Collaborative Review – Prostate Cancer

Positive Surgical Margins in Radical Prostatectomy: Outlining the Problem and Its Long-Term Consequences

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Article info

Article history:
Accepted September 23, 2008
Published online ahead of print on October 1, 2008

Keywords:
Prostate cancer
Positive surgical margins
Radical prostatectomy
Nerve sparing
PSA
Biochemical recurrence
Radiation therapy
Frozen section analysis
Endorectal MRI

Abstract

Context: This review focuses on positive surgical margins (PSM) in radical prostatectomy (RP).
Objective: To address the etiology, incidence, and oncologic impact of PSM and discuss technical points to help surgeons minimize their positive margin rate. An evidence-based approach to assist clinicians in counseling patients with a PSM is provided.
Evidence acquisition: A literature search in English was performed using the National Library of Medicine database and the following key words: prostate cancer, surgical margins, and radical prostatectomy. Seven hundred sixty-eight references were scrutinized, and 73 were selected for rigorous review based on their pertinence, study size, and overall contribution to the field.
Evidence synthesis: In contemporary series, PSM are reported in 11–38% of patients undergoing RP. Although variability exists in the pathologic interpretation of surgical margins, PSM are associated with an increased hazard of biochemical recurrence (BCR) and local disease recurrence as well as the need for secondary cancer treatment. A posterolateral PSM appears to confer the greatest risk of recurrence, whereas the prognostic significance of positive apical margins remains controversial. The role of preoperative imaging and intraoperative frozen section analysis are being investigated to reduce margin positivity rates. Level-1 evidence indicates that adjuvant radiotherapy (RT) in men with PSM reduces BCR rates and clinical progression and possibly improves overall survival (OS).
Conclusions: PSM in RP specimens are uniformly considered an adverse outcome. Regardless of approach (open or laparoscopic), attention to surgical detail is essential to minimize rates. For patients with a PSM destined to experience a cancer recurrence, RT is the only established treatment with curative potential. A randomized trial in patients with PSM comparing immediate postoperative RT to salvage RT is critically needed before definitive recommendations can be made.

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1. Introduction

The ultimate success of any cancer operation with curative intent relies on complete surgical extirpation of the tumor. Cancer cells at the inked surgical resection margin may suggest an incomplete local resection and suboptimal patient outcome [1]. The importance of achieving negative surgical margins to reducing the risk of recurrence is paramount and has been recognized in all solid malignancies, including prostate cancer (PCa). However, despite the evolution of surgical technique and the introduction of novel surgical approaches, positive surgical margins (PSM) in radical prostatectomy (RP) specimens are not uncommon, leading to an increased risk of biochemical, local, and possibly systemic disease progression. Unfortunately, the optimal treatment strategy for men with PSM remains open to disagreement.

In this review, we focus on the issue of PSM in PCa, addressing the pathologic pitfalls confounding surgical margins interpretation and the impact of PSM on long-term oncologic outcomes, providing technical recommendations to help surgeons minimize their positive margin rate, and discussing available data to assist clinicians in counseling patients with PSM after RP.

2. Evidence acquisition

A literature search in English was performed using the National Library of Medicine database and the following key words: prostate cancer, surgical margins, and radical prostatectomy. A free-text strategy was applied without limiting the year of publication. Seven hundred sixty-eight references were initially scrutinized, and 115 pertinent publications were identified and rigorously reviewed. Reference lists of retrieved articles were scrutinized for additional relevant articles. Seventy-three papers were selected for this review based on their pertinence (favoring recent publications), study size, and overall contribution to the field.

2.1. Assessing margin status in radical prostatectomy specimens: anatomical considerations and pathologic pitfalls

The pathologic definition of PSM seems straightforward: “A tumor extending to the inked surface of the prostatectomy specimen that the surgeon has cut across” [1]. Although tumor biology (volume, distribution, and aggressiveness) and surgical factors (type of procedure, technique, and experience) are the primary determinants of margin status, adequate specimen handling and accurate interpretat-

Fig. 1 – Whole mount section of a nerve-sparing radical prostatectomy specimen. The cancer lies in the left peripheral zone as indicated by (a) the two arrows and (b) the dotted line; (c) cancer cells reaching the inked margin in an area of capsular incision at which extraprostatic tissue is absent (pT2+).
tion of the RP slides remain imperative. Several considerations must be emphasized in this respect.

There are two types of positive margins: iatrogenic and noniatrogenic [1]. Iatrogenic positive margins result from capsular incision in organ-confined tumors (pT2+; Fig. 1 a–c), or cutting across an area of extraprostatic tumor extension (Fig. 2 a and b). Iatrogenic implies that with wider dissection, the positive margins could have been avoided. 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. Irrespective of cause, the difficulty with applying a uniform definition is that PSM may not always represent residual cancer cells that have been left in situ.

