Evidence-Based Series 17-3 IN REVIEW

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


Report Date: September 11, 2008

An assessment conducted in November 2014 placed Evidence-based Series (EBS) 17-3 IN REVIEW. This means that it is undergoing assessment for currency and relevance. The Surgical Oncology Group has determined that it is still appropriate for this document to continue to be available while this updating process unfolds. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol).

EBS 17-3 is comprised of 3 sections and is available on the CCO Website on the PEBC Surgery page.

Section 1: Surgical and Pathological Guidelines
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

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Evidence-Based Series #17-3: Section 1

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


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
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) with an effective date of April 2007 (endorsed by Cancer Care Ontario [CCO] and the Expert Panel on Prostate Cancer Surgery and Pathology). The full protocol and checklist for RP are included in Section 2: Appendix 1 and can be found at:

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 attaining a positive margin rate of <25% for pT2 disease should be an achievable goal.

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.

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). CCO has recommended as a minimum standard that all mandatory elements on the CAP checklist (Section 2: Appendix 2) be included in the RPS pathology report.

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.
- The full CAP checklist and protocol for RP are available at [http://www.cap.org/apps/docs/cancer_protocols/2006/prostate06_pw.pdf](http://www.cap.org/apps/docs/cancer_protocols/2006/prostate06_pw.pdf) and are included in Section 2: Appendix 1 of this EBS report.

RELATED GUIDELINES

For a current listing of the following relevant guideline documents, please visit the Program in Evidenced-Based Care (PEBC) at [http://www.cancercare.on.ca](http://www.cancercare.on.ca):

- **Multidisciplinary Case Conference Standards**, June 2006
- Evidence Summary 3-10: *The Use of Brachytherapy in T1 or T2 Prostate Cancer*, May 2001 Update
- Practice Guideline 3-11: *The Use of Conformal Radiotherapy and the Selection of Radiation Dose in T1 or T2 Prostate Cancer*, October 2002
- Evidence-Based Series 3-15: *Non-hormonal Systemic Therapy in Men with Metastatic Hormone-refractory Prostate Cancer*, November 2005
- Evidence-Based Series 3-17: *Adjuvant Radiotherapy Following Radical Prostatectomy for Pathologic T3 or Margin-Positive Prostate Cancer*, February 2008.
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REFERENCES


Evidence-Based Series #17-3: Section 2

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


A Quality Initiative of the Surgical Oncology Program, Cancer Care Ontario and the Program in Evidence-based Care, Cancer Care Ontario
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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 (available at: http://www.cap.org/apps/docs/cancer_protocols/2006/prostate06_pw.pdf), 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 metastasis', '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 tumour’ were used. These results were combined with the term ‘prostatectomy’ 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 noncomparative 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).

<table>
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<th>Topic</th>
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<th>Number of EMBASE hits</th>
<th>Number ordered for full-publication review</th>
<th>Number of articles included in this report</th>
<th>Table #</th>
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<td>479</td>
<td>56</td>
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<td>Margins</td>
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<td>31</td>
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<td>Complications</td>
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<tr>
<td>Guidelines/Systematic reviews</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
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<tr>
<td>Cochrane Reviews</td>
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<td>23</td>
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</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>PLND</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masterson 2006 (57)</td>
<td>4,611,</td>
<td>Extended</td>
<td>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.</td>
</tr>
<tr>
<td>Berglund 2007 (55)</td>
<td>4,693,</td>
<td>Limited</td>
<td>Nine lymph nodes removed</td>
</tr>
<tr>
<td>Allaf 2004 (58)</td>
<td>4,000,</td>
<td>Extended</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>4,000,</td>
<td>Limited</td>
<td>Limited pelvic lymph node dissection differed in that the posterior extent of the dissection terminated with the fibrofatty tissue along the obturator nerve.</td>
</tr>
</tbody>
</table>
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 mandatory, 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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Please see Appendix 5 for the full membership of the Expert Panel on Prostate Cancer Surgery and Pathology.

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REFERENCES


72. Weckermann D, Goppelt M, Dorn R, Wawroschek F, Harzmann R. Incidence of positive pelvic lymph nodes in patients with prostate cancer, a prostate-specific antigen (PSA) level of <10 ng/mL and biopsy Gleason score of <6, and their influence on PSA progression-free survival after radical prostatectomy. BJU Int. 2006;97:1173-8.


Surgical Pathology Cancer Case Summary (Checklist)
Protocol web posting date: July 2006
Protocol effective date: April 2007
Applies to invasive carcinomas only
Based on AJCC/UICC TNM, 6th edition

PROSTATE GLAND: Radical Prostatectomy
Patient name:
Surgical pathology number:
Note: Check 1 response unless otherwise indicated.
MACROSCOPIC (rarely applicable; see “Background Documentation”)

**MICROSCOPIC**

Histologic Type
___ Cannot be determined
___ Adenocarcinoma (conventional, not otherwise specified)
___ Prostatic duct adenocarcinoma
___ Mucinous (colloid) adenocarcinoma
___ Signet-ring cell carcinoma
___ Adenosquamous carcinoma
___ Small cell carcinoma
___ Sarcomatoid carcinoma
___ Other (specify): ____________________________
___ Undifferentiated carcinoma, not otherwise specified

* Data elements with asterisks are not required for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Histologic Grade
Gleason Pattern
(if 3 patterns are present, record the most predominant and second most common patterns; the tertiary pattern should be recorded if higher than primary and secondary patterns but does not get incorporated into the Gleason score)
___ Not applicable
___ Cannot be determined
Primary Pattern
___ Grade 1
___ Grade 2
___ Grade 3
___ Grade 4
___ Grade 5
Secondary Pattern
___ Grade 1
___ Grade 2
___ Grade 3
___ Grade 4
___ Grade 5
*Tertiary Pattern
___ Grade 3
___ Grade 4
___ Grade 5
Total Gleason Score: ____

*Tumor Quantitation
*Proportion (percent) of prostate involved by tumor: ____%
*Tumor size (dominant nodule, if present):
*Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm

Extraprostatic Extension (check all that apply)
___ Absent
___ Present
*___ Focal
*Specify site(s):
*___ Nonfocal (established, extensive)
*Specify site(s):
___ Indeterminate

Seminal Vesicle Invasion (invasion of muscular wall required)
___ Absent
___ Present
___ No seminal vesicle present

Pathologic Staging (pTNM)
Primary Tumor (pT)
___ Not identified
___ pT2: Organ confined
*___ pT2a: Unilateral, involving one-half of 1 side (“lobe”) or less
*___ pT2b: Unilateral, involving more than one-half of 1 side (“lobe”) but not both sides (“lobes”)
*___ pT2c: Bilateral disease
pT3: Extraprostatic extension
___ pT3a: Extraprostatic extension
___ pT3b: Seminal vesicle invasion
___ pT4: Invasion of bladder and/or rectum (see Explanatory Note J)
Note: Subdivision of pT2 disease is problematic and has not been proven to be of importance; hence, the subcategories pT2a,b,c are considered optional.

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in regional lymph node or nodes
Specify: Number examined: ___
Number involved: ___
Distant Metastasis (pM)

___ pMX: Distant metastasis cannot be assessed

pM1: Distant metastasis

___ pM1a: Distant metastasis, non-regional lymph node(s)

___ pM1b: Distant metastasis, bone(s)

___ pM1c: Distant metastasis, other site(s)

*Note: When more than 1 site of metastasis is present, the most advanced category (pM1c) is used.

Margins (check all that apply)

___ Cannot be assessed

*___ Benign glands at surgical margin

___ Margins uninvolved by invasive carcinoma

___ Margin(s) involved by invasive carcinoma

*___ Unifocal

*___ Multifocal

___ Apical

___ Bladder neck

___ Anterior

___ Lateral

___ Postero-lateral (neurovascular bundle)

___ Posterior

___ Other(s) (specify): ____________________________

*Perineural Invasion

*___ Absent

*___ Present

*Venous (Large Vessel) Invasion (V)

*___ Absent

*___ Present

*___ Indeterminate

*Lymphatic (Small Vessel) Invasion (L)

*___ Absent

*___ Present

*___ Indeterminate

*Additional Pathologic Findings (check all that apply)

*___ None identified

*___ High-grade prostatic intraepithelial neoplasia (PIN)

*___ Inflammation (specify type):

*___ Atypical adenomatous hyperplasia (adenosis)

*___ Nodular prostatic hyperplasia

*___ Other (specify): ____________________________

*Comment(s)
Background Documentation
Protocol web posting date: July 2006
Protocol effective date: April 2007

IV. Radical Prostatectomy

A. Clinical Information
1. Patient identification
   a. Name
   b. Identification number
   c. Age (birth date)
2. Responsible physician(s)
3. Date of procedure
4. Clinical information
   a. Relevant history (previous diagnosis, treatment, includes prostate-specific antigen [PSA], imaging)
   b. Relevant findings
   c. Procedure
      (1) perineal procedure
      (2) retropubic procedure
         i. nerve sparing
         ii. standard radical
      (3) laparoscopic procedure
   d. Operative findings
   e. Anatomic site(s) of specimen(s)

