

Significance and management of positive surgical margins at the time of radical prostatectomy

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ABSTRACT

Positive surgical margins (PSM) at the time of radical prostatectomy (RP) result in an increased risk of biochemical recurrence (BCR) and secondary treatment. We review current literature with a focus on stratifying the characteristics of the PSM that may define its significance, the impact of modern imaging and surgical approaches in avoidance of PSM, and management strategies when PSM do occur. We performed a review of the available literature to identify factors associated with PSM and their management. PSM have been repeatedly demonstrated to be associated with an increased risk of BCR following RP. The specific characteristics (size, number, location, Gleason score at the margin) of the PSM may influence the risk of recurrence. Novel imaging and surgical approaches are being investigated and may allow for reductions of PSM in the future. The use of adjuvant treatment for a PSM remains controversial and should be decided on an individual basis after a discussion about the risks and benefits. The goal of RP is complete resection of the tumor. PSM are associated with increased risk of BCR and secondary treatments. Of the risk factors associated with BCR after RP, a PSM is directly influenced by surgical technique.

Key words: Biochemical recurrence, prostate cancer, radical prostatectomy, robotic, surgical margin

INTRODUCTION

Wide variations in the incidence of positive surgical margins (11-48%) have been reported at the time of radical prostatectomy (RP).^[1-8] Centers of excellence tend to report PSM in the lower end of this range^[2] while population-based studies demonstrate results on the upper end which may be more reflective of most clinicians experience.^[1] Cancer registries such as Surveillance, Epidemiology and End Results Program (SEER) have been shown to grossly underreport PSM and may be inaccurate.^[5] Regardless, the incidence of PSM depends on both the characteristics of the cancer

and the technique of the surgeon. Achieving a negative surgical margin may be the most significant opportunity the surgeon has to influence the natural history of the disease, as patients with PSM have been repeatedly demonstrated to have greater rates of biochemical recurrence (BCR).^[2,4,6-8] Additionally, some clinicians view PSM as a trigger for adjuvant radiation therapy.

Attaining a negative surgical margin at the time of RP is the primary goal of the surgeon, but it is not an isolated goal. Preserving the neurovascular tissue and maintaining maximal urethral length are crucial for erectile functional and continence outcomes. Balancing oncologic and functional goals which are at odds with one another is fundamental to successfully performing RP regardless of surgical approach.

When a PSM is encountered, the specific characteristics of the PSM may influence the risk of BCR and subsequent disease progression. The specific pathologic characteristics of the PSM (length, number, location and Gleason score at the PSM) may all influence the risk of BCR. Because of the increased risk of BCR with PSM, some advocate immediate adjuvant treatment; however this may result in deterioration in quality of life and over treatment for many patients. In this review we will consider the definition and significance of a PSM, the pathologic

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Access this article online

Quick Response Code:	Website:
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	DOI:
	10.4103/0970-1591.134240

characteristics that influence the significance of the margin, recent surgical and imaging techniques that may reduce the rates of PSM and management of PSM when they are encountered.

DEFINITION OF A SURGICAL MARGIN

In theory, the definition of a PSM is clear; “tumor that extends to the surface of the prostate wherein the surgeon has cut across the tissue plane.”^[9] However, because the prostate lacks a true histologic capsule, in practice the definition can become confusing. In order to facilitate defining surgical margins (SM) status upon receipt by the pathologist, the entire surgical specimen should be inked and fixed. A positive margin is simply identified as “cancer cells extending to the inked surface of the specimen”. Margin status is negative if tumor cells are microscopically close to (<0.1 mm), but not actually in contact with the inked surface or when they are at the surface of the tissue lacking any ink.^[10] Even with proper handling of the specimen by the pathologist, SM assessment may be complicated by crush, thermal, or electrocautery artifact, partial tearing of the extraprostatic soft tissue during processing or tissue banking and incomplete or irregular tracking of ink.^[11] Such findings may contribute to interobserver variation with reported kappa values of 0.45 (moderate agreement) between local pathologists and expert pathologists and values of 0.74 between expert pathologists.^[11,12]

