

Mini-reviews

This month there are two mini-reviews on aspects of prostate cancer. The first, from the USA, presents the implications of surgical margin status after radical prostatectomy and the potential role of adjuvant radiation therapy. The second, from the USA and Belgium, discusses the use of hormonal therapy for PSA-only recurrence of prostate cancer after previous local therapy.

In the third mini-review, the condition known as hypoactive sexual desire disorder is described, and that it is often ignored or erroneously treated as erectile dysfunction suggests to the authors that education of doctors and patients is required. Finally, there is a mini-review of conventional and alternative methods for providing analgesia in renal colic.

Surgical margin status after radical retropubic prostatectomy

MASOOD A. KHAN and ALAN W. PARTIN

James Buchanan Brady Urological Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Accepted for publication 13 August 2004

KEYWORDS

prostate adenocarcinoma, radical prostatectomy, surgical margin, prognosis

INTRODUCTION

Since the early 1980s, improved knowledge of male pelvic anatomy, along with the refinement of surgical technique, have led to a dramatic change in the management of localized prostate cancer. There has been a dramatic increase in the number of radical prostatectomies (RPs) in the USA over the past 20 years (peaking at 104 000 in 1992–93) [1]. In addition, the incidence of lymph node and/or seminal vesicle involvement has decreased considerably over the past few years [2,3]. As a result, interest has recently focused on the relationship between surgical margin status and disease progression after RP. In this mini-review we discuss the implications of surgical margin status after RP and the potential role of adjuvant radiation therapy.

DEFINITION OF SURGICAL MARGIN STATUS

Current reports give several definitions of a positive surgical margin after RP; notably, Zeitman *et al.* [4] assign a positive margin status if tumour is present at or within 1 mm of the surgical margin. However, Epstein *et al.* [5,6] found that if the tumour is not actually

cut across and/or at the inked surface (the external surface of the prostate is covered with India ink before sectioning), a 'close surgical margin' (<0.1 mm) should not be designated as a positive surgical margin. The authors state that 'close margins' are unrelated to the tumour that would have been left within the patient, nor do they indicate any greater risk of disease progression after RP. Therefore, a positive surgical margin is generally defined as extension of tumour to the inked surface of the resected specimen.

CAUSE AND SITE OF POSITIVE MARGINS

Accidental incision into the prostate and a site of tumour that may not extend beyond the prostate often result in positive surgical margins. This 'capsular incision' most frequently occurs in the apex and may account for >70% of cases with a positive surgical margin [7]. Accordingly, Stamey *et al.* [8] and Ackerman *et al.* [9] found that capsular incision represented 45% and 87% of positive apical margins, respectively, seemingly resulting from an artefact of sectioning the apex [10]. Another important factor is the 'detrusor apron', a continuation of the anterior bladder wall with the pubis, which constitutes a large portion of the anterior fibromuscular stroma [11]. This stroma covers the entire anterior and anterolateral surface of the glandular prostate, hence transection can typically produce a capsular incision and lead to a potential 'false-positive' margin [11].

Positive margins resulting from capsular incision are also typically found in the posterior margin and the mid portion of the gland [8,9]. Encouragingly, a higher risk of progression after RP is not usually linked with positive surgical margins arising from capsular incisions [7,12–14].

Failure to adequately address extraprostatic extension of tumour, which most often occurs posterolaterally in the region of the neurovascular bundles (NVBs), may lead to a positive margin. NVBs are often spared despite bulky disease, in an attempt to safeguard potency. The value of this practice has been questioned, as recent evidence indicates that margin status is not significantly different between nerve-sparing and non-nerve-sparing surgery (retropubic or perineal) when patients are matched for stage and grade [7]. However, it is notable that attempts to preserve adjacent vital structures such as the rectum, rather than NVBs, more commonly result in an extraprostatic extension [7].

INCIDENCE OF POSITIVE SURGICAL MARGINS

Epstein *et al.* [7,13] examined RPs undertaken by one surgeon at the Johns Hopkins Hospital, and found that over time there was a striking change in the incidence of positive margins. Reviews from 1982 to 1988 showed that 41% of RP specimens had positive margins, decreasing to 16% between 1994 and 1995 [7,13]; when only stage T1c disease was considered, this rate decreased further to 8%. In 1999, the incidence of positive margins for all patients operated by the same surgeon was 5.8% [7]. Other institutions have also reported this trend in the decrease in positive margins [15,16].