B. Macroscopic Examination
1. Specimen
   a. Organ(s)/tissues included
   b. Unfixed/fixed (specify fixative)
   c. Opened/unopened
   d. Orientation, if indicated by surgeon
   e. Structures included in specimen
      (1) prostate
      (2) seminal vesicles
      (3) segments of vasa deferentia
      (4) other(s) (specify)
   f. Size (3 dimensions)
   g. Weight
   h. Obstruction of urethra (partial/complete)
   i. Descriptive features (e.g., necrosis, nodular hyperplasia)
   j. Results of intraoperative consultation
2. Tumor, if identified
   a. Location(s)
   b. Size(s)
   c. Descriptive features
   d. Extent of local invasion
Prostate • Genitourinary For Information Only

3. Regional lymph nodes
   a. Location
   b. Number (each location, if possible)

4. Blocks submitted for microscopic evaluation (include diagrams, if appropriate) (Note G)
   a. Tumor(s) (each grossly recognizable tumor)
   b. Blocks from other anatomic locations within the prostate (to evaluate for multicentricity) or systematic sampling of prostate when tumor not grossly identified (Note G)
   c. Blocks to determine extent of invasion (Note I)
      (1) prostatic capsule and periprostatic tissue adjacent to each tumor, including inked margins
      (2) seminal vesicles
      (3) periprostatic tissue at bases of seminal vesicles
   d. Apex (Note J)
   e. Vesical neck margin (Note J)
   f. All lymph nodes
   g. Frozen section tissue fragment(s) (unless saved for special studies)
   h. Other tissues (specify)

5. Special studies (specify)

C. Microscopic Evaluation

1. Tumor
   a. Histologic type (Note A)
   b. Gleason score with primary, secondary, and tertiary grades (Note B)
   c. Location(s)
   d. Extent of local invasion (Note I)
      (1) extraprostatic extension
      (2) seminal vesicle involvement

2. Margins (location and extent of margins involved with tumor) (Note H)

3. Regional lymph nodes
   a. Number (specify location)
   b. Number involved by tumor
      (1) specify location, if possible
      (2) size of metastatic deposit (optional)
      (3) extracapsular extension, if present (optional)

4. Additional pathologic findings, if present
   a. High-grade prostatic intraepithelial neoplasia (PIN)
   b. Therapy-related changes
   c. Other(s)

5. Metastasis to other organ(s) or structure(s) (specific sites)

6. Other tissue(s)/organ(s)

7. Results/status of special studies (specify)

8. Comments, as appropriate, including correlation with intraprocedural consultation, results of other specimens, and clinical information
Explanatory Notes

A. Histologic Type
This protocol applies only to carcinomas of the prostate gland. The histologic classification of prostate carcinoma is recommended and shown below. However, this protocol does not preclude the use of other systems of classification or histologic types. Mixtures of different histologic types should be indicated.

Histologic Classification of Carcinoma of the Prostate
Adenocarcinoma (conventional, not otherwise specified)
Special variants of adenocarcinoma and other carcinomas
Prostatic duct adenocarcinoma
Mu
inuous (colloid) adenocarcinoma
Signet-ring cell carcinoma
Adenosquamous carcinoma
Squamous cell carcinoma#
Basaloid and adenoid cystic carcinoma#
Urothelial (transitional cell) carcinoma#
Small cell carcinoma
Sarcomatoid carcinoma
Lymphoepithelioma-like carcinoma#
Undifferentiated carcinoma, not otherwise specified
# This protocol does not apply to these carcinomas.

B. Gleason Score
The Gleason grading system is recommended for use in all prostatic specimens containing adenocarcinoma, with the exception of those showing treatment effects, usually in the setting of androgen withdrawal. The Gleason score is an important parameter used in nomograms, such as the Partin tables, which guide individual treatment decisions. Readers are referred to the recommendations of a recent consensus conference dealing with the contemporary usage of the Gleason system. The Gleason score is the sum of the primary (most predominant in terms of surface area of involvement) Gleason grade and the secondary (second most predominant) Gleason grade. Where no secondary Gleason grade exists, the primary Gleason grade is doubled to arrive at a Gleason score. The primary and secondary grades should be reported in addition to the Gleason score, e.g., Gleason score 7(3,4) or 7(3+4).
In needle biopsy specimens, it is recommended that Gleason scores be assigned for each specimen (container). In addition, a global or composite score reflecting all specimens may be provided.
In needle biopsy specimens where there is a minor secondary component (<5% of tumor) and where the secondary component is of higher grade, the latter should be reported. For instance, a case showing >95% Gleason 3 and <5% Gleason 4 should be reported as Gleason score 7 (3,4 or 3+4). Conversely, if a minor secondary pattern is of lower grade, it need not be reported. For instance, where there is >95% Gleason score 4 and <5% Gleason 3, the score should be reported as Gleason 8 (4,4).
In needle biopsy specimens where more than 2 patterns are present, and the worst grade is neither the predominant nor the secondary grade, the predominant and highest grade should be chosen to arrive at a score (e.g., 75% grade 3, 20%-25% grade 4, <5% grade 5) is scored as 3+5=8.
Rules of grading similar to the above apply to transurethral resection and enucleation specimens.
Tertiary Gleason patterns are common in radical prostatectomy specimens. When Gleason pattern 5 is present as a tertiary pattern, its presence should be recognized in the report. For instance, in a situation where the primary Gleason grade is 3, the secondary is 4 and there is <5% Gleason 5, the report should indicate a Gleason score.
of 7 (3,4) with tertiary Gleason pattern 5.
In most radical prostatectomy specimens, a dominant nodule is not present, and the
Gleason score is based on the tumor present in the entire gland. Where more than 1
separate tumor is clearly identified, the Gleason scores of individual tumors can be
recorded separately, or, at the very least, a Gleason score of the dominant or most
significant lesion should be recorded. For instance, if there is a large Gleason score
4 (2,2) transition zone tumor and a separate smaller Gleason score 8 (4,4) peripheral
zone cancer, both scores should be reported, or, at the very least, the latter score
should be reported rather than these scores being averaged.

C. Quantitation of Tumor
There are many methods of estimating the amount of tumor in prostatic specimens.8-17
In core biopsies, the absolute number or percentage of cores involved, the linear extent
of involvement in millimeters, and the proportion (percent) of surface area of prostatic
tissue involved may be used. In transurethral resections, the proportion (percent) of
tissue involved by carcinoma, the number of positive chips and the ratio or percentage
positive chips to total chips may be used. In subtotal and radical prostatectomy
specimens, the percentage of tissue involved by tumor can also be “eyeballed.”
Additionally, in these latter specimens, it may be possible to measure a dominant tumor
nodule in at least 2 dimensions and/or to indicate the number of blocks involved by tumor
over the total number of prostatic blocks submitted.
For the purpose of this protocol, it is suggested that, at the very least, the estimated
proportion (percent) of prostatic tissue involved by tumor be included for all specimens.

D. Local Invasion in Needle Biopsies
Occasionally in needle biopsies, periprostatic fat is present and involved by tumor.8,9 This
observation should be noted since it indicates that the tumor is at least pT3a in the TNM
system. Furthermore, if seminal vesicle tissue is present (either unintentionally or
intentionally, as in a directed biopsy) and involved by tumor, this should be reported since
it indicates that the tumor is at least pT3b. Seminal vesicle invasion is defined by
involvement of the muscular wall.8,9,18 At times, especially in needle biopsy specimens, it
is difficult to distinguish between seminal vesicle and ejaculatory duct tissue. It is
important not to overinterpret ejaculatory duct as seminal vesicle since involvement of the
former by tumor does not constitute pT3b disease. If there is doubt as to whether the
involved tissue represents seminal vesicle or ejaculatory duct, then invasion of seminal
vesicle should not be definitively diagnosed.

E. Perineural Invasion
Perineural invasion in core needle biopsies has been associated with extraprostatic
extension in some correlative radical prostatectomy studies, although its exact prognostic
significance remains to be determined.9,19-22 Perineural invasion has also been found to be
an independent risk factor for predicting an adverse outcome in patients treated with
external beam radiation. The value of perineural invasion as an independent prognostic
factor, however, has been questioned in a multivariate analysis.22

F. Prostatic Intraepithelial Neoplasia (PIN)
The diagnostic term prostatic intraepithelial neoplasia (PIN), unless qualified, refers to
high-grade PIN.23 Generally, low-grade PIN is not reported. The presence of isolated PIN
should be reported in all biopsy specimens.9 The reporting of PIN in biopsies with
carcinoma is considered optional but may be important, especially in the context of limited
(minimal) adenocarcinoma. High-grade PIN in a biopsy without evidence of carcinoma is a
risk factor for the presence of carcinoma on subsequent biopsies.24,25 The reporting of
high-grade PIN in prostatectomy specimens is optional.