Surgical margins in the presence of extra-prostatic extension (EPE) may represent an over enthusiastic effort on the part of the surgeon to preserve the neurovascular bundle (NVB) or tumor that invades into vital structures and could not be completely resected [Figure 1a]. PSM in the absence of EPE, usually represent a capsular incision into tumor, an iatrogenic positive margin, due to an improper dissection plane with incision into the prostate and into the tumor [Figure 1b].^[13] Importantly this scenario, pT2+, has prognostic significance. Such patients have greater rates of biochemical recurrence than patients with either pT2 cancers with negative SM or cancers with EPE and negative SM (pT3a, SM negative).^[14]

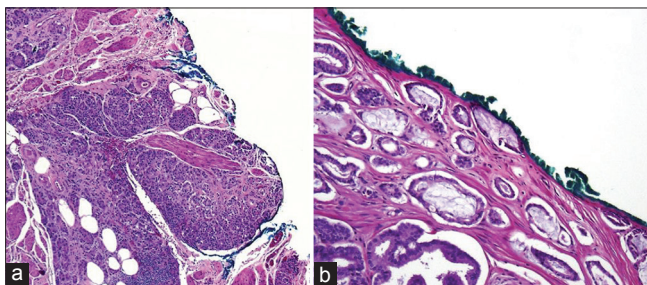


Figure 1: (a) Prostatectomy specimen demonstrating extraprostatic extension with tumor extending beyond the capsule of the prostate and a positive surgical margin (pT3a+). (b) Prostatectomy specimen demonstrating an organ confined tumor with tumor extending to the inked margin due to capsular incision (pT2+) (Figure adapted from Meeks and Eastham^[13])

PATHOLOGIC CHARACTERISTICS OF SURGICAL MARGINS

Patients with PSM have increased risk of BCR.^[2,4,6-8,12] For example in a multi-institutional study of more than 7000 patients the 5 and 10 year BCR rate for PSM were 0.53 (95% CI 0.494, 0.566) and 0.36 (95% CI 0.28, 0.45), [Figure 2], a Kaplan-Meier curve adapted from this publication demonstrating BCR stratified according to margin status.^[4] This figure also demonstrates that many patients, despite the presence of PSM will not develop BCR even with 10 years of follow. Many investigators have attempted to better define the pathologic characteristics of PSM in order to better risk stratify patients and potentially offer adjuvant intervention for those at high risk of progression while sparing over treatment for others.

“Amount” of positive margin

Multiple investigators have sought to quantify the “amount” of PSM either by counting the number of positive margins in a given specimen, or the extent of the positive margin quantified as binary variable such as focal versus extensive often seen in older studies or as a more reproducible linear extent. The rationale behind these attempts assumes that a greater amount of PSM is associated with greater quantity of tumor left behind and a greater potential for growth, biochemical recurrence, and metastases. Multiple analyses from our institution and others have demonstrated that multiple PSM confer increased risk of BCR when compared with a solitary margin.^[2,6-8] Although the number of positive margins may be an independent predictor in multivariable analysis for BCR, the number of positive margins may not significantly impact the predictive accuracy of nomogram predictions compared to a PSM modeled more simply as positive or negative.^[7]

Multiple investigators have attempted to determine if the extent of the positive margin has prognostic significance. Examining our data as focal compared to extensive as