In many sites, the prostate is surrounded by <1 mm of periprostatic soft tissue. Because close margins are not associated with increased risk of progression [2], even the smallest amount of unin- volved tissue separating tumor from ink should designate the surgical margins as negative.

The scant amount of flimsy connective tissue surrounding the prostate can be readily disrupted during intraoperative or postoperative handling of the surgical specimen. As a result, ink could seep into the gland, leading to a false impression of positive margins (Fig. 3 a and b). Even for dedicated uropathologists with considerable experience, the presence of crush, thermal, or electrocautery artifacts can complicate surgical margins interpretation [3].

Finally, an area in which the definition of positive margins may vary is the apex. Lack of a distinct capsule and periprostatic tissue and the presence of benign glands admixed with skeletal muscle render the histologic boundaries in the apical region rather vague [4]. Pathologists must recognize that the distal margin is not a “distal urethral margin”—that is,
<table>
<thead>
<tr>
<th>Author</th>
<th>Yr</th>
<th>No.</th>
<th>Surgical technique</th>
<th>No. PSM (%)</th>
<th>No. PSM in OC tumors (%)</th>
<th>No. PSM in NOC tumors (%)</th>
<th>Median follow-up (mo)</th>
<th>PSA relapse: +SM vs –SM</th>
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<td>NR</td>
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<td>498</td>
<td>ORP</td>
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PSM = positive surgical margins; OC = organ confined; NOC = non-organ confined (pT3–4N0 or pTxN1); PSA = prostate-specific antigen; NR = not reported; +SM = positive margins; –SM = negative margins; HR = hazard ratio; CI = confidence interval; LRP = laparoscopic radical prostatectomy; ORP = open radical prostatectomy; RLRP = robot-assisted laparoscopic radical prostatectomy; SVI = seminal vesical invasion.

a Cox proportional hazards regression controlling for additional adverse clinical and pathologic features (preoperative PSA, pathologic Gleason score, extracapsular extension, SVI, and lymph node metastasis).

b Statistically significant as indicated in text; p log rank not specified.
c Men with pT3b/pT4 tumors were excluded.
d HR varies depending on the statistical model used.
*e HR varies depending on whether solitary or multiple margins were involved.
rather than digging into the prostate to obtain urothelium (the urethra often retracts proximally), one should assess the prostatic tissue exterior to the urethra. Several definitions of positive apical margins have been proposed, largely dependent upon the pathologist’s view and the technique used to process the apex (the apex may be shaved tangentially or handled as perpendicular sections) [5]. Comparative data are unavailable on clinical outcomes when these differing definitions and techniques are employed.

2.2. Positive surgical margins: oncologic outcomes

From an oncologic standpoint, the presence of a tumor at the inked margin indicates—at least in theory—inadequate cancer clearance. Most investigators agree and methodologically sound studies support PSM as an independent predictor of PCa recurrence after RP (Table 1). Positive margins have been reported in 11–38% of patients undergoing RP in contemporary series and have been associated with an increased hazard of biochemical recurrence (BCR) and local disease recurrence as well as the need for secondary cancer treatment [6–16]. A few studies have contested these findings, arguing that when adverse pathologic features such as % Gleason grade 4/5, seminal vesicle invasion (SVI), or lymph node metastasis are accounted for, margin status no longer plays a role in determining clinical outcomes [17–19]. The impact of PSM on more robust clinical end points (eg, metastatic progression and cancer-specific mortality) has yet to be reported.

The debate over whether positive margins represent unfavorable tumor biology, technical error, or both remains pertinent. It is conceivable that an iatrogenic capsular incision of a low-grade organ-confined cancer (pT2+) provides different prognostic information than a PSM associated with extraprostatic extension of high-grade tumor. In the latter scenario, cancer cells have acquired the biologic aggressiveness to invade through the capsule and hence, if left in the patient, likely pose a greater threat of growing locally and spreading beyond the pelvis. Alternatively, one might argue that the presence of micrometastatic disease in men with high-risk disease should virtually offset the influence of the surgical margins on ultimate clinical outcomes. In this context, Karakiewicz and associates have provided data highlighting the singular importance of achieving negative margins in the presence of adverse pathologic features [10]. Conducting a large multi-institutional assessment of 5831 patients undergoing RP, the authors found that the greatest risk of prostate-specific antigen (PSA) relapse may be expected if PSM are present concomitantly with Gleason sum 7–10 or lymph node invasion (LNI). The synergy of the combined adverse effects exceeded the contribution of either factor alone to the overall probability of treatment failure. In contrast, Freedland et al found that the presence of both PSM and extraprostatic extension did not portend a worse prognosis than the presence of either one alone [7]. Using the Shared Equal Access Regional Cancer Hospital database to study PSA outcomes in men with PSM, the authors concluded that PSM in otherwise organ-confined tumors are as ominous as the finding of extraprostatic extension. This suggests that the TNM staging system should be modified to include PSM as pT3. Other studies have demonstrated no difference in PSA failure rates between patients with pT2+ tumors and those with organ-confined, margin-negative cancers (pT2) [20]. Despite these uncertainties as to the prognostic significance of margin status in various clinical and pathologic settings, PSM are uniformly acknowledged as an adverse outcome and should unequivocally be avoided.