G. Submission of Tissue for Microscopic Evaluation in Transurethral
Resection and Radical Prostatectomy Specimens

Specimens weighing 12 g or less should be submitted in their entirety, usually in 6 to 8 cassettes.26,27 For specimens greater than 12 g, the initial 12 g are submitted (6 to 8 cassettes), and 1 cassette for every additional 5 g may be submitted. In general, random chips are submitted; however, if some chips are firmer or have a yellow or orange-yellow appearance, they should be preferentially submitted. If an unsuspected carcinoma is found in tissue submitted, and it involves 5% or less of the tissue examined, the remaining tissue may be submitted for microscopic examination, especially in younger patients.

A radical prostatectomy specimen may be submitted in its entirety or partially sampled in a systematic fashion.28,29 For partial sampling in the setting of a grossly visible tumor, the tumor and associated periprostatic tissue and margins, along with the entire apical and bladder neck margins and the junction of each seminal vesicle with prostate proper, should be submitted. If there is no grossly visible tumor, a number of systematic sampling strategies may be used. One that yields excellent prognostic information involves submitting the posterior aspect of each transverse slice along with a mid anterior block from each side. The anterior sampling detects the T1c cases arising in the transition zone and extending anteriorly. The entire apical and bladder neck margins and junction of each seminal vesicle with prostate should also be submitted.

H. Margins

The entire surface of the prostate should be inked to evaluate the surgical margins.28-36 Usually, surgical margins should be designated as “negative” if tumor is not present at the inked margin and as “positive” if tumor cells touch the ink at the margin. When tumor is located very close to an inked surface but is not actually in contact with the ink, the margin is considered negative. Positive surgical margins should not be interpreted as extraprostatic extension. Intraprostatic margins are positive in the setting of capsular incision (so-called pT2+ disease).28 If the surgical margin is positive, the pathologist should state this explicitly, although this finding is not relied upon for pathologic staging. The specific locations of the positive margins are useful to report, and there should be some indication of the extent of margin positivity (eg, unifocal versus multifocal, number of positive sites [blocks], linear extent in millimeters).

I. Extraprostatic Extension

Extraprostatic extension (EPE) is the preferred term for the presence of tumor beyond the confines of the prostate gland.28,30,31 Tumor abutting on or admixed with fat constitutes extraprostatic extension. Tumor involving loose connective tissue in the plane of fat or beyond, even in the absence of direct contact between tumor and adipocytes, indicates EPE. Extraprostatic extension also may be reported when tumor involves perineural spaces in the neurovascular bundles, even in the absence of periprostatic fat involvement. In certain locations, such as the anterior prostate and bladder neck regions, there is a paucity of fat, and in these locations EPE is determined when the tumor extends beyond the confines of the normal glandular prostate. Sometimes there is a distinct bulging tumor nodule, which may be associated with a desmoplastic stromal reaction. The specific location(s) and the number of sites (blocks) of EPE are useful to report. Descriptors of EPE (focal, nonfocal) may be used. The definition of focal versus nonfocal is subjective, but focal EPE equates with only a few neoplastic glands outside the prostate, and nonfocal EPE is more extensive spread beyond the prostatic edge. Focal or nonfocal EPE may involve 1 or more sites.

J. Apex and Bladder Neck

The apex should be carefully examined because it is a common site of margin positivity.28-31 At the apex, tumor admixed with skeletal muscle elements does not constitute extraprostatic extension. The apical and bladder neck surgical margins should be submitted entirely, preferably with a perpendicular sectioning technique. Microscopic
involvement of bladder neck muscle fibers in radical prostatectomy specimens should not be equated with a pT4 designation. The latter requires gross involvement of the bladder neck, generally with margin positivity. A recent study has shown that patients with microscopic bladder neck involvement have recurrence rates similar to patients with seminal vesicle involvement (pT3b).37

K. TNM and Stage Groupings
The protocol recommends the use of the TNM Staging System for carcinoma of the prostate of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), as shown below.38,39 By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible. Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible), and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

Primary Tumor (T): Clinical Classification
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Clinically inapparent tumor neither palpable nor visible by imaging
T1a Tumor incidental histologic finding in 5% or less of tissue resected
T1b Tumor incidental histologic finding in more than 5% of tissue resected
T1c Tumor identified by needle biopsy (eg, because of elevated PSA)
T2 Tumor confined within prostate#
T2a Tumor involves one-half of 1 lobe or less
T2b Tumor involves more than one-half of 1 lobe but not both lobes
T2c Tumor involves both lobes
T3 Tumor extends through the prostate capsule##
T3a Extracapsular extension (unilateral or bilateral)
T3b Tumor invades seminal vesicle(s)
T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall
# Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.
## Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.

Primary Tumor (pT): Pathologic Classification
pT2# Organ confined
pT2a Unilateral, involving one-half of 1 lobe or less
pT2b Unilateral, involving more than one-half of 1 lobe but not both lobes
pT2c Bilateral disease
pT3 Extraprostatic extension
pT3a Extraprostatic extension##
pT3b Seminal vesicle invasion
pT4 Invasion of bladder and/or rectum
# There is no pathologic T1 classification.
## Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

**Regional Lymph Nodes (N)**
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in regional lymph node or nodes

**Distant Metastasis# (M)**
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
M1a Non-regional lymph node(s)
M1b Bone(s)
M1c Other site(s)
# When more than 1 site of metastasis is present, the most advanced category (pM1c) is used.

**Stage Groupings (TNM) Grade**
Stage I T1a N0 M0 G1
Stage II T1a N0 M0 G2, G3-4
T1b N0 M0 Any G
T1c N0 M0 Any G
T1 N0 M0 Any G
T2 N0 M0 Any G
Stage III T3 N0 M0 Any G
Stage IV T4 N0 M0 Any G
Any T N1 M0 Any G
Any T Any N M1 Any G

**TNM Descriptors**
For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.
The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.
The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy). The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.
The “a” prefix designates the stage determined at autopsy: aTNM.

**Additional Descriptors**
Residual Tumor (R)
Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.
RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor
For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

Vessel Invasion
By AJCC/UICC convention, vessel invasion (lymphatic or venous) does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category. In all other cases, lymphatic and venous invasion by tumor are coded separately as follows.
Lymphatic Vessel Invasion (L)
LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion
Venous (Large Vessel) Invasion (V)
VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

Regional Lymph Nodes (pN0): Isolated Tumor Cells
Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Lymph nodes or distant sites with ITCs found by either histologic examination, immunohistochemistry, or nonmorphologic techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) should be classified as N0 or M0, respectively. Specific denotation of the assigned N category is suggested as follows for cases in which ITCs are the only evidence of possible metastatic disease.40,41 The assessment of ITCs in the context of prostatic adenocarcinoma is considered investigational and their biologic significance is unknown.
pN0 No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITCs)
pN0(i-) No regional lymph node metastasis histologically, negative morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(i+) No regional lymph node metastasis histologically, positive morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(mol-) No regional lymph node metastasis histologically, negative nonmorphologic (molecular) findings for ITCs
pN0(mol+) No regional lymph node metastasis histologically, positive nonmorphologic (molecular) findings for ITCs

References for Explanatory Notes
EVIDENTIARY BASE - page 38


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

The following elements on the College of American Pathologists (CAP) Radical Prostatectomy Checklist should be included in the radical prostatectomy report:

(a) Histological tumour type
(b) Gleason grading - primary pattern, secondary pattern, score
(c) Presence or absence of extraprostatic extension
(d) Presence or absence of seminal vesicle invasion (invasion of muscle wall required)
(e) pT and pN designation
(f) Margin status - involved or uninvolved by invasive carcinoma; location of positive margin(s)

- Other desirable although not mandatory elements include:
  (a) Presence of tertiary Gleason patterns
  (b) Tumour quantitation - proportion (%) of prostate involved by tumour (eyeball method) or tumour diameter if dominant nodule is present.
  (c) Extent of extraprostatic extension - focal or non-focal (established, extensive)
  (d) Presence or absence of lymphatic (small vessel) invasion
  (e) Presence or absence of venous (large vessel) invasion

- Other optional elements include:
  (a) Perineural invasion
  (b) Presence of benign prostatic glands at surgical margin
  (c) Additional pathological findings (high grade PIN, inflammation, nodular hyperplasia, atypical adenomatous hyperplasia (adenosis) etc.)