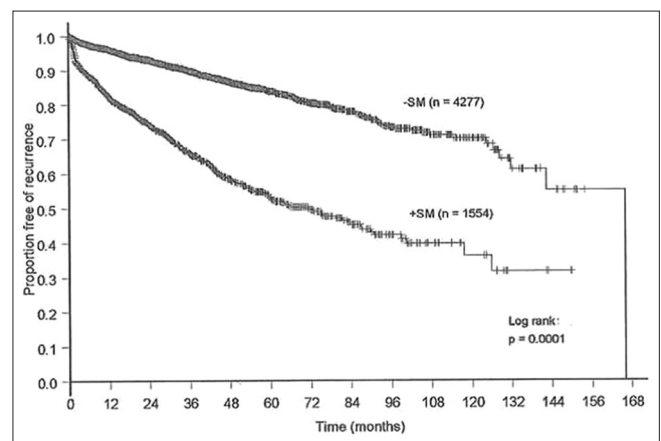


Figure 2: Kaplan-Meier curve demonstrating BCR according to SM status based on the collected data from 7816 consecutively treated patients from eight institutions. PSM are associated with greater rates of BCR over time, adapted from Karakiewicz *et al.*^[4]

part of a multicenter analysis and then more rigorously examining linear length at our institution alone, both analyses demonstrated that longer PSM were associated with greater rates of BCR. However, both analyses demonstrated that the concordance index in a model incorporating length of positive margin was not meaningfully enhanced compared to a model that just included the status of the margin (positive versus negative).^[7,15] Other groups have independently corroborated these findings and repeatedly demonstrated that the length of PSM is associated with BCR.^[16,17] The International Society of Urological Pathologists (ISUP) reviewed the available data and reached a consensus in 2008 that PSM should be recorded as millimeters of involvement.^[9]

Anatomic location of positive surgical margin

Efforts to reduce PSM have lead surgeons and pathologists to define their anatomic location and determine if the site-specific location impacts rates of recurrence. Repeatedly studies have demonstrated that the two most likely locations for PSM are the apex of the prostate and the posterolateral margins. Together these sites make up the majority of PSM accounting for 60-75% of PSM in most reported series of either open retropubic or robotic approaches.^[2,18] The apex of the prostate has less supporting tissue than the rest of the gland, it contains the least amount of capsule, and even benign glands can become admixed with skeletal muscle at this location.^[19] This coupled with the increased traction placed on the apex during various parts of the procedure and efforts to maintain urethral length may explain the increased rates of PSM in this location. The posterolateral margin of the prostate is the second most common location of PSMs and this is likely due to attempts to preserve as much of the neurovascular bundle as possible which run in this location.

Gleason score at positive surgical margin

Recently, investigators have begun to investigate the importance of the Gleason score at the PSM. Theoretically when a higher Gleason score is found at the PSM, a more aggressive tumor remains in the patient with potentially higher rates of BCR. Several studies have demonstrated that grade of cancer at the PSM is associated with greater rates of BCR.^[15,16,20] Gleason score in the primary tumor is highly correlated with Gleason score at the margin for Gleason 6 tumors but this concordance rate diminishes rapidly as the primary tumor Gleason score increases.^[21] At MSKCC, Udo and colleagues noted that Gleason grade was associated with increased risk of BCR in a univariate analysis but it did not significantly enhance the concordance index of a model incorporating specimen Gleason Score and overall SM status.^[15] While ISUP currently recommends that reporting Gleason score at PSM remain at the discretion of the reporting pathologist, it may remain an important discriminator for determining the importance of a positive margin, particularly for those with Gleason 7 or greater disease, further study will be needed to verify the importance of these findings.

All together these data suggest that length of the PSM, the number of PSMs, the Gleason score at the PSM, and potentially even the location of the PSM may each play important roles in defining the risk of BCR following RP. Inter-institution variability in reporting makes comparisons or collaborations difficult. Potentially one could envision a scenario in which the characteristics (length, location, number, Gleason score) of a margin would have value in determining who should receive adjuvant therapy; however, this has yet to be demonstrated convincingly. Furthermore, while each of these factors may have significance on their own they have not demonstrated benefit in predicting outcomes when added to existing models.

