><td>0.0</td></tr><tr><td>4</td><td>17</td><td>0.4</td><td>23.5</td></tr><tr><td>5</td><td>279</td><td>6.0</td><td>14.7</td></tr><tr><td>6</td><td>1806</td><td>39.0</td><td>13.6</td></tr><tr><td>7</td><td>2206</td><td>47.7</td><td>23.9</td></tr><tr><td>8</td><td>218</td><td>4.7</td><td>35.8</td></tr><tr><td>9</td><td>96</td><td>2.1</td><td>42.7</td></tr><tr><td>10</td><td>3</td><td>0.0</td><td>100</td></tr></table></td><td></td><td>Most surgeries NS-RP</td></tr>
<tr><td>Chun (2006) (76)
N=2402</td><td>RP
Gleason ≤7 = 98.9%</td><td>Pro CS</td><td>20.2% (range 21.4-32.9)
16.4-27.4% over time (p=0.06)</td><td></td><td></td><td>+SM and surgical volume not significantly related. (p=0.7)</td></tr>
<tr><td>Blute (1997) (28)
N=2334</td><td>Stage: pT2N0</td><td>Retro CS</td><td>Overall : 18.7%
1 +SM: 79.6%
≥ 2 +SM: 20.4%</td><td></td><td>Apex/Urethra 58%
Prostate Base 19%
Anterior Prostate 2.5%
Posterior Prostate 40%
In 42% of +SM, apex/urethra only positive site</td><td></td></tr>
<tr><td>Khan (2003) (17)
N=1955</td><td>RRP
Gleason 2-10</td><td>Retro CS</td><td>Overall: 9.8%</td><td>Gleason =6: 4.2%
Gleason=7: 9.8%
Gleason>7: 17.7%</td><td></td><td>Single surgeon.</td></tr>
<tr><td>Bianco (2005) (38)
N=1746</td><td>RRP
cT1a-3</td><td>Retro CS</td><td>12% overall</td><td></td><td></td><td>+SM rates 20% in 1983-1988; 10.5% since 1995</td></tr>
</table>

<table>
<tr><th rowspan="2">Study</th><th rowspan="2">Surgical Type Stage</th><th rowspan="2">Study Design</th><th colspan="3">Positive Margin (%)</th><th rowspan="2">Other</th></tr>
<tr><th>Overall</th><th>By Stage</th><th>By Location</th></tr>
<tr><td>Freedland (2003) (77)
N=1621</td><td>RP
cT1-3
Gleason 2-10</td><td>Retro
CS</td><td>25%;</td><td></td><td></td><td>+SM & no seminal vesicle invasion (n=402):
53% no ECE

With ECE (n=300):
37% with -SM</td></tr>
<tr><td>Swindle (2005) (14)
N=1389</td><td>RP
cT1-3
Gleason 2-10</td><td>Retro
CS</td><td>12.9 overall</td><td>% positive surgical margins by clinical and pathological stage
Stage | % (N)
cT1a | 0
cT1b | 26.4 (14)
cT1c | 11.2 (55)
cT2a | 9.2 (24)
cT2b | 14.3 (46)
cT2c | 15.3 (23)
cT3 | 22.4 (22.4)
Gleason 2-6 | 10.9 (110)
Gleason 7 (3+4) | 12.1 (31)
Gleason 7 (4+3) | 18.6 (13)
Gleason 8-10 | 33.3 (24)
pT2 | 6.8% (58/847)
pT3 | 23% (121/522)</td><td></td><td>+SM rate for pT3a:
31.7% before 1990
11.1% after 2000</td></tr>
<tr><td>Palisaar (2005) (25)
N=1343</td><td>RRP
BLNS; ULNS; NNS
cT1c-3
pT2-3b</td><td>Retro
CS</td><td>NS: 15.1%
NNS: 25.0%</td><td>Overall positive margins:
pT2: 10.6%
pT3a: 26.9%
pT3b: 36.7%
pT4: 44.4%

% positive margins
pT2 | NS | 6.5
NNS | 5.1
pT3a | NS ECE | 24.0
NS Non-ECE | 4.2
NNS ECE | 24.7
NNS Non-ECE | 3.4
pT3b | NS | 15.0
NNS | 25.1</td><td>Location of positive surgical margins in relation to pT stage and surgical procedure for each prostate lobe separately
pT2: NS 843; NNS 669; p
pT3a: NS 174; NNS 510; p
pT3b: NS 80; NNS 338; P
Apex | 15 (1.8%) | 21 (3.1%) | 0.091 | 6 (3.4%) | 43 (8.4%) | 0.039 | 3 (3.8%) | 21 (6.2%) | 0.593
Lateral | 26 (3.1%) | 4 (0.6%) | 0.001 | 8 (4.6%) | 20 (3.9%) | 0.662 | 3 (3.8%) | 11 (3.3%) | 0.737
Others | 14 (1.7%) | 9 (1.3%) | 0.677 | 4 (2.3%) | 25 (4.9%) | 0.191 | 6 (7.6%) | 53 (15.7%) | 0.073</td><td></td></tr>
</table>

<table>
<tr><th rowspan="2">Study</th><th rowspan="2">Surgical Type Stage</th><th rowspan="2">Study Design</th><th colspan="3">Positive Margin (%)</th><th rowspan="2">Other</th></tr>
<tr><th>Overall</th><th>By Stage</th><th>By Location</th></tr>
<tr><td>Orvieto (2006) (24)
N=996</td><td>RRP
cT1b-2b
Gleason 3-10</td><td>Retro CS Cohort</td><td>8.8%</td><td><table><tr><td>pT2</td><td>1.7%</td></tr><tr><td>pT3a</td><td>24.2%</td></tr><tr><td>pT3b</td><td>27.1%</td></tr></table></td><td></td><td>A significant decrease in:
+SM rates over time in patients with ECE
OR= 0.77, 0.67-0.89
P< 0.001
+SM rates over time in patients with OC disease
OR= 0.66, 0.45-0.95
P= 0.027)</td></tr>
<tr><td>Berger (2002) (78)
N=845</td><td>RRP</td><td>Cohort</td><td>13%</td><td></td><td></td><td></td></tr>
<tr><td>Kausik (2002) (30)
N=842</td><td>pT3a/b NOMO, excluded pre & postop therapy</td><td>Retro CS</td><td>n= 354, 42%

≥ 2 +SM = 13%</td><td></td><td><table><tr><td colspan="5">Site of positive surgical margins</td></tr><tr><td># +SM</td><td>Site</td><td>No. pts.</td><td>Overall</td><td>+SM %</td></tr><tr><td>1</td><td>Overall</td><td>243</td><td>29</td><td>69</td></tr><tr><td></td><td>Apex</td><td>83</td><td>10</td><td>23</td></tr><tr><td></td><td>Base</td><td>21</td><td>2.5</td><td>6</td></tr><tr><td></td><td>Posterior</td><td>135</td><td>16</td><td>38</td></tr><tr><td></td><td>Anterior</td><td>4</td><td>0.5</td><td>1.2</td></tr><tr><td>≥ 2</td><td></td><td>111</td><td>13</td><td>31</td></tr></table></td><td></td></tr>
<tr><td>Marcovich (2000) (27)
N=751</td><td>BNS RRP (n=222), Std. RRP (n=529) pT2-4</td><td>Retro CS</td><td>27% in standard surgeries

28% in BNS surgeries</td><td><table><tr><td>% pos▫tive margins</td><td>BNS</td><td>standard</td></tr><tr><td>T2</td><td>19.5</td><td>19.4</td></tr><tr><td>T3a</td><td>46.7</td><td>19.6</td></tr><tr><td>T3b</td><td>52.2</td><td>50.0</td></tr><tr><td>T3c</td><td>36.4</td><td>48.6</td></tr><tr><td>T4</td><td>100</td><td>85.7</td></tr></table></td><td>Site of the positive margin was adjacent to or at the bladder neck in:
7% of standard RRP
22% of BNS</td><td>pT3a cancers:
BNS surgery had significantly higher rates of +SM
47% vs. 20%
chi-square = 6.32
P= 0.01</td></tr>
<tr><td>Sofer (2002) (19)
N=734</td><td>RRP
Stage <cT3cN0 M0</td><td>Retro CS</td><td>29%
75% one +SM
20% two +SM
5% > 2 +SM</td><td><table><tr><td colspan="2">Characteristics of patents with positive margins (N=210)</td></tr><tr><td>Gleason 2-6</td><td>65 (31%)</td></tr><tr><td>Gleason 7</td><td>87 (41%)</td></tr><tr><td>Gleason 8-10</td><td>58 (27%)</td></tr><tr><td>T1</td><td>126 (60%)</td></tr><tr><td>T2</td><td>82 (39%)</td></tr><tr><td>T3</td><td>2 (1%)</td></tr><tr><td>NS</td><td>58 (28%)</td></tr></table></td><td><table><tr><td colspan="3">Location of positive margins</td></tr><tr><td rowspan="8">Single margin</td><td>Apex</td><td>45%</td></tr><tr><td>Posterolateral</td><td>17%</td></tr><tr><td>Posterior</td><td>15%</td></tr><tr><td>Anterior</td><td>12%</td></tr><tr><td>Bladder neck</td><td>5.7%</td></tr><tr><td>Lateral</td><td>5%</td></tr><tr><td rowspan="3">Multiple margins</td><td>Bladder neck + 1 other +SM</td><td>7%</td></tr><tr><td>Bladder neck + 3 or more +SM</td><td>5.1%</td></tr><tr><td>Total with a positive bladder neck margin</td><td>17.8%</td></tr></table></td><td></td></tr>
</table>

<table>
<tr><th rowspan="2">Study</th><th rowspan="2">Surgical Type Stage</th><th rowspan="2">Study Design</th><th colspan="3">Positive Margin (%)</th><th rowspan="2">Other</th></tr>
<tr><th>Overall</th><th>By Stage</th><th>By Location</th></tr>
<tr><td>Sofer (2002) (31)
N=734</td><td>RRP
Stage <cT3cN0 M0</td><td>Retro CS</td><td>Nerve-sparing (NS): 24%

Non-nerve-sparing (NNS): 31%</td><td></td><td><table><tr><td>Location</td><td colspan="3">NS Surgery</td></tr><tr><td></td><td>Any (%)</td><td>None (%)</td><td>Overall</td></tr><tr><td>Apex</td><td>38</td><td>32</td><td>34</td></tr><tr><td>Posterolateral</td><td>14</td><td>13</td><td>13</td></tr><tr><td>Posterior</td><td>10</td><td>12</td><td>11</td></tr><tr><td>Anterior</td><td>9</td><td>9</td><td>9</td></tr><tr><td>Other</td><td>29</td><td>35</td><td>33</td></tr></table></td><td>No evidence of higher +SM rate with NS surgery.</td></tr>
<tr><td>Fesseha (1997) (79)
N=590</td><td>RRP</td><td>Retro CS</td><td>36.8% with +SM and/or ECE</td><td></td><td>5.5% had an apical positive margin in an otherwise prostate confined tumour.</td><td></td></tr>
<tr><td>Salomon (2003) (26)
N=538</td><td>Radical
cT1a-2b
Gleason 2-10
pT2a-3b</td><td>Retro CS</td><td>26.6%</td><td>pT2 (n=371):
Overall:17.8%
Solitary positive margin: 16.1%</td><td>Apex: 31.4%
Bladder neck: 20.9%
Posterolateral: 32.1%
Multiple: 15.3%

<table><tr><td colspan="4">Location of margin by stage for pT2 patients</td></tr><tr><td>Stage</td><td>Apex N=26</td><td>Bladder Neck N=14</td><td>Posterolateral N=20</td></tr><tr><td>cT1a+b</td><td>2 (8%)</td><td>1 (7%)</td><td>0</td></tr><tr><td>cT1c</td><td>13 (50%)</td><td>7 (50%)</td><td>17 (85%)</td></tr><tr><td>cT2a</td><td>11 (43%)</td><td>5 (36%)</td><td>3 (15%)</td></tr><tr><td>cT2b</td><td>0</td><td>1 (7%)</td><td>0</td></tr><tr><td>Gleason 2-4</td><td>4 (15%)</td><td>5 (36%)</td><td>3 (15%)</td></tr><tr><td>Gleason 5-6</td><td>16 (62%)</td><td>8 (57%)</td><td>13 (65%)</td></tr><tr><td>Gleason 7-10</td><td>6 (23%)</td><td>1 (7%)</td><td>4 (20%)</td></tr><tr><td>pT2a</td><td>1 (3.8%)</td><td>2 (14%)</td><td>1 (5%)</td></tr><tr><td>pT2b</td><td>25 (96%)</td><td>12 (86%)</td><td>19 (95%)</td></tr></table></td><td></td></tr>
<tr><td>Lepor (2004) (80)
N=500</td><td>RRP
cT1a-2</td><td>Retro CS</td><td></td><td></td><td>Apex: 21 cases; 2 (9.5%) occurred with +SM at other sites.</td><td>Intraoperative biopsy of the apical soft-tissue margin reduced +SM by 3.8%</td></tr>
<tr><td>Pettus (2004) (34)
N=498</td><td>RRP
pT2-3a N0, SV-
No adjacent organ involvement</td><td>Retro CS</td><td>Overall: 19.7%</td><td></td><td><table><tr><td colspan="6">Positive margin location by stage</td></tr><tr><td></td><td colspan="4">Margin status stratification</td><td rowspan="2">p</td></tr><tr><td></td><td>-SM (%)</td><td>+AM (%)</td><td>+OM (%)</td><td>+MM (%)</td></tr><tr><td>Overall</td><td>400 (80)</td><td>28 (5.6)</td><td>57 (11)</td><td>13 (2.6)</td><td></td></tr><tr><td>Gleason 2-4</td><td>66 (18)</td><td>5 (21)</td><td>7 (13)</td><td>3 (25)</td><td rowspan="3">0.97</td></tr><tr><td>Gleason 5-6</td><td>228 (61)</td><td>13 (54)</td><td>35 (66)</td><td>5 (42)</td></tr><tr><td>Gleason 7</td><td>64 (17)</td><td>5 (21)</td><td>10 (19)</td><td>4 (33)</td></tr></table></td><td></td></tr>
</table>

Study	Surgical Type Stage	Study Design	Positive Margin (%)			Other
			Overall	By Stage	By Location	
					Gleason 8-10: 17 (4) / 1 (4) / 1 (2) / 0 T1: 169 (43) / 12 (44) / 20 (37) / 6 (50) 0.86 T2: 219 (56) / 15 (56) / 34 (63) / 6 (50) T3: 2 (1) / 0 / 0 / 0	
Cannon (2005) (50) N=402	RRP Median PSA =5.5 ng/ml	Retro CS	5.6% with perineural invasion 6.4% without perineural invasion.			Of patients (n=61) with NS on the side of the PNI: only 1 had a +SM. Of patients (n=11) with NS on the side of PNI: none had +SM on that side. +SM rate on the side of the PNI: 2% 0% with NS Of those with PNI who had BLNS (n=57): 4 had +SM PNI alone is not associated with +SM.
Rapp (2005) (9) N=403	RRP cT1c Gleason 3-9 pT2-3b	Retro CS	4% of patients with an abnormal IOPE 5% in patients with a normal IOPE.		With extraprostatic extension at NVB: 23% In different location: 14%	IOPE revealed a palpable abnormality in NVB not previously detected in 12%. 37% of these had an extraprostatic extension at the site of the abnormality. 2% of these had +SM 2% had apical +SM
Cohn (2002) (21) N=382	RRP cT1c (27%) cT2 (73%)	Retro CS	9% 7% in last four years 4% in most recent year	pT3a: 39% pT3b: 12.5%	Apex: 41% Lateral positivity: 38% Posterior positivity: (9%) Anterior positivity: 6% Bladder neck: 6%	Patients: pT2 (71%) pT3a (20%) pT3b (5%) pT4a (3%) pT3aN1+pT4aN1 1% 52% of patients had BLNS 27% of patients had ULNS

Study	Surgical Type Stage	Study Design	Positive Margin (%)			Other
			Overall	By Stage	By Location	
Emerson (2005) (81) N=369	RRP	Retro CS	23%			Extent: mean 6.76 (0.01 to 68) mm For margin positive patients: Gleason 5-9 pT2a-3b
Cheng (2000) (82) N=339	RRP cT1c-3 pT2a-T3b Gleason 3-9	Retro CS	24%			Patients with: serum PSA < 4 ng/ml <10% cancer in biopsy 14% risk of +SM Patients with: serum PSA > 20 ng/ml >40% cancer in biopsy 79% risk of +SM Significant independent predictors of margin status: preoperative PSA (P<0.001) percentage of cancer in biopsy: (P<0.001)
Graefen (1998) (22) N=289	Unilateral Nerve-sparing RRP cT1-2 pT2-3c	Retro CS	15.9%	(N) / NNS (220) % / NS (69) % pT2 / 1.5 / 0 pT3a / 39.5 / 37.0 pT3b / 71.4 / 0 pT3c / 39.7 / 16.7		Only 3 patients (4.3%) had a positive margin on the NS side.
Vis (2006) (20) N=281	RRP pT2-4 Gleason 2-10	Retro CS	23.5%	Positive margins by stage Stage / +SM % pT2 / 18.0 pT3a / 36.7 pT3b-4 / 47.6 Gleason 2-6 / 17.0 Gleason 7 / 30.3 Gleason 8-10 / 71.4	9.3% (or 39.4% of those with positive margins) had positive margin at the apex only	

<table>
<tr><th>Study</th><th>Surgical Type Stage</th><th>Study Design</th><th colspan="3">Positive Margin (%)</th><th>Other</th></tr>
<tr><th></th><th></th><th></th><th>Overall</th><th>By Stage</th><th>By Location</th><th></th></tr>
<tr><td>Rabbani (1998) (13)
N=242</td><td>BNS-RRP
cT1a-2c
Gleason 2-10
Bilateral NS: 62%
Unilateral NS : 16%
NNS: 13%
Unknown: 9%</td><td>Retro CS</td><td>36%
Of these, 69% were solitary sites</td><td colspan="2">
Positive margins by stage and location
<table>
<tr><th rowspan="2">Stage</th><th rowspan="2">No. +SM (%)</th><th colspan="6">Number of positive margins</th></tr>
<tr><th>Apex</th><th>Bladder Neck</th><th>Left Posterior</th><th>Right Posterior</th><th>Left Anterior</th><th>Right Anterior</th></tr>
<tr><td>cT1a/b/c</td><td>44 (37)</td><td>20</td><td>5</td><td>15</td><td>11</td><td>3</td><td>5</td></tr>
<tr><td>cT2a</td><td>8 (22)</td><td>3</td><td>2</td><td>2</td><td>3</td><td>1</td><td>0</td></tr>
<tr><td>cT2b</td><td>26 (38)</td><td>9</td><td>8</td><td>10</td><td>8</td><td>3</td><td>3</td></tr>
<tr><td>cT2c</td><td>8 (44)</td><td>5</td><td>0</td><td>5</td><td>2</td><td>1</td><td>2</td></tr>
<tr><td>Gleason 2-4</td><td>4 (22)</td><td>1</td><td>1</td><td>1</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Gleason 5-7</td><td>74 (36)</td><td>32</td><td>12</td><td>31</td><td>20</td><td>6</td><td>7</td></tr>
<tr><td>Gleason 8-10</td><td>6 (40)</td><td>4</td><td>1</td><td>0</td><td>3</td><td>2</td><td>2</td></tr>
<tr><td>pT2a</td><td>2 (10)</td><td>0</td><td>0</td><td>0</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>pT2b</td><td>3 (21.4)</td><td>2</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>pT2c</td><td>32 (24.2)</td><td>17</td><td>2</td><td>10</td><td>4</td><td>2</td><td>2</td></tr>
<tr><td>pT3a</td><td>27 (64.3)</td><td>11</td><td>0</td><td>13</td><td>6</td><td>3</td><td>3</td></tr>
<tr><td>pT3b</td><td>4 (80)</td><td>2</td><td>0</td><td>2</td><td>2</td><td>1</td><td>2</td></tr>
<tr><td>pT3c</td><td>4 (40)</td><td>1</td><td>1</td><td>3</td><td>3</td><td>0</td><td>0</td></tr>
<tr><td>pT4a</td><td>14 (93.3)</td><td>4</td><td>12</td><td>4</td><td>6</td><td>2</td><td>3</td></tr>
</table>

Isolated positive margins by stage and location
<table>
<tr><th rowspan="2">Stage</th><th rowspan="2">No. +SM (5)</th><th colspan="6">Number of isolated positive margins</th></tr>
<tr><th>Apex</th><th>Bladder neck</th><th>Left posterior</th><th>Right posterior</th><th>Left anterior</th><th>Right Anterior</th></tr>
<tr><td>cT1a/b/c</td><td>35 (80)</td><td>14</td><td>2</td><td>9</td><td>8</td><td>1</td><td>1</td></tr>
<tr><td>cT2a</td><td>5 (63)</td><td>1</td><td>1</td><td>2</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>cT2b</td><td>16 (62)</td><td>4</td><td>2</td><td>6</td><td>3</td><td>1</td><td>0</td></tr>
<tr><td>cT2c</td><td>3 (38)</td><td>2</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Gleason 2-4</td><td>4 (100)</td><td>1</td><td>1</td><td>1</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Gleason 5-7</td><td>51 (69)</td><td>19</td><td>3</td><td>17</td><td>10</td><td>2</td><td>0</td></tr>
<tr><td>Gleason 8-10</td><td>2 (33)</td><td>1</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>pT2a</td><td>2 (100)</td><td>0</td><td>0</td><td>0</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>pT2b</td><td>3 (100)</td><td>2</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>pT2c</td><td>28 (88)</td><td>14</td><td>2</td><td>8</td><td>3</td><td>1</td><td>0</td></tr>
<tr><td>pT3a</td><td>20 (74)</td><td>5</td><td>0</td><td>9</td><td>4</td><td>1</td><td>1</td></tr>
<tr><td>pT3b</td><td>1 (25)</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>pT3c</td><td>2 (50)</td><td>0</td><td>0</td><td>1</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>pT4</td><td>3 (21)</td><td>0</td><td>3</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
</table>
</td><td></td><td>Patients with:
3 ≤ positive cores
no neoadjuvant androgen deprivation therapy
had higher (24%) incidence of +SM

Patients with:
PSA > 10ng/ml
Higher (16%) incidence of +SM at bladder neck

When stratified by clinical stage:
no significant difference in apical +SM for BLNS, ULNS, or NNS</td></tr>
<tr><td>Hsu (2007) (83)
N=200</td><td>Radical Unilateral cT3 disease</td><td>Retro CS</td><td>33.5</td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th rowspan="2">Study</th><th rowspan="2">Surgical Type Stage</th><th rowspan="2">Study Design</th><th colspan="3">Positive Margin (%)</th><th rowspan="2">Other</th></tr>
<tr><th>Overall</th><th>By Stage</th><th>By Location</th></tr>
<tr><td>Lowe (1996) (42)
N=188</td><td>BNS, bladder neck resecting
Clinical stage A2-B2</td><td>Pro CS</td><td>10.2% after bladder neck resection

16.7% after BNS</td><td></td><td></td><td></td></tr>
<tr><td>Lee (2006) (48)
N=169</td><td>RRP
pT2a-3b</td><td>Retro CS</td><td>21%</td><td></td><td></td><td></td></tr>
<tr><td>Aydin (2004) (33)
N=164</td><td>RRP
T1a-3a</td><td>Retro CS</td><td></td><td></td><td>
<table>
<tr><th>Stage</th><th>Bladder neck positive %</th><th>Bladder neck negative %</th></tr>
<tr><td>T1a</td><td>2.6</td><td>-</td></tr>
<tr><td>T1b</td><td>-</td><td>5.6</td></tr>
<tr><td>T1c</td><td>71.0</td><td>23.0</td></tr>
<tr><td>T2a</td><td>13.2</td><td>44.4</td></tr>
<tr><td>T2b</td><td>7.9</td><td>20.6</td></tr>
<tr><td>T2c</td><td>2.6</td><td>5.6</td></tr>
<tr><td>T3a</td><td>2.6</td><td>0.8</td></tr>
<tr><td>Total</td><td>100</td><td>100</td></tr>
</table>
</td><td>Study of patients with positive margins.