- 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.
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.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study Design</th>
<th>Positive Margin (%)</th>
<th>Biochemical Recurrence (%)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OPEN SURGERY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ward (2004)</td>
<td>7268</td>
<td>Retro CS</td>
<td>38%</td>
<td>Progression free survival:</td>
<td>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&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No adjuvant hormonal</td>
<td></td>
<td>5 year: 76% (SE: ± 1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or radiation therapy</td>
<td></td>
<td>10 year: 63% (SE: ± 1)</td>
<td></td>
</tr>
<tr>
<td>Karakiewicz</td>
<td>5831</td>
<td>Pro CS</td>
<td>Overall: 26.7%</td>
<td>Recurrence-free survival:</td>
<td>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&lt;0.001</td>
</tr>
<tr>
<td>(2005)</td>
<td></td>
<td>No adjuvant hormonal</td>
<td></td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or radiation therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blute (1997)</td>
<td>2334</td>
<td>Retro CS</td>
<td>Overall: 26%</td>
<td>Freedom from PSA recurrence:</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage: All pT2NO,</td>
<td></td>
<td>5 yr. survival free of clinical or PSA failure: -SM: 86% (SE: ± 1%) +SM: 75% (SE: ± 3%) p&lt; 0.001</td>
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<tr>
<td></td>
<td></td>
<td>No prior adjuvant</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>therapy</td>
<td></td>
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</tr>
<tr>
<td>Bianco (2005)</td>
<td>1746</td>
<td>Retro CS</td>
<td>Overall: 12%</td>
<td>Probability at 10yr Progression-free:</td>
<td>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</td>
</tr>
<tr>
<td>(Urology)</td>
<td></td>
<td>No prior adjuvant</td>
<td></td>
<td>-SM: 81% ± 3% +SM: 58% ± 12%</td>
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<tr>
<td></td>
<td></td>
<td>hormonal or radiation</td>
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<tr>
<td></td>
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<td>therapy</td>
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</tr>
<tr>
<td>Swindle</td>
<td>1389</td>
<td>Retro CS</td>
<td>Overall: 12.9</td>
<td>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</td>
<td>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</td>
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<tr>
<td>(2005)</td>
<td></td>
<td>Excluded pts. With</td>
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<tr>
<td></td>
<td></td>
<td>adjuvant therapy</td>
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</tr>
<tr>
<td>Palisaar</td>
<td>1343</td>
<td>Retro CS</td>
<td>Overall: 19.6%</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>(2005)</td>
<td></td>
<td>Excluded neo-</td>
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<td>adjuvant hormonal</td>
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<td></td>
<td>treatment</td>
<td></td>
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<tr>
<td>Guillonneau</td>
<td>1000</td>
<td>Retro CS</td>
<td>pT2c: 16% pT2a: 14%</td>
<td>Median followup: 12 months (1 to 48) Progression-free survival: 3 year: +SM: 90% +SM: 67% p&lt;0.001</td>
<td>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&lt;0.001</td>
</tr>
<tr>
<td>(2003)</td>
<td></td>
<td></td>
<td>pT2b: 41%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Study</th>
<th>Surgical Type</th>
<th>Study Design</th>
<th>Positive Margin (%)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage</td>
<td>Stage</td>
<td>Overall</td>
<td>By Stage</td>
</tr>
<tr>
<td>Ward (2004)</td>
<td>RP</td>
<td>cT1a-T3</td>
<td>Retro CS</td>
<td>38%</td>
</tr>
<tr>
<td>(32) N=7268</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Karaskiewicz</td>
<td>RRP</td>
<td>Gleason 2-10</td>
<td>Pro CS</td>
<td>26.7%</td>
</tr>
<tr>
<td>(2005) (75) N=5831</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastham (2003)</td>
<td>RP</td>
<td>Stage: cT1- T3NxMO</td>
<td>Retro CS</td>
<td>20%</td>
</tr>
<tr>
<td>(16) N=4629</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chun (2006)</td>
<td>RP</td>
<td>Gleason ≤7 = 98.9%</td>
<td>Pro CS</td>
<td>20.2%</td>
</tr>
<tr>
<td>(76) N=2402</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blute (1997)</td>
<td>Stage</td>
<td>pT2N0</td>
<td>Retro CS</td>
<td>Overall: 18.7% 1 +SM: 79.6% ≥ 2 +SM: 20.4%</td>
</tr>
<tr>
<td>(28) N=2334</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(17) N=1955</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bianco (2005)</td>
<td>RRP</td>
<td>cT1a-3</td>
<td>Retro CS</td>
<td>12% overall</td>
</tr>
<tr>
<td>(38) N=1746</td>
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</table>
### EBS 17-3 IN REVIEW

<table>
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<tr>
<th>Study</th>
<th>Surgical Type</th>
<th>Stage</th>
<th>Study Design</th>
<th>Overall</th>
<th>By Stage</th>
<th>By Location</th>
<th>Positive Margin (%)</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>Freedland (2003) (77) N=1621</td>
<td>RP</td>
<td>cT1-3</td>
<td>Retro CS</td>
<td>25%;</td>
<td></td>
<td></td>
<td></td>
<td>+SM &amp; no seminal vesicle invasion (n=402): 53% no ECE With ECE (n=300): 37% with -SM</td>
</tr>
<tr>
<td>Palisaar (2005) (25) N=1343</td>
<td>RRP</td>
<td>cT1c-3</td>
<td>Retro CS</td>
<td>15.1% NS, 25.0%</td>
<td></td>
<td></td>
<td></td>
<td>Location of positive surgical margins in relation to pT stage and surgical procedure for each prostate lobe separately</td>
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<table>
<thead>
<tr>
<th>Stage</th>
<th>%</th>
<th>(N)</th>
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<tr>
<td>cT1a</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>cT1b</td>
<td>26.4 (14)</td>
<td></td>
</tr>
<tr>
<td>cT1c</td>
<td>11.2 (55)</td>
<td></td>
</tr>
<tr>
<td>cT2a</td>
<td>9.2 (24)</td>
<td></td>
</tr>
<tr>
<td>cT2b</td>
<td>14.3 (46)</td>
<td></td>
</tr>
<tr>
<td>cT2c</td>
<td>15.3 (23)</td>
<td></td>
</tr>
<tr>
<td>cT3</td>
<td>22.4 (22.4)</td>
<td></td>
</tr>
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<table>
<thead>
<tr>
<th>Gleason 2-6</th>
<th>%</th>
<th>(N)</th>
</tr>
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<tbody>
<tr>
<td>10.9 (110)</td>
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</table>

<table>
<thead>
<tr>
<th>Gleason 7 (3+4)</th>
<th>%</th>
<th>(N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.1 (31)</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Gleason 7 (4+3)</th>
<th>%</th>
<th>(N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.6 (13)</td>
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<table>
<thead>
<tr>
<th>Gleason 8-10</th>
<th>%</th>
<th>(N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.3 (24)</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>pT2</th>
<th>%</th>
<th>(N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.8% (58/847)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>pT3</th>
<th>%</th>
<th>(N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23% (121/522)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>pT2</th>
<th>pT3a</th>
<th>pT3b</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td>NNS</td>
<td>p</td>
</tr>
<tr>
<td>843</td>
<td>669</td>
<td>0.091</td>
</tr>
<tr>
<td>14</td>
<td>4</td>
<td>0.662</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>0.593</td>
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<tr>
<th>Apex</th>
<th>Lateral</th>
<th>Others</th>
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<tr>
<td></td>
<td></td>
<td>p</td>
</tr>
<tr>
<td>15</td>
<td>1.8%</td>
<td>0.091</td>
</tr>
<tr>
<td>21</td>
<td>3.1%</td>
<td>0.662</td>
</tr>
<tr>
<td>3</td>
<td>3.8%</td>
<td>0.593</td>
</tr>
<tr>
<td>26</td>
<td>3.1%</td>
<td>0.001</td>
</tr>
<tr>
<td>4</td>
<td>0.6%</td>
<td>0.662</td>
</tr>
<tr>
<td>0.091</td>
<td>8.4%</td>
<td>0.593</td>
</tr>
<tr>
<td>8</td>
<td>0.6%</td>
<td>0.662</td>
</tr>
<tr>
<td>4</td>
<td>4.6%</td>
<td>0.593</td>
</tr>
<tr>
<td>0.001</td>
<td>3.9%</td>
<td>0.593</td>
</tr>
<tr>
<td>8</td>
<td>3.8%</td>
<td>0.593</td>
</tr>
<tr>
<td>3</td>
<td>3.3%</td>
<td>0.593</td>
</tr>
<tr>
<td>14</td>
<td>1.7%</td>
<td>0.191</td>
</tr>
<tr>
<td>9</td>
<td>1.3%</td>
<td>6</td>
</tr>
<tr>
<td>0.677</td>
<td>4.9%</td>
<td>0.073</td>
</tr>
<tr>
<td>6</td>
<td>7.6%</td>
<td>0.073</td>
</tr>
<tr>
<td>25</td>
<td>15.7%</td>
<td>0.073</td>
</tr>
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</table>