Various factors have contributed to this sharp decline in positive surgical margins, including a better understanding of periprostatic anatomy, and improved surgical techniques. These include wide excision of the NVBs when necessary, and a lateral approach to the NVBs, allowing complete resection of the apex, while preserving the NVBs when appropriate [15,17]. Furthermore, the early 1990s saw a marked stage migration of prostate cancer at diagnosis, with 75% of men in the USA presenting with clinical stage T1c disease [16]. Compared to men with palpable disease, this cohort have more favourable pathological

findings, including more organ-confined disease and lower positive surgical margins [18–20]. During the past decade, patient selection has also been important. Men with high biopsy Gleason scores (≥ 7) and/or elevated serum PSA levels (>10 ng/mL) are less likely to have organ-confined disease, and hence are less likely to be recommended to undergo surgery [21,22].

To improve continence rates, interest has been generated in bladder-neck preserving prostatectomy, but there is concern that this might be associated with more positive surgical margins. Unfortunately, although recent studies indicate that for selected patients (i.e. T1c–T2a, low-volume and -grade disease) preserving the bladder neck does not result in more positive surgical margins or disease progression, continence rates have not greatly improved either [23–24].

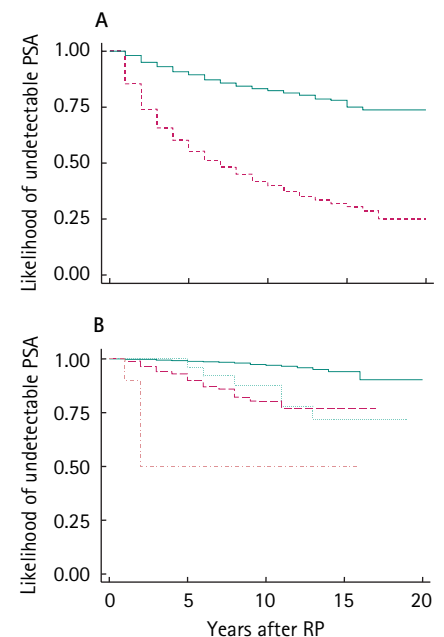
MARGIN STATUS AND DISEASE PROGRESSION

The likelihood of progression is considered to be significantly greater for men with true positive surgical margins than men with negative margins [25]. Two studies predicted the progression-free probability at 5 years after RP to be 81–83% for margin-negative disease, decreasing to 58–64% for margin-positive disease [15,17]. Multifocal and extensive positive margins are regarded as higher risks for progression than solitary and focally-positive margins [7]. Similarly, margins positive at the bladder base indicate a higher risk of biochemical failure [26].

In keeping with other reports, Fig. 1A (data from our institution) shows that a positive margin status confers higher biochemical disease recurrence. Despite the importance of margin status in predicting progression, it would be a mistake to ignore the impact of other variables, including seminal vesicle and lymph-node status, extraprostatic extension, and prostatectomy Gleason score, all of which affect the prognosis adversely.

The Gleason score is the most powerful predictor of progression after RP [7]. Fig. 1B shows the influence of Gleason score on margin status in biochemical recurrence-free survival estimates after RP. Biochemical recurrence rates for positive margins with a Gleason score of 2–6 are similar to those for negative margins with a Gleason score of

FIG. 1. Biochemical survival estimates for: **A**, all 2897 men after RP by surgical margin status (negative, green, 2560 men; positive, red, 337 men). **B**, the influence of RP Gleason score on biochemical survival estimates for men after RP by surgical margin status (green line, surgical margin, SM, –ve, seminal vesicle, SV, –ve and lymph node, LN, –ve, Gleason < 7 ; red line, SM, SV and LN all –ve, Gleason 7–10; light green line, SM +ve, SV –ve, LN –ve, Gleason < 7 ; light red line, SM +ve, SV –ve, LN –ve, Gleason 7–10). All data derived from the series of P.C. Walsh, The Johns Hopkins Hospital, 1982–2001. As only nine men in B were SM +ve and a Gleason score of 7–10 with LN –ve and SV –ve, the long-term biochemical survival estimates are, misleadingly, much better than normally expected for this subset of men.



7–10. However, when seminal vesicles and lymph nodes are negative and the Gleason score is 7–10, a positive surgical margin predicts a high rate of failure.

ADJUVANT RADIATION THERAPY FOR POSITIVE MARGINS

There is no current consensus on the need for or the best treatment for positive surgical margins. Nevertheless, intuitively, men with positive margins are likely to fail locally, and so are suitable candidates for adjuvant external beam radiotherapy (EBRT). Recently, Leibovich *et al.* [27] studied 76 men with organ-confined disease (T2N0) and a single

positive margin, who received early EBRT (within 3 months of surgery), and matched them 1 : 1 with controls who did not receive adjuvant EBRT; the estimated 5-year clinical and biochemical progression-free survival was higher in the early EBRT group. Notably, although similar results were reported by others [28,29], no studies have yet shown an overall survival benefit. Many margin-positive tumours reflect high-grade and/or -stage disease with occult distant metastases, despite presenting with presumed clinically localized disease. Thus although a positive margin may indicate local disease recurrence, unfortunately it does not exclude occult distant disease. Han *et al.* [30] recently determined whether biochemical failure after RP in men with Gleason score 7 disease and positive surgical margins is associated with distant metastasis or local tumour recurrence. Isolated clinical local recurrence was rare amongst these men; hence EBRT given when PSA levels increased controlled the disease poorly. Accordingly, men with a Gleason score of ≥ 7 and positive surgical margins should be considered for a systemic approach to adjuvant therapy.