Of +SM patients:
23.2% had bladder neck +SM</td></tr>
<tr><td>Deliveliotis (2002) (29)
N=149</td><td>RRP
Gleason ≤7
cT1-2</td><td>Retro CS</td><td>Group 1: 21%
Group 2: 18%
Group 3: 22%</td><td></td><td>
<table>
<tr><th colspan="4">Margin Positive status among groups</th></tr>
<tr><th></th><th>BNS (%)</th><th>PLS (%)</th><th>Both (%)</th></tr>
<tr><td>Overall</td><td>21</td><td>18</td><td>22</td></tr>
<tr><td>Bladder neck</td><td>6</td><td>2</td><td>4</td></tr>
<tr><td>Bladder neck only</td><td>2</td><td>0</td><td>2</td></tr>
<tr><td>Apex</td><td>6</td><td>4</td><td>8</td></tr>
<tr><td>Apex only</td><td>0</td><td>2</td><td>4</td></tr>
</table>
</td><td>Group 1: BNS (N=48)
Group 2: PLS (N=51)
Group 3: Both (N=50)</td></tr>
<tr><td>Alsikafi (1998) (15)
N=144</td><td>RRP
T1b-2c
Gleason 2-9</td><td>Retro CS</td><td>11.1%</td><td>T1: 10.3%
T2: 12.0%

0%: Gleason 2-4
14.6%: Gleason 5-6
7.9%: Gleason 7-9</td><td>Apex: 35%
Posterolateral: 40%
Anterior: 15%
Bladder neck: 10%</td><td>45% of patients had organ-confined disease.

Positive margins:
Focal: 8%
Extensive: 3%

NVB surgery more often in men with high grade disease.</td></tr>
<tr><td>Salomon (2003) (10)
N=137
Adult Urology</td><td>RRP
pT3bNOM0</td><td>Retro CS</td><td>45.2%</td><td></td><td></td><td></td></tr>
</table>

Study	Surgical Type Stage	Study Design	Positive Margin (%)			Other
			Overall	By Stage	By Location	
Richman (2005) (18) N=100	RRP cT1-2 Gleason 6-10 pT2a-3b	Retro CS	13%	Positive margin by stage pT2a: 0/11 (0%) pT2b: 9/69 (13.0%) pT3a: 6/17 (35.3%) pT3b: 1/3 (33.3%) Gleason 6: 2/43 (4.7%) Gleason 7: 8/47 (17.0%) Gleason 8-10: 3/10 (30%) Low (pT2, Gleason 6): 1/40 (2.5%) Moderate (pT2, Gleason 7): 5/36 (14%) High (pT3 or Gleason ≥8: 7/24 (29.2%)	Apex: 10% Base/bladder neck 2% Posterolateral: 1% Site of capsular penetration: 0%	All performed by one surgeon.
LAPAROSCOPIC SURGERY						
Guillonneau (2002) (11) N=550	LRP, <cT2b, Gleason 2-8	Retro CS	16.7%	pT2a: 3.3% pT 2b: 15% pT3a: 33% pT3b: 47%		
Guillonneau (2003) (12) N=1000	LRP, cT1a-2b, Gleason 2-10	Retro CS		Positive margin by stage % cT1a: 33 cT1b: 0 cT1c: 16 cT2a: 14 cT2b: 41 pT2aN0/Nx: 6.9 pT2bN0/Nx: 18.6 pT3aN0/Nx: 30 pT3bN0/Nx: 32 pT1-3N1: 67 Gleason Score 2-4: 0 5-6: 15 7: 21 8-10: 30	Apex: 50% Posterolateral: 30% Prostate base: 20%	

<table>
<tr><th rowspan="2">Study</th><th rowspan="2">Surgical Type Stage</th><th rowspan="2">Study Design</th><th colspan="3">Positive Margin (%)</th><th rowspan="2">Other</th></tr>
<tr><th>Overall</th><th>By Stage</th><th>By Location</th></tr>
<tr><td>Martinez-Pineiro (2006) (23) N=604</td><td>LRP, T1-3, Gleason 5-9</td><td>Pro CS</td><td></td><td>pT2 19.2%
pT3 53.2%
pT4 75%

cT1: 26.7%
cT2-3: 37.8%</td><td>Location of positive margin
Stratified by surgical technique
<table><tr><th>Location</th><th>Combined technique %</th><th>Descending Technique%</th><th>Total %</th></tr><tr><td>Postero-lateral</td><td>9.0</td><td>12.5</td><td>40.3</td></tr><tr><td>Apical</td><td>11.4</td><td>6.7</td><td>26.1</td></tr><tr><td>Combined -multiple</td><td>12.3</td><td>4.1</td><td>19.8</td></tr><tr><td>Anterior</td><td>4.1</td><td>1.2</td><td>6.2</td></tr><tr><td>Bladder neck</td><td>0.8</td><td>2.1</td><td>6.2</td></tr><tr><td>Seminal vesicle</td><td>-</td><td>0.4</td><td>1.1</td></tr><tr><td>Total</td><td>37.7</td><td>27.1</td><td>29.3</td></tr></table></td><td>Over time, most surgeons showed:
a reduction of +SM in pT2
no change in pT3-4
fewer isolated posterolateral positive margins
more isolated apical margins with time.</td></tr>
</table>

Notes: AM = apical margin; BLNS = bilateral nerve-sparing; BNS = bladder neck sparing; CI = confidence interval; ECE = extracapsular extension; IOPE = intraoperative prostate exam; LRP = laparoscopic radical prostatectomy; MM = multiple positive margins; N = number; N+ = node positive; N- = node negative; N0M0 = negative nodes no metastases; NNS = non-nerve-sparing; NS = nerve-sparing; NVB = neurovascular bundles; OC = organ confined; OM = non-apical isolated margin; OR = Odds Ratio; PNI = perineural invasion; Pro CS = prospective case series; PSA = prostate specific antigen; PLS = puboprostatic ligament sparing ; Retro CS = retrospective case series; RP = radical prostatectomy; RPP = radical perineal prostatectomy; RRP = radical retropubic prostatectomy; +SM = positive surgical margin; -SM = negative surgical margin; SV- = no seminal vesicle involvement; ULNS = unilateral nerve sparing.

Appendix 3. Table 3. Studies reporting surgical complications for radical prostatectomy.

<table>
<tr><th>Study</th><th>N</th><th>Study Design</th><th>Surgical Method</th><th>Urinary Function (% incontinent) Continence definition</th><th>Erectile Function %</th><th>Rectal Injury (RI) Blood Transfusion (BT) %</th><th>Other Postoperative Complications</th></tr>
<tr><td colspan="8">OPEN</td></tr>
<tr><td>Begg (2002) (36)</td><td>10,737</td><td>Retro CS (SEER data)</td><td>RP</td><td>At 24 months:
Severe incontinence: 11%

Severe incontinence: leakage or absence of urinary control occurring more than twice per day, plus a response to questionnaire that this represented a “big” or “moderate” problem.</td><td></td><td></td><td>Surgery related death: 0.5% at 30 days.
Rates varied significantly among surgeons in:
postop complications (p≤ 0.001)
late urinary complications (p≤ 0.001)
long-term incontinence (p≤ 0.001).</td></tr>
<tr><td>Kundu (2004) (37)</td><td>3477</td><td>Retro CS</td><td>RRP</td><td>7%
0.3% underwent placement of an artificial urinary sphincter because of severe stress incontinence.

Continence: At a minimum of 18 months, patients did not require pads or other protection to keep outer garments dry.</td><td>BLNS surgery:76%
ULNS surgery: 53%</td><td></td><td>Perioperative mortality: 0%
Postoperative complications: 9% excluding impotence
Anastomotic stricture: 2.7%.
Inguinal hernia: 2.5%
Thromboembolism: 1.3%

Overall the complication rate reduced significantly by era:
1983-1991:16.9%
1992-2003:7.4%

All surgeries performed by one surgeon</td></tr>
<tr><td>Catalona (1999) (40)</td><td>1870</td><td>Retro CS</td><td>RRP</td><td>92% recovered urinary continence at 18 months.
<table>
<tr><th>Age</th><th>% Incontinent</th></tr>
<tr><td>40-49</td><td>8</td></tr>
<tr><td>50-59</td><td>3</td></tr>
<tr><td>60-69</td><td>8</td></tr>
<tr><td>70+</td><td>13</td></tr>
<tr><td>Total</td><td>8</td></tr>
</table></td><td>
<table>
<tr><th>Age</th><th>BLNS %</th><th>ULNS %</th><th>Total %</th></tr>
<tr><td>40-49</td><td>91</td><td>50</td><td>90</td></tr>
<tr><td>50-59</td><td>82</td><td>33</td><td>80</td></tr>
<tr><td>60-69</td><td>61</td><td>51</td><td>60</td></tr>
<tr><td>70+</td><td>48</td><td>40</td><td>47</td></tr>
<tr><td>Total</td><td>68</td><td>47</td><td>66.5</td></tr>
</table></td><td>RI: 0.05%</td><td>Perioperative mortality: 0%
Post operative complications excluding impotence and urinary incontinence:10%
Anastomotic stricture: 4%
Thromboembolic: 2%
Inguinal hernia: 1%</td></tr>
<tr><td>Bianco (2005) (38)</td><td>1746</td><td>Retro CS</td><td>RP</td><td>6.7% had long-term incontinence, required surgical procedure</td><td></td><td></td><td>Perioperative death: 0.11% within 30 days
Major postop complications: 28.6%
Late urinary complications: 25.2% (major events 16%)
Cause-specific survival: 89% at 15 years.</td></tr>
</table>

Study	N	Study Design	Surgical Method	Urinary Function (% incontinent) Continence definition	Erectile Function %	Rectal Injury (RI) Blood Transfusion (BT) %	Other Postoperative Complications
Lance (2001) (45)	1698	Retro CS	RRP (N=1382) RPP (N=316)	RRP: 40.1% RPP 35.2% P= 0.34	RRP 91.1% RPP 91.8%	RI: Higher rate in RPP vs. RRP (p=0.01) BT: Non-homologous transfusion: RRP: 1.4% RPP: 9.5%	No differences between RRP vs. RPP for: Incontinence Impotence bladder neck contracture short term complication rates
Bianco (2005) (52)	1472	Retro CS (SEER data)	RRP	9% at 12 months 5% at 24 months	63% by 18months 70% by 24 months Median time to recovery of erectile function: 12 months.		Perioperative death: 0.11% At 24 months: 60% were potent, continent, and cancer-free 28% were cancer-free but not potent or continent 12% had experienced recurrence or received other treatments for their disease.
Orvieto (2006) (24)	977	Retro CS	RRP				Symptomatic BNC: 3% of patients. Continence rate at 12 months: 58% with BNC 77% without BNC p= 0.01
Burkhard (2006) (41)	536	Retro CS	RRP	At one year: 5.8% Grade I stress incontinence: 5.0% Grade II stress incontinence: 0.8% Grade III stress incontinence: 0 Artificial sphincter implantation: 0 Grade I: requiring 1-2 pads daily Grade II: 4-8 pads daily Incontinence by surgical technique: BLNS 1.3% ULNS 3.4% NNS 13.7%			
Nuttall (2002) (49)	438	Retro CS	RRP			BT: Allogenic RBC transfusion rate: 69% in 1985/6 16.2% in 1990 7.1% in 1999	

Study	N	Study Design	Surgical Method	Urinary Function (% incontinent) Continence definition	Erectile Function %	Rectal Injury (RI) Blood Transfusion (BT) %	Other Postoperative Complications
Cohn (2002) (21)	382	Retro CS	Anatomical RP	18 or more months follow up: Partially continent: 6% Incontinent: 10% (95% CI ± 4) Two or more pads daily: 4% Completely continent: dry, no pads Partially continent: single pad, patient stated they got "damp but not wet" Incontinent: > 1 pad daily.	BLNS: 71% of previously potent patients ULNS: 64% of previously potent patients		2 patients died of prostate cancer.
Maffezzini (2003) (46)	300	Retro CS	Anatomical RRP	Median followup 29 months: Overall: 11.2% Stress incontinence: 8.8% Incontinent: 2.3% Stress incontinence: 1-3 pads per day. Incontinent: 4 or more pads per day.		RI: 0.3% BT: Autologous: first 12% Allogenic: on the basis of hematocrit levels of 28%, 10.6% Median number of blood units transfused: 3 (1-6)	Perioperative mortality: 0% Overall intraoperative and early postoperative complication rate: 6.3%. Surgical repair required: 1% of cases. Second intervention: 1.7% of cases. Left obturator nerve severed: 0.3%. Complete section right pelvic ureter: 0.3%. Pulmonary embolism: 0.3% Lymphocele 1.0%
Lowe (1996) (42)	188	Pro CS	Bladder neck preservation vs. bladder neck resection	At 1 year: with bladder neck resection 13.7% with bladder neck preservation 10.6% Continence was classified as total if the patient wore no protective pads or tissues and did not change underwear because of wetness. Incontinence was defined as any degree of loss of urinary control sufficient to require the patient to use some form of protection.			
Lee (2006) (48)	169	Retro CS	RRP	20% Most use one pad/day or occasionally		BT: 23% averaged 2.13 (1-7) units of packed RBC	Perioperative mortality: 0% 8% developed complications including: pelvic hematoma ICU for cardiac/respiratory monitoring lymphocele formation clot retention 9% developed PSA recurrence.

Study	N	Study Design	Surgical Method	Urinary Function (% incontinent) Continence definition	Erectile Function %	Rectal Injury (RI) Blood Transfusion (BT) %	Other Postoperative Complications
Deliveliotis (2002) (29)	149	Retro CS	RRP BNS RP PLS RP	At 12 months: BNS: 8% PLS: 8% BNS & PLS: 6% Continent: No need for any pads daily, not even for occasional leakage of a few drops of urine.			
Richman (2005) (18)	100	Retro CS	RP	After 1 year: 6% overall 4% needed one pad/day 2% required 2 pads per day Incontinence defined by number of pads used per day	57% of patients were potent 1 year after surgery. Potency was defined as "erections sufficient for intercourse to your and your partner's satisfaction".		
Tewari (2003) (47)	100	Pro CS	Anatomical RRP		50% return to potency at 440 days	RI: 1% BT: 67%	Lymphocele: 2% Deep vein thrombosis: 1%
Heidenreich (2002) (44)	203	Pro CS	RRP and ascending RRP			RI: 1%	Lymphocele: 9% Deep vein thrombosis: 6% Pulmonary embolism: 2% Myocardial infarction: 2% Pneumonia : 2%
Ponholzer (2006) (39)	552	Cross-sectional Survey	RPE	45.6% (a) 67% (b) 21% 1-3 episode per week 11% reported on a permanent loss of urine. 35.8% of RPE patients used pads. a) Any involuntary loss during the past 4 weeks b)daily episode	Deterioration of sexual life: reported by 94.4% 52% had used medications for ED		Mean follow up time was 3.3 years
Lilleby (1999) (51)	108	Cross sectional survey	RP	Moderate or severe incontinence: 35%	Erectile dysfunction: 48% Psychological distress due to erectile dysfunction: 59%		Patients were evaluated using EORTC QLQ-C30, IPSS, and PAIS.
LAPAROSCOPIC							
Guillonneau (2002) (11)	550	Retro CS	LP	At 12 months: 11.2% incontinent 5.9% severe incontinence Incontinent: one pad per day. Severe incontinence: > 2 pads per day.	-85% recovered spontaneous erections. -66% have experienced intercourse, with 1/3 using sidenafil.	RI: 1.45% BT: 5.27% Regular reduction in transfusion rate with experience	Postoperative death: 0%
OPEN AND LAPAROSCOPIC							

Study	N	Study Design	Surgical Method	Urinary Function (% incontinent) Continence definition	Erectile Function %	Rectal Injury (RI) Blood Transfusion (BT) %	Other Postoperative Complications
Anastasiadis (2003) (43)	300	Retro CS	RRP (N=70) L P (N=230)	At 1 year: Diurnal incontinence: RRP 22.3%, LP 11.0% Nocturnal incontinence: RRP 10.0%, LP 4.0% Continence included: use of pad for precaution without any leakage.	At one year: RRP 30%, LP 41% Preserving one NVB: RRP 27%, LP 46% Preserving both NVB: RRP 44%, LP 53%		Surgical complications: RRP 13.1% LP 9.6% Includes: rectal injury anastomotic leakage wound infection hematoma temporary ileus
Guazzoni (2006) (35)	120	Pro, RCT	Comparison: RRP (N=60) vs. LP (N=60)			RI: 1.7% in LRP BT: Homologous transfusion: 9% in RRP 0% in LRP Autologous transfusion: 45% in RRP 13.3% in LRP	Final Pathology: No differences between RRP and LP

Notes: BLNS = bilateral nerve sparing; BNC = bladder neck constriction; BNS = bladder neck sparing; BT = blood transfusion; CS = case series; LP = laparoscopic prostatectomy; LRP = laparoscopic radical prostatectomy; N = number; NNS = non-nerve-sparing; PLS = Puboprostatic ligament sparing; Pro = prospective; RBC = red blood cell?; RCT = randomized controlled trial; Retro = retrospective; RI = rectal injury; RP = radical prostatectomy; RRP = radical retropubic prostatectomy; RPP= radical perineal prostatectomy; ULNS = unilateral nerve sparing.

Appendix 3. Table 4. Summary of the staging and therapeutic value information found in pelvic lymph node dissection (PLND) studies.

Study (Year) N	Study Design	Stage	PLND Extent	Outcomes	Comments
Open Radical Prostatectomy - Therapeutic Value					
Joslyn (2006) (56) N=9182	Retro CS (SEER database)	Histological grade I-IV SEER code 1-3	None, Extent varied	Cancer specific mortality by number of nodes examined: For all patients: 0: HR=1.00 (ref) 1-3: HR=0.85, CI(0.68-1.06) p=0.1580 4-6: HR=0.77, CI(0.64-0.93) p=0.0069 7-9: HR=0.82, CI(0.67-0.99) p=0.0390 ≥10: HR=0.81, CI(0.70-0.94) p=0.0047 For patients with negative nodes: 0: HR=1.00 (ref) 1-3: HR=0.96, CI(0.76-1..21) p=0.7373 4-6: HR=0.86, CI(0.70-1.05) p=0.1321 7-9: HR=0.87, CI(0.71-1.07) p=0.1957 ≥10: HR=0.85, CI(0.72-0.99) p=0.0382	
Dimarco (2005) (61) N=7036	Retro CS (RRP prostate cancer database)	pT1-3N0 Gleason 2-10	Bilateral, extent varied	Extent not associated with: PSA progression: RR=0.99, CI(0.96-1.02, p=0.90 Systemic progression: RR=0.99, CI(0.96-1.03), p=0.68 Cause-specific survival: RR=1.01, CI(0.96-1.06) (p=0.75)	
Berglund (2007) (55) N=4693	Retro CS (CaPSURE database)	T1-4 Gleason 2-10	Limited bilateral N=3961 None N=732	Failure free survival at 5 years: No PLND 70% Limited PLND 74% (p=0.11) No significance in any of the risk categories	Groups were significantly different in age and disease status.
Masterson (2006) (57) N=4611	Retro RV of Pro CS	T1-3	Extended PLND	Extent to freedom from BCR: Overall: not significant Men with negative nodes: HR 0.91; p=0.01	
Allaf (2004) (58) N=4000	Retro RV	Gleason 4-10 68% organ confined Mean PSA 7.1 Mean PSA for limited: 7.2	Limited (N=1865) Extended (N=2135)	PSA Progression free survival at 5 years: Limited PLND: 16.5% Extended PLND: 34.4% (p=0.07) <15% positive nodes: Limited PLND 10% (95% CI 0.6% to 35.5%) Extended PLND 42.9% (95% CI 28.4% to 56.7%) (p=0.01)	Differences remained after stratification for: Gleason score Organ confined disease Seminal vesicle invasion Surgical margin status

Study (Year) N	Study Design	Stage	PLND Extent	Outcomes	Comments
Fergany (2000) (60) N=575	Retro CS	T1-2	PLND (N=372) no PLND (N=203) PLND type not defined	Biochemical failure at 38 months: Overall: 7% PLND: 8.9% no PLND: 3.4% Estimated biochemical relapse-free survival at 4 years: PLND: 91% no PLND: 97% (p=0.16)	The follow up in the no PLND group was substantially shorter
Bhatta-Dhar (2004) (59) N=336	Retro RV	PSA ≤ 10ng/ml, Gleason ≤ 6, T1-2	PLND N=140; No PLND N=196	Biochemical relapse-free rate at 6 years: PLND: 86% No PLND: 88% (p=0.28)	Complication rate for PLND is about 1%. A greater likelihood of a complication resulting from PLND (1%) than of finding positive lymph nodes (0.7%).
Briganti (2006) (54) N=963	Pro CS	T1c to T3	Extended (≥10 nodes removed) N= 767 Limited (1-9 nodes removed) N=196		Complication rate: Overall: 17.4%. Extended: 19.8% Limited: 8.2% OR 2.7, p<0.001 Lymphocele was higher in ePLND (10.3% vs. 4.6%) Staging benefit should be juxtaposed to complication rates.
Study (Year) N	**Study Design**	**Stage**	**PLND Extent**	**Outcomes**	**Comments**
Staging Value					
Open					
Kawakami (2006) (84) N=4303	Retro CS (CaPSURE database)	D'Amico risk groups T1-4 Gleason 2-10	Not specified	Positive nodes: Low risk 0.87% Intermediate risk 2.0% High risk 7.1%	80% of intermediate risk patients undergo PLND
Allaf (2004) (58) N=4000	Retro RV	Gleason 4-10 68% organ confined Mean PSA 7.1	Limited (N=1865) Extended (N=2135)	Positive nodes found: Limited PLND: 1.2% Extended PLND: 3.3% p<0.0001	Differences remained after stratification for: Gleason score Organ confined disease Seminal vesicle invasion Surgical margin status

Study (Year) N	Study Design	Stage	PLND Extent	Outcomes	Comments
Weckermann (2006) (72) N=474	Retro CS	pT2b to pT4 PSA level ≤10 ng/ml, Gleason ≤6	Radio-guided PLND	Standard PLND would have understaged 4% of patients. 57% of N+ were micrometastases	In group 1, only sentinel lymph nodes were biopsied.
Burkhard (2002) (65) N=463	Pro CS	pT2a to pT4 Median PSA 11.0 µg/l (range 0.42-172 µg/l) Cytological grading 1-3	Meticulous bilateral PLND	7% of patients would have been understaged, left with N+ Comparing preoperative and postoperative grading: 24% undergraded 12% overgraded.	Meticulous PLND required for accurate staging.
Bader (2003) (63) N=367	Pro CS	pT1-pT4 Gleason 2-10	Meticulous PLND	Incidence of N+: 3 times higher for the extended PLND vs. modified Of patients with clinically localized disease: 25% had histologically proven N+	Meticulous PLND: provides accurate staging may impact progression and survival
Bader (2002) (62) N=365	Pro CS	Median PSA 11.9 ng/ml (range 0.4-172 ng/ml)	Open lymph node dissection	Positive nodes in: external iliac vein: 36% obturator fossa: 60% internal iliac vessel:58% 39% would be understaged with limited PLND 19% would be understaged without PLND along the internal iliac vessels	CT imaging has low sensitivity and accuracy for lymph node metastases No preferential site of lymph node metastases Positive nodes in: pT1: 0% pT2a-b: 13% pT3a: 22% pT3b: 52% pT4: 50%
Alagiri (1997) (68) N=303	Retro CS	T1a-3c	Bilateral modified PLND	Unnecessary in vast majority of patients. Predictive of nodal involvement: PSA (P<0.001) Gleason score (P<0.001) Combined (P<0.001)	At a PSA level of ≥ 20 ng/ml, and a Gleason score ≥ 8: Overall accuracy: 91% Positive predictive value: 67% Negative predictive value: 92%.
Weckermann (2005) (71) N=319	Pro CS	PSA ≤ 10ng/ml Gleason ≤ 6,	radio-guided sentinel, Sentinel	52% would be understaged with standard PLND in low risk group. All men with positive lymph nodes also had positive sentinel lymph nodes.	