Several groups have now investigated the prognostic significance of the site, number, and extent of PSM. The difference in the risk of recurrence between a focal or solitary positive margin and an extensive or multifocal margins has been highlighted by some [5,21] and refuted by others [16,22]. Sofer et al showed that biochemical progression was significantly more prevalent among men with multiple PSMs compared to a single PSM (hazard ratio [HR]: 2.19; 95% confidence interval [CI]; 1.11–4.32) but not associated with the location of the positive margin. Conversely, in a detailed analysis of 2442 whole-mount prostatectomy specimens, Eastham and colleagues demonstrated that the effect on BCR was highly influenced by the specific location of the positive margin, with the posterolateral site conferring the greatest probability of relapse [9]. Focusing on the two most commonly involved sites and adjusting for all known adverse pathologic features, the estimated HR for progression was 2.8 (95% CI; 1.76–4.44) for the posterolateral site and 0.94 (95% CI; 0.59–1.51) at the apex. In fact, whether a positive apical margin truly portends a dismal prognosis remains moot. Some studies reported that a solitary positive apical margin is associated with higher recurrence rates and a shorter interval to progression [5,12,23], whereas others failed to demonstrate any association between the apical margin status and PSA relapse [24,25]. Ohori et al, for example, concluded that the presence of cancer in the apical region was merely the reflection of a more aggressive tumor. After adverse pathologic factors
were accounted for, the status of the apical margin was not an independent predictor of PSA relapse [25]. In other studies, patients with PSM at the prostate base appeared to carry a higher risk for biochemical progression than those with positive margins elsewhere [6,26].

It remains perplexing as to why a positive margin at one location but not at another can predict disease recurrence. Several theories have been proposed, including higher rates of artifactual positive margins at the apex [9,12]; lack of apical supporting tissue leading to reduced vascularity and destruction of residual tumor; and an abundance of neurovascular tissue at the posterolateral site, allowing cancer cells to migrate more easily along the nerves [9]. This site-specific variation in PSA outcomes raises the question of whether a new, selective stratification based on the pattern (location, extent, and number) of involved margins would be more appropriate when PSM are incorporated into outcome-prediction tools or used to consider adjuvant therapy.

3. Evidence synthesis

3.1. Surgical recommendations and lessons learned

The goals of RP are to remove the cancer completely with negative surgical margins, minimize perioperative complications, and optimize recovery of potency and urinary continence. No surgeon uniformly achieves these results [27]. RP is one of the most complex operations urologists perform, and outcomes are highly sensitive to technique. The success of surgery and the incidence of PSM vary greatly among surgeons [28,29]. Even among highly experienced surgeons, intraoperative video documentation review can help decrease the rate of PSM [30,31], further underscoring the imperative role of the individual surgeon’s performance on margins outcome. Currently, the majority of RPs are performed via the retropubic or laparoscopic/robotic approaches (with fewer cases done perineally). There does not appear to be a significant difference in the rate of PSM between the various techniques [32].

The following section is meant to provide technical highlights thought to reduce the likelihood of PSM. The hope is that readers will discern the important anatomic and surgical tenets that allow them to refine their own technique and potentially improve their results.

3.1.1. The anterior margins

Anterior prostate tumors may be underestimated preoperatively, despite having higher overall tumor volumes and associated higher rates of PSM [33]. To minimize the risk of positive anterior margins, the dorsal venous complex (DVC) must be carefully dissected and secured to ensure that no adherent tumor is retained. In open RP, one option is to pass a 22-gauge surgical wire or a right-angle clamp beneath the DVC anterior to the urethra just distal to the prostatic apex. The wire or clamp will later serve as a template for dividing the DVC sharply with a knife. Other techniques work as well, provided that a clear and safe cleavage plane between the prostate and DVC is guaranteed [34]. Care must be taken to avoid incising into the apex anteriorly while dividing the DVC. This is facilitated by placing a sponge stick on the anterior surface of the prostate to retract it cephalad and by using the sucker to further retract the apex away from the wire. In laparoscopic and robot-assisted RP, the DVC is often dissected from the prostate as the final step before division of the urethra and removal of the specimen [35,36]. The minimally invasive approach may facilitate a safe and accurate division of the DVC, because the pneumoperitoneum-induced tamponade helps control excessive venous bleeding, and the magnification that optics provide improves visualization. Nevertheless, in terms of positive margins rate, no data exist to suggest any advantage of laparoscopic or robot-assisted RP over traditional open surgery.