EVIDENTIARY BASE - page 43
<table>
<thead>
<tr>
<th>Study</th>
<th>Surgical Type</th>
<th>Stage</th>
<th>Study Design</th>
<th>Overall</th>
<th>By Stage</th>
<th>By Location</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orvieto (2006) (24) N=996</td>
<td>RRP cT1b-2b G</td>
<td>Gleason 3-10</td>
<td>Retro CS Cohort</td>
<td>8.8%</td>
<td>P12: 1.7%</td>
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<td>P13a: 24.2%</td>
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<td></td>
<td>P13b: 27.1%</td>
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</tr>
<tr>
<td>Berger (2002) (78) N=845</td>
<td>RRP</td>
<td></td>
<td>Cohort</td>
<td>13%</td>
<td></td>
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</tr>
<tr>
<td>Kausik (2002) (30) N=842</td>
<td>pT1a/b NOMO, excluded pre &amp; postop therapy</td>
<td>n= 354, 42%</td>
<td>Retro CS</td>
<td></td>
<td></td>
<td>Site of positive surgical margins</td>
<td># +SM</td>
</tr>
<tr>
<td>Marcovich (2000) (27) N=751</td>
<td>BNS RRP (n=222), Std. RRP (n=529) pT2-4</td>
<td>27% in standard surgeries</td>
<td>Retro CS</td>
<td>28% in BNS surgeries</td>
<td>Site of the positive margin was adjacent to or at the bladder neck in:</td>
<td></td>
<td>7% of standard RRP</td>
</tr>
<tr>
<td>Sofer (2002) (19) N=734</td>
<td>RRP Stage &lt;cT3cNO M0</td>
<td></td>
<td>Retro CS</td>
<td>29% 75% one +SM 20% two +SM 5% &gt; 2 +SM</td>
<td>Characteristics of patients with positive margins (N=210)</td>
<td>Location of positive margins</td>
<td>Single margin</td>
</tr>
<tr>
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</tbody>
</table>

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)
## EBS 17-3 IN REVIEW

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgical Type</th>
<th>Stage</th>
<th>By Location</th>
<th>Positive Margin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofer (2002) (31) N=734</td>
<td>RRP</td>
<td>cT3cN0 M0</td>
<td>Overall: 26.6%</td>
<td>Apex: 38%, Bladder Neck: 32%, Posterolateral: 13%, Anterior: 9%, Other: 29%</td>
</tr>
<tr>
<td>Fesseha (1997) (79) N=590</td>
<td>RRP</td>
<td>NS Surgery</td>
<td>Overall: 36.8% with +SM and/or ECE</td>
<td>Location: Any (%) None (%) Overall</td>
</tr>
<tr>
<td>Salomon (2003) (26) N=538</td>
<td>Radical</td>
<td>cT1a-2b Gleason 2-10 pT2a-3b</td>
<td>Location of margin by stage for pT2 patients</td>
<td></td>
</tr>
<tr>
<td>Lepor (2004) (80) N=500</td>
<td>RRP</td>
<td>cT1a-2</td>
<td>Overall: 19.7%</td>
<td>Positive margin location by stage</td>
</tr>
<tr>
<td>Pettus (2004) (34) N=498</td>
<td>RRP</td>
<td>pT2-3a N0, SV-No adjacent organ involvement</td>
<td>Overall: 19.7%</td>
<td></td>
</tr>
</tbody>
</table>

Intraoperative biopsy of the apical soft-tissue margin reduced +SM by 3.8%
<table>
<thead>
<tr>
<th>Study</th>
<th>Surgical Type</th>
<th>Study Design</th>
<th>Positive Margin (%)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Overall</td>
<td>By Stage</td>
<td>By Location</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Glyeson 8-10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 (4)</td>
<td>1 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Cannon (2005) (50)</td>
<td>RRP</td>
<td>Retro CS</td>
<td>5.6% with perineural invasion 6.4% without perineural invasion.</td>
<td></td>
</tr>
<tr>
<td>N=402</td>
<td>Median PSA =5.5 ng/ml</td>
<td></td>
<td></td>
<td>Of patients (n=61) with NS on the side of the PNI: only 1 had a +SM.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Of patients (n=11) with NS on the side of PNI: none had +SM on that side.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+SM rate on the side of the PNI:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2% with NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Of those with PNI who had BLNS (n=57):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 had +SM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PNI alone is not associated with +SM.</td>
</tr>
<tr>
<td>Rapp (2005) (9)</td>
<td>RRP</td>
<td>Retro CS</td>
<td>4% of patients with an abnormal IOPE 5% in patients with a normal IOPE.</td>
<td></td>
</tr>
<tr>
<td>N=403</td>
<td>cT1c Gleason 3-9 pT2-3b</td>
<td></td>
<td></td>
<td>With extraprostatic extension at NVB: 23% In different location: 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IOPE revealed a palpable abnormality in NVB not previously detected in 12%.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37% of these had an extraprostatic extension at the site of the abnormality.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2% of these had +SM 2% had apical +SM</td>
</tr>
<tr>
<td>Cohn (2002) (21)</td>
<td>RRP</td>
<td>Retro CS</td>
<td>9% 7% in last four years 4% in most recent year pT3a: 39% pT3b: 12.5%</td>
<td></td>
</tr>
<tr>
<td>N=382</td>
<td>cT1c (27%) cT2 (73%)</td>
<td></td>
<td></td>
<td>Apex: 41% Lateral positivity: 38% Posterior positivity: 9% Anterior positivity: 6% Bladder neck: 6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients: pT2 (71%) pT3a (20%) pT3b (5%) pT4a (3%) pT3aN1+pT4aN1 1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>52% of patients had BLNS 27% of patients had ULNS</td>
</tr>
<tr>
<td>Study</td>
<td>Surgical Type</td>
<td>Stage</td>
<td>Study Design</td>
<td>Overall</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>-------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>Emerson</td>
<td>RRP</td>
<td>N=369</td>
<td>Retro CS</td>
<td>23%</td>
</tr>
<tr>
<td>(2005) (81)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheng</td>
<td>RRP</td>
<td>N=339</td>
<td>Retro CS</td>
<td>24%</td>
</tr>
<tr>
<td>(2000) (82)</td>
<td>cT1c-3 pT2a-T3b Gleason 3-9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graefen</td>
<td>Unilateral Nerve-sparing RRP cT1-2 pT2-3c</td>
<td>N=289</td>
<td>Retro CS</td>
<td>15.9%</td>
</tr>
<tr>
<td>(1998) (22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vis</td>
<td>RRP</td>
<td>N=281</td>
<td>Retro CS</td>
<td>23.5%</td>
</tr>
<tr>
<td>(2006) (20)</td>
<td>pT2-4 Gleason 2-10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<p>| Study          | Surgical Type | Stage | Study Design | Overall | By Stage | By Location | Other                                                                 |
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<table>
<thead>
<tr>
<th>Study</th>
<th>Surgical Type</th>
<th>Study Design</th>
<th>Overall</th>
<th>By Stage</th>
<th>Positive Margin (%)</th>
<th>By Location</th>
<th>Positive margins by stage and location</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbani (1998) (13)</td>
<td>BNS-RRP cT1a-2c</td>
<td>Retro CS</td>
<td>36%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients with: 3 ≤ positive cores no neoadjuvant androgen deprivation therapy had higher (24%) incidence of +SM</td>
</tr>
<tr>
<td></td>
<td>Gleason 2-10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients with: PSA &gt; 10ng/ml Higher (16%) incidence of +SM at bladder neck</td>
</tr>
<tr>
<td></td>
<td>NS: 62% Unilateral NS: 16% NNS: 13% Unknown: 9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>When stratified by clinical stage: no significant difference in apical +SM for BLNS, ULNS, or NNS</td>
</tr>
<tr>
<td>Hsu (2007) (83)</td>
<td>Radical Unilatera l cT3 disease</td>
<td>Retro CS</td>
<td>J3.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Surgical Type</td>
<td>Stage</td>
<td>Study Design</td>
<td>Positive Margin (%)</td>
<td>Other</td>
<td></td>
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<td>--------------------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lowe (1996)</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>
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<td></td>
</tr>
<tr>
<td>Lee (2006)</td>
<td>RRP pT2a-3b</td>
<td>Retro CS</td>
<td>21%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aydin (2004)</td>
<td>RRP T1a-3a</td>
<td>Retro CS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deliveliotis (2002)</td>
<td>RRP Gleason ≤7 cT1-2</td>
<td>Retro CS</td>
<td></td>
<td>Study of patients with positive margins. Of +SM patients: 23.2% had bladder neck +SM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alsikafi (1998)</td>
<td>RRP T1b-2c Gleason 2-9</td>
<td>Retro CS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salomon (2003)</td>
<td>RRP pT3bNOM O</td>
<td>Retro CS</td>
<td>45.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Positive Margin (%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgical Type</th>
<th>Stage</th>
<th>Positive Margin (%)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Lee (2006)</td>
<td>RRP pT2a-3b</td>
<td>Retro CS</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Aydin (2004)</td>
<td>RRP T1a-3a</td>
<td>Retro CS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deliveliotis (2002)</td>
<td>RRP Gleason ≤7 cT1-2</td>
<td>Retro CS</td>
<td></td>
<td>Study of patients with positive margins. Of +SM patients: 23.2% had bladder neck +SM</td>
</tr>
<tr>
<td>Alsikafi (1998)</td>
<td>RRP T1b-2c Gleason 2-9</td>
<td>Retro CS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salomon (2003)</td>
<td>RRP pT3bNOM O</td>
<td>Retro CS</td>
<td>45.2%</td>
<td></td>
</tr>
</tbody>
</table>