<table>
<tr><th>Study (Year)
N</th><th>Study Design</th><th>Stage</th><th>PLND Extent</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td>Pagliarulo (2006) (66)
N=274</td><td>Retro CS</td><td>pT3N0
pT3a N=137
pT3b N=137</td><td>extended bilateral PLND</td><td>13.3% of node negative patients were OLN+

21% of these had multiple OLN+</td><td>Recurrence at 10 years:
N+ 69% ±5 RR 2.78
OLN+ 61% ±10 RR 2.27
OLN- 36% ±4 RR 1 (P<0.001)

Overall deaths at 10 years:
N+ 31% ±5 RR 1.40
OLN + 44% ±11 RR 2.07
OLN - 20% ±3 RR 1 (P=0.032)</td></tr>
<tr><td>Heidenreich (2002) (44)
N=203</td><td>Pro CS</td><td>T1c-T3</td><td>103 extended bilateral

100 standard</td><td>Lymph node metastases:
Extended: 26.2%.
Standard: 12%

42% of metastases were outside of the regions of standard PLND

In low risk group : false negative rate of 2.8%.</td><td></td></tr>
<tr><td>Wawroschek (2003) (70)
N=194</td><td>Retro CS</td><td>T1-T4
Gleason 2-9</td><td>Sentinel PLND, followed by modified PLND or extended PLND</td><td>Number of node-positive patients who would have been detected with a PLND limited to the following regions:
<table><tr><th>Region</th><th>Node-positive patients (%)</th></tr><tr><td>Obturator fossa</td><td>44.2 (30.5-58.7)*</td></tr><tr><td>Obturator fossa, external iliac</td><td>65.4 (50.9-78)*</td></tr><tr><td>Obturator fossa, internal iliac</td><td>82.7 (69.7-91.8)**</td></tr><tr><td>Obturator fossa, external and internal iliac</td><td>98 (89.7-100)</td></tr><tr><td>Obturator fossa, external and internal iliac, presacral, pararectal, paravesical</td><td>100 (93.2-100)</td></tr></table>* p< 0.01
** p<0.05</td><td>Extent of PLND was dependent on the preoperative risk factors

No patients in the low-risk group had metastases.

IHC in serial sections histopathological technique found highest percentage of positive nodes, regardless of location</td></tr>
<tr><td>Miyake (2005) (69)
N=178</td><td>Retro CS</td><td>cT1-2,
Gleason 2-10
pT2-4</td><td>Bilateral, external iliac nodes and obturator fossa</td><td>Of 13 N+ patients:
external iliac nodes alone : 53.8%
obturator fossa alone: 30.8%
both: 15.4%
single N+ : 46.2%
For those (n=6) with a single N+:
83.3% located in the external iliac region</td><td>Positive lymph nodes were significantly related to other clinicopathological factors</td></tr>
</table>

<table>
<tr><th>Study (Year)
N</th><th>Study Design</th><th>Stage</th><th>PLND Extent</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td>Clark (2003) (53)
N=123</td><td>Prospective-randomized to either a right or left extended PLND</td><td>T1c-3
Gleason ≤6 (68%)
Gleason 7 (20%)
Gleason ≥ 8 (12%)
PSA > 10ng/ml (84%)
cT1c (72%)</td><td>Extended one side, limited on other side</td><td>Positive nodes found in 6.5% of patients

Lymph node metastases:
4/123 extended
3/123 limited dissections
1 person had positive nodes bilaterally.</td><td>Randomization as to side of extended PLND was performed as there is some laterality to prostate lymphatic drainage.
<table><tr><th>Complication</th><th>EPLND</th><th>Total</th></tr><tr><td>Lymphocele</td><td>3</td><td>4</td></tr><tr><td>Deep venous thrombosis</td><td>2</td><td>2</td></tr><tr><td>Ureteral injury</td><td>1</td><td>1</td></tr><tr><td>Lower extremity edema</td><td>3</td><td>5</td></tr><tr><td>Pelvic abscess</td><td>1</td><td>1</td></tr><tr><td>Total</td><td>10</td><td>13</td></tr></table></td></tr>
<tr><td colspan="6">Laparoscopic</td></tr>
<tr><td>Parra (1996) (64)
N=155</td><td>Retro CS</td><td>cT1a-2c
Low risk: PSA< 10ng/ml and Gleason<7
High risk:
PSA ≥ 10ng/ml.
Gleason ≥ 7</td><td>Modified staging laparoscopic</td><td>27.5% of low risk patients upstaged by PLND</td><td>To select patients who do not require PLND use:
Preoperative PSA
primary tumour grade
local clinical stage</td></tr>
<tr><td colspan="6">Open and Laparoscopic</td></tr>
<tr><td>Rogers (1996) (67)
N=689</td><td>Retro CS</td><td>cT1a-3c
Gleason 2-10</td><td>Modified PLND
Open = 676,
Laparoscopic = 13</td><td>Lymph node metastases increased significantly (P=0.001) with increasing clinical stage.

8% of patients understaged without PLND</td><td>Stage, DRE, PSA, biopsy Gleason sum were not sufficiently sensitive to predict nodal metastases.</td></tr>
</table>

Notes: BCR = biochemical recurrence; N+ = positive nodes; N- = negative nodes; OLN = occult lymph node; OLN+ = positive occult lymph nodes; OLN- = negative occult lymph node; Pro CS = prospective case series; Retro CS = retrospective case series; Retro RV = retrospective review.

Appendix 4. Technical considerations.

a) Technical Considerations for Radical Prostatectomy

- The prostatic apex area is the location with the highest rate of positive resection margins and is also the area where troublesome bleeding may occur. Proper hemostasis with secure control of the dorsal venous complex of the penis and other bleeding sources is crucial as it improves visualization and appreciation of the anatomy and surgical planes, facilitating accurate dissection in order to:
  (a) avoid inadvertent incision into the apex, leading to incomplete excision of all apical prostatic tissue, and compromise of the surgical resection margin.
  (b) avoid injury to the striated sphincter musculature surrounding the urethra at that location, which might lead to urinary incontinence.
  (c) enable optimal preservation of urethral length.
  (d) facilitate preservation of the neurovascular bundles at the apex of the prostate on the dorsolateral aspects of the membranous urethra.
- Clips should be used for hemostasis and the use of electrocautery near the neurovascular bundles should be avoided.
- The site of transection of the urethra should be 1-3 mm beyond the prostatic apex.
- The investing periurethral musculature should be left intact.
- Division of the posterior aspect of the urethra should be followed by sharp dissection of the rectourethralis muscle and remaining attachments of the prostate to the rectum.
- With the retrograde approach, the rectourethralis muscle and remaining attachments of the prostate to the rectum should be sharply and carefully dissected, minimizing the chance of rectal injury, which most commonly occurs during the dissection and division of the posterior aspect of the urethra and manipulation of the prostatic apex with cephalad traction on the specimen.
- There is consensus that seminal vesicle invasion is associated with poorer prognosis; however, tumour involvement of the seminal vesicles most commonly occurs in the proximal one-third of the vesicles in patients with Low Risk tumours.
- Sparing of the tip of the seminal vesicles is not likely to compromise cancer control, and may avoid injury to the pelvic neural plexus that affects erectile function.
- A small amount (5 mm) of bladder neck tissue should be excised with the prostate specimen.
- Absorbable sutures should be used for the urethral-bladder neck anastomosis, which should be tension-free with mucosa-to-mucosa coaptation.

b) Technical considerations for handling and processing the RPS in the laboratory

- In the Pathology Laboratory, the RPS (with or without lymph nodes) is accessioned in the usual fashion.
- The RPS should be fixed (if not done so already) in appropriate volume of neutral buffered formalin (minimum 10:1 ratio). In general, the specimen should be fixed for a minimum of 18-24 hours prior to sectioning. A microwave-assisted technique may be used to reduce fixation time.
- The prostate gland should be weighed and measured in three dimensions; seminal vesicles should be measured; accompanying lymph node specimens should also be measured and a record made of the number and size of grossly identified nodes.
- The outer aspects of the RPS should be carefully inked to identify the surgical margins. Various techniques are suitable. Some pathologists prefer India ink while others use multi-coloured dyes.

- After appropriate fixation and inking, the distal apical segment is transected and then serially sectioned, perpendicular to the inked surface. An en face (shave) technique is to be discouraged at the apex, as this approach can result in false-positive margin interpretation.
- The basal (bladder neck) aspect is commonly doughnut shaped and irregular. It is transected from the main specimen and should also be submitted in a perpendicular fashion to minimize the possibility of a false-positive margin at this location.
- Seminal vesicles may be sectioned in transverse or longitudinal fashion. It is not necessary to block the whole seminal vesicle, although the junction between the seminal vesicle and prostate should be entirely blocked.
- The portion of the RPS between apical and basal aspects should be serially sectioned at 3-5 mm intervals perpendicular to the rectal surface. These sections are carefully examined to identify gross tumour (often not visible in T1c disease). Macroscopic features should be discussed in the pathology report.
- For purposes of tissue submission, the entire apical and basal portions are submitted. The intervening transverse sections can be either totally or subtotally submitted using regular-sized blocks. The submission protocol should be a documented with an appropriate diagramatic or written block legend.
- For subtotal submissions, a systematic approach to include the posterolateral peripheral zone should be used.
- A whole organ sectioning technique is a reasonable alternative to the above-described process.
- All lymph nodes accompanying the RPS should be submitted for histological analysis. It is not necessary to submit all perinodal fat, although it is often difficult to distinguish between adipose tissue and fatty lymph nodes.

Appendix 5. Members of the Expert Panel on Prostate Cancer Surgery and Pathology.

Dr. Joseph Chin, Chair (Surgeon) London Health Science Centre London, Ontario	Dr. Alexander Boag (Pathologist) Kingston General Hospital Kingston, Ontario
Dr. John Srigley (Pathologist) The Credit Valley Hospital Mississauga, Ontario	Mr. Paul Darby, CEO Peterborough Regional Health Centre Peterborough, Ontario
Dr. Bish Bora (Surgeon) Sudbury Regional Hospital Sudbury, Ontario	Dr. Andrew Evans (Pathologist) University Health Network, Toronto General Hospital Toronto, Ontario
Dr. Dimitrios Divaris (Pathologist) Grand River Hospital–Kitchener-Waterloo Health Centre Kitchener, Ontario	Amber Hunter, Program Manager Surgical Oncology Program Cancer Care Ontario Toronto, Ontario
Dr. Neil Fleshner (Surgeon) University Health Network, Princess Margaret Hospital Toronto, Ontario	Dr. John Kell President, Society of Urological Surgery in Ontario Toronto, Ontario
Dr. Angelo Iocca (Surgeon) Royal Court Medical Centre Barrie, Ontario	Dr. Arun Mathur (Surgeon) Oshawa Clinic Oshawa, Ontario
Dr. Bernard Langer, Consultant Cancer Care Ontario Toronto, Ontario	Linda Mayhew, Research Coordinator Program in Evidence-based Care, McMaster University Hamilton, Ontario
Dr. Edward Matsumoto (Surgeon) St. Joseph's Hospital Hamilton, Ontario	Dr. Madeleine Moussa (Pathologist) London Health Sciences Centre London, Ontario
Dr. Tom McGowan (Radiation Oncology) Credit Valley Hospital Mississauga, Ontario	Dr. Linda Rabeneck, RVP Toronto Sunnybrook Regional Cancer Centre Toronto, Ontario
Dr. Christopher Morash (Surgeon) The Ottawa Hospital - Civic Campus Ottawa, Ontario	Dr. Thomas Short (Surgeon) Credit Valley Medical Arts Centre Mississauga, Ontario
Bryan Rumble, Research Coordinator Program in Evidence-based Care, McMaster University Hamilton, Ontario	Dr. John Tsihlias (Surgeon) William Osler Health Centre Etobicoke, Ontario
Eric Winquist (Medical Oncology) London Health Science Centre London, Ontario	Dr. Robin McLeod, Quality Lead Cancer Care Ontario Toronto, Ontario
Dr. Sheila McNair, Assistant Director Program in Evidence-based Care, McMaster University Hamilton, Ontario	

Evidence-Based Series #17-3 Version 2: Section 3

Guideline for Optimization of Surgical and Pathological Quality Performance for Radical Prostatectomy in Prostate Cancer Management: EBS Development Methods and External Review Process

The 2008 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making. See Section 4 for updated references.
The content of Section 3 is the original Development & Review Process from the 2008 guideline and is unchanged.

J. Chin, J. Srigley, L.A. Mayhew, R.B. Rumble, C. Crossley, A. Hunter, N. Fleshner, B. Bora, R. McLeod, S. McNair, B. Langer, A. Evans, and the Expert Panel on Prostate Cancer Surgery and Pathology

A Quality Initiative of the Surgical Oncology Program, Cancer Care Ontario
and the Program in Evidence-based Care, Cancer Care Ontario
A Special Project of the Expert Panel on Prostate Cancer Surgery and Pathology

Report Date: September 11, 2008

THE SURGICAL ONCOLOGY PROGRAM AND THE PROGRAM IN EVIDENCE-BASED CARE COLLABORATION

The Surgical Oncology Program (SOP) and the Program in Evidence-based Care (PEBC) are initiatives of Cancer Care Ontario (CCO). The mandate of the SOP is to improve the delivery of cancer surgery in Ontario through initiatives designed to increase access to care and improve the quality of care through cancer surgery service planning and prediction, supporting the recruitment and retention of cancer surgeons, and facilitating knowledge transfer and evidence-based practice. The mandate of the PEBC is to improve the lives of Ontarians affected

by cancer, through the development, dissemination, implementation, and the evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care. The SOP and PEBC have worked collaboratively on a number of occasions to develop evidence-based materials relevant to the surgical community in Ontario.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

As part of its quality improvement mandate, the SOP convenes expert panels for the selection of quality indicators and the development of clinical guidelines and organizational standards. The panels are comprised of surgeons, other clinicians, health care administrators, other health care professionals, and methodologists and are established on an as-needed basis for specific quality initiatives.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Expert Panel on Prostate Cancer Surgery and Pathology of CCO. See Section 2, Appendix 5 for a complete list of Expert Panel members. The series is a convenient and up-to-date source of the best available evidence on surgical and pathological quality performance for radical prostatectomy in prostate cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Report Approval Panel included:

- Since the recommended rates are aggressive compared with current provincial data, the authors should provide a more explicit rationale for the recommendations for positive margin, rectal injury and blood transfusion rates.

- The authors should provide more background to associate positive margin rates with relevant clinical outcomes, drawing on the clinical reports.
- This document provides clinical recommendations about surgical management when surgical management has been determined to be the best options for the patient. This document is not about what is the best treatment approach for prostate cancer. This is a subtle but very important difference that should be highlighted in the introduction and, more explicitly recognized in the recommendations.
- The role and parameters to be included in the multidisciplinary case conferencing of high-risk patients should be expanded upon.

Modifications in Response to Report Approval Panel Feedback:

- In addition to the evidence review outlined in section 2 of the draft document, a group of urologists and pathologists were invited to participate in a survey and follow-up meeting in October 2007, to obtain feedback and opinions on the draft recommendations developed by the working group. While not a formal consensus process, the details (process and outcomes) of the consultation have been included in the methods and results sections of the revised document.
- A new table was compiled (Appendix 3: Table 1) presenting the evidence of association between positive margin rates and relevant outcomes (recurrence, survival) to support the recommendation for reducing margin rates.
- The title states that this guideline is specific to radical prostatectomy. The wording for the target population and for the first surgical recommendation has been revised to capture the scope of this document.
- The recommendation regarding multidisciplinary case conferencing were expanded to include the processes involved before recommendations to proceed to surgery are given.

External Review by Ontario Clinicians

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and review and approval of the report by the PEBC Report Approval Panel, the Expert Panel on Prostate Cancer Surgery and Pathology circulated Sections 1 and 2 to external review participants in Ontario for review and feedback.

Methods

Feedback was obtained through a mailed survey of 113 external review participants in Ontario (60 urologists, 29 pathologists, 11 surgical leads, eight radiation oncologists, and five medical oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The survey was mailed out on May 28, 2008. Follow-up reminders were sent at four weeks (postcard) and six weeks (complete package mailed again). The Expert Panel on Prostate Cancer Surgery and Pathology reviewed the results of the survey.

Results

Forty-seven responses were received out of the 113 surveys sent (42% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the participants who responded, 38 (81%) indicated that the report was relevant to their practice or organizational position, and they completed the survey. One respondent only answered two questions. Results of the feedback survey are summarized in Table 5.

Table 5. Responses to items on the external review feedback survey.

Item	Number (%)			
	Strongly agree or agree	Neither agree nor disagree	Disagree or disagree strongly	No response/ Not applicable
The rationale for developing a guideline, as stated in the "*Introduction*" section of the draft report, is clear.	34(87)	3(8)		2(5)
There is a need for a guideline on this topic.	30(77)	8(21)		1(3)
The literature search is relevant and complete (i.e., no key trials were missed nor any included that should not have been).	29(74)	8(21)	1(3)	1(3)
I agree with the methodology used to summarize the evidence.	31(80)	5(13)	2(5)	1(3)
The results of the trials described in the draft report are interpreted according to my understanding of the data.	33(85)	5(13)		1(3)
The draft recommendations in the report are clear.	34(87)	3(8)	2(5)	
I agree with the draft recommendations as stated.	30(77)	6(15)	3(8)	
The draft recommendations are suitable for the patients for whom they are intended.	33(85)	3(8)	1(3)	2(5)
The draft recommendations are too rigid to apply to individual patients.	5(13)	7(18)	25(64)	2(5)
When applied, the draft recommendations will produce more benefits for patients than harms.	24(62)	12(31)	2(5)	1(3)
The draft report presents options that will be acceptable to patients.	29(74)	9(23)		1(3)
To apply the draft recommendations will require reorganization of services/care in my practice setting.	7(18)	6(15)	25(64)	1(3)
To apply the draft recommendations will be technically challenging.	5(13)	9(23)	24(62)	1(3)
The draft recommendations are too expensive to apply.	2(5)	7(18)	29(74)	1(3)
The draft recommendations are likely to be supported by a majority of my colleagues.	29(74)	8(21)		2(5)
If I follow the draft recommendations, the expected effects on patient outcomes will be obvious.	16(41)	17(44)	5(13)	1(3)
The draft recommendations reflect a more effective approach for improving patient outcomes than is current usual practice.	10(26)	2(5)	2(5)	3(8) N/A 22(56)
When applied, the draft recommendations will result in better use of resources than current usual practice.	4(10)	2(5)	3(8)	2(5) N/A 28(72)
I would feel comfortable if my patients received the care recommended in the draft report.	32(82)	4(10)	1(3)	2(5)
This draft report should be approved as a practice guideline.	26(67)	10(26)	2(5)	1(3)
If the draft report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Likely or very likely**	**Unsure**	**Not at all likely or unlikely**	
	29(74)	4(10)	4(11)	2(5)
If the draft report were to become a practice guideline, how likely would you be to apply the recommendations to your patients?	32(82)	1(3)	4(10)	2(5)

Summary of Written Comments and Expert Panel Responses

Twenty-four respondents (62%) provided written comments. The main points contained in the written comments are summarized in Table 6.

Table 6. Summary of external review comments and Expert Panel responses.