BLADDER NECK MARGIN

Extraprostatic extension with microscopic invasion of the bladder neck-previously designated as T4 according to the American joint commission on cancer (AJCC)-has recently been revised to be included in T3a category. This reclassification is based on the work of several retrospective series which have demonstrated that patients with isolated positive bladder neck margins have outcomes that more closely approximate T3 lesions.^[22-24] Typically, direct extension of cancer from the organ of origin into surrounding structures is designated as T4; however, at the bladder neck, the interwoven nature of the outer layers of the bladder with the smooth muscle of the prostate obscure distinct tissue boundaries. It is unclear if a PSM at the bladder neck is associated with a worse prognosis than PSM in other locations, as isolated bladder neck margins are rare and often associated with multiple high-risk features.^[22] Further investigation is needed to more clearly define whether isolated bladder neck margin truly does have a worse prognosis than margins in other locations, if confirmed, clarification of the AJCC might be to define bladder neck invasion as T3b and seminal vesicle invasion as T3c as suggested by some groups.^[23]

SURGICAL APPROACH

With the huge shift towards robotics and away from open RP that has occurred over the last decade, invariable the question is asked does the surgical approach influence SM status.^[25] Currently, there are no large prospective randomized surgical trials designed to answer this question and even if there were, a larger problem might still remain. Large heterogeneity in PSM exists between individual surgeons performing RP through the same approach even after adjusting for case mix, surgery date, and surgery volume. In a review of the SMS of 44 different surgeons at two large urban centers PSM ranged, for each surgeon, from 10% to 48%.^[3] Substantial variation in outcomes remained even when analyses are limited to high or very high volume surgeons and are likely to dwarf differences between surgical approaches limiting the utility of comparative studies.

Despite these limitations various investigators have compared margin rates, location, and length for one surgical approach with another. Because of the increased use of robotic-assisted laparoscopic prostatectomy investigators have been interested in the impact that this novel surgical approach has on SM status. In a recently published meta-analysis with propensity adjustment for patient, surgeon, and hospital factors, the authors found no difference in PSM for open and robotic surgery.^[26] A prior meta-analysis that limited its analysis to comparative studies only demonstrated that PSM rates were similar between approaches.^[27] Administrative care datasets have not been able to directly compare PSM for differing surgical approaches but have demonstrated similar rates in the use of secondary therapies between different surgical approaches as a surrogate.^[28] At our institution we have found no significant difference in PSM or BCR for one surgical approach compared with another, but again individual surgeon variation is likely to be of greater importance than surgical approach.^[29,30]

IMAGING TOOLS PREDICT OR PREVENT POSITIVE MARGINS

Partial preservation of the neurovascular bundle (NVB) is likely the best compromise between oncologic and erectile functional outcomes in men at risk for EPE in the area of the NVB. Key to this approach is identification of the specific location of the cancer in relation to the NVB. Pre-operative MRI has been demonstrated to alter surgical plan prior to RP in approximately 40% of patients; however, MRI is reader dependent with significant interobserver variability.^[31,32]

Another strategy has been the use of a real-time transrectal ultrasound during RP to help outline the suspected area of EPE. Using this technology, one group demonstrated a reduction in their PSM rates from 29% to 9%.^[33] More recently urologists have begun to incorporate the use of a transrectal ultrasound probe with concurrent use of the TilePro to display the ultrasound images on the da Vinci surgical system console.^[34] Mounting interest in MR-US fusion technology is likely to result in utilizing this technology in a similar fashion to attempt to minimize PSM and maximize preservation of the NVB.

Near-infrared fluorescence imaging has been used for the identification of renal tumors^[35] and sentinel lymph nodes for prostate cancer.^[36] In the future similar types of technology may assist in the identification of the NVB or the location of the prostate tumor in order to reduce the rates of PSM.

MANAGEMENT OF POSITIVE MARGINS

Large multi-institutional studies have demonstrated that patients with PSM are more than twice as likely to experience BCR as patients without, even after adjusting

for age, PSA, pathologic Gleason score, pathologic stage, and year of surgery.^[7] This leaves clinicians and patients in the challenging position of considering the role for additional treatment in the absence of any detectable disease. Unfortunately, adjuvant radiotherapy comes at the cost of increased risk of urinary incontinence, urinary stricture disease, proctitis, and rectal bleeding. Furthermore, although patients with PSM are at an increased risk of developing BCR many never do and are exposed to the potential harms of adjuvant radiotherapy without benefit.