### Margin Positive status among groups

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgical Type</th>
<th>Stage</th>
<th>Positive Margin (%)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowe (1996)</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>
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</tr>
<tr>
<td>Lee (2006)</td>
<td>RRP pT2a-3b</td>
<td>Retro CS</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Aydin (2004)</td>
<td>RRP T1a-3a</td>
<td>Retro CS</td>
<td></td>
<td></td>
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<tr>
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<td>RRP Gleason ≤7 cT1-2</td>
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</tr>
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<td>RRP T1b-2c Gleason 2-9</td>
<td>Retro CS</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>RRP pT3bNOM O</td>
<td>Retro CS</td>
<td>45.2%</td>
<td></td>
</tr>
</tbody>
</table>
## EBS 17-3 IN REVIEW

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgical Type</th>
<th>Stage</th>
<th>Study Design</th>
<th>Overall</th>
<th>Positive Margin (%)</th>
<th>By Stage</th>
<th>By Location</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richman (2005) (18) N=100</td>
<td>RRP cT1-2 Gleason 6-10 pT2a-3b</td>
<td>Retro CS</td>
<td>13%</td>
<td>Positive margin by stage</td>
<td>Apex: 10% Base/bladder neck 2% Posterolateral: 1% Site of capsular penetration: 0%</td>
<td>All performed by one surgeon.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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%)

### By Location
- Apex: 10%
- Base/bladder neck: 2%
- Posterolateral: 1%
- Site of capsular penetration: 0%

### Laparoscopic Surgery

<table>
<thead>
<tr>
<th>Guillonneau (2002) (11) N=550</th>
<th>LRP, &lt;cT2b, Gleason 2-8</th>
<th>Retro CS</th>
<th>16.7%</th>
<th>Positive margin by stage</th>
<th>Apex: 50% Posterolateral: 30% Prostate base: 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cT1a: 33</td>
<td>cT1b: 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-4: 0</td>
<td>5-6: 15</td>
</tr>
</tbody>
</table>

### Positive Margin by Stage
- cT1a: 33
- cT1b: 0
- cT1c: 16
- cT2a: 14
- cT2b: 41
- pT2aNO/Nx: 6.9
- pT2bNO/Nx: 18.6
- pT3aNO/Nx: 30
- pT3bN0/Nx: 32
- pT1-3N1: 67
- Gleason Score
- 2-4: 0
- 5-6: 15
- 7: 21
- 8-10: 30

### By Location
- Apex: 10%
- Posterolateral: 30%
- Prostate base: 20%
<table>
<thead>
<tr>
<th>Study</th>
<th>Surgical Type</th>
<th>Stage Design</th>
<th>Positive Margin (%)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinez-</td>
<td>LRP,</td>
<td>Pro CS</td>
<td>Overall</td>
<td></td>
</tr>
<tr>
<td>Pineiro (2006) (23)</td>
<td>T1-3,</td>
<td></td>
<td>pT2 19.2% pT3 53.2% pT4 75%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gleason 5-9</td>
<td></td>
<td>cT1: 26.7% cT2-3: 37.8%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of positive margin</th>
<th>Stratified by surgical technique</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Combined technique %</td>
<td>Descending Technique %</td>
</tr>
<tr>
<td>Postero-lateral</td>
<td>9.0</td>
<td>12.5</td>
</tr>
<tr>
<td>Apical</td>
<td>11.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Combined -multiple</td>
<td>12.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Anterior</td>
<td>4.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Bladder neck</td>
<td>0.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Seminal vesicle</td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Total</td>
<td>37.7</td>
<td>27.1</td>
</tr>
</tbody>
</table>

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.

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; MA = 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; PL5 = 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; SY- = no seminal vesicle involvement; ULNS = unilateral nerve sparing.
### Appendix 3. Table 3. Studies reporting surgical complications for radical prostatectomy.

<table>
<thead>
<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>
</thead>
<tbody>
<tr>
<td>OPEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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></td>
<td>BLNS surgery: 76% ULNS surgery: 53%</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.</td>
<td>Age</td>
<td>BLNS %  ULNS %  Total % 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>
<tr>
<td>Study</td>
<td>N</td>
<td>Study Design</td>
<td>Surgical Method</td>
<td>Urinary Function (% incontinent) Contiuence definition</td>
<td>Erectile Function %</td>
<td>Rectal Injury (RI) Blood Transfusion (BT) %</td>
<td>Other Postoperative Complications</td>
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<tr>
<td>Lance (2001)</td>
<td>1698</td>
<td>Retro CS</td>
<td>RRP (N=1382) RPP (N=316)</td>
<td>RRP: 40.1% RPP 35.2% P= 0.34</td>
<td>RRP 91.1% RPP 91.8%</td>
<td>RI: Higher rate in RRP vs. RPP (p=0.01) BT: Non-homologous transfusion: RRP: 1.4% RPP: 9.5%</td>
<td>No differences between RRP vs. RPP for: Incontinence Impotence bladder neck contracture short term complication rates</td>
</tr>
<tr>
<td>Bianco (2005)</td>
<td>1472</td>
<td>Retro CS (SEER data)</td>
<td>RRP</td>
<td>9% at 12 months 5% at 24 months</td>
<td>63% by 18months 70% by 24 months Median time to recovery of erectile function: 12 months.</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Orvieto (2006)</td>
<td>977</td>
<td>Retro CS</td>
<td>RRP</td>
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<td></td>
<td>Symptomatic BNC: 3% of patients. Continence rate at 12 months: 58% with BNC 77% without BNC p= 0.01</td>
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<tr>
<td>Burkhard (2006)</td>
<td>536</td>
<td>Retro CS</td>
<td>RRP</td>
<td>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: BLSN 1.3% ULNS 3.4% NNS 13.7%</td>
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### EBS 17-3 IN REVIEW