CLARIFYING RISK STRATIFICATION: One respondent suggested clarifying risk stratification since patients can have a low Gleason score but still be very advanced.
Response: Under Target Population in Section 1 and Definitions used in this Document in Section 2, "and/or" was added to intermediate risk and "or" was added to high-risk definitions.
STANDARD FOR MORTALITY RATES: One respondent requested that mortality rates of <1% should be a standard.
Response: Under surgical recommendations, the last bullet under radical prostatectomy, <1% mortality was added as a goal.
NERVE SPARING: One respondent felt that there are patients with intermediate risk who should not have nerve sparing. (ie. cT2 Gleason 4+3>50%) They suggested to reword the recommendation.
Response: The recommendation under radical prostatectomy (bullet 4) was reworded accordingly.
IMPACT OF POSITIVE SURGICAL MARGINS: One respondent suggested that the report indicate that positive surgical margins have not been demonstrated to directly impact metastasis-free, disease-specific, or overall survival.
Response: Under the Results section, Surgical Questions 1. (first paragraph), a statement was added to indicate the above.
PATIENT PREFERENCES: One respondent commented that patient preferences were not addressed adequately.
Response: Under the recommendations for radical prostatectomy (first bullet), "after full discussion with patient and taking into account patient preferences" was added. In the Introduction (fifth paragraph, 3rd line), "with the patient regarding treatment options" was added.
GOALS OF RADICAL PROSTATECTOMY: One respondent felt that the three goals of radical prostatectomy, cancer control, continence and erectile function, should be encouraged, not just hitting a target positive margin rate.
Response: The three main goals of radical prostatectomy already listed under surgical recommendations were also added to the end of the first paragraph in the Introduction.
MULTIDISCIPLINARY ASSESSMENT: Several respondents were concerned about requiring input from a multidisciplinary team for all high-risk patients considering surgical options.
Response: The recommendation was changed to "The decision to offer surgery to high-risk patients should be made with careful consideration. High-risk patients should be offered a referral for radiation consultation or review at a Multidisciplinary Cancer Conference (MCC)."
TARGET RATES: Given that most contemporary series publish blood transfusion rates of <1%, one respondent commented that this should be the standard, not <10%. Also, another respondent suggested that a target should be given for achievable rates of urinary continence as this is the most common long term side effect.
Response: The panel felt that the recommendation for blood transfusion rates was reflective of the literature and should not be changed. Since there was heterogeneity in the definition of urinary continence, the panel felt that a recommendation for urinary continence rates should not be included.
SHORT-TERM OUTCOMES: One respondent noticed that several studies were missing from the systematic review.
Response: The articles mentioned were about short-term (30-day) outcomes that were outside of the scope of this guideline and did not meet the inclusion criteria for the systematic review.
RATING QUALITY OF STUDIES AND META-ANALYSIS: One respondent inquired as to the lack of the levels of evidence, ranking of quality of recommendations and meta-analysis.

Response: The panel felt the evidence was not of high enough quality for a quality assessment or meta-analysis.
QUANTIFYING THE TUMOUR: One respondent asked whether pathologists should be quantifying the tumour and by what method.
Response: Pathologists at the very least should provide a percent of prostate tissue involved by tumour. This can be expressed in "bins" such as <1%, 1-5%, 6-10%, 11-20%, etc.
PERPENDICULAR SECTIONS DIFFICULT: One respondent said that perpendicular sections of the bladder neck margin were difficult to obtain and should be changed to "every attempt should be made to get perpendicular sections."
Response: The Panel felt that perpendicular sections at the bladder neck were not difficult to obtain. In fact they are easier to obtain than good "en face" sections and the latter can lead to spurious margin positivity.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Expert Panel on Prostate Cancer Surgery and Pathology and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the questions of interest emerges.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:

Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.

Evidence-Based Series #17-3 Version 2: Section 4

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Guideline for Optimization of Surgical and Pathological Quality Performance for Radical Prostatectomy in Prostate Cancer Management

Guideline Review Summary

J. Srigley, J. Chin, L. Durocher-Allen, and Members of the Expert Panel on Prostate Cancer Surgery and Pathology

October 13, 2017

The 2008 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2008. In December 2014, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review.

A PEBC methodologist updated the original search of the literature and the results were reviewed by two clinical experts, Drs. Joseph Chin and John Srigley. Although the reviewers found that the new evidence continued to support the 2008 recommendations, they noted that some of the original content was in need of revision. Specifically, the surgical recommendation on positive margin rate for pT2 disease was revised and the pathology recommendations have been modified to align with the most recent version of the College of American Pathologists (CAP) checklist and the WHO/IAARC staging classification. An Expert Panel of urologists and pathologists was convened (see Appendix 1) to consider the original recommendations for endorsement and the proposed modifications of the surgical and pathology recommendations.

The Expert Panel agreed that the recommendations and modifications found in Section 1 (Guideline Recommendations) including the updated pathology protocols should be endorsed (on October 13, 2017).

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered:

Surgical Questions:

What are the recommended surgical procedures and outcomes for radical prostatectomy (RP), specifically:

1. What is the recommended extent of procedures and what is an acceptable positive margin rate?
2. What are the reported rates for surgical complications, specifically incontinence, erectile dysfunction, rectal injury, and blood transfusion, and does surgical technique (e.g. nerve sparing, bladder neck preservation) affect complication rates?
3. Under what circumstances should nerve-sparing techniques be used?
4. Which patients should receive pelvic lymph node dissection (PLND) and what is the recommended extend of PLND?

Pathological Questions:

1. What are the recommended procedures for handling the RP specimen in the operating room and for handling and processing the RP specimen (with or without lymph nodes) in the pathology lab?
2. What diagnostic and prognostic elements should be included in the pathology report, what format should be used, and what reporting elements should be included?

Literature Search and New Evidence

A total of 7557 citations were identified from MEDLINE and EMBASE via OVID from March 2007 to May 2016. Of those, 151 were selected for full text review. A total of 70 articles met inclusion criteria. Of the 70 identified publications, there were 2 guidelines identified, 1 publication of systematic reviews and 67 publications of primary studies. The results of the guidelines identified can be found in Table 1 (1,2) and the results of the systematic review can be found in Table 2 (3). The publications of the primary studies can be found in Table 3 (4-72).

At the request of CCO's Surgical Oncology Program, a reviewer from CCO's Evidence Search and Review Service (ESRS) further evaluated the 70 included publications to identify articles reporting positive surgical margins, surgical margins and/or recurrence rates. A total of 40 publications were deemed relevant and included in the ESRS report (39 primary articles and a single guideline). The finalized list of articles identified by the ESRS reviewer was confirmed by the Surgical Oncology Program's Clinical Quality Lead. The ESRS results can be found in Table 4.

Impact on the Guideline and its Recommendations

The new evidence did not contradict the original surgical and pathology recommendations in the guideline and they were endorsed with the following modifications by the expert panel who agreed that the recommendations are still relevant and supported by the available evidence. The panel convened by the Surgical Oncology Program included 7 urologists, 7 pathologists and 1 radiation oncologist representing 10 regions.

The original recommendations for pathology were out of date with respect to current classification and staging and they have been updated to align with the most recent CAP protocol released in June 2017 (73), based on the International Society of Urological Pathology (ISUP) consensus conferences in 2009 (74-79) and 2014 (80,81), the (2016) WHO/IARC classification of urological tumours (82), and the seventh edition AJCC cancer staging manual. The eighth edition of the AJCC (83) will come into effect January 1, 2018 and a corresponding version of the CAP protocol was released June 2017 (84). The current documents may be obtained from the CAP website: http://www.cap.org/web/oracle/webcenter/portalapp/pagehierarchy/cancer_protocol_templates.jspx?_adf.ctrl-state=i6f2zyq5p_9&_afrLoop=481147013012490#! See Appendix 2 for the summary of required elements for reporting of specimens.

The panel reviewed the ESRS evidence summary and a Webinar was convened to discuss the findings and potential updates to the positive margin rate target. Based on the available but limited evidence and expert consensus at the Webinar, the panel unanimously agreed to update the positive margin rate target recommendation. It was decided that the existing positive margin rate target recommendation of "Attaining a positive margin rate of < 25% for pT2 disease should be an achievable goal" should be changed to "Radical Prostatectomy should aim at achieving a negative margin, while ensuring a balance between margin rates and functional outcomes," thus removing the reference to a specific target and not limiting that patient population to pT2 cases. The expert panel voted at the meeting to accept the changes and all participants agreed to the revision.

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program in evidence-based care | programme de soins fondé sur des preuves

Document Review Tool

Number and title of document under review	17-3 Guideline for Optimization of Surgical and Pathological Quality Performance for Radical Prostatectomy in Prostate Cancer Management
Current Report Date	September 1, 2008
Clinical Expert	Joseph Chin, John Srigley
Research Coordinator	Lisa Durocher-Allen
Date Assessed	December 1, 2014
Approval Date and Review Outcome (once completed)	October 13, 2017 ENDORSE

Original Question(s):

Surgical Questions:

What are the recommended surgical procedures and outcomes for radical prostatectomy (RP), specifically:

1. What is the recommended extent of procedures and what is an acceptable positive margin rate?
2. What are the reported rates for surgical complications, specifically incontinence, erectile dysfunction, rectal injury, and blood transfusion, and does surgical technique (e.g. nerve sparing, bladder neck preservation) affect complication rates?
3. Under what circumstances should nerve-sparing techniques be used?
4. Which patients should receive pelvic lymph node dissection (PLND) and what is the recommended extend of PLND?

Pathological Questions:

1. What are the recommended procedures for handling the RP specimen in the operating room and for handling and processing the RP specimen (with or without lymph nodes) in the pathology lab?
2. What diagnostic and prognostic elements should be included in the pathology report, what format should be used, and what reporting elements should be included?

Target Population: Adult males with potentially curable prostate cancer for whom RP is the preferred treatment option.

Study Section Criteria:

Inclusion Criteria

1. Randomized trials comparing RP with any other treatment
2. Prospective case series studies of RP
3. Retrospective review of RP patient reports
4. Studies with more than 100 subjects
5. Systematic reviews
6. Clinical Practice Guidelines
7. Studies concerning PLND regardless of primary treatment
8. Database reviews

Exclusion Criteria

1. Review papers that were no systematic reviews
2. Letters to the editor
3. Single-patient case reports
4. Studies in which prostatectomy was salvage treatment
5. Studies that combined prostatectomy with other procedures (e.g. cystoprostatectomy)
6. Studies with less than 100 subjects
7. Studies concerning robotic surgery and techniques

Further exclusions mentioned after initial search (2008) Surgical questions: studies were excluded if the articles were not directly on topic or if they did not report any of the following outcomes: Positive margin rate or information on surgical margins, Rate of incontinence, Rate of impotence, Rate of rectal injury, Blood loss, Blood transfusion, biochemical failure rate (five year or ten year), time to biochemical failure, clinical recurrence rate (local or distant), time to recurrence, biochemical progression-free survival, cancer-specific death or survival, recurrence-free survival, or progression-free survival. PLND section- excluded if they did not present data on PLND separately from other data.

Search Details:

Original Search (2008 document)
The MEDLINE and EMBASE databases were searched for evidence related to the surgical questions during the month of March 2007, using the following text, MeSH, and EMBASE subject headings: 'prostatic neoplasms', 'prostate cancer', and 'prostate tumo?r'. These results were combined with the term 'prostatectom:' to provide a base pool of literature on surgical treatment of prostate cancer. These aggregate results were then combined with the terms 'nerve sparing', 'neurovascular bundles', 'nerve bundle', 'continence', 'incontinence', 'incontinent', 'urinary incontinence', 'pelvis lymphadenectomy', 'lymph node metastas?s', 'pelvis lymph node', 'lymph node dissection', 'pelvic lymph node dissection', 'pelvis surgery', 'lymph node excision', 'pelvic lymph node resection', 'lymph node resection', 'sentinel lymph node biopsy', 'neoplasm invasiveness', 'neoplasm residual', 'surgical margin$', 'margin status', 'surgical resection margin', 'margin clearance', and 'positive margin', with the total results being limited to human studies in the English language published from 1996 through to March 2007. These searches produced 5,311 references.

Brief Summary/Discussion of New Evidence: A total of 7557 citations were identified from MEDLINE and EMBASE via OVID from March 2007 to May 2016. Of those, 151 were selected for full text review. A total of 70 articles met inclusion criteria.

Of the 70 identified publications, there were 2 guidelines identified, 1 publication of systematic reviews and 67 publications of primary studies. The results of the guidelines identified can be found in Table 1 and the results of the systematic review can be found in Table 2. The publications of the primary studies can be found in Table 3.

The ESRS summary reported that the overall positive surgical margin rates varied from 6.3% to 57.5% for open prostatectomy (RP), 10% to 35.8% for laparoscopic RP, and 13.9% to 38.3% for studies that did not report the type of approach used. For positive surgical margin rates by T-stage, pT2 rates ranged from 3.7% to 35% for open RP, and 7.4% to 18.9% for laparoscopic RP; pT3 positive margin rates were higher than pT2 and ranged from 17.4% to 67% for open RP, and 25.3% to 42% for laparoscopic RP. In general, there was a large range and variability in the data. See Table 4 for details.

Clinical Expert Interest Declaration: None to declare.

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No
2. Does the newly identified evidence support the existing recommendations?	Yes
3. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	No

Review Outcome	ENDORSE
If the outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	Not applicable

DSG/GDG Approval Date	October 13, 2017
DSG/GDG Commentary	This guideline should be endorsed. The pathology sections should be revised to include the most recent College of American Pathology (CAP) criteria.

Table 1. Guidelines meeting inclusion criteria for EBS #17-3

Author, year, reference	Inclusion criteria	Methods	Intervention/ Comparison	Brief results
Heidenreich et al 2004 [1] **Nerve sparing** **PLND**	Studies on screening, diagnosis and local treatment with curative intent of clinically organ-confined PC	Lit search: date search was 2011-2013 (update to EAU PC guideline). Databases searched unknown. Evidence level was graded 1-4 Methods for assessing the quality of included studies was not reported.	Nerve sparing PLND	Recommendations: Nerve sparing surgery may be attempted in preoperatively potent patients with low risk for extracapsular disease (T1c and Gleason score < 7 and PSA > 10ng/ml). (Level of evidence = 3). Unilateral nerve-sparing procedures are an option in stage T2z-T3a disease (Levels of evidence = 4). Nerve sparing: Nerve-sparing RP can be performed safely in clinically localized high-risk PC, provided that intraoperative frozen sections are taken without compromising oncologic and functional outcomes PLND: Men with intermediate and high risk PCs, an ePLND should always be performed to obtain optimal information about the extent of lymph node involvement for use in counseling patients concerning the potential need for adjuvant treatment options. The true therapeutic benefit of ePLND however is still unclear.
Tanaka et al. 2009 [2] **Positive Margin** **Surgical complications**	Studies with a focus on urological laparoscopic surgeries related to indications, diagnosis and surgical techniques. Of interest was the laparoscopic radical prostatectomy for prostate cancer	Lit search: Date search from database inception to May 2005. Keyword based search, keywords not provided. Searched PubMed and Japana Centra Revuo Medicina. Articles were included in English and Japanese. Evidence level was graded I to VI Methods for assessing the quality of included studies was not reported.	Urinary continence, erectile function Positive Margin Biochemical recurrence	N = 132 studies laparoscopic radical prostatectomy -Favourable results are obtained with PSA level <10ng/mL, Gleason score ≤7, and T1c-T2b disease (ideal criteria). -PSA level ≥ 8ng/mL, Gleason score ≥ 8 or localized T3 disease are not necessarily contraindications for laparoscopic radical prostatectomy, but consideration of QoL and life expectancy in choosing treatment options. - 1 systematic review results: Urinary continence at 12 months: 60-94% for laparoscopic surgery and 61-98% for retropubic open surgery, no difference between groups. Potency: 34-67% for laparoscopic surgery and 31-79% for retropubic open surgery, no difference between groups -1 non-randomized prospective controlled trial found that urinary continence was achieved earlier following retropubic open surgery than laparoscopic surgery. Positive margins: -drawing from reports collating results of at least 100 laparoscopic procedures: overall PSM was 16-26%. -when stratified by pathological stage, PSM = 7.4-18.9% (pT2), 25.3-42.0% (pT3) Biochemical recurrence (measured by PSA levels) - Overall was 9-5-11% of all patients - when stratified by pathological stage: 3.2-8.2% (pT2a), 6.5-12.0% (pT2b), 15.9-23.0% (pT3a), and 23-9-56.0% (pT3b)

PC = prostate cancer; LRP: laparoscopic radical prostatectomy; PLND = Pelvic Lymph Node Dissection; ePLND = Extended PLND; RRP= Radical retropubic prostatectomy; lPLND = Limited PLND; LNI = Lymph Node Invasion; BCR = Biochemical Recurrence; CR = clinical recurrence; EAU = European Association of Urology; PSA = Prostate-specific antigen

Table 2. Systematic reviews meeting inclusion criteria for EBS #17-3

Author, year, reference	Inclusion criteria	Methods	Intervention/ Outcomes of interest	Brief results
Briganti et al., 2009[3] **Systematic review** **PLND**	Original articles, editorials, or review articles with a focus on the role of PLND in PC stating and outcomes	Lit search: Years searched unknown. Search terms (keywords) were provided in the article. Searched Medline (PubMed). No formal methods for assessing quality of the included studies were reported.	Extent of PLND Low risk patients	The authors did not report the total number of included studies or include a PRISMA flow diagram. Extent: -A matter of debate, some consider ePLND the removal of obturator, external iliac, and hypogastric nodes. Others the removal of presacral nodes, which are a part of the hypogastric package in some series. Others advocate the additional removal of the common iliac nodes, at least up to the ureteric crossing. - General agreement that extended nodal dissection should always include removal of lymph nodes along the hypogastic artery. - lPLND is associated with dismal staging accuracy that is falsely biased towards low rates of LNI due to inadequate nodal sampling PLND in low-risk patients: -rate of LNI in lPLND is invariably low, ranging from 0.5-0.7% - rate of LNI in ePLND increase slightly, ranging from 5.8%-8.0% - still unknown whether PLND might confer significant BCR, lack of prospective studies

PC = prostate cancer; LRP: laparoscopic radical prostatectomy; PLND = Pelvic Lymph Node Dissection; ePLND = Extended PLND; RRP= Radical retropubic prostatectomy; lPLND = Limited PLND; LNI = Lymph Node Invasion; BCR = Biochemical Recurrence; CR = clinical recurrence; EAU = European Association of Urology; PSA = Prostate-specific antigen

Table 3. Primary studies meeting inclusion criteria for EBS #17-3

Author, year, etc	Procedure and population	Methods	Intervention/Outcomes of Interest	Brief results
Overall SM + rates and +SM rates by margin site, pathological stage, and surgical technique				
Abdollah et al. 2014 [4]	Patients treated with RP and anatomically ePLND	Evaluated the data of 315 M0 pN1 PC patients treated with RP and ePLND between 2000 and 2012 at one tertiary care centre.	PSM Cancer Specific Mortality	PSM = 57.5% Predicting Cancer Specific Mortality *Univariate* PSM: HR = 1.76 (0.85-3.63), p=0.1 *Multivariate* PSM HR = 0.92 (0.40-2.13), p=0.08
Albayrak et al. 2010 [5]	Patients undergoing RPP by a single surgeon between March 2004 and	Prospective analysis of 120 consecutive patient undergoing RPP. Patients whose prostate volume was <60 cc with a Gleason score of ≤7 (3+4)/10 and PSA level <10ng/mL were accepted as	PSM	N = 120, mean age 62 (48-75), mean PSA level 7.4 (1.5-21) ng/mL Overall PSM = 9.1% (N = 11)

<table>
<tr><td></td><td>September 2009.</td><td>eligible. Patients with a probability of nodal metastasis of >5% were excluded. Patients were followed up for 24 (3-48) months in outpatient clinics.

Also looked at surgical outcomes. Data shown in specific table.</td><td></td><td>Incident of margin involvement at the bladder neck, the anterior prostate, the lateral and apical prostate was 4, 3, 3, and 1 case.</td></tr>
<tr><td>Atlay et al. 2015 [6]</td><td>Patients undergoing RPP from April 2006 to December 2013</td><td>Retrospective analysis of RP patients categorized into 3 groups based on their BMI and compared on postoperative oncologic and functional outcomes. High risk patients (Gleson score >7, or 4+2, PSA >10, and clinical stage ≥T3) were excluded</td><td>BMI: normal <25kg/m^2

Overweight 25-<30kg/m^2

Obese ≥30kg/m^2</td><td>N =298, Clinical stageT1c (87%), T2a (8%) and T2b (5%)

PSM = 6.3% (n=19), of these 31.5% (n=6) peripheral, 10.5% (n=2) apical, and 57.8% (n =11) prostate base.

PSM (normal, overweight, obese) = 6.9%, 5.8%, 6.1%, p = ns

BCR (normal, overweight, obese) = 2.6%, 2.9%, 2.4%, p = ns

Nerve sparing, no sig. difference between groups.

<table><tr><td></td><td>Normal</td><td>Overweight</td><td>Obese</td></tr><tr><td>Bilateral (ns)</td><td>42 (36.5%)</td><td>38 (37.2%)</td><td>31 (38.2%)</td></tr><tr><td>Unilateral (ns)</td><td>33 (28.6%)</td><td>28 (27.4%)</td><td>25 (30.8%)</td></tr><tr><td>Non-nerve sparing (Ns)</td><td>40 (34.7%)</td><td>36 (35.2%)</td><td>25 (30.8%)</td></tr></table></td></tr>
<tr><td>Barre 2007 [7]</td><td>Patients undergoing RRP for localised PC (pT2 and pT3)</td><td>Prospective series of patients with localised PC.</td><td>NS, Margin rate</td><td>N = 231 patients, mean age 63 yrs (46-75 yr).