In the absence of lymph node involvement with negative seminal vesicles and Gleason score < 8 disease, delayed biochemical recurrence (> 1 year after surgery) predicts local recurrence. Hence, these patients may benefit from EBRT [31,32]. Both immediate and delayed adjuvant EBRT decrease PSA levels and produce modest improvements in 5-year biochemical progression-free survival rates [31,32], but no improvements in overall survival have been reported.

In summary, some positive surgical margins might be controlled locally with immediate or delayed adjuvant EBRT, but there is no evidence that adjuvant EBRT improves survival for this cohort, nor are there sufficient data to support early vs late adjuvant EBRT. To manage margin-positive patients, it is vital to review the pathology accurately, to determine the grade, location and extent of margins, and the status of seminal vesicles and lymph nodes. For example, systemic therapy (e.g. hormonal) should be considered in the presence of positive surgical margins with positive seminal vesicles, lymph nodes or a Gleason score of ≥ 7 . However, adjuvant EBRT should be considered for biochemical recurrence > 1 year after RP with a Gleason score of 2–6 and negative seminal vesicle and lymph node

involvement, as this is more likely to reflect local recurrence.

CONCLUSIONS

The prevalence of positive surgical margins has declined steadily since the early 1990s. Explanations include a better understanding of pelvic anatomy, developments in surgical techniques, stage shift of the disease at presentation, and improved patient selection. Positive margins are predominantly apical and posterior, caused by capsular incisions, and do not appear to affect disease recurrence. However, a true positive margin increases the risk of progression, and therefore is an important factor for men undergoing RP. Despite the importance of margin status, other variables, including extraprostatic extension, seminal vesicle and lymph nodes status, and Gleason score, all affect the prognosis adversely, and must also be considered. At present, little consensus exists about the treatment of positive surgical margins, but there is some evidence that EBRT might benefit selected cases. Prospective randomized controlled trials comparing immediate vs delayed EBRT are required, as current studies have produced mixed results.

CONFLICT OF INTEREST

None declared.

REFERENCES

- 1 Wingo PA, Guest JL, McGinnis L *et al.* Patterns of inpatient surgeries for the top four cancers in the United States, National Hospital Discharge Survey, 1988–95. *Cancer Causes Control* 2000; **11**: 497–512
- 2 Pound CR, Partin AW, Epstein JI, Walsh PC. Prostate-specific antigen after anatomic radical retropubic prostatectomy. Patterns of recurrence and cancer control. *Urol Clin North Am* 1997; **24**: 395–406
- 3 Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. *Urol Clin North Am* 2001; **28**: 555–65
- 4 Zietman AL, Coen JJ, Shipley WU, Althausen AF. Adjuvant irradiation after radical prostatectomy for adenocarcinoma of prostate: analysis of freedom from PSA failure. *Urology* 1993; **42**: 292–9
- 5 Epstein JI. Evaluation of radical prostatectomy capsular margins of resection. The significance of margins designated as negative, closely approaching, and positive. *Am J Surg Pathol* 1990; **14**: 626–32
- 6 Epstein JI, Sauvageot J. Do close but negative margins in radical prostatectomy specimens increase the risk of postoperative progression? *J Urol* 1997; **157**: 241–3
- 7 Epstein JI. Pathologic assessment of the surgical specimen. *Urol Clin North Am* 2001; **28**: 567–94
- 8 Ackerman DA, Barry JM, Wicklund RA, Olson N, Lowe BA. Analysis of risk factors associated with prostate cancer extension to the surgical margin and pelvic node metastasis at radical prostatectomy. *J Urol* 1993; **150**: 1845–50
- 9 Stamey TA, Villers AA, McNeal JE, Link PC, Freiha FS. Positive surgical margins at radical prostatectomy. importance of the apical dissection. *J Urol* 1990; **143**: 1166–73
- 10 Wieder JA, Soloway MS. Incidence, etiology, location, prevention and treatment of positive surgical margins after radical prostatectomy for prostate cancer. *J Urol* 1998; **160**: 299–315
- 11 Myers RP. Detrusor apron, associated vascular plexus, and avascular plane: relevance to radical retropubic prostatectomy – anatomic and surgical commentary. *Urology* 2002; **59**: 472–9
- 12 Watson RB, Civantos F, Soloway MS. Positive surgical margins with radical prostatectomy: detailed pathological analysis and prognosis. *Urology* 1996; **48**: 80–90
- 13 Epstein JI, Pizov G, Walsh PC. Correlation of pathologic findings with progression after radical retropubic prostatectomy. *Cancer* 1993; **71**: 3582–93
- 14 Barocas DA, Han M, Epstein JI *et al.* Does capsular incision at radical retropubic prostatectomy affect disease-free survival in otherwise organ-confined prostate cancer? *Urology* 2001; **58**: 746–51
- 15 Ohori M, Wheeler TM, Kattan MW,