<table>
<thead>
<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>
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<tbody>
<tr>
<td>Cohn (2002) (21)</td>
<td>382</td>
<td>Retro CS</td>
<td>Anatomical RP</td>
<td>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: &gt; 1 pad daily.</td>
<td>BLNS: 71% of previously potent patients ULNS: 64% of previously potent patients</td>
<td></td>
<td>2 patients died of prostate cancer.</td>
</tr>
<tr>
<td>Maffezzini (2003) (46)</td>
<td>300</td>
<td>Retro CS</td>
<td>Anatomical RRP</td>
<td>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.</td>
<td></td>
<td>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)</td>
<td>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%</td>
</tr>
<tr>
<td>Lowe (1996) (42)</td>
<td>188</td>
<td>Pro CS</td>
<td>Bladder neck preservation vs. bladder neck resection</td>
<td>At 1 year: with bladder neck resection 13.7% with bladder neck preservation 10.6% Continencc 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.</td>
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<tr>
<td>Lee (2006) (48)</td>
<td>169</td>
<td>Retro CS</td>
<td>RRP</td>
<td>20% Most use one pad/day or occasionally</td>
<td>BT: 23% averaged 2.13 (1-7) units of packed RBC</td>
<td></td>
<td>Perioperative mortality: 0% 8% developed complications including: pelvic hematoma ICU for cardiac/respiratory monitoring lymphocele formation clot retention 9% developed PSA recurrence.</td>
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<tr>
<td>Deliveliotis (2002) (29)</td>
<td>149</td>
<td>Retro CS</td>
<td>RRP BNS RP PLS RP</td>
<td>At 12 months: BNS: 8% PLS: 8% BNS &amp; PLS: 6%</td>
<td>Continent: No need for any pads daily, not even for occasional leakage of a few drops of urine.</td>
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<td>Richman (2005) (18)</td>
<td>100</td>
<td>Retro CS</td>
<td>RP</td>
<td>After 1 year: 6% overall 4% needed one pad/day 2% required 2 pads per day</td>
<td>57% of patients were potent 1 year after surgery. Potency was defined as “erections sufficient for intercourse to your and your partner’s satisfaction”.</td>
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<tr>
<td>Tewari (2003) (47)</td>
<td>100</td>
<td>Pro CS</td>
<td>Anatomical RRP</td>
<td></td>
<td>50% return to potency at 440 days</td>
<td>RI: 1% BT: 67%</td>
<td>Lymphocele: 2% Deep vein thrombosis: 1%</td>
</tr>
<tr>
<td>Heidenreich (2002) (44)</td>
<td>203</td>
<td>Pro CS</td>
<td>RRP and ascending RRP</td>
<td></td>
<td></td>
<td>RI: 1%</td>
<td>Lymphocele: 9% Deep vein thrombosis: 6% Pulmonary embolism: 2% Myocardial infarction: 2% Pneumonia: 2%</td>
</tr>
<tr>
<td>Ponholzer (2006) (39)</td>
<td>552</td>
<td>Cross-sectional Survey</td>
<td>RPE</td>
<td>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</td>
<td>Deterioration of sexual life: reported by 94.4% 52% had used medications for ED</td>
<td></td>
<td>Mean follow up time was 3.3 years</td>
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<tr>
<td>Lilleby (1999) (51)</td>
<td>108</td>
<td>Cross-sectional survey</td>
<td>RP</td>
<td>Moderate or severe incontinence: 35%</td>
<td>Erectile dysfunction: 48% Psychological distress due to erectile dysfunction: 59%</td>
<td></td>
<td>Patients were evaluated using EORTC QLQ-C30, IPSS, and PAIS.</td>
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<tr>
<td>LAPAROSCOPIC</td>
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<tr>
<td>Guillonneau (2002) (11)</td>
<td>550</td>
<td>Retro CS</td>
<td>LP</td>
<td>At 12 months: 11.2% incontinent 5.9% severe incontinence Incontinent: one pad per day. Severe incontinence: &gt; 2 pads per day. -85% recovered spontaneous erections. -66% have experienced intercourse, with 1/3 using sildenafil.</td>
<td>RI: 1.45% BT: 5.27% Regular reduction in transfusion rate with experience</td>
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<td>Postoperative death: 0%</td>
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<td>OPEN AND LAPAROSCOPIC</td>
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<tr>
<td>Anastasiadis (2003) (43)</td>
<td>300</td>
<td>Retro CS</td>
<td>RRP (N=70) L P (N=230)</td>
<td>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.</td>
<td>At one year: RRP 30%, LP 41% Preserving one NVB: RRP 27%, LP 46% Preserving both NVB: RRP 44%, LP 53%</td>
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<tr>
<td>Guazzoni (2006) (35)</td>
<td>120</td>
<td>Pro, RCT</td>
<td>Comparison: RRP (N=60) vs. LP (N=60)</td>
<td></td>
<td>RI: 1.7% in LRP BT: Homologous transfusion: 9% in RRP 0% in LRP Autologous transfusion: 45% in RRP 13.3% in LRP</td>
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</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Study Design</th>
<th>Stage</th>
<th>PLND Extent</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td><strong>Open Radical Prostatectomy - Therapeutic Value</strong></td>
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<tr>
<td>Joslyn (2006) (56) N=9182</td>
<td>Retro CS (SEER database)</td>
<td>Histological grade I-IV SEER code 1-3</td>
<td>None, Extent varied</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Dimarco (2005) (61) N=7036</td>
<td>Retro CS (RRP prostate cancer database)</td>
<td>pT1-3NO Gleason 2-10</td>
<td>Bilateral, extent varied</td>
<td>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)</td>
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<tr>
<td>Berglund (2007) (55) N=4693</td>
<td>Retro CS (CaPSURE database)</td>
<td>T1-4 Gleason 2-10</td>
<td>Limited bilateral N=3961 None N=732</td>
<td>Failure free survival at 5 years: No PLND 70% Limited PLND 74% (p=0.11) No significance in any of the risk categories</td>
<td>Groups were significantly different in age and disease status.</td>
</tr>
<tr>
<td>Masterson (2006) (57) N=4611</td>
<td>Retro RV of Pro CS</td>
<td>T1-3</td>
<td>Extended PLND</td>
<td>Extent to freedom from BCR: Overall: not significant Men with negative nodes: HR 0.91; p=0.01</td>
<td></td>
</tr>
<tr>
<td>Allaf (2004) (58) N=4000</td>
<td>Retro RV</td>
<td>Gleason 4-10 68% organ confined Mean PSA 7.1 Mean PSA for limited: 7.2</td>
<td>Limited (N=1865) Extended (N=2135)</td>
<td>PSA Progression free survival at 5 years: Limited PLND: 16.5% Extended PLND: 34.4% (p=0.07) &lt;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)</td>
<td>Differences remained after stratification for: Gleason score Organ confined disease Seminal vesicle invasion Surgical margin status</td>
</tr>
<tr>
<td>Study (Year)</td>
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<tr>
<td>Fergany (2000) (60) N=575</td>
<td>Retro CS</td>
<td>T1-2</td>
<td>PLND (N=372) no PLND (N=203) PLND type not defined</td>
<td>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)</td>
<td>The follow up in the no PLND group was substantially shorter</td>
</tr>
<tr>
<td>Bhatta-Dhar (2004) (59) N=336</td>
<td>Retro RV</td>
<td>PSA ≤ 10ng/ml, Gleason ≤ 6, T1-2</td>
<td>PLND N=140; No PLND N=196</td>
<td>Biochemical relapse-free rate at 6 years: PLND: 86% No PLND: 88% (p=0.28)</td>
<td>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%).</td>
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<tr>
<td>Briganti (2006) (54) N=963</td>
<td>Pro CS</td>
<td>T1c to T3</td>
<td>Extended (≥10 nodes removed) N= 767 Limited (1-9 nodes removed) N=196</td>
<td>Complication rate: Overall: 17.4%. Extended: 19.8% Limited: 8.2% OR 2.7, p&lt;0.001 Lymphocele was higher in ePLND (10.3% vs. 4.6%) Staging benefit should be juxtaposed to complication rates.</td>
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**Staging Value**

**Open**

<table>
<thead>
<tr>
<th>Study (Year)</th>
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<th>Stage</th>
<th>PLND Extent</th>
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<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Kawakami (2006) (84) N=4303</td>
<td>Retro CS (CaPSURE database)</td>
<td>D’Amico risk groups T1-4 Gleason 2-10</td>
<td>Not specified</td>
<td>Positive nodes: Low risk 0.87% Intermediate risk 2.0% High risk 7.1%</td>
<td>80% of intermediate risk patients undergo PLND</td>
</tr>
<tr>
<td>Allaf (2004) (58) N=4000</td>
<td>Retro RV</td>
<td>Gleason 4-10 68% organ confined Mean PSA 7.1</td>
<td>Limited (N=1865) Extended (N=2135)</td>
<td>Positive nodes found: Limited PLND: 1.2% Extended PLND: 3.3% p&lt;0.0001</td>
<td>Differences remained after stratification for: Gleason score Organ confined disease Seminal vesicle invasion Surgical margin status</td>
</tr>
<tr>
<td>Study (Year) N</td>
<td>Study Design</td>
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<tr>
<td>Weckermann (2006) (72) N=474</td>
<td>Retro CS</td>
<td>pT2b to pT4 PSA level ≤10 ng/ml, Gleason ≤6</td>
<td>Radio-guided PLND</td>
<td>Standard PLND would have understaged 4% of patients. 57% of N+ were micrometastases</td>
<td>In group 1, only sentinel lymph nodes were biopsied.</td>
</tr>
<tr>
<td>Burkhard (2002) (65) N=463</td>
<td>Pro CS</td>
<td>pT2a to pT4 Median PSA 11.0 µg/l (range 0.42-172 µg/l) Cytological grading 1-3</td>
<td>Meticulous bilateral PLND</td>
<td>7% of patients would have been understaged, left with N+ Comparing preoperative and postoperative grading: 24% undergraded 12% overgraded.</td>
<td>Meticulous PLND required for accurate staging.</td>
</tr>
<tr>
<td>Bader (2003) (63) N=367</td>
<td>Pro CS</td>
<td>pT1-pT4 Gleason 2-10</td>
<td>Meticulous PLND</td>
<td>Incidence of N+: 3 times higher for the extended PLND vs. modified Of patients with clinically localized disease: 25% had histologically proven N+</td>
<td>Meticulous PLND: provides accurate staging may impact progression and survival</td>
</tr>
<tr>
<td>Bader (2002) (62) N=365</td>
<td>Pro CS</td>
<td>Median PSA 11.9 ng/ml (range 0.4-172 ng/ml)</td>
<td>Open lymph node dissection</td>
<td>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</td>
<td>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%</td>
</tr>
<tr>
<td>Alagiri (1997) (68) N=303</td>
<td>Retro CS</td>
<td>T1a-3c</td>
<td>Bilateral modified PLND</td>
<td>Unnecessary in vast majority of patients. Predictive of nodal involvement: PSA (P&lt;0.001) Gleason score (P&lt;0.001) Combined (P&lt;0.001)</td>
<td>At a PSA level of ≥ 20 ng/ml, and a Gleason score ≥ 8: Overall accuracy: 91% Positive predictive value: 67% Negative predictive value: 92%.</td>
</tr>
<tr>
<td>Weckermann (2005) (71) N=319</td>
<td>Pro CS</td>
<td>PSA ≤ 10ng/ml Gleason ≤ 6, radio-guided sentinel, Sentinel</td>
<td>52% would be understaged with standard PLND in low risk group. All men with positive lymph nodes also had positive sentinel lymph nodes.</td>
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<tr>
<td>Study (Year)</td>
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<tr>
<td>Pagliarulo (2006)</td>
<td>Retro CS</td>
<td>pT3NO 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&lt;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)</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)</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:</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)</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>
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<tr>
<td>Study (Year)</td>
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<tr>
<td>Clark (2003) N=123</td>
<td>Prospective-randomized to either a right or left extended PLND</td>
<td>T1c-3 Gleason ≤6 (68%)</td>
<td>Extended one side, limited on other side</td>
<td>Positive nodes found in 6.5% of patients</td>
<td>Randomization as to side of extended PLND was performed as there is some laterality to prostate lymphatic drainage.</td>
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<td></td>
<td>Gleason 7 (20%)</td>
<td></td>
<td>Lymph node metastases: 4/123 extended</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gleason ≥ 8 (12%)</td>
<td></td>
<td>3/123 limited dissections</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA &gt; 10ng/ml (84%)</td>
<td></td>
<td>1 person had positive nodes bilaterally.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cT1c (72%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>Parra (1996) N=155</td>
<td>cT1a-2c</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></td>
<td></td>
<td>Low risk: PSA&lt; 10ng/ml and Gleason&lt;7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk: PSA ≥ 10ng/ml, Gleason ≥ 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rogers (1996) N=689</td>
<td>cT1a-3c</td>
<td>Modified PLND</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>
<tr>
<td></td>
<td></td>
<td>Gleason 2-10</td>
<td>Open = 676, Laparoscopic = 13</td>
<td></td>
<td></td>
</tr>
</tbody>
</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 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.