NS bilateral N = 131, unilateral = 17

No nerve sparing = 83

<table><tr><td></td><td>Monofocal margin % (n)</td><td>Multifocal margins % (n)</td><td>Total

% (n)</td></tr><tr><td>pT2 (n = 162)</td><td>3.7 (6)</td><td>0</td><td>3.7 (6)</td></tr><tr><td>pT3 (n = 69)</td><td>11.6 (8)</td><td>5.8 (4)</td><td>17.4 (12)</td></tr><tr><td>Total (n = 231)</td><td>6 (14)</td><td>1.7 (4)</td><td>7.8 (18)</td></tr></table></td></tr>
</table>

<table>
<tr>
<td>Billis 2008 [8]</td>
<td>Patients undergoing RRP</td>
<td>Retrospective study of the surgical specimens of 230 consecutive patients submitted to RRP between January 1997-June 2005 were whole-mount processed</td>
<td>PSM (iatrogenic and non-iatrognic)</td>
<td>N = 230

Frequency of overall PSM and stratified according to iatrogenic and non-introgenic

<table>
<tr><td>Characteristic</td><td>N (%)</td></tr>
<tr><td>PSM</td><td>95/230 (41.30%)</td></tr>
<tr><td>Iatrogenic (pT2+)</td><td>61/230 (26.52%)</td></tr>
<tr><td>Non-iatrogenic (EPE)</td><td>34/230 (14.78%)</td></tr>
</table>
Nerve-sparing (iatrogenic vs non-iatrogenic) = 51.85% vs 50.00%, p >0.99

Extension (iatrogenic vs non-iatrogenic) (Mean ±SD)

= 37.18 ± 28.77 vs 86.38 ±57.82 , p <0.01

Biochemical progression: pT2+ stage, 20/59 (33.90%); EPE of the tumour, 13/33 (39.39%)</td>
</tr>
<tr>
<td>Budaus 2009 [9]</td>
<td>Patients treated with nsRP</td>
<td>Prospective study of 1150 patients treated with nsRP by two high-volume surgeons from April 2005-December 2007</td>
<td>PSM

10 yr BCR free survival

10 yr CSM free survival</td>
<td>N = 1150
Positive Margin , % (n) = pT2 5.2 (24), pT3 = 27.1 (48)
Nerve sparing (both sides), % (n) = pT2 82.3 (379) pT3 = 36.2 (64)
Nerve sparing (one side), % (n) = pT2 17.6 (81) pT3 = 63.8 (113)
10 yr BCR free survival (pT2, pT3a, pT3b, pT4) = 87.0%, 53.3%, 26.7%, 5.9%
10 yr CSM free survival (pT2, pT3a, pT3b, pT4) = 98.3%, 95.6%, 84.9%, 72.2%</td>
</tr>
<tr>
<td>Buschemeyer et al. 2008 [10]</td>
<td>Patients treated with RP between 1988 and 2006 at Veterans Affair Medical Centers</td>
<td>Retrospective analysis of RP without lymph node metastases patients from the SEARCH Database comparing time to prostate specific antigen recurrence in positive and negative bladder neck margins</td>
<td>Margin rate

BCR</td>
<td>N = 1772 men, N = +BN = 79 (5%)

Extracapsular extension (%): -BN vs + BN = 361 (22) vs 40

(51), p <0.001

Adjusting for multiple clinical and pathological variable,

including the number of nonBN positive margins, +BN remained associated with increased risk of BCR (HR = 1.52, 95% CI 1.06-2.19, p=0.02)

Isolate +BN vs +BN associated with other +ve margin

Extracapsular extension (%) = 37 (58%) vs 3 (20), p = 0.008</td>
</tr>
</table>

<table>
<tr>
<td>Comploj et al. 2011 [11]</td>
<td>Patients undergoing RP, performed by a single experience surgeon at one institution</td>
<td>Prospective study between January 2001 and Deember 2010 investigating positive margins and biochemical recurrence.

Also looked at postoperative complications and nerve sparing. Data shown below</td>
<td>Margin Rate, biochemical recurrence</td>
<td>N = 212, mean age = 63 (45-74) years
<table>
<tr><td>Stage</td><td>Total</td><td>PSM % (n)</td></tr>
<tr><td>pT2a</td><td>47</td><td>6.4 (3)</td></tr>
<tr><td>pT3b</td><td>20</td><td>5 (1)</td></tr>
<tr><td>pT2c</td><td>99</td><td>19.2 (19)</td></tr>
<tr><td>pT3b</td><td>27</td><td>40.7 (11)</td></tr>
<tr><td>pT3b</td><td>11</td><td>54.5 (6)</td></tr>
<tr><td>pT4</td><td>8</td><td>87.5 (7)</td></tr>
</table>
62% of Patients with PSM who did not develop biochemical recurrence after a mean follow up time of 48 months</td>
</tr>
<tr>
<td>De La Roca 2014 [12]</td>
<td>Patients undergoing open RRP for clinically localized PC between March 1991 and June 2008</td>
<td>Retrospective analyses on the outcome of 161 patients with PSMs, compared to a control group of 67 patients without PSMs, with a total of 228 cases.</td>
<td>PSM

BCR</td>
<td>Correlation between PSM and BCR and CR
<table>
<tr><td></td><td>Category</td><td>No PSM N (%)</td><td>PSM N (%)</td><td>p</td></tr>
<tr><td rowspan="2">BCR</td><td>No</td><td>60 (38)</td><td>100 (62)</td><td rowspan="2"><0.001</td></tr>
<tr><td>Yes</td><td>7 (10)</td><td>61 (90)</td></tr>
<tr><td rowspan="2">CR</td><td>No</td><td>67 (31)</td><td>151 (69)</td><td rowspan="2">0.06</td></tr>
<tr><td>Yes</td><td>0</td><td>10 (100)</td></tr>
</table>
PSM as one variable predicting BCR in 5 years

Univariate: RR = 3.51 (CI 95% 1.51-8.13), p=0.003

Multivariate: RR= 1.47 (CI 95% 0.27-7.96), p=0.653</td>
</tr>
<tr>
<td>Di Benedetto et al. (2015)[13]</td>
<td>Patients with high risk prostate cancer (PSA level of ≥20ng/mL ± biopsy Gleason ≥ 8± clinical T stage ≥2c) undergoing LRP with standard PLND</td>
<td>Prospective analyses of 446 high risk patients from 2000 to 2013 investigating positive margins, PSM.</td>
<td>PSM

BCR</td>
<td>Data reported on both salvage and non-salvage, and total patient. Only data for non-salvage is reported below.

N = 417 (93.5% of total)

NVB preservation (n) = none 235, unilateral 66, bilateral 116

PSM, n/N (%) = pT2 26/237 (11.0), pT3 78/177 (44.0), pT4 3/3 (100)</td>
</tr>
<tr>
<td>Dobruch et al. (2014)[14]</td>
<td>Patients undergoing RP and extended endoscopic PLND.</td>
<td>In February 2011 to June 2013 165 patients undergoing RP were prospectively collected and evaluated. Seventy eight had ePLND, this was only done on subjects with intermediate or high risk, localized PC, specifically PSA above 10ng/ml, Gleason score ≥ 7, or clinical stage of prostate cancer ≥ cT2b.</td>
<td>ePLND</td>
<td>Mean LN removed = 19, LN metastases was 16.6%

PSM: Lymph node positive =3 (23%) vs lymph node negative = 9 (14%), p = ns</td>
</tr>
</table>

<table>
<tr>
<td>Gacci et al. 2013 [15]</td>
<td>Patients undergoing RP and patients previously treated with transurethral resection of the prostate (TURP)</td>
<td>2,408 patients treated with RP for clinically localized PC were enrolled in 135 departments and PSM rates and all preoperative, surgical and pathological features were investigated. Also, differences between 75 patients who had undergone previous TURP and the remaining sample were compared.</td>
<td>PSM

TURP vs no TURP</td>
<td>N = 2,408, of those 75 had TURP

29% with PSM (n =702), of them, 66% (n=464) presented solidary PSM, while 34% (n = 238) had multifocal PSM. 167 patients presented PSM in 2 sites, 46 in 3 sites and 19 in 4 sites, and 6 in 5 different sites.

<table>
<tr><th></th><th>Overall</th><th>Apex</th><th>Base</th><th>Posterior</th><th>Lateral right</th><th>Lateral left</th></tr>
<tr><td>All</td><td>702 (29%)</td><td>325</td><td>51</td><td>132</td><td>281</td><td>253</td></tr>
<tr><td>Unique</td><td>464 (66%)</td><td>177</td><td>23</td><td>60</td><td>113</td><td>91</td></tr>
<tr><td>Multifocal</td><td>238 (34%)</td><td>148</td><td>28</td><td>72</td><td>168</td><td>162</td></tr>
</table>

Multivariate analysis predicting PSM in total N : Preopeartive PSA (ns),Clinical Stage (Standardized β = -0.113, p<0.001), Biopsy GS (β = --0.078, p<0.001), number of biopsy cores (β = 0.971 p<0.001), number of positive biopsy cores (β = -0.964, p<0.001), percent of positive biopsy cores (ns), and Nerve Sparing (β = 0.051, p<0.024)

TURP vs no TURP

No difference in PSA, pathological GS and pT, however had lower rate of NS approach compare with no TURP (χ2 p = 0.0015, t test p = 0.038).

No difference in overall PSM (23 vs 32%, p =0.101), however significant difference in the sites of PSM, men with TURP resented with high rates in the bladder neck (5 vs 2%, p =0.049) and lower rates in the Apex (5 vs 14%, p=0.036)</td>
</tr>
<tr>
<td>Golabek et al. 2014 [16]</td>
<td>PC patients treated with laparoscopic radical extraperitoneal prostatectomy (LRP)</td>
<td>Clinical and histological data of 295 consecutive patients who had undergoing LRP for clinically localized prostate cancer in a single institution between January 2007 and December 2012 were reviewed from prospectively maintained database. The aim was to evaluate the effect of bladder neck sparing on urinary continence and SM.

UC data shown in appropriate table.</td>
<td>Surgical margins (SM)</td>
<td>N = 295, mean age 62 (42-78)

Overall SM = 29.15

Bladder neck +SM in 16.3% and in 85.7% of those cases were in combination with an SM at 1 or 2 other sites.

Logistic regression indicated that preoperative PSA and pathological T stage correlated with +SM (p =0.008, r = 0.154 and p<0.001 r = 0.371).

Men with PSA > 10ng/ml had significantly shorter time to BCR (83.3% vs 92.3% in cases with –SM, p =0.047, and 39.2% vs 65.4% in patients with +SM, p = 0.027</td>
</tr>
<tr>
<td>Gözen et al. 2015 [17]</td>
<td>Patients undergoing LRP with cT1, cT2, and cT3 prostate cancer</td>
<td>Prospective analysis between March 1999 and December 2013 of patients undergoing LRP at a single institution. Patients were divided into 3 groups (cT1, cT2, cT3) and compared on various outcomes. Also reported on surgical complications and PLND. Shown in tables below.</td>
<td>Clinical stage groups (cT1, cT2, cT3)

Surgical margins</td>
<td>N = 1751: cT1 (417) cT2 (842) cT3 (492)

PSM (%): cT1= 51 (12.2); cT2= 164 (19.5); cT3 = 188 (38.2), p <0.001</td>
</tr>
<tr>
<td>Izard et al. 2014 [18]</td>
<td>Patients undergoing RP for PC</td>
<td>Prospective analysis of all RP specimens since 1998 comparing margin status (positive, close, negative) and BCR. Patients were excluded</td>
<td>Margin status (positive, close (tumour cells</td>
<td>N = 158</td>
</tr>
</table>

		if they received neoadjuvant therapy, had node-positive disease and if their postoperative PSA did not reach an undetectable level.	within 0.1mm of inked margin) or negative). BCR	Margin status (N, %) : negative 1058 (67%) Close 232 (15%), positive 298 (19%) *Unadjusted:* Margin status and BCR : negative 86 (8.1%), close 33 (14.2%), positive 74 (24.8%) *Adjusted (univariate) : Margin status and risk of recurrence:* Close HR = 1.72 (CI 1.14 to 2.57), p = 0.008 Positive HR = 2.91 (CI 12.13-3.98), p <0.001 *Adjusted (multivariate): Margin status and risk of recurrence:* Close HR 1.53 (CI 1.00 to 2.32), p =0.047 Positive HR 2.10 (CI 1.48 to 2.99), p < 0.001
Kamecki et al. 2013 [19]	Patients undergoing RP with PC in stage cTI-3	Prospective study evaluating the incidences of positive margins in PC undergoing RP in the years 2010 and 2011. .	Margin status	N = 114, mean age 61.5 years (44-78 years) PSM was found in 45 (39.47% patients, and in 20 (17.54%) margins were assessed as close (1-2mm). Among the patients with PSM about 22% had biochemical recurrence. Mean follow up was 12 months (range 6-18). During this period, a biochemical relapse after radical treatment (PSA > 0.2ng/ml) occurred in 16.36% of the patients (patients with pN1 were excluded, as the resection was recognized as incomplete)
Kates et al., 2016 [20]	Patients undergoing RP and PLND for localized PC	Retrospective analysis of PC patients between 2010 and 2014, comparing PSM length and Gleason score and their relations with grade and adverse pathological characteristics of the final specific and whether PSM affect risk of early BCR	Margin BCR Pathological features include organ confined, focal EPE, non-focal EPE, Seminal vesicle invasion and positive LN.	N = 4082 PSM = 14.4%, Of patients with PSM, BCR was identified in 22% and clinical signs of metastases in 3% Lower GS at the margin was associated with shorter margin length (p = 0.02). In a linear regression model a longer positive margin was independently associated with higher GS at the margin (b =0.78, p=0.016) *Logistic regression predicting risk of a lower GS at the positive margin* Margin length HR = 0.77 (CI = 0.64 to 0.94), p =0.01 Staging characteristics (organ confined was reference group) F-EPE HR 0.97 (CI = 0.40 to 2.37), p = ns NF-EPE HR = 0.83 (CI 0.38 to 1.82), p = ns SVI/LN invasion HR = 0.53 (CI 0.22 to 1.27), p =ns *Cox proportional hazards model predicting BCR* Lower GS at margin HR = 0.50 (CI 0.25 to 0.97), p = 0.04 Margin Length HR = 1.05 (CI 0.82 to 1.35), p =ns Staging characteristics (organ confined was reference group):

				F-EPE HR =1.16 (CI 0.11-11.84), p = ns NF-EPE HR = 0.70 (CI 0.07 to 6.42), p =ns SVI/LN invasion HR = 2.04 (CI 0.22-18.90), p = ns
Khoder et al. 2012[21]	Patients with clinically localized PC undergoing open intrafascial Retropublic radical prostatectomy (OIF-RP)	Prospective study between January 2007 to December 2009 comparing functional outcomes at 3 and 12 months.	PSM	N = 231, f/u data available for 179 pts PSM was 10% in pT2 cases and 65% in pT3 cases.
Kumano et al. 2008 [22]	Patients with clinically organ-confined PC undergoing LRP without any neo-adjuvant therapies	Retrospective analysis investigating the influence of the number of PSM and their location on BCR in 159 PC patients between April 2000 and June 2006..	PSM PSM location BCR	N = 159, PSM = 35.8% (n = 57), of whom 56.1% and 43.9% had organ confined disease and non-organ confined disease. Of these 57, 63.2% and 36.8% had solitary and multiple PSM. Location of PSM of the 57 patients was: 64.9% Apex, 14.0% anterior site, 24.6% posterior site, and 36.8% bladder neck. During observation period (median 38 months), BRC developed in 31/159 (19.5%) patients. *Predictors of BCR (univariate)* No of PSM HR 2.93, p=0.0066 Apex margin HR 3.35, p <0.001 Bladder neck margin HR 4.37, p <0.001 Anterior and Posterior margin were ns *Predictors of BCR (Multivariate)*

				Bladder neck margin HR =6.69, p >0.001 Apex margin HR =4.47, p = 0.0018 No of PSM, Anterior and Posterior were ns
Lee et al. 2015[23]	Patients who underwent RP	Retrospective analysis from 1995 to 2013 of men undergoing RRP RPP and MIRP comparing PSM and BCR-free survival rates, and 5 yr metastases-free survival rates. *Note.* MIRP data will not be reported and robot-assisted laparoscopic was included in this group.	PSM	Total N = 2581, RPP = 689. RRP = 402 *Patient and PC features: N(%)* Intermediate risk :RPP 411 (59.7) vs RRP 214 (53.2), p = 0.04 High Risk : RPP 278 (40.3) RRP 188(46.8), p<0.001 Neurovascular bundle preservation: RPP 387 (56.2) vs RRP 120 (29.9), p <0.001 PSM: RPP 164 (23.8) vs RRP 105 (26.1), p =0.39 Biochemical Recurrence RPP 156 (24.7) RRP 90 (24.7), no p value reported BCR-free survival rates % PSM: RPP 3 years 64.5; RPP 5 years 53.0; RRP 3 years 63.8; 5 years 59.4, p = ns
Li et al. 2011 [24]	Patients with PC receiving RP at a single centre between 2000 and 2009	From 2000 to 2009, 149 patients with PC received RP were followed up. All patients were followed up on the 3rd month, 6th month and from that point on every 6 months after operation.	PSM	PSM RRP 36.9% (41/111) PSM LRP 42% (16/38) Most common location of PSM was the apex (63% 36/37) and 64% (23/36) in the prostate lobe. PSM (% (n/N)) : BCR vs No BCR : 52 (11/21) vs 35.2 (44/125) p<0.001
Lu et al. 2012[25]	Patients undergoing RP for localized PC in one institution	Prospective analysis of 894 consecutive patients who underwent RP for localized pc between 1993 to 1999 at one institution	PSM (negative, close, positive). CSM were tumour approached the margin by less than 0.1mm	Margin location: CSM vs PSM: Apex (17 vs 24%), Peripheral (81 vs 51%), Bladder Neck (1 vs 4%) and Multiple (1 vs 21%), p <0.001 BCR = Overall (31%), NSM (21%), CSM (39.0%), PSM (49.6%), p< 0.001 *Univariate analysis:* CSM HR =1.93 (95% CI 1.34-2.78), p <0.001 PSM HR =2.97 (95% CI 2.30-3.83), p<0.001 *Multivariate analysis:* CSM HR =2.12 (95% CI 1.04-4.33), p=0.039 PSM HR =3.52 (95% CI 1.97-6.29), p <0.001 *Multivariate analysis (CSM considered negative)* PSM HR =2.98 (95% CI 1.75-5.05), p<0.001

Mann et al. (2008)[26]	Patients undergoing PC	Retrospective analysis of Columbia University Urologic Oncology database of patients who had undergoing RP from 1991 to 2005 and had sufficient pathologic data and ≥1 year of follow up. Three epochs were chosen: 1991-1995. 1996-2000, and 2001-2005	PSM	Of 2215 pts analyzed, 631 (18%) had ≥ 1PSM after RP Using a log rank test, Surgical Margin Status (SMS) was shown to be a predictor of Biochemical failure (BCF), (p<0.01), remained significant in multivariate model adjusted for PSA, Gleason score, and pathological stage. *Adjusted HR of BCF for PSM:* 1991-1995- HR 1.79 (95% CI 1.43-2.24) p <0.01 1996-2000 HR 3.22 (95% CI 1.23-8.47) p<0.01 2001-2006 HR 12.43 (95%CI 7.78-19.86) p<0.01
Mauermann et al., 2012 [27]	Patients undergoing RP	Prospective analysis of patients undergoing RP at one institution between January 1987 and April 2010. 89.4% of patients underwent open retropublic approach and 10.6%	PSM (solitary vs multiple)	16.4% had solitary PSM and 18.1% had multiple PSM. Mean lymph node removed was 14.14, for NSM was 14.43, solitary PSM was 13.83, and multiple PSM was 13.38, p =0.021 BCR in solitary PSM was 22.1%, and 31.0% in multiple PSM *Univariate for risk of BCR* sPSM HR 1.951 (95% CI 1.436-2.649), p<0.0001 mPSM HR 3.102 (95% CI 2.374-4.054), p<0.0001 *Multivariate for risk of BCR* sPSM HR 1.711 (95% CI 1.255-2.332), p=0.001 mPSM HR 2.075 (95% CI 1.552-2.773), P<0.0001
Mithal et al. 2016[28]	Patients who were treated with RP	Retrospective study of men in the SEARCH cohort treated by RP from 1988 to 2013. Patients treated with preoperative androgen deprivation or RT were excluded.	BCR	N = 4051 Median f/u was 6.6 (3.2-10.6) yrs PSM = 1600 (40%) Extracapsular extension (PSM vs NSM) = 519 (32%) vs 263 (11%), p<0.001 *HR for PSM outcomes after RP* BCR: Crude HR =2.58 (95% CI 2.31-2.88), p<0.001 Adjusted HR = 1.98 (95% CI 1.75-2.23), p<0.001 *Adjusted for age, race, preoperative PSA level, pathological Gleason score, seminal vesicle invasion, extracapsular extension, years of surgery, surgical centre and receipt of ART.

