Significance of positive surgical margin and how to minimize in robotic radical prostatectomy

Abstract

The success of any cancer operation with curative intent relies on complete surgical removal of the tumor. The goal of RP is complete resection of the tumor. Positive surgical margins [PSM] after radical prostatectomy [RP] associated with an increased risk of biochemical recurrence [BCR] and secondary treatment. We conducted the current literature to focus on the characteristics of the PSM that may define its significance, the impact of robotic radical prostatectomy 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. The specific characteristics [size, number, location, Gleason score at the margin] of the PSM may affect the risk of recurrence. Novel imaging and surgical approaches are being investigated and may allow for reductions of PSM in the future. Of the risk factors associated with BCR after RP, a PSM is directly influenced by surgical technique.

Keywords: Biochemical recurrence; Radical prostatectomy; Positive surgical margins; Robotic radical prostatectomy

Introduction

Prostate cancer [PCa] is the second leading cause of cancer related deaths in men, with continuously increasing incidence, particularly as a result of aging of the population and the large-scale use of PSA measurements.1 Radical prostatectomy [RP] is one of the major treatment options for localized PCa, with a high 5-year disease-specific survival rate of > 95%.1 Interestingly, positive surgical margin [PSM] rates differ substantially [10–48%] in contemporary RP series, irrespective of the surgical technique applied.2 The reasons for these findings are not completely clear, but compact anatomy of the prostate, experience of the surgeon, technique applied, lack of precision in outlining the prostate or tumor and pathological protocol may play a role. A recent study showed that the surgical approach did not affect the rate but did affect the location of PSMs: open RP was associated with a higher apical PSM rate [38.5%], while robot-assisted RP led to higher posterolateral PSM rates [52.3%].3

The diagnosis of a PSM after RP has several implications; it has been associated with higher rates of BCR and shorter time to progression and could lead to a significant fear in the patient, with an impact on quality of life. It could also trigger potentially unnecessary adjuvant radiation therapy and evoke associated side effects in patients with high safety needs.7 A PSM implies incomplete cancer resection, resulting in complementary treatments such as adjuvant radiotherapy or androgen deprivation therapy.3 Robot-assisted radical prostatectomy [RARP] has become the dominant surgical approach for treatment of prostate cancer in the United States and was expected to account for more than 80% of all radical prostatectomies performed in 2013.6 RARP facilitates nerve-sparing procedures with less damage to sexual function, and nerve-sparing RARP may yield better postoperative continence and potency.7 However, sparing the neurovascular bundles reduces the safety distance between cancerous tissue and surgical margins, and thus, nerve-sparing RARP may lead to higher rates of surgical margins that are positive for cancer [positive surgical margins].8

Definition of 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”.6 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 [&lt;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 Surgical margins in the presence of extraprostatic 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. PSM in the absence of EPE, usually represent a capsular breach extending into the periprostatic fat, an iatrogenic positive margin, due to an improper dissection plane with incision into the prostate and into the tumor [c/o Figure 1 & 2 in ref 12].12

Characteristic of surgical margin

Patients with PSM have increased risk of BCR.13 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. 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.

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. 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.13

Anatomic location of positive surgical margin

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.14 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. 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.15

Gleason score at positive surgical margin

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.16 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.16

Types of positive surgical margin

There are two types of positive margins: iatrogenic and noniatrogenic.17 Iatrogenic positive margins result from capsular incision in organ-confined tumors [pT2+], or cutting across an area of extraprostatic tumor extension. Iatrogenic implies that with wider dissection, the positive margins could have been avoided.18 With noniatrogenic margins, the cancer simply extends through the capsule and periprostatic tissue, reaching the edge of the surgical specimen. When this is the case, the cancer has been either completely removed or resection of additional tissue will result in unacceptable morbidity [eg. cutting through the rectal wall]. Pathologists are generally able to discern iatrogenic from noniatrogenic margins; however, in pT2+ cases, one cannot determine with certainty whether there is extraprostatic tumor extension where a capsular gap is observed.18 Positive surgical margins in robotic-assisted radical prostatectomy; robotic urologic surgery, a new and exciting emerging frontier in the field of urology, has tremendous potential to progress as a treatment option for prostate cancer in the future. Robotic-assisted laparoscopic radical prostatectomy [RARP] is gaining popularity for the treatment of clinically localised prostate cancer.19