Three randomized trials have examined the role of adjuvant radiotherapy in men with 'adverse' pathologic features in the RP specimen.^[37-39] Eligible patients were randomized to either adjuvant radiotherapy or "wait and see". All three trials documented improvement in BCR free-survival with adjuvant radiotherapy compared to a "wait and see" approach. Two of these trials also demonstrated a reduction in clinical locoregional failure with adjuvant radiotherapy.^[37,38] In all three studies the group gaining the most benefit from adjuvant radiotherapy was men with PSM. Based largely on the results of these three trials the American Urological Association (AUA) and the American Society for Therapeutic Radiology Organization (ASTRO) released joint guidelines stating that patients with adverse pathologic features (including but not limited to a PSM) should be offered ART.^[40] The guidelines continue on to state that the decision of whether to receive adjuvant radiotherapy should be based on a shared decision making process by a multidisciplinary team and the patient with consideration of the "patient's history, functional status, values, preferences, and tolerance for potential toxicities and QoL effects of radiotherapy."

A remaining and important limitation of the existing data is that none of these randomized trials have compared adjuvant radiotherapy to early salvage radiotherapy. It has been demonstrated that salvage therapy administered at lower PSA levels is associated with greatest effectiveness. The ability to detect PSA at very low levels has led many to conclude that a preferable strategy would be to offer early salvage treatment when patients have low but detectable PSA rather than adjuvant radiotherapy. Such a strategy may reduce the over treatment of patients who are never destined to develop BCR while maintaining the potential advantage of radiotherapy. Two ongoing randomized clinical trials, RADICALS (Radiotherapy and Androgen Deprivation In Combination After Local Surgery, NCT # 00541047) and RAVES (Radiotherapy Adjuvant vs. Early Salvage, NCT # 00860652), are evaluating whether progression-free and/or prostate cancer specific and overall survival are significantly prolonged by the use adjuvant radiotherapy compared to early salvage radiotherapy at the time of PSA failure.

Lastly, some practitioners use androgen deprivation therapy (ADT) alone for patients with adverse pathologic

characteristics including a PSM. In one small randomized trial, whose results have not been confirmed, ADT following prostatectomy for patients with lymph node positive disease was demonstrated to result in overall survival benefit^[41] but for node negative patients ADT has never been demonstrated to have similar benefit. ADT has the potential for significant harm, reduces QoL, and should only be considered for patients with a positive lymph node or those undergoing adjuvant or salvage radiotherapy.

CONCLUSIONS

PSM are associated with an increased risk of BCR. The presence of a PSM may be more influenced by the individual surgeon than the surgical approach used to perform RP. Longer PSM (>3 mm), multiple PSM, and higher Gleason score at the PSM are associated with an increased likelihood of BCR, while isolated apical PSM have a lower risk of BCR. MRI and intra-operative imaging modalities may help to reduce the incidence of PSM although further study is needed to ascertain the role of pre- or intra-operative imaging in improving outcomes. Finally when a PSM is encountered consistent with the AUA/ASTRO recommendations a thoughtful discussion should be had about the risks and benefits of immediate ART.^[37] Until the results of two ongoing randomized trials evaluating the impact of ART versus early salvage radiotherapy report results, a nuanced strategy which considers the specific characteristics of the individuals oncologic factors as well as those of the PSM-with a tendency toward ART for multiple high risk features and toward early salvage for those with few-may be the most rational approach.

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How to cite this article: Silberstein JL, Eastham JA. Significance and management of positive surgical margins at the time of radical prostatectomy. *Indian J Urol* 2014;30:423-8.

Source of Support: Nil, **Conflict of Interest:** None declared.