Moore et al. 2012 [29]	Patients who had not received neoadjuvant hormonal or radiation therapy and were undergoing RP by a single surgeon.	Prospective analysis of patients undergoing RP between 2002 and 2007 by a single surgeon. Bilateral, unilateral and non-nerve sparing data were collected	PSM	BNSS N = 704, UNSS N =171, NNSS = 70 PSM: Total 19.6%, BNSS 18.2%, UNSS 21.1%, 30.0% NNSS RR for PSM in multivariate binary logistic regression: UNSS RR =0.585 (95% CI 0.300-1.135), p = ns BNSS RR =0.639 (95% CI 0.349-1.170), p = ns PSM by stage pT2 tumours: 61 BNSS (11.4%), 8 UNSS (12.5%), 4 NNSS (14.3%), p ns pT3 tumours: 51 BNSS (42.1%), 17 UNSS (29.3%), 6 NNSS (28.6%) p ns pT3b tumours: 16 BNSS (35.6%), 11UNSS (28.2%), 9 NNSS (47.4%) p ns
Nelles et la. 2009 [30]	Patients treated with RP	Retrospective analysis using the SEARCH database of patients treated with RP from 1988 to 2006. Patients were excluded if treated with preoperative androgen deprivation or radiation.	PSM BCR	N = 1018 PSM by nerve sparing technique (BNS, UNS, NNS) (%): 38, 40, 43, p=ns Apical PSM (BNS, UNS, NNS) (%): 19,18,10, p =ns Bladder neck PSM (BNS, UNS, NNS) (%): 3,2,7, p=0.007 OR for PSM BNS OR =0.95 (95% CI 0.63-1.45), p=0.82 UNS OR =0.99 (95% CI 0.59-1.66), p=0.97 HR for positive BCR BNS HR = 0.61 (95% CI 0.43-0.87), p=0.006 UNS HR = 0.71 (95% CI 0.45-1.11), p=0.13
Peterson & Chen 2012 [31]	Patients treated with RP	Prospective analysis of 4,374 patients undergoing RP (retropubic approach) between 1990 and 2007 investigating margin status and UC. *UC data reported below.*	Margin status	PSM = 22% Multivariate Cox HR model predicting UC Margin status (Pos vs Neg) = 0.963 (CI 95% = 0.757-1.225), p = 0.7589
Pettenati et al. 2015[32]	Patients undergoing RP using open retropubic approach or laparoscopy for localized PC who did not receive adjuvant radiotherapy or androgen-deprivation therapy	Retrospective analysis of a database from a single institution between 2005 and 2008 comparing surgical margins BCR free survival and recurrence risk factors.	Margin status 5 year BCR	N = 630 PSM N =206 (32.7%) Mean surgical margins length was 3.0 ± 3.1 mm (median 2.0 mm, range 0.1-15.0mm). The BCR rate was 30% (n=33) with a 5 year BCR-free survival of 83.9 ± 0.04% BCR risk (only sig values reported) Tumor volume OR 4.29 (95% CI 1.011-1.483), p =0.038 Length of PSM OR 4.35 (95% CI 1.011-1.421), p = 0.037

Pfitzenmaier et al. 2008 [33]	Patients without neoadjuvant and direct postoperative adjuvant therapy who underwent RP	Prospective analysis of 406 consecutive men who underwent RP for PC between 1990 and 2006 at a single institution.	PSM	PSM by stage: pT2 22 (8.2%), pT3a 32 (30.5%), pT3b-4 16 (48.5%) PSM by number (N/%) = 1 PSM = 46 (11.3%), 2 PSM 19 (4.7%), ≥3 5 (1.2%) PSM by location: apical 24 (5.9%), nonapical 22 (5.4%), several 24 (5.9%) At median f/u of 5.2 years, 114 patients (28.1%) developed biochemical relapse after median of 0.9 (0.2-11.9) years, 22 patients (5.4%) had local recurrence after a median of 3.2 (0.5-8.5) years and 16 patients (3.9%) developed distant metastatic disease after a median of 3.7(0.9-9.7) years. The risk of patients with a PSM of developing PSA recurrence was 3.213 (2.126-4.855) times higher of developing local recurrence was 4.643 (1.785-12.079) times higher, or of developing distant metastasis was 6.649 (1.1915-23.088) times higher compared with patients with a NSM.
Porpiglia et al. 2011 [34]	Patients undergoing laparoscopic RP for PC who were not undergoing neoadjuvant and adjuvant therapy	Retrospective analysis from a prospectively maintain database of 300 patients who underwent LRP between 2000 and 2009 from a hospital in Italy to investigate the prognostic value of PSM in the biochemical free survival rate (BFSR). After LRP, patients were followed every 3 month	PSM	N 68 PSM (22.7%), overall BFSR in PSM group = 67.6% HR for time to biochemical recurrence PSM HR =3.7888 (95% CI =1.911-7.5119), p = 0.0001 PSM extension HR = 5.6807 (95% CI 1.4889-21.674), p =0.011 PSM location HR = 1.2951 (95%CI 0.2-4.0539), p =0.0602 PSM number HR = 1.7044 (95% CI 0.5-5.8102), p = 0.3941
Rabbani et al. 2009 [35]	Patients undergoing open or laparoscopic RP with no previous radiotherapy or hormonal therapy	Prospective analysis between January 1999 and June 2007 of patients undergoing open or laparoscopic RP to determine BCR in patients with PSM on the prostate specimen, who have additional negative tissue resected from that site (M+-) compared with patients with negative margins (M-) and those with persistent PSM (M+)	PSM	N = 4217, RRP 76.3% and LRP (23.7%) Pathological OC cancer: total = 2901, M- 2659, M+ 216, M+- 26 ECE alone (no seminal vesicle or lymph node involvement): Total = 843, M- 657, M+ 174, M+- 12 PSM Overall (13.9%); Apex 5.2%, Bladder neck 1.2%, Posterior 6.6%, Anterior 2.8% For OC patients, 36 actuarial BCR free probability was 97.9% (97.3-98.5) for M-, 89.0% (84.1-93.9) for M+, 100% for M+- For patients with ECE, 36 month actuarial BCR free probability was 83.7% (80.0-87.4) for M-, 73.7 (66.1-81.3) for M+, 90.0 (71.4-100%) for M+-
Servoll et al. 2014 [36]	Patients who underwent RP for localized PC	The RP specimens of 300 consecutive patients operated with RP for localized PC between 1985-2009 to investigate the relationship between the known pathological characteristics of PSM (PSM length, single vs multiple PSM, the GS at the PSM, and the location) and clinical outcomes with long term follow up. Patients were followed at 3 months intervals for the first year posoperatively and then	Length of PSM Single vs multiple PSM Location of PSM	N = 300 Single PSM = 135 (83%) Multiple PSM 28 (17%) Linear extent ≤ 3.0mm = 63 (39) >3.0mm = 100 (61%) Median Linear extent 4 (1-28) PSM location: Base 33 (20), Apex 57 (35), Anterior 16 (10) Posterior-lateral 57 (35) Multivariate proportional HR: effects of margin length on clinical progression *PSM ≤3.0 is reference group.* PSM cohort (n = 163): PSM > 3.0 mm= HR =1.95 (1.12-3.38), p =0.017

<table>
<tr><td></td><td></td><td>semiannually until the fifth year and annually thereafter.</td><td></td><td>Entire cohort (n =300): PSM > 3.0 mm = HR =2.49 (1.48-4.20), p =0.001</td></tr>
<tr><td>Stolzenburg et al. 2010 [37]</td><td>Patients who underwent BN-sparing and BN resection EERPE</td><td>Retrospective analysis for 240 patients who had undergone EERPE for localized PC between June 2005 and December 2008 to investigate the effects of BN procedure used on UC and margin status. Patients were divided into 2 groups according to BN method used: BN preservation and without BN preservation with racket handle repair of BN at 12 o'clock position.

UC data presented in table below.</td><td>SM</td><td>Group 1 BN preservation : N = 150

Group 2 no BN preservation but with racket handle repair N = 90

<table><tr><td></td><td>Group 1</td><td>Group 2</td></tr><tr><td>Overall SM +</td><td>16 (10.7%)</td><td>9 (10.0%)</td></tr><tr><td>BN</td><td>1</td><td>1</td></tr><tr><td>Apex</td><td>12</td><td>6</td></tr><tr><td>Other</td><td>3</td><td>2</td></tr><tr><td>pT2</td><td>5.1%</td><td>2.9%</td></tr><tr><td>pT3</td><td>30.3%</td><td>33.3%</td></tr></table></td></tr>
<tr><td>Udo et al., 2013 [38]</td><td>Men with pT2 or pT3a cancer at RP. Patients with seminal vesicle invasion or lymph node involvement were</td><td>Retrospective analysis of 2150 men with pathological stage pT2 orpT3 cancer at RP from 2004 to 2007 to investigate surgical margin and progression free probability.</td><td>PSM</td><td>PSM in 207 (10%) of men, pT2 in 93 and pT3a in 114 patients.

Univariate analysis of predictors of progression at RP, % (95% CI)

Total PSM linear length : 1 or less 91 (81-96), 1.1 to 3 (83 (69-91) greater than 3 47 (31-61), log rank test, p < 0.001

Location: no apex or posterolat 85 (51-96), Apex alone 77 (68-84), Nonapical posterolat alone 84 (67-92), log rank test p <0.05

Pathological stage: pT2, NSM 97 (96-98), pT2 PSM 85 (96-98), pT3a NSM 90 (87-93), pT3a PSM 72 (62-80), log rank test p <0.001</td></tr>
<tr><td>Van Oort et al. 2010 [39]</td><td>Patients with PSM in the prostatectomy specimen</td><td>Between 1995 and 2005, 267 consecutive patients with PSM in the prostatectomy specimen were analyzed for associations between the length of the PSM and different prognostic variables. Patients were followed at 3 month intervals for the first year and 6 monthly thereafter.</td><td>PSM length

BCR</td><td>Total N = 267, N for BCR f/u = 174

5 year risk of BCR was 29%

Significant difference between pts with PSM ≤10 mm with a 5 year risk of BCR of 21% and pts with PSM of > 10mm with a 5 year risk of BCR of 29%, p= 0.011

Using a cox regression or time to PSA recurrence, length of PSM was a significant predictor (HR = 2.26, (95% CI 1.19-4.31, p= 0.013).

Multivariate analyses revealed that risk of BCR was associated with increasing length of PSM (≤ 10 mm vs > 10 mm HR =2.15 (95% CI = 1.12-4.15), p = 0.022).

# of PSM (%): Total group (1 PSM vs > 1 PSM) = 161 (60.3) vs 106 (39.7)

BCR group (1 PSM vs > 1 PSM) = 123 (70.7) vs 51 (29.3)</td></tr>
<tr><td>Vesely et al. 2014[40]</td><td>Patients who underwent open or laparoscopic RP for localized PC and that were no treated with radiation or hormonal therapy.</td><td>Patients who underwent open or laparoscopic RP for clinically localized PC between May 2001 and March 2012 at one institution. Of these patients, only 116 patients who had PSM were evaluated further for BCR.</td><td>PSM

BCR</td><td>N = 116, 47% experienced BCR

Median duration of time to BCR was 12 months (range 2-66).

The frequency of BCR did not differ significantly (p = 0.08) between clinical T categories: T1c (38%), T2a (54%), T2b (71%) and T2c (60%)

Of all PSM locations, 14 (13%) were apical, 20 (17%) at the bladder neck and 81 (70%) at the posterolateral site. A total of 46 patients (40%) had PSM ≤ 1mm. Neither the location (p =0.216) nor the extent of PSM (p =0.405) had any significant impact on the frequency of BCR.</td></tr>
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Von Bodman et al. 2010 [41]	Men undergoing RPP without neoadjuvant androgen deprivation therapy	Using a prospective prostatectomy database, men undergoing RRP between November 2001 and June 2007 were analysed. At each postoperative visit (every 3-4 months in the first year, then every 6 months through year 5, then annually) outcomes regarding EF were evaluated.	Surgical Margins	N = 644 pts, bilateral group =504 pts nonnerve sparing = 140 PSM, N (%): Total: 89 (13.8%), bilateral NS: 62 (12.3%), non bilateral: 27 (19.3%)
Weiner et al. 2015 [42]	Men with low risk PC undergoing RP	Retrospective population based data from the NCDB from 2010 to 2011 to investigate PSM at RP and time from diagnosis to RP. The study population was stratified by length of time from diagnosis to RP (0-6 months were considered initial RP, and then 6-9 months, 9-12 months and > 12 months).	PSM	N = 16,818 underwent RP within 6 months of diagnosis Delayed N : 6-9 months : 894 (5%), 9-12 months 169 (0.9%), > 12 months 62 (0.3%) PSM rate was 15.8% Univariate analysis showed delaying RP among low risk patients had no effects on rates of upgrading, upstaging, surgical margins, nodal metastasis or at least one adverse pathological event (all p were ns). A total of 9,649 (65%) were very low risk. When compared with those who were no very low risk, men with very low risk tumours were less likely to have PSM (12% vs 18%, p <0.001).
Author, year, etc	**Procedure and population**	**Methods**	**Intervention /Outcome of interest**	**Brief results**
Surgical complications				
Albayrak et al. 2010 [5]	Patients undergoing RPP by a single surgeon between March 2004 and September 2009.	Prospective analysis of early continence results of 120 consecutive patients. Patients whose prostate volume was <60 cc with a Gleason score of ≤7 (3+4)/10 and PSA level <10ng/mL were accepted as eligible. Patients with a probability of nodal metastasis of >5% were excluded. Patients were followed up for 24 (3-48) months in outpatient clinics. *Also looked at surgical margins. Data shown in specific above.*	Continence	N = 120, mean age 62 (48-75), mean PSA level 7.4 (1.5-21) ng/mL Bilateral nerve sparing 60.8% and 10% as unilateral. Non nerve sparing was 29.2% Early continence: bilateral 79.4%, and unilateral 58.3%, p = ns non-nerve sparing 54.2%, p= ns (bilateral vs non-nerve sparing) Continence across time Immediate continence 36.7%, month 1 54.1%, and month 3 72.5% One year follow up (13 patients were out of f/u after 9 months) = 95.3% Age and continence: ≤49 (77.7%), 50-59 (73.3%), 60-69 (73.4%) and ≥70 (64.7%), p =ns
Antebi et al. 2011 [43]	Patients with localized PC undergoing RP from 1992-2007 by a single surgeon.	Prospective analysis of patients undergoing RP and assessing the likelihood of achieving the Trifecta (achieve disease recurrence free, urinary continence, and sexual potency). BR is defined as PSA ≥ 0.2ng/mL, urinary continence defined as	Disease recurrence free (BR) Urinary continence (UC)	N = 831, mean age 59 (35-77), median preoperative PSA 5.8ng/mL Unilateral nerve sparing 17.5%, Bilateral nerve sparing 63.5%, non-nerve sparing 19% At median follow up of 52-54 months: Overall rates: BR 19%, SP 71%, UC 94.5%

<table>
<tr><td></td><td></td><td>wearing no pad and sexual potency as having erections sufficient for intercourse with or without phosphodiesterase-5 inhibitor.</td><td>Sexual potency (SP)</td><td>BR (low, int., high, %) = 12.7, 22.4, 40.8, p <0.001

SP (low, int, high, %) = 73.5, 69.5, 67.0, p = ns

UC (low, int, high, %) = 93.7, 94.2, 93.1, p = ns</td></tr>
<tr><td>Atlay et al. 2015 [6]</td><td>Patients undergoing RPP from April 2006 to December 2013</td><td>Retrospective analysis of RP patients categorized into 3 groups based on their BMI and compared on postoperative oncologic and functional outcomes. High risk patients (Gleson score >7, or 4+2, PSA >10, and clinical stage ≥T3) were excluded</td><td>BMI: normal <25kg/m^2

Overweight 25-<30kg/m^2

Obese ≥30kg/m^2

Urinary Continence
Erectile Function</td><td>N =298, Clinical stageT1c (87%), T2a (8%) and T2b (5%)

Continence:

At catheter removal (normal, overweight, obese)= 88.6%, 87.2%, 88.8%, p=ns

3 mths (normal, overweight, obese)= 89.5%, 87.2%, 88.8%, p=ns

6 mths (normal, overweight, obese) = 89.5%, 88.2%, 91.3%, p = ns

12 mths (normal, overweight, obese) = 94.7%, 95.0%, 95.0%, p=ns

Erectile Function

3 months (normal, overweight, obese) 9.1. ±3.1, 8.9 ±4.4, 8.7 ±3.8, p =ns

6 months (normal, overweight, obese) 9.8 ±6.2, 9.1 ±7.9, 9.5 ± 8.5, p = ns

12 months ((normal, overweight, obese) 13.8 ±5.4, 13.1 ±4.8, 12.8 ±3.7, p =ns

Authors' notes: Results reveal being overweight is not a risk factor in RPP patients.</td></tr>
<tr><td>Barre 2007 [7]</td><td>Patients undergoing RP for localised PC (pT2 and pT3)</td><td>Prospective series of patients with localised PC. Patients completed self-administered questionnaires on continence and sexual activity after RP at 1, 3, 6, and 12 months</td><td>Erectile function, Continence</td><td>N –=231 patients, mean age 63 yrs (46-75 yr).

Erectile function

<table>
<tr><td>1 month</td><td>3 month</td><td>6 month</td><td>12 month</td></tr>
<tr><td>108/134 evaluated</td><td>105/108 evaluated</td><td>48/79 evaluated</td><td>37/37 evaluated</td></tr>
<tr><td>27 (25%)</td><td>51 (48.6%)</td><td>24 (50%)</td><td>6 (16.2)</td></tr>
</table>
Of the 54 patients at 1 yr of follow up, 37 had undergone NS sparing

Of them, 70.3% (n = 26) had erections satisfactory for intercourse without the need for medication.

<table>
<tr><td>Pre RP</td><td>No ED</td><td>Mild</td><td>Mild-moderate</td><td>Moderate</td><td>Severe</td></tr>
<tr><td>22-25</td><td>5</td><td>7</td><td>5</td><td>4</td><td>4</td></tr>
<tr><td>17-21</td><td>2</td><td>2</td><td>3</td><td>0</td><td>2</td></tr>
<tr><td>Total</td><td>7 (20.5 %)</td><td>9 (26.5%)</td><td>8 (23.5%)</td><td>4 (11.8%)</td><td>6 (17.7%)</td></tr>
</table>

Continence</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>54 of 231 patients had 1 yr of follow up, 94% total continent (never used pads)</td>
</tr>
<tr>
<td>Budaus 2009 [9]</td>
<td>Patients treated with nsRP</td>
<td>Prospective study of 1150 patients treated with nsRP by two high-volume surgeons from April 2005-December 2007</td>
<td>Urinary Continence

Erectile Function</td>
<td>N = 1150

Urinary Continence:
<table>
<tr><th></th><th colspan="2"><60 yr</th><th colspan="2">60-70 yr</th><th colspan="2">>70yr</th></tr>
<tr><th># pads per 24hrs</th><th>BNS (%)</th><th>UNS (%)</th><th>BNS (%)</th><th>UNS (%)</th><th>BNS (%)</th><th>UNS (%)</th></tr>
<tr><td>0-1</td><td>95.9</td><td>97.4</td><td>93.8</td><td>93.2</td><td>94.5</td><td>84.1</td></tr>
<tr><td>2</td><td>3.3</td><td>2.6</td><td>5.5</td><td>6.8</td><td>3.7</td><td>10.7</td></tr>
<tr><td>>2</td><td>0.7</td><td>-</td><td>0.7</td><td>-</td><td>1.8</td><td>5.2</td></tr>
</table>
Erectile Function
<table>
<tr><th></th><th>< 60yr</th><th>60-70 yr</th><th>>70 yr</th></tr>
<tr><td>Bilateral</td><td>59</td><td>56</td><td>59</td></tr>
<tr><td>Unileteral</td><td>44</td><td>35</td><td>25</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><td>Comploj et al. 2011 [11]</td><td>Patients undergoing RP, performed by a single experience surgeon at one institution</td><td>Prospective study between January 2001 and December 2010 investigating positive margins and biochemical recurrence.

Also looked at surgical margins and nerve sparing.</td><td>Urinary Continence

Erectile Function</td><td>N = 212, mean age = 63 (45-74) years

Urinary Continence at 48 months: 81 % completely continent, 14% not wearing any protected, but some leakage, 3.7% grade II stress urinary incontinence, and 0.4% complained of grade III stress urinary incontinence.

Erectile function: 70% recovered spontaneous erections occurred within 6 months, but only 16% of them stated that the erection was the same quality before RPP.</td></tr>
<tr><td>Gandaglia et al. 2012 [44]</td><td>Patients with low risk PC who underwent bilateral nerve-sparing RP (BNSRP), performed by 2 high-volume surgeons</td><td>Between January 2008 and June 2010, patients underwent BNSRP at a single tertiary referral center. Baseline EF was assessed a day prior to surgery and categorized into severed, moderate, mild to moderate, mild and no ED group. Patients were also retrospectively divided into no PLND and ePLND group. Patients were evaluated every 3 months during the first year, and every 6 months thereafter.</td><td>ePLND vs no PLND

EF recovery</td><td>N = 396, ePLND group = 235, no PLND = 161, mean number of lymph nodes removed was 20.3

Preoperative EF (no PLND vs ePLND): severe 39 vs 69, moderate 10 vs 17, mild to moderate 10 vs 18, mild 23 vs 18, and no ED 79 vs 113), p =0.04

At mean f/u of 33.2 months after surgery, 46.2% recovered EF after BNSRP. Overall EF recovery rate at 1 yr and 2 yr was 42% and 48.4%, no sig difference between ePLND and no PLND.

Univariate analyses predicting ED (HR; p value): Age at surgery (<60 vs ≥70 = 4.2; 0.001; 60-69 vs ≥ 70 = 2.8; 0.002); no PLND vs ePLND (0.8; ns); and Preoperative IIEF-EF (11-17 vs 0-10 = 0.9; ns ; 18-21 vs 0-10 = 0.7; 0.5; 22-25 vs 0-10 = 2.15;0.009 ; ≤ 26 vs 0-10 = 2.42; 0.001)

Multivariate analyses predicting ED (HR; p value): Age at surgery (<60 vs ≥70 = 2.5;0.02; 60-69 vs ≥70 = 2.4; 0.03); no PLND vs ePLND (0.9;</td></tr>
<tr><td>Golabek et al. 2014 [16]</td><td>PC patients treated with laparoscopic radical extraperitoneal prostatectomy (LRP)</td><td>Clinical and histological data of 295 consecutive patients who had undergoing LRP for clinically localized prostate cancer in a single institution between January 2007 and December 2012 were reviewed from prospectively maintained database. The aim was to evaluate the effect of bladder neck sparing on urinary continence and SM.

Surgical margin data shown in appropriate table.</td><td>Urinary continence</td><td>Total N = 295, mean age 62 (42-78)

UC assessed in 196 patients at 3, 6, 12 months

<table><tr><th>Postoperative time</th><th>Continence rate (RXT+)</th><th>Continence rate (RXT-)</th></tr><tr><td>3</td><td>55.61%</td><td>59.23%</td></tr><tr><td>6</td><td>80.61%</td><td>85.86%</td></tr><tr><td>12</td><td>84.69%</td><td>90.21%</td></tr></table></td></tr>
<tr><td>Gözen et al. 2015 [17]</td><td>Patients undoing LRP with cT1, cT2, and cT3 prostate cancer</td><td>Prospective analysis between March 1999 and December 2013 of patients undergoing LRP at a single institution. Patients were divided into 3 groups (cT1, cT2, cT3) and compared on various outcomes. Also reported on surgical margins and PLND. Shown in appropriate tables</td><td>Clinical stage groups (cT1, cT2, cT3)

Urinary continence

Erection sufficient for intercourse</td><td>N = 1751: cT1 (417) cT2 (842) cT3 (492)

Urinary continence (%): cT1= 391 (93.8); cT2= 776 (91.7); cT3 = 446 (90.7), p= ns

Erection sufficient for intercourse with or without med (%): cT1= 194 (46.6); cT2= 266 (31.6); cT3 = 83 (17), p<.001</td></tr>
<tr><td>Graso et al. 2012 [45]</td><td>Patients undergoing RRP with bladder neck preservation</td><td>Prospective analysis between February 1995 and May 2010 of 692 patients diagnosed with PC and underwent RRP with bladder neck preservation. Of those, 180 patients were followed for a mean postoperative follow up of 82 months</td><td>Urinary Continence (post-operative within 2 weeks, 3 months, 6 months and 12 months after the operation)</td><td>N = 180

2 weeks: 73%, 3 months: 89%; 6 months: 95.5%; 12 months : 97.7%</td></tr>
</table>

Kafkasli et al. 2013[46]	Patients with localized PC undergoing RRP and RPP	Retrospective analysis of RRP and RPP procedures from on clinic between December 2006 and December 2010. The continence level of the patients was evaluated based on the number or urinary pads used and frequency of incontinent episodes. All patients underwent bladder-sparing surgery.	Urinary Continence	N = 37 RRP and 122 RPP Continence rates: RPP : 50.8% at catheter removal and 70.5% (1 month), 79.5% (3 months) 86.9% (6 months) 93.4% (12 months) RRP: 59.5% at catheter removal and 78.4% (1 month), 89.2% (3 months) 91.9% (6 months) 91.9% (12 months) No statistical difference between RPP and RRP for frequency of
Khoder et al. 2012[21]	Patients with clinically localized PC undergoing open intrafascial Retropublic radical prostatectomy (OIF-RP)	Prospective study between January 2007 to December 2009 comparing functional outcomes at 3 and 12 months.	EF (IIEF score) Continence	N = 231, f/u data available for 179 pts *Continence:* After 3 months 60% of patients had full continence and after 12 months 86% had full continence (P <.001). In patients younger than 60 years, the proportion of patients with full continence was 64% and 95% after 3 and 12 months (p<.001) *EF* The median preoperative IIEF-5 score was 23 (range 15-25) After 3 months, median IIEF-5 score was 14 (range 0-25). After 12 months, the median IIEF-5 score was 19 (range 0-25). After 3 months, the patients' baseline score reach by 50% of patients. After 12 months, this proportion was significantly higher, reaching baseline in
Kübler et al. 2007[47]	Patients undergoing RPP with non-nerve sparing and nerve sparing	Prospective analysis between January 2001 and December 2004 where patients completed the EPIC questionnaire, a validated patient self-assessment quality of life instrument preoperatively, and at 3 to 6 months intervals following surgery. *Also included information on nerve sparing shown in table below.*	EF Urinary Continence	N = 265, 42.3% underwent nerve sparing approach *Erectile Function:* Median time to recovery was 23.8 months in nerve sparing group and was not reached in the nonnerve sparing group (p=0.011) Independent predictors of earlier recovery of erectile function were nerve sparing technique (HR 4.0, 95% CI 1.5 to 10.3, p =0.018) and better preoperative erectile function (HR 2.3, 95% CI 1.2 to 4.6, p =0.005) *Urinary Continence:* Median recovery time to recovery was 4.8 months in the nerve sparing group and 6.1 month in the nonnerve sparing group (p<0.001).