- Goto Y, Scardino PT. Prognostic significance of positive surgical margins in radical prostatectomy specimens. *J Urol* 1995; **154**: 1818–24
- 16 Stamey TA, Donaldson AN, Yemoto CE, McNeal JE, Sozen S, Gill H. Histological and clinical findings in 896 consecutive prostates treated only with radical retropubic prostatectomy: epidemiologic significance of annual changes. *J Urol* 1998; **160**: 2412–7
- 17 Epstein JI, Partin AW, Sauvageot J, Walsh PC. Prediction of progression following radical prostatectomy. A multivariate analysis of 721 men with long-term follow-up. *Am J Surg Pathol* 1996; **20**: 286–92
- 18 Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA* 1994; **271**: 368–74
- 19 Geary ES, Stamey TA. Pathological characteristics and prognosis of nonpalpable and palpable prostate cancers with a Hybritech prostate specific antigen of 4–10 ng/ml. *J Urol* 1996; **156**: 1056–8
- 20 Han M, Partin AW, Chan DY, Walsh PC. An evaluation of the decreasing incidence of positive surgical margins in a large retropubic prostatectomy series. *J Urol* 2004; **171**: 23–6
- 21 Partin AW, Yoo JK, Carter HB *et al*. The use of prostate-specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. *J Urol* 1993; **150**: 110–4
- 22 Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Contemporary update of prostate cancer staging nomograms (Partin tables) for the new millennium. *Urology* 2001; **58**: 843–8
- 23 Lowe BA. Comparison of bladder neck preservation to bladder neck resection in maintaining postprostatectomy urinary continence. *Urology* 1996; **48**: 889–93
- 24 Marcovich R, Wojno KJ, Wei JT, Rubin MA, Montie JE, Sanda MG. Bladder neck-sparing modification of radical prostatectomy adversely affects surgical margins in pathologic T3a prostate cancer. *Urology* 2000; **55**: 904–8
- 25 van den Ouden D, Hop WC, Kranse R, Schroder FH. Tumour control according to pathological variables in patients treated by radical prostatectomy for clinically localized carcinoma of the prostate. *Br J Urol* 1997; **79**: 203–11
- 26 Obek C, Sadek S, Lai S, Civantos F, Rubinowicz D, Soloway MS. Positive surgical margins with radical retropubic prostatectomy. anatomic site-specific pathologic analysis and impact on prognosis. *Urology* 1999; **54**: 682–8
- 27 Leibovich BC, Engen DE, Patterson DE *et al*. Benefit of adjuvant radiation therapy for localized prostate cancer with a positive surgical margin. *J Urol* 2000; **163**: 1178–82
- 28 Stein A, deKernion JB, Dorey F, Smith RB. Adjuvant radiotherapy in patients post-radical prostatectomy with extending through capsule or positive seminal vesicles. *Urology* 1992; **39**: 59–62
- 29 Cheng WS, Frydenberg M, Bergstralh EJ, Larson-Keller JJ, Zincke H. Radical prostatectomy for pathologic stage C prostate cancer. influence of pathologic variables and adjuvant treatment on disease outcome. *Urology* 1993; **42**: 283–91
- 30 Han M, Pound CR, Potter SR, Partin AW, Epstein JI, Walsh PC. Isolated local recurrence is rare after radical prostatectomy in men with Gleason 7 prostate cancer and positive surgical margins: therapeutic implications. *J Urol* 2001; **165**: 864–6
- 31 Partin AW, Pearson JD, Landis PK *et al*. Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. *Urology* 1994; **43**: 649–59
- 32 Cadeddu JA, Partin AW, DeWeese TL, Walsh PC. Long-term results of radiation therapy for prostate cancer recurrence following radical prostatectomy. *J Urol* 1998; **159**: 173–8

Correspondence: Alan W. Partin, James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Jefferson Building Rm. 157, 600 North Wolfe Street, Baltimore, MD 21287–2101, USA.
e-mail: apartin@jhmi.edu

Abbreviations: EBRT, external beam radiotherapy; RP, radical prostatectomy; NVB, neurovascular bundle.