Reducing positive surgical margins rates

Regardless of their oncologic implications, PSMs are likely to generate anxiety among affected patients and often trigger additional therapy. Urologists should strive to reduce their rates of positive margins while attempting to maintain patient quality of life with respect to postoperative urinary and erectile function.4

Surgical experience

Cumulative evidence suggests that margin status is associated with surgical experience: Higher-volume surgeons tend to have fewer positive margins. Surgical learning curves have been developed for open RP [20], laparoscopic RP;21 and RALRP,22 attesting to the importance of surgeon experience in optimizing outcome. The incidence of PSMs is expected to be relatively high initially, but it generally plateaues with accumulating experience. Studies have provided different estimates of the number of surgeries required to reduce the positive margin rate to a minimum; estimates range from 200–250 cases in the laparoscopic series23 to 1000–1500 cases using the robotic approach.22 For surgeons who are novices at the robotic technique, experience with open or laparoscopic RP and fellowship training appear to expedite the transition to the robotic interface and to eliminate an unwarranted increase in margin positivity.21

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.24 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 feature.25 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.25

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.26 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.27 A prior meta-analysis that limited its analysis to comparative studies only demonstrated that PSM rates were similar between approaches.28 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.
Significance of positive surgical margin and how to minimize in robotic radical prostatectomy

between different surgical approaches as a surrogate.\textsuperscript{29}

**Technical modification during robot-assisted laparoscopic radical prostatectomy**

Based on the premise that infiltrating cancer cells may generate changes in tissue elasticity, surgeons performing open surgery have traditionally used tactile feedback to modify the resection as needed to reduce their PSM rates. Nonetheless, concerns over the lack of tactile feedback in RALRP have been largely refuted by accumulating evidence demonstrating that oncologic safety can be maintained by trading tactile sensation for intraoperative visual cues to delineate key anatomic landmarks.\textsuperscript{30}

**Apical margins**

Precise dissection of the apex is one of the most challenging aspects of RP, for several reasons. First, the apex is in a fairly inaccessible location, deep beneath the pubic arch and intermingled with vital structures such as the dorsal venous complex, erectile nerves, rectum, and sphincter. Second, the apex lacks the distinct capsule and periprostatic tissues that are present on the posterolateral surface of the prostate, rendering the accurate planes of dissection in this area imperceptible. Third, the configuration of the apex is highly variable, with some glands demonstrating pronounced asymmetry and others harboring a distal beak of apical tissue protruding posterior to the urethra [also known as a posterior apical notch]. This concealed posterior extension might be violated during surgery, particularly if the dissection is carried out in a plane perpendicular to the axis of the urethra. Therefore, to optimize the recovery of sexual and urinary function without compromising the surgical margin, surgeons have sought ways to optimally dissect the apex.\textsuperscript{31}

**Posterolateral margins**

Irrespective of surgical technique, the close contact between the prostate and surrounding neurovascular tissue inevitably translates into a conflict between the desire to preserve as much erectile function as possible and the risk of compromising cancer control by leaving residual tumor behind. The area of nerve sparing is particularly predisposed to PSMs, which can result from iatrogenic intraprostatic incision into an otherwise organ confined tumor or failure to excise the extraprostatic extension of the prostate carcinoma.\textsuperscript{32}

Classically, PSMs occur most commonly at the apex followed by the posterolateral prostate in stage pT2 and pT3 disease. Positive margins occur at the apex for several reasons. The primary reason is that anteriorly there is no capsule and the prostatic apex interdigitates with the striated muscle of the external sphincter. This can be further complicated from obscured vision or access by the pubic bone, anterior prostatic fat, or bleeding from the dorsal venous complex. Insufficient mobilization of the fibro-muscular bands that tether the apex also increases positive margins.\textsuperscript{33}

Because several planes of dissection can be entertained to ensure oncologic safety at the posterolateral site, nerve sparing should not be considered an all-or-none phenomenon. Before deciding how wide to dissect the neurovascular bundles, surgeons must apply available tools [clinical biopsy data, rectal examination, endorectal magnetic resonance imaging] to preoperatively estimate the location and volume of the tumor.\textsuperscript{34}