<table>
<thead>
<tr>
<th>Surgeon/Pathologist</th>
<th>Hospital/Institution</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Joseph Chin, Chair (Surgeon)</td>
<td>London Health Science Centre</td>
<td>London, Ontario</td>
</tr>
<tr>
<td>Dr. John Srigley (Pathologist)</td>
<td>The Credit Valley Hospital</td>
<td>Mississauga, Ontario</td>
</tr>
<tr>
<td>Dr. Bish Bora (Surgeon)</td>
<td>Sudbury Regional Hospital</td>
<td>Sudbury, Ontario</td>
</tr>
<tr>
<td>Dr. Dimitrios Divaris (Pathologist)</td>
<td>Grand River Hospital-Kitchener-Waterloo Health Centre</td>
<td>Kitchener, Ontario</td>
</tr>
<tr>
<td>Dr. Neil Fleschner (Surgeon)</td>
<td>University Health Network, Princess Margaret Hospital</td>
<td>Toronto, Ontario</td>
</tr>
<tr>
<td>Dr. Edward Matsumoto (Surgeon)</td>
<td>St. Joseph’s Hospital</td>
<td>Hamilton, Ontario</td>
</tr>
<tr>
<td>Dr. Tom McGowan (Radiation Oncology)</td>
<td>Credit Valley Hospital</td>
<td>Mississauga, Ontario</td>
</tr>
<tr>
<td>Dr. Christopher Morash (Surgeon)</td>
<td>The Ottawa Hospital - Civic Campus</td>
<td>Ottawa, Ontario</td>
</tr>
<tr>
<td>Bryan Rumble, Research Coordinator</td>
<td>Program in Evidence-based Care, McMaster University</td>
<td>Hamilton, Ontario</td>
</tr>
<tr>
<td>Eric Winquist (Medical Oncology)</td>
<td>London Health Science Centre</td>
<td>London, Ontario</td>
</tr>
<tr>
<td>Dr. Sheila McNair, Assistant Director</td>
<td>Program in Evidence-based Care, McMaster University</td>
<td>Hamilton, Ontario</td>
</tr>
<tr>
<td>Dr. Alexander Boag (Pathologist)</td>
<td>Kingston General Hospital</td>
<td>Kingston, Ontario</td>
</tr>
<tr>
<td>Mr. Paul Darby, CEO</td>
<td>Peterborough Regional Health Centre</td>
<td>Peterborough, Ontario</td>
</tr>
<tr>
<td>Dr. Andrew Evans (Pathologist)</td>
<td>University Health Network, Toronto General Hospital</td>
<td>Toronto, Ontario</td>
</tr>
<tr>
<td>Amber Hunter, Program Manager</td>
<td>Surgical Oncology Program</td>
<td>Cancer Care Ontario</td>
</tr>
<tr>
<td>Dr. John Kell</td>
<td>President, Society of Urological Surgery in Ontario</td>
<td>Toronto, Ontario</td>
</tr>
<tr>
<td>Dr. Arun Mathur (Surgeon)</td>
<td>Oshawa Clinic</td>
<td>Oshawa, Ontario</td>
</tr>
<tr>
<td>Linda Mayhew, Research Coordinator</td>
<td>Program in Evidence-based Care, McMaster University</td>
<td>Hamilton, Ontario</td>
</tr>
<tr>
<td>Dr. Madeleine Moussa (Pathologist)</td>
<td>London Health Sciences Centre</td>
<td>London, Ontario</td>
</tr>
<tr>
<td>Dr. Linda Rabeneck, RVP</td>
<td>Toronto Sunnybrook Regional Cancer Centre</td>
<td>Toronto, Ontario</td>
</tr>
<tr>
<td>Dr. Thomas Short (Surgeon)</td>
<td>Credit Valley Medical Arts Centre</td>
<td>Mississauga, Ontario</td>
</tr>
<tr>
<td>Dr. John Tsihlias (Surgeon)</td>
<td>William Osler Health Centre</td>
<td>Etobicoke, Ontario</td>
</tr>
<tr>
<td>Dr. Robin McLeod, Quality Lead</td>
<td>Cancer Care Ontario</td>
<td>Toronto, Ontario</td>
</tr>
</tbody>
</table>
Guideline for Optimization of Surgical and Pathological Quality Performance for Radical Prostatectomy in Prostate Cancer Management: EBS Development Methods and External Review Process


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.

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

<table>
<thead>
<tr>
<th>CLARIFYING RISK STRATIFICATION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>One respondent suggested clarifying risk stratification since patients can have a low Gleason score but still be very advanced.</td>
</tr>
<tr>
<td><strong>Response:</strong> 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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STANDARD FOR MORTALITY RATES:</th>
</tr>
</thead>
<tbody>
<tr>
<td>One respondent requested that mortality rates of &lt;1% should be a standard.</td>
</tr>
<tr>
<td><strong>Response:</strong> Under surgical recommendations, the last bullet under radical prostatectomy, &lt;1% mortality was added as a goal.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NERVE SPARING:</th>
</tr>
</thead>
<tbody>
<tr>
<td>One respondent felt that there are patients with intermediate risk who should not have nerve sparing. (ie. cT2 Gleason 4+3&gt;50%) They suggested to reword the recommendation.</td>
</tr>
<tr>
<td><strong>Response:</strong> The recommendation under radical prostatectomy (bullet 4) was reworded accordingly.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IMPACT OF POSITIVE SURGICAL MARGINS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td><strong>Response:</strong> Under the Results section, Surgical Questions 1. (first paragraph), a statement was added to indicate the above.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PATIENT PREFERENCES:</th>
</tr>
</thead>
<tbody>
<tr>
<td>One respondent commented that patient preferences were not addressed adequately.</td>
</tr>
<tr>
<td><strong>Response:</strong> 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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GOALS OF RADICAL PROSTATECTOMY:</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td><strong>Response:</strong> 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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MULTIDISCIPLINARY ASSESSMENT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Several respondents were concerned about requiring input from a multidisciplinary team for all high-risk patients considering surgical options.</td>
</tr>
<tr>
<td><strong>Response:</strong> 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).”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TARGET RATES:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Given that most contemporary series publish blood transfusion rates of &lt;1%, one respondent commented that this should be the standard, not &lt;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.</td>
</tr>
<tr>
<td><strong>Response:</strong> 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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SHORT-TERM OUTCOMES:</th>
</tr>
</thead>
<tbody>
<tr>
<td>One respondent noticed that several studies were missing from the systematic review.</td>
</tr>
<tr>
<td><strong>Response:</strong> 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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RATING QUALITY OF STUDIES AND META-ANALYSIS:</th>
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<td>One respondent inquired as to the lack of the levels of evidence, ranking of quality of recommendations and meta-analysis.</td>
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| **Response:** The panel felt the evidence was not of high enough quality for a quality assessment or meta-
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.

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REFERENCES