Le et al. 2010[48]	Men with localized PC treated with RP	Retrospective analysis using the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) longitudinal database at 40 clinical sites. Men are recruited by urologists at each site and they complete self-administered questionnaires upon enrolment into the study and every 6 months thereafter. Patients with ≥4 years follow-up data who were newly diagnosed at enrollment and who had RP as the primary treatment between 1995 and 2001 were included in the study. Neoadjuvant and/adjuvant therapy were excluded.	Sexual Function	N = 620, most patients had low- to intermediate risk characteristics including a PSA level of ≤10 ng/ml (86%) stage T1 and T2 (98%) and a Gleason score of ≤6 (76%). Trends in overall SF over time stratified in two groups: low (0-79) and high (80-100): High (28% of total sample): overall SF score of 53 (25) at 2 years after RP. Low: overall SF score of 25 (22) at 2 years. There was no additional improvement in mean overall SF score in either group at 4 years after RP.
Lee et al. 2015[49]	Patients who underwent RP	Retrospective analysis from 1995 to 2013 of men undergoing RRP RPP and MIRP comparing PSM and BCR-free survival rates, and 5 yr metastases-free survival rates. *Note.* MIRP data will not be reported and robot-assisted	Continence rate	Total N = 2581, RPP = 689. RRP = 402 *Continence rate at 1 year N (%)* RPP 496/578 (85.8) , RRP 252/358 (70.4), p<0.001
Lee, JK et la. 2015[50]	PC patients who underwent RP who reported poor UF or EF at 12 mo after RP	Retrospective identified men who underwent open and minimally invasive RP for localized PC from 2007 through 2013 with ≥ 12 month follow up on Urinary function (UF) and EF to determine the probability of achieving good UF or EF. Patients were excluded if they achieved function by 12 ± 2 months. Note. *Robotic assisted surgery was included in some of the analyses and thus was excluded from data*	UF EF	N = 3187 Urinary dysfunction N(%): open 273 (34); laparoscopic 226 (28) Erectile dysfunction N (%): open 432 (43); laparoscopic 289 (29)
Mao et al. 2015[51]	Patients treated with RRP at one institution (non-nerve sparing)	Prospective study between July 2010 and November 2013 of 493 consecutive patients treated with RRP at one institution. UC after RP was assessed after catheter was removed and at follow up visits or telephone interviews at 3 months after surgery.	UC	Predictors of UC after catheter removal (only sig. values shown) Age OR =1.13 (95% CI 1.00-1.28), p = 0.06 Preoperative Pelvic floor muscle exercise OR =0.19 (95% CI = 0.04-0.94) p =0.04 Predictors of UC after 3 months (only sig. values shown) Age OR =1.055 (95% CI 1.01-1.09) p =0.003 BMI OR=0.89 (95% CI 0.82-0.97), p =0.006

<table>
<tr>
<td>Marien & Lepor 2008 [52]</td>
<td>Patients undergoing open retropubic RP</td>
<td>Prospective analysis of 1110 consecutive men undergoing open retropubic RP between October 2000 and September 2005. Men were followed up at 3, 6, 12, and 24 months after ORRP.</td>
<td>UC

EF</td>
<td>N = 1110

97% and 64% of men regained UC and were engaging in sexual intercourse at 24 months
<table>
<tr><td>Group</td><td>% Total Control</td><td>% Continent</td><td>% Potent</td></tr>
<tr><td>Bilateral</td><td>56</td><td>96</td><td>60</td></tr>
<tr><td>Unilateral</td><td>54</td><td>99</td><td>44</td></tr>
<tr><td>P value</td><td>0.75</td><td>0.50</td><td>0.01</td></tr>
</table>
</td>
</tr>
<tr>
<td>Nandipati et al. 2007[53]</td>
<td>Patients who underwent RP</td>
<td>Prospective analysis of patients who underwent RP between 1995 and 1998 at one clinic. Incontinence was evaluated by the number of pads per day. Follow up data were collected at 3, 6, 12 and 24 months, and annually.</td>
<td>UC</td>
<td>N = 152

Unilateral NS UC at 3,6,12,24, <60 (%) = 56,76,92,96,88

Bilateral NS UC at 3,6,12,24, <60 (%) = 59,77,86,94,91</td>
</tr>
<tr>
<td>Penson et al. 2005 [54]</td>
<td>Patients with localized PC undergoing RP.</td>
<td>Between October 1, 1994 and October 31st, 1995, 1,288 men 39-79 years old at diagnosis with localized PC who underwent PC. Patients completed self-administered surveys on Urinary Function and EF at diagnosis and 6, 12, 24 and 60 months after diagnosis.</td>
<td>EF

Urinary Function</td>
<td>N = 1288

Urinary function summary score (baseline, 6,12,24 and 60 months): 91, 59, 71, 75, 75

EF summary score (baseline, 6,12,24 and 60 months): 72, 26, 36, 38, 39

Men in whom bilateral nerve sparing surgery was attempted were more likely to report erection firm enough for intercourse at 60 months than men who records indicated they underwent unilateral</td>
</tr>
<tr>
<td>Peterson & Chen 2012 [31]</td>
<td>Patients treated with RP</td>
<td>Prospective analysis of 4,374 patients undergoing RP (retropubic approach) between 1990 and 2007 investigating margin status and UI.

UC data reported below.</td>
<td>UI</td>
<td>Of the 4,374 patients, 1,616 (37%) had at least one continence f/u after 1 year post surgery.

Of the 1,616, 1459 (90.3%) reported UI more than 1 year after RP with a median f/u time of 50.7 months (range 12-216 months), significantly shorter than men who did not report UI (mean 63.2 months, range 12.9-199.6 months, p= 0.0010)</td>
</tr>
<tr>
<td>Razi et al. 2009 [55]</td>
<td>Patients undergoing RRP</td>
<td>Retrospective analysis of patients undergoing RRP between 1999 and 2006 was divided into 2 groups: bladder neck preservation and bladder neck reconstruction, and compare UI between the 2 groups.</td>
<td>UI

Continence was defined as no need to use sanitary pads/diapers</td>
<td>N= 103 (51 bladder neck preservation, 52 bladder neck reconstruction).

Overall UI = 5.8%

Bladder neck Preservation vs Reconstruction UC = 51 (100) vs 46 (88.5), p =0.03</td>
</tr>
</table>

Suardi et al. 2013 [56]	Patients with PC treated with bilateral NS, unilateral NS or non-NS retropubic RP with or without PLND	Prospective analysis of patients with PC treated with bilateral NS, unilateral NS or non-NS retropubic RP with or without PLND at a single tertiary referral centre between January 2003 and July 2010 investigating rates of UC. No patient received either neoadjuvant or adjuvant hormonal or radiation therapy. Continence rates were assessed by the patient reported pad usage over 24h and were followed up 1, 3,6, 12 months postoperatively and every 6 months after.	UC	N = 1249 Complete UC in 993 patients (79.5%) at mean f/u of 42.2 months after surgery UC recovery rate at 1 and 2 years: all : 76% and 79% UC recovery rate at 1 and 2 years by NS status: BNSRP 79.5% and 84%, UNSRP 62.8% and 75.9% and non-NSRP 44.6% and 44.6%, log rank P <0.001 UC recovery rate at 1 and 2 years by preoperative risk group : Low 79.9% and 83%, Intermediate 69.9% and 75.2%, and high 54.7% and 56.2%, log rank P < 0.001 Cox regression analyses predicting UC recovery after RP Risk group: Intermediate vs low: Univariate : HR = 0.82, p=0.01, Multivariate HR = 0.92, p =ns High vs low: Univariate: HR = 0.5 p<0.001, Multivariate HR 0.56, p=0.005
Stolzenburg et al. 2010 [37]	Patients who underwent BN-sparing and BN resection EERPE	Retrospective analysis for 240 patients who had undergone EERPE for localized PC between June 2005 and December 2008 to investigate the effects of BN procedure used on UC and margin status. Patients were divided into 2 groups according to BN method used: BN preservation and without BN preservation with racket handle repair of BN at 12 o'clock position. Postoperative continence was measured at 24 hr after catheter removal, 3, 6, and 12 months after EERPE.	UC	Group 1 BN preservation : N = 150 Group 2 no BN preservation but with racket handle repair N = 90 UC (0-1 pad, 2-3 pad, >3): After catheter: Group 1 19.9, 50.0, 30.1; Group 2 9.4, 50.6, 40.0, p =0.038 3 months: Group 1 73.3, 16.8, 9.9; Group 2 61.3, 27.5, 11.2, p = 0.045 6 months : Group 1 86.5, 8.1, 5.4; Group 2 80.6, 14.5, 4.9, p =0.416 12 months: Group 1 93.5, 4.8, 1.7l Group 2 91.5, 6.4, 2.1, p = 0.92

Takenake et al. (2009) [57]	Patients undergoing RP using the retropubic or laparoscopic approach who did not receive neoadjuvant hormonal therapy or preoperative radiotherapy.	Retrospective analysis from April 2000 to June 2006 compared continence rate in the early period after surgery between RRP and LRP and evaluated both preoperative EF and attempted NS procedure as predictors of early recovery of UC.		N = 146, Group 1 RRP = 37 Group 2 LRP = 109 Overall rates of UC: 18%, 49%, 68%, and 80% at 1, 3, 6, and 12 months. Group 1 UC : 27%, 54%, 77%, and 91% at 1,3, 6, and 12 months Group 2 UC : 15%, 47%, 65%, and 77% at 1,3, 6, and 12 months No statistically significant differences were found between these two groups. *Univariate Analysis* Group 1: Attempted NS procedure (one or both NVBs) was associated with recovery of urinary continence at 6 months (P = 0.0316), however a significant association between preoperative IIEF-5score (≥14) and the recovery of UC was not shown. Group 2: Attempted NS procedure was associated with UC at 1, 3, and 6 months (P = 0.0323, P = 0.0335, and P = 0.0090). Preoperative IIEF-5 score (≥14) was associated with UC at 6 months (P = 0.0475). *Multivariate Analysis:* Group 1: attempted NS procedure or Preoperative IIEF-5 score were non significant
Tzou et al. 2009[58]	Patients undergoing RRP by one surgeon	Prospective cohort study from September 1999 to February 2006 where 285 consecutive men underwent RRP with either attempted bilatereal, unilateral or non-nerve sparing surgery and completed questionnaires on continence at preop, 1 year and 2 year post-op.	UC	N = 285, 235 (82%) at year 1 and 182 (64%) at year 2 UC Pad free: Year 1 (81%), Year 2 (87%), p > 00.05 Non nerve sparing: Year 1 (84%) Year 2 (83%), p > 00.05 Unilateral NS: Year 1 (77%) Year 2 (85%), p > 00.05 Bilateral NS: Year 1 (85%) Year 2 (93%), p > 00.05 UC by EF Non nerve sparing and no erection: Year 1 27/32 pts, 84%, Year 2 22/25, 88% Nerve sparing and no erections: Year 1 33/39, 85%, Year 2 18/24 75%
Von Bodman et al. 2010 [41]	Men undergoing RPP without neoadjuvant androgen deprivation therapy	Using a prospective prostatectomy database, men undergoing RRP between November 2001 and June 2007 were analysed. At each postoperative visit (every 3-4 months in the first year, then every 6 months through year 5, then annually) outcomes regarding EF were evaluated.	EF	N = 644 IIEF Q3 + Q4, mean (95% CI) EF levels 1-3: 8.3 (7.9-8.7) EF levels 4-5: 3.9 (3.2- 4.6) Multivariate Cox regression analysis for prediction of recovery of EF: Recovery of level 1 EF: Pre-treatment EF (2 vs 1): Hr = 0.50 (95% CI 0.30-0.83), p = 0.007 Recovery of level 2 or better EF: Pre-treatment EF (2 vs 1) : HR = 0.69 (95% CI 0.48-0.99), p = 0.042

Author, year, etc	Procedure and population	Methods	Intervention	Brief results
Nerve-sparing				
Antebi et al. 2011 [43]	Patients with localized PC undergoing RP from 1992-2007 by a single surgeon.	Prospective analysis of patients undergoing RP and assessing the likelihood of achieving the Trifecta (achieve disease recurrence free, urinary continence, and sexual potency). BR is defined as PSA ≥ 0.2ng/mL, urinary continence defined as wearing no pad and sexual potency as having erections sufficient for intercourse with or without phosphodiesterase-5 inhibitor. *Also looked at surgical complication. Data shown in specific table.*	Nerve Sparing	N = 831 Unilateral nerve sparing 17.5%, Bilateral nerve sparing 63.5%, non-nerve sparing 19% The ability to perform a nerve sparing procedure was assessed from the surgeon's operative note defining whether on or both neurovascular bundles were spared. A procedure was recorded as non-nerve sparing when there was no intention to spare the neurovascular bundles and when there was uncertainty the nerves were preserved.
Comploj et al. 2011 [11]	Patients undergoing RP, performed by a single experience surgeon at one institution	Prospective study between January 2001 and December 2010 investigating positive margins and biochemical recurrence. *Also looked at surgical margins and surgical complication. Data shown in specific table.*	Nerve Sparing	N = 212, mean age = 63 (45-74) years 103/212 patients (48.6%) underwent nerve-sparing procedure. 77 cases were bilateral preservation and 26 unilateral. Nerve preservation was only considered in fully potent patients with no more than 2/5 positive cores per side.
Kübler et al. 2007[47]	Patients undergoing RPP with non-nerve sparing and nerve sparing	Prospective analysis between January 2001 and December 2004 where patients completed the EPIC questionnaire, a validated patient self-assessment quality of life instrument preoperatively, and at 3 to 6 months intervals following surgery. *Also looked at surgical complication. Data shown in specific table.*	Nerve Sparing	N = 265 and 42.3% underwent nerve sparing approach. The nerve sparing approach was performed in patients who had varying degrees of potency and sought nerve sparing surgery. Patients considered for nerve sparing usually had less than 20% biopsy core involvement, a Gleason score of 7 or less, and PSA 20ng/ml or less. The decision to spare or sacrifice a given neurovascular bundle was guided by the presence of palpable nodule and the cancer volume. A PLND was performed in select, high risk patients only.
Takenake et al. (2009) [57]	Patients undergoing RP using the retropubic or laparoscopic approach who did not receive neoadjuvant hormonal therapy or preoperative radiotherapy.	Retrospective analysis from April 2000 to June 2006 compared continence rate in the early period after surgery between RRP and LRP and evaluated both preoperative EF and attempted NS procedure as predictors of early recovery of UC.	Nerve Sparing	Bilateral nerve-sparing procedure was offered to patients with prostate-specific antigen (PSA) \10 ng/ml, Gleason score of B7, and location of biopsy of cancer positive specimen not close to the neurovascular bundle (NVB). Unilateral nerve-sparing procedure was offered to patients when one side of the apex was free of cancer and no more than one biopsy was positive on the ipsilateral side.

Tzou et al. 2009[58]	Patients undergoing RRP by one surgeon	Prospective cohort study from September 1999 to February 2006 where 285 consecutive men underwent RRP with either attempted bilateral, unilateral or non-nerve sparing surgery.	Nerve Sparing	Whether nerve sparing was performed or not was based primarily on biopsy findings, clinical stage, patient age, preoperative sexual function, and intraoperative neurovascular bundle assessment.
Author, year, etc	**Procedure and population**	**Methods**	**Intervention/Outcomes**	**Brief results**
Pelvic Lymph Node Dissection				
Abdollah et al. 2014 [4]	Patients treated with RP and anatomically ePLND	Evaluated the data of 315 M0 pN1 PC patients treated with RP and ePLND between 2000 and 2012 at one tertiary care centre. ePLND consisted of excision of fibrofatty tissue along the external iliac vein, the distal limit being the deep circumflex vein and the femoral canal. Proximally, ePLND was performed up to and including the bifurcation of the common iliac artery.	ePLND Cancer Specific Mortality	N = 315 Predicting Cancer Specific Mortality *Univariate* Removed Lymph nodes HR = 1.03 (1-1.07), p=0.05 Positive Lymph nodes: HR = 1.12 (1.07-1.17), p<0.001 *Multivariate* Removed Lymph nodes HR = 0.93 (0.88-0.99), p=0.02 Positive Lymph nodes: HR = 1.16 (1.09-1.24), p<0.001 10 yrs, CSM free survival rate was 74.7%, 85.9%, 92.4%, 96.0% and 97.9% for patients with 8, 17, 26, 36, and 45 nodes removed (p=0.02). The most informative cut-off for the number of RLN was 14. At 10 yr, the CSM free survival rates were significantly higher for patients with ≥14RLNs compared to the counterparts with <14 RLNs (p= 0.04)
Daimon et al. 2012[59]	Low risk prostate cancer patients who had undergone LRP	Between January 2002 and December 2006, 286 patients without previous endocrine treatment underwent LRP; 139 patients with PSA level <10ng/mL, biopsy Gleason sum of 6 of less, and T stage of T2a or less were divided into 2 groups: PLND or no PLND, as per surgeon's discretion.	PLND/No PLND Biochemical relapse-free survival rate	Median age = 64.9 (47-75 years) Median preoperative PSA = 6.4 ng/ML (3.6-9.9); Median Gleason score = 5.2 Median follow up time = 69.4 months The 5 year and 7 year biochemical relapse-free survival rate were 90.1% and 88.3% in patients with limited PLND, and 82.4% and 82.4% in those without PLND (log rank, P = 0.278). Laparoscopic PLND in patients with low-risk prostate cancer did not improve biochemical relapse free survival rate at 5 and 7 years after LRP.

<table>
<tr>
<td>Dobruch et al. 2014 [14]</td>
<td>Patients undergoing RP and extended endoscopic PLND.</td>
<td>In February 2011 to June 2013 165 patients undergoing RP were prospectively collected and evaluated. Seventy eight had ePLND, this was only done on subjects with intermediate or high risk, localized PC, specifically PSA above 10ng/ml, Gleason score ≥ 7, or clinical stage of prostate cancer ≥ cT2b.</td>
<td>ePLND</td>
<td>Mean LN removed = 19, LN metastases was 16.6%

In comparison to those without LN involvement, patients with LN metastases had: greater number of positive biopsy cores (3.7 vs 5.3, p<0.01), maximum percentage of cancer in biopsy core (47.0 vs 67.6, p< 0.01) and great biopsy and specimen Gleason scores (7.0 vs 7.7 and 7.0 vs 7.8).
<table>
<tr><th>Removed lymph nodes</th><th>Mean number removed lymph nodes</th><th>% positive among removed lymph nodes</th></tr>
<tr><td>Presacral</td><td>2.8</td><td>28</td></tr>
<tr><td>Common iliac</td><td>5.0</td><td>10</td></tr>
<tr><td>External iliac</td><td>7.5</td><td>23</td></tr>
<tr><td>Obturator</td><td>7.0</td><td>26</td></tr>
<tr><td>Internal iliac</td><td>2.0</td><td>0</td></tr>
</table>
</td>
</tr>
<tr>
<td>Gözen et al. 2015 [17]</td>
<td>Patients undoing LRP with cT1, cT2, and cT3 prostate cancer</td>
<td>Prospective analysis between March 1999 and December 2013 of patients undergoing LRP at a single institution. Patients were divided into 3 groups (cT1, cT2, cT3) and compared on various outcomes. Also reported on surgical margins and complications. Shown in appropriate tables.</td>
<td>Clinical stage groups (cT1, cT2, cT3)

ePLND

ePLND included external, internal iliac lympth nodes, and the nodes within the obturator fossa.</td>
<td>N = 1751: cT1 (417) cT2 (842) cT3 (492)

Mean lymph nodes removed = 13.9

Extracapsular extension:

Extraprostatic (pT3a) (%): cT1= 56 (13.4); cT2= 146 (17.3); cT3 = 174 (35.4)

Focal (pT3a) (%): cT1= 56 (13.4); cT2= 126 (14.9); cT3 = 121 (24.6);

none (pT2) (%): cT1= 305 (73.2); cT2= 570 (67.8); cT3 = 197 (40);</td>
</tr>
<tr>
<td>Hu et al. 2011 [60]</td>
<td>Men ≥65 diagnosed with PC undergoing RP</td>
<td>A population based study of men ≥ 65 years undergoing RRP and MIRP during 2004 to 2006 from the SEER linked data to determine clinical and pathologic characteristics associated with performing PLND during RP and assess the variation in yielded and morbidity of PLND by surgical approach, surgeon volume, and extent of dissection.</td>
<td>PLND vs no PLND</td>
<td>N = 5448 (no PLND = 1415; PLND = 4033)

No PLND vs PLND (%) D'Amico risk: Low (37.0 vs 24.8), Intermediate (39.8 vs 43.7), High (16.4 vs 26.4), unknown (6.8 vs 5.2), p<0.001

MIRP vs RRP

PLND performed (%): 38.3 vs 87.6, p<.001

Median LN removed: 3 vs 4, p<.001

Regression for use of PLND

D'Amico Risk (low is referent)

Intermediate OR 1.83 (CI 1.44 to 2.32), p <.001

High OR = 2.57 (CI 1.94 to 3.4), p<.001

Surgical approach (referent = MIRP) : RRP OR =16.7 (CI 11.1 to 25.0), p<.001</td>
</tr>
<tr>
<td>Ji et al., 2012[61]</td>
<td>Patients undergoing open RP for clinically localized PC</td>
<td>A prospective randomized study of patients being treated with open RP for clinically localized PC in one department between January 2000 and December 2003. Patients were allocated to</td>
<td>sPLND vs ePLND</td>
<td>N = 360 (180 ePLND and 180 standard PLND at RP)

Median follow up was 74 (SD 24.5), mean patient age at surgery was 68 (48-81)

Risk levels (%) : low (29.4%) intermediate (45.6) and high (25.0)</td>
</tr>
</table>

		standard or extended PLND. sPLND includes lymph nodes in the obturator fossa and along the external iliac vein. ePLND is a complete lymph node dissection along the obturator fossa and the external and internal vessels.		sPLND vs ePLND (%) Disease risk: Low 30.0 vs 28.9; Intermediate 46.1 vs 45.0, high 23.9 vs 26.1, p ns Number of lymph nodes removed: 10 vs 23, p <.0001 Positive lymph nodes = 10 vs 22.2, p =.002 *Hazard model of risk factors for biochemical progression* Disease risk (referent = low) Intermediate HR 2.452 (CI 1.173 to 5.125), p = .017 High HR 5.599 (CI 2.689 to 11.655)p =<.0001 Positive Margin HR 2.412 (CI 1.820 to 3.571), p<.0001 Lymph node involvement HR 2.826 (CI 1.720 to 4.645), p<.0001 Extended PLND HR 2.056 (CI 1.291 to 3.275), p = .002
Lindberg et al. 2009 [62]	Patients undergoing RP and PLND at one hospital	Prospective analysis of a series of patients undergoing RP and PLND from January 2002 to September 2007. Before Nov 2003, all PLND were limited to the obturator fossae. At that time ePLND was gradually introduced in December 2005.	Limited PLND and Extended PLND	N = 172 lPLND = 64 and ePLND 108 Clinical stage: T1-2 lPLND 97%, ePLND 81%; T3 lPLND 3%, ePLND 19% Preoperative Gleason score (2-6, 7, 8-10) lPLND: 23%, 48%, 28% ePLND 14%, 55% 31% Median lymph node retrieved was 17, ePLND range 5-40, lPLND range 3-18 Metastases were identified in 4 /64 in lPLND (6%) and 22/108 in ePLND (20%)
Mitsuzuka et al. 2013 [63]	Patients undergoing open RP who had not undergone neoadjuvant therapy	Retrospective analysis of 1268 patients between January 2000 and December 2009. Patients with low risk disease were classified according to whether they underwent PLND or not. The extent of PLND included the external iliac vein, the pelvic side wall and the obturator nerve.	PLND vs no PLND	N = 222, 66.2% underwent PLND PLND group was more likely to be older, have higher PSA and have clinical T2a when compared with no-PLND group 5 year PSA recurrence free survival was nearly identical when comparing the two groups. 87.6 (PLND) vs 87.1 (no PLND) (P =0.65, log rank test) PSA, pathological T stage, and PSM in univariate analysis and pathological T stage in multivariate analysis were significant predictors of PSA recurrence, but PLND was not.