Depending on how the extent of the tumor at base is appreciated, surgeons may choose the carry the dissection in an intra-fascial plane [complete nerve sparing ascertained by the glistening view of the prostate], an interfascial plane [partial nerve sparing confirmed by a whitish coloration of the prostate], or an extrafascial plane [non-nerve sparing determined by fatty tissue seen on the prostate]. This counterintuitive finding is likely related to tumor characteristics [candidates for interfascial and extrafascial nerve sparing have worse disease] and, possibly, a technical error [forcing a plane with blunt dissection is prone to produce a capsular flap at areas of adhesions or entry of capsular arteries].\textsuperscript{35}

**Frozen-section analysis**

Preoperative measures may not be an entirely adequate guide to safe nerve sparing, so some surgeons propose the use of real-time histologic monitoring of the surgical margins by intraoperative frozen-section analysis combined with excision of additional tissue when indicated. Although this concept was initially shown to be of clinical benefit,\textsuperscript{36} its general necessity in all patients remains controversial, as does the optimal technique. In early studies, frozen-section analysis during RP was targeted to specific areas considered suspicious by the surgeon. The results were generally discouraging.\textsuperscript{37}

More recently, however, a systematic approach was introduced involving the assessment of the entire gland circumference. Schlomm et al.,\textsuperscript{38} concluded that systematic frozen-section analysis is a useful adjunct to surgical preplanning, yielding a substantial decrease in the rate of PSMs and safe preservation of the neurovascular bundles in high-risk patients who would otherwise have been considered candidates for non–nerve-sparing surgery.

The long-term oncologic and functional benefits of this approach remain to be confirmed. One noteworthy finding in the aforementioned studies is the consistently low rate of histopathologically detected cancer [approximately 25%] in secondary-excised specimens when the margin was deemed positive by frozen section study. On the one hand, the high false-negative rate might be justified by the fact that secondary resection was not carried out exactly at the corresponding anatomic location. On the other hand, malignant cells contacting the inked surface [PSMs] do not necessarily indicate that cancer was left behind. Obviously, the latter condition has explicit implications for secondary therapy.\textsuperscript{39}

**Imaging tools predict or prevent positive margins**

**Pre-operative MRI**

MRI has been demonstrated to alter surgical plan prior to RP in approximately 40% of patients; however, it has significant interobserver variability.\textsuperscript{39}

**A real-time transrectal ultrasound**

A real-time transrectal ultrasound during RP to help outline the suspected area of EPE with a reduction in their PSM rates from 29% to 9%. 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. 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.\textsuperscript{40}
Near-infrared fluorescence imaging

Near-infrared fluorescence imaging has been used for the identification of renal tumors and sentinel lymph nodes for prostate cancer.

Management of positive margins after radical prostatectomy

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. 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 stricturedisease, 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 harms of adjuvant radiotherapy without benefit.

Three randomized trials potential have examined the role of adjuvant radiotherapy in men with ‘adverse’ pathologic features in the RP specimen. All documented improvement in BCR free-survival with adjuvant radiotherapy compared to a ‘wait and see’ approach. 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.

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.” 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.

Lastly, some practitioners use androgen deprivation therapy [ADT] alone for patients with adverse pathologic features 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 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.

Conclusion

PSM are associated with an increased risk of BCR. The presence of a PSM may be more influenced Tumor biology [volume, distribution, and aggressiveness] and by the individual surgeon experience than the surgical approach [type of procedure and technique] 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. Although a PSM at the posterolateral location appears to confer the greatest probability of relapse, the prognostic significance of PSM at the apex remains uncertain. Regardless of surgical approach [open, laparoscopic, or robotic], attention to detail and increased surgical experience remain imperative in reducing the rate of PSM. Preoperative planning with eMRI and frozen section analysis during surgery may play a role in reducing the incidence of PSM, particularly for patients at high risk of a PSM. For men with PSM on final pathology, RT is the only established treatment with curative potential.

While compared to the open approach, early studies indicate that robotic prostatectomy has promising outcomes in short-term oncological control, potency, and continence compared to open radical prostatectomy. The results suggest that the experience gained with RARP leads to a decrease in the incidence of positive surgical margins. RARP can provide comparable surgical margin results for patients found to have both low- and high-risk disease. Further, lack of tactile sensation can be mitigated with a combination of careful preoperative evaluation, clinical algorithms for excision of the NVB, intraoperative visual clues, and surgeon experience. Until long-term biochemical recurrence and survival data become available, surgical margin rates provide the best surgeon-related surrogate endpoint to predict oncological outcomes after radical prostatectomy.

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Conflict of interest

None.

References


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