Schiavina et al 2010 [64]	Patients treated with RP	From October 1995 to June 2009, 1510 consecutive PC patients underwent RP. A retrospective analysis was performed on 614 patients with a minimum follow up of 12 months. All patients underwent limited or extended PLND during RP.	Group 1 (1-9 LN removed) Group 2 (10 or more nodes removed)	Total mean number of nodes at RP =10.8 ± 6.4 (median 10, range 1-36) Group 1 (n = 295, 48.0%, with a mean of 5.7 ± 2.3 LNs (median 6) Group 2 (n = 319, 52.0%, with a mean of 15.6± 5.1 LNs (median 14) 5 and 10 year cancer-specific survival rates were 98.8% and 95.8%, and BCR free survival rates were 77.2% and 60.7%. BCR was observed in 21.2% patients. Clinical characteristic correlated with BCR Univariate: LN groups (2 vs 1): HR =0.658 (95% CI 0.464-0.934), p =0.019 Multivariate: LN group (2 vs 1): HR =0.564 (95% CI 0.390-0.814), p =0.002 Pathological characteristics correlated with BCR Univariate: LN groups (2 vs 1): HR =0.658 (95% CI 0.464-0.934), p =0.019 Multivariate: LN groups (2 vs 1): HR = 0.478 (95% CI 0.321-0.711), p <0.001
Schiavina et al 2011 [65]	Patients treated with RP	From October 1995 to June 2009, 1510 consecutive PC patients underwent RP. A retrospective analysis of 872 patients who had a follow- up period > 12 months and did not receive neoadjuvant hormonal therapy or adjuvant hormonal therapy. All patients underwent limited or extended PLND during RP.	Clinical risk groups (low risk, intermediate risk, high risk) LN groups (group 1 0-9 LN removed and group 2 10 or more LN removed)	Low risk N =402, Intermediate N = 347, High N = 123 LN Group 1 N = 573 LN Group 2 N =299 Total mean number of LNS obtained 10.9 ± 6.4 (11.0, 1-6), Group 1 mean = 5.7 ± 6.3 (5.0) and Group 2 = 15.7 ± 5.1 (14.0) 5 and 10 year BCR free survival rates were 74.9 and 58.7%. BCR was observed in 180 (20.6%). Clinical and pathological characteristics correlated with BCR (Low Risk) Univariate: LN groups (2 vs 1) : HR = 0.828 (0.409-1.674), p =0.599 Univariate: Number of positive LNs: HR = 1.319 (1.067-1.630), 0.010 Clinical and pathological characteristics correlated with BCR (Intermediate and high risk patients) Univariate: LN groups (2 vs 1): HR = 0.668 (0.471-0.947), p =0.023 Multivariate: LN groups (2 vs 1): HR = 0.498 (0.329-0.754), p =0.001 Univariate: # of positive LNs (2 vs 1) HR = 1.845 (1.623-2.098), p <0.001 Multivariate: # of positive LNs (2 vs 1) HR = 1.529 (1.296-1.805, p< 0.001
Schumacher et al. 2008 [66]	Node positive patients with negative preoperative staging examinations, no neoadjuvant hormonal or	A total of 122 consecutive patients with positive nodes detected at extended PLND were identified from a series of 602 patients with clinically localized PC (N0M0) based on negative staging examinations. Among the	Localization of positive nodes BCR	N = 122, median of 22 nodes (range 10-75) were removed per patient. Of these node-positive patients, 47 (39%) had 1 positive node, 27 (22%) had 2 positive nodes, and 48 (39%) had ≥ 3 positive nodes Location of positive nodes:

	radiotherapy, and who underwent extended PLND (≥10 lymph nodes in the surgical specimen) followed by RRP. None of the patients received immediate ADT.	122 patients were treated by open RRP between April 1989 and January 2007.		External iliac vein 11/122 (9%), internal iliac artery 26/122 (21.3%) In 60/122 (49.2%) found in internal iliac vessels in combination with positive nodes in the area f the obturator fossa and/or the external iliac vein. Median BCR (95% CI) 5 years: all 122 patients 13.9% (0.07-0.21), 1pN+ 24.7% (0.39-0.11), 2 pN+ 11.8% (0.27-0.03), ≥3pN+ 4.9% (0.09-0.02) 10 years: all 122 patients 2.9% (0.01-0.07) Risk factors after extended PLND followed by RRP in 122 pN+ Total number of pN+ removed : HR = 1.375 (95%CI 1.10-1.25) p<0.001 2pN+ removed: HR = 0.909 (95% CI 0.22-3.71), p =0.894 3pN+ removed: HR = 5.637 (95% CI 2.02 -15.71) p<0.001
Touijer et al. 2011 [67]	Patients with clinical localized PC undergoing LRP	Retrospective analysis of data collected prospective from January 2003 to June 2007 to investigate the rate of lymph node metastases according to the extent of PLND	Extent (standard vs limited PLND)	Limited N = 174 Standard N = 595 # lymph nodes retrieved, median (IQR): lPLND = 9 (6-13), sPLND = 13 (9-18) Lymph node involvement, n (%): lPLND 6 (3.4) sPLND 42 (7.1) In the subgroup of patients with a LNI ≥ 2%, standard PLND was a superior operation than the limited PLND in detecting nodal metastases (14.3% vs 4.5%, respectively; P = 0.003) The risk/benefit of standard vs limited PLND would be one additional grade 3 complication per 20 additional patients with nodal metastases. In the subgroup of patients with LNI < 2%, three patients (1.0%) had positive nodes after a standard PLND
Withrow et al. 2010 [68]	Patients with low-to intermediate risk PC and underwent PLND	Retrospective analysis of a subset of patients meeting inclusion criteria from a population-based case cohort study that between January 1st 1990 and December 31st 1998 who were treated with prostatectomy and had PLND.		N = 313 Men nodes removed was 6.3 (SD 4.5) HR for PC specific mortality: Lymph nodes HR = 0.97 (95% Ci 0.91-1.03), p =ns Patients with positive lymph nodes had on average 3.8 more nodes removed than those with negative results (p = 0.08). Using the 2008 CCO guideline, a cohort to mimic the target group, patients with known PSA, Gleason and T category values (n= 567) were stratified according to CCO risk category. Risk category Low (CCO PLND recommendation is optional): 196 (75.1%) received PLND in the cohort Risk category Medium (CCO PLND recommendation is recommended): 184 (84.8%) received PLND in the cohort Risk category High (CCO PLND recommendation is mandatory): 83 (93.3%) received PLND in the cohort.

Author, year, etc	Procedure and population	Methods	Intervention/outcomes of interest	Brief results
Handling and Processing RP specimen				
Egevad et al. 2008 [69]	European Network of Uropathology (ENUP) members from 321 laboratories in 15 countries completed an anonymous questionnaire on routines and handling of RP specimens	A multiple questions web-based anonymous questionnaire was launched with 37 questions about routines for the handling and reporting of RP specimens. Participants were invited by email in June 2007 and reminders were sent 3 times until September 2007.	Various handling of specimens outcomes	Response rate was 67.6%, of those, 63.6% said they report on RP specimens. Those replies were analysed and percentages for how they handled specimens is below. *Inking, tissue harvesting, and fixation (%)*: Inking of specimen [or dipped it in silver nitrate (96.6)] and were painted with 1 (37.6), 2 (28.9), 3 (23.7) or 4 (8.9) colours; harvesting of fresh tissue for research (29.1) for either academic institutions (55.4) or other laboratories (7.2); techniques for tissue harvesting (more than 1 reply was possible) were core biopsy specimens (31.3), punch biopsy from cut surfaces (37.5), shave sampling from cut surfaces (31.3) and cytological sampling from cut surfaces (6.3); and enhanced fixation (14.8). *Cutting, slicing, and embedding (%):* special equipment to slice the gross specimen (12.3), techniques for cutting the apex with 'cone method' with sagittal sections (73.5), 'cone method' with radial sections (15.7), shave method (8.3) and other (2.5); techniques for cutting the base with 'cone method' with sagittal sections (61.8), 'cone method' with radial sections (9.3), shave method (25.5) and other (3.4); total submission of seminal vesicle (63.4); embedding of prostate: always (71.6), some partial/full (17.6) and always partial (10.8); and embedding technique: whole mounts in all cases (37.5), standard blacks in all cases (55.5) and variable (7). *Grading of RP specimens (%):* Gleason system (99.5) with separate GS for main tumour (20.2), GS based on all cancer present (67) and both of these reported (12.8). *Stage, tumour volume and margins (%):* Stratification of EPE (88.2); definition of focal of minimal EPE: a few glands outside the prostate (43.6), less than one high power field of cancer outside (12.8), subjective assessment (30.2) and other (13.4); estimation of tumour volume (60.1) using planimetry method (1), grid method (4.8), largest diameter and calculate through formula (11.4), visual estimation of percentage (49.5) and largest diameter (no calculation; 33.3). Gross examination was usually performed by a qualified medical pathologist (70.4), resident pathologist (24.6) or either of them (2.5). Few said laboratory technician (2.5).
Vainer et al. 2011 [70]	RPS slices were evaluated	During a 1 year period, 238 RPS were sectioned into horizontal slices. Apex and basis was cut sagittally, and remaining slices were embedded in quadrants. Glass slides from every second horizon slice were withheld. The remaining slices were		A median of 12 slides (30%) were withheld during initial assessment 8 RPS (3.2%) the pTNM stage had to be changed: 6 cases (2.6%) from pT2b to pTc and in 2 cases (0.8%) from pT2c to pT3a. In one RPS (0.4%), the surgical margin status was changed.

<table>
<tr><td></td><td></td><td>evaluated microscopically, and essential pathological parameters were recorded. The aim of this study was to determine whether significant information is lost when only half of the horizontal tissue sections are examined.</td><td></td><td>Only little information is lost with systematic partial embedding, overlooking features significant for the postoperative treatment in only 1.2%.</td></tr>
<tr><td>Author, year, etc</td><td>Procedure and population</td><td>Methods</td><td>Intervention/ outcomes of interest</td><td>Brief results</td></tr>
<tr><td colspan="5">Pathology Reporting</td></tr>
<tr><td>Aumann et al. 2012 [71]</td><td>All pathology reports of prostatectomy specimens between January 2002-August 2010 (N = 1049) were classified into descriptive reports (DR), structured reports (SRs) and template-based synoptic reports (TBSRs) and compared on 11 organ-specific essential data items.</td><td>Development and validation of a TNM-adapted toolset that comprises an electronic instruction manual for grossing and PIS integrated template for synoptic diagnoses. Templates included all the organ specific essential information, considering the requirements of UICC TNM system. They are adapted to the cancer protocols and checklists of the CAP.</td><td>Type of report (DR, SR, TBSRs)</td><td>N = 1049

DR = 411, SR = 333, TBSR = 305

Organ-specific Essential data items:

<table>
<tr><td>ED</td><td>DR</td><td>SR</td><td>TBSR</td></tr>
<tr><td>Median EDs</td><td>7</td><td>10</td><td>11</td></tr>
<tr><td>Intraprostatic tumour spread</td><td>75.2%</td><td>85.0%</td><td>99.3%</td></tr>
<tr><td>Extraprostatic extension</td><td>25.6%</td><td>70.3%</td><td>98.3%</td></tr>
<tr><td>Seminial vesicle involvement</td><td>79.8%</td><td>88.6%</td><td>100%</td></tr>
<tr><td>Perineural invasion</td><td>33.8%</td><td>85.0%</td><td>100%</td></tr>
<tr><td>Lymph vessel invasion</td><td>24.8%</td><td>83.5%</td><td>100%</td></tr>
<tr><td>Blood vessel invasion</td><td>21.4%</td><td>83.5%</td><td>100%</td></tr>
<tr><td>Histological tumour type</td><td>92.9%</td><td>99.7%</td><td>99.7%</td></tr>
<tr><td>Gleason score</td><td>98.8%</td><td>99.4%</td><td>100%</td></tr>
<tr><td>Surgical margin status complete</td><td>81.3%</td><td>97.1%</td><td>99.7%</td></tr>
<tr><td>Nodal status</td><td>99.5%</td><td>100%</td><td>100%</td></tr>
<tr><td>TNM classification complete</td><td>85.3%</td><td>97.9%</td><td>99.7%</td></tr>
</table>

Evaluation revealed that the format of the report correlates significantly with the completeness of essential data needed to further information processing.</td></tr>
</table>

Egevad et al. 2008 [69]	European Network of Uropathology (ENUP) members from 321 laboratories in 15 countries completed an anonymous questionnaire on routines and handling of RP specimens	A multiple questions web-based anonymous questionnaire was launched with 37 questions about routines for the handling and reporting of RP specimens. Participants were invited by email in June 2007 ad reminders were sent 3 times until September 2007.	Various reporting of specimens outcomes	Response rate was 67.6%, of those, 63.6% said they report on RP specimens. Those replies were analysed and percentages for how they report specimens is below. Report TNM stage (88.6), surgical margin (location reported; 98); surgical margins (extent reported; 88.7); methods for estimation of extent in mm (36.1) in subjective description (e.g. focal or extensive; 56.7) or other (7.2) Image was routinely attached to reports (15.3), most commonly scan glass slides with tumour marked with ink or computer or to mark tumour on a schematic drawing. No one attached microscopic images to t he report.
Mossanen et al. 2014 [72]	The readability of pathology reports of RP were analyzed.	The test from the pathology report was copied into Microsoft Word and was edited to convert phrases into complete sentences and to ensure correct spelling, syntax and punctuation. No adjustments were made to the content of any report. Reports were then modified in a stepwise fashion. First descriptions of the gross specimen and immunohistochemistry performed were deleted from the report and revised readability level was calculated. Complex medical vocabulary and pathology terms were then replaced with simpler alternatives where possible with the aim of reducing readability.	Readability index (RI) (lower score means easier reading). *the Flesch-Kincaid readability formula considers the average number of words per sentence and the average number of syllables per word to evaluate readability of a given text.	Standard report mean RI = 10.5 Modified report mean RI= 11.5, $p < 0.05$ Modified report mean RI = 10.6. $p<0.05$ - removing gross descriptions and immunohistochemistry terms resulted in an increase in RI. - indicates that the remaining elements of the report describing each biopsy core remain challenging to read and interpret.

PC = prostate cancer; LRP: laparoscopic radical prostatectomy; PLND = Pelvic Lymph Node Dissection; ePLND = Extended PLND; RRP= Radical retropubic prostatectomy; lPLND = Limited PLND; LNI = Lymph Node Invasion; BCR = Biochemical Recurrence; CR = clinical recurrence; EAU = European Association of Urology; PSA = Prostate-specific antigen

Table 4. ESRS Summary (Pathological Stage and Prostate Surgical Margin Rates)

	pT2	pT2a	pT2b	pT2c	pT3	pT3a	pT3b
Open	3.7% to 35%				17.4% to 67%	30.5% to 77%	
Laparoscopic	7.4% to 18.9%*	0% to 14.1%	15.4% to 29.4%	13.8% to 20.6%	25.3% to 42%*	33.3% to 74%	12.5% to 63.6%

*Based on one study

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Appendix 1. Members of the Expert Panel

Local Health Integration Network Region	Name	Role
1	Yasser El-Gohary	Pathologist
2	Madeleine Moussa	Pathologist
2	Joseph Chin	Urologist
5 & 6	Munir Jamal	Urologist
5 & 6	John Srigley	Pathologist
7N	Rajiv Singal	Urologist
7S	Padraig Warde	Provincial Head, Radiation Treatment Program, Cancer Care Ontario
7S	Aaron Pollett	Provincial Head, Pathology and Laboratory Medicine, Cancer Care Ontario
7S	Andy Evans	Pathologist
7S	Antonio Finelli	Urologist
9	Joan Sweet	Pathologist
10	Michael Leveridge	Urologist
11	Christopher Morash	Urologist
13	Lian Widjanarko	Pathologist
14	Owen Prowse	Urologist
	Jonathan Irish	Provincial Head, Surgical Oncology, Cancer Care Ontario
	Alice Wei	Lead, Quality Improvement & Knowledge Transfer, Cancer Care Ontario

	Michelle Lee	Quality Improvement Specialist, Cancer Care Ontario

Appendix 2. College of American Pathologists Checklist elements to include in radical prostatectomy report.

[Note: This appendix (formerly Appendix 2 in Section 2 of the 2008 version of the guideline) has been rewritten to correspond to the current versions of the College of American Pathologist protocols]

The College of American Pathologists indicates that the following are required elements for examination and reporting of specimens from patients with carcinoma of the prostate gland (version 4.0.0.0, June 2017)*

- Procedure
- Histologic Type
- Histologic Grade
  - Gleason Patterns - primary, secondary (and tertiary if applicable)
  - Gleason score
  - Grade Group/ISUP grade
- Tumor Quantitation - proportion (%) of prostate involved by tumour (eyeball method) or tumour diameter if dominant nodule is present.
- Extraprostatic Extension (EPE)
  - Extent of EPE – focal or non-focal (established or extensive)
- Urinary Bladder Neck Invasion
- Seminal Vesicle Invasion (invasion of muscular wall required)
- Margin Status
  - Location(s) of positive margin(s)
  - Linear extent of positive margin(s)
    - Limited <3mm, not limited >3mm
- Treatment Effect on Carcinoma
- Regional Lymph Nodes
  - Number of Lymph Nodes Involved (required only if applicable)
  - Number of Lymph Nodes Examined (required only if applicable)
- Pathologic Stage Classification (pTNM, AJCC 8th Edition)†
  - TNM Descriptors (required only if applicable)

* Select "Download the SUMMARY OF REQUIRED ELEMENTS", which may be found on the on the College of American Pathologists website http://www.cap.org by selecting *Protocols and Guidelines* then *Cancer Protocols*. A revised version incorporating AJCC 8th edition requirements was released June 2017 to be effective January 1, 2018.

† AJCC 8th Edition should be used effective January 1, 2018. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al., editors. AJCC cancer staging manual, 8th edition. American Joint Committee on Cancer. New York, NY: Springer International Publishing. Chapter 58. 2016 (2017).

- Primary Tumor (pT)
- Regional Lymph Nodes (pN)
- Distant Metastasis (pM) (required only if applicable)

Other desirable although not required (core) elements include:

- Percent Gleason pattern 4 and/or 5 (of total tumour)
- Presence or absence of intraductal carcinoma (IDC)
- Location of extraprostatic extension
- Margin Descriptors
  - Focality (unifocal vs multifocal)
  - Nature (incised vs soft tissue)
  - Gleason pattern present at positive margins – pattern (3 vs pattern 4 or 5)
- Presence or absence of lymphovascular invasion – present or not identified
- Regional Lymph Node Descriptors
  - Size of largest metastatic deposit
  - Size of largest involved lymph node
  - Extranodal extension - present or absent

- Comments on the distance of a tumour from the resection margin are not useful as such features have no biological significance

- In cases where neoadjuvant treatment has been used (hormones, radiation, chemotherapy), and histological treatment effects are identified, the Gleason score is generally not rendered. Treatment effects often lead to spurious upgrading of the tumour.

Where relevant, appropriate clinicopathological comments should be used to clarify problems and issues related to macroscopic or microscopic components of the report.

DEFINITIONS OF REVIEW OUTCOMES

1. **EDUCATION AND INFORMATION** – EDUCATION AND INFORMATION means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "EDUCATION AND INFORMATION."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.