3.1.2. The apical margins

Surgeons are generally reluctant to remove “excess” healthy tissue in the apical region because of the proximity of the sphincter mechanism and neurovascular bundles (NVB). Yet, to minimize the risk of positive apical margins, wide excision around the apex of the prostate should be sought. Poor visualization from uncontrolled bleeding or insufficient mobilization of the distal portion of the prostate may lead to inadvertent violation into the apex. To gain maximal exposure prior to dividing the urethra, the fibromuscular bands and DVC that tether the apex must be completely transected. Some investigators advocate preserving the puboprostatic ligaments to provide augmented support to the sphincter mechanism, thereby improving the recovery of urinary continence. Whether this maneuver adversely affects the rate of positive apical margins is unknown [11,37], although identification and preservation of accessory pudendal arteries does not seem to confer greater risk of positive apical margins [38]. Some prostates have a notch that allows the urethra to enter the prostate proximally and anterior to the apex, leaving a distal rim of apical tissue protruding posteriorly to the
urethra. Dividing the urethra in a straight perpendicular plane may result in inadvertent incision into this concealed extension of the apex posteriorly [39]. Although surgeons ought to recognize and address this anatomic variant, care should be taken to avoid overdissecting the urethra and periurethral muscles distally, as this may result in prolonged postoperative incontinence.

3.1.3. The posterolateral margins
As long as oncologic safety is maintained, preservation of the NVB should be a part of standard of care. The imperative role of nerve preservation with regard to recovery of erectile function cannot be overstated. Yet even for experienced surgeons, sparing the NVB while simultaneously attaining clear surgical margins remains a challenge, particularly when operating on bulky, high-risk tumors. If the cancer lies in close proximity to or involves the NVB, all or part of the bundle must be resected to ensure complete surgical extirpation. When sacrificing an ipsilateral nerve is required, the dissection should begin over the rectal wall in the fat beneath and lateral to the prostate [39]. Alternatively, if extension of cancer into the capsule is suspected but not grossly apparent, the NVB may be only partially resected, leaving sufficient tissue on the prostate to ensure negative margins while preserving as many of the nerves and vessels adjacent to the prostate as possible.

Nowadays, with the recognition of the downward clinical and pathologic stage migration of newly diagnosed cancers [15], dissection of the NVB is no longer perceived as an all-or-none phenomenon. Even in men with the highest risk of extraprostatic disease, a portion of the neurovascular tissue can often be preserved. This approach has been fostered by improved comprehension of the periprostatic anatomy [37,40,41]: Dissection of the NVB can be done in an interfascial plane (complete nerve sparing, directly adjacent to the prostatic capsule and medial to the prostatic fascia); an interfascial plane (partial nerve sparing, with part or all of the prostatic fascia staying on the prostate rather than covering the medial aspect of the NVB); or an extrafascial plane (nerve resection, outside the endopelvic fascia covering the prostate) (Fig. 4).

Ample evidence is available to attest that nerve sparing during RP is not an independent adverse risk factor for either PSM or progression-free survival after controlling for various clinical and pathologic features [42,43]. Although some authors feel that surgical margin status is a variable set forth by tumor biology independent of surgical technique [42], others have convincingly demonstrated the impact of surgical technique [28] and surgical volume [29] in reducing the likelihood of PSM. Use of endorectal magnetic resonance imaging (eMRI) [44,45], intraoperative transrectal ultrasound (TRUS) [46], or models developed to identify patients at high risk for extraprostatic extension and NVB involvement [41,47,48] may allow surgeons to more expeditiously choose an accurate plane of dissection in an individual patient based on tumor location and extent.

Fig. 4 – Schematic drawing of two different surgical techniques for nerve-sparing prostatectomy: (a) interfascial nerve-sparing prostatectomy and (b) intrafascial nerve-sparing prostatectomy.*

EF = endopelvic fascia; PF = periprostatic fascia; PC = prostatic capsule; PP = prostatic vascular pedicle; NBV = neurovascular bundle.

* Reprinted with permission from European Urology [37].
3.1.4. The posterior margins
Deep dissection beneath Denonvilliers’ fascia should be performed routinely, as invasion of this fascia by cancer is fairly common [49], and deep dissection will likely reduce the incidence of posterior PSM. Denonvilliers’ fascia should be sharply perforated at the angle between the NVB and the prostate, completely releasing the bundles away from the lateral aspect of the gland. The appearance of perirectal fat emerging between the cut edges of this fascia will assure that the layer has been incised completely and violation into the posterior surface of the prostate or seminal vesicles has been avoided. Although blunt dissection is quicker, it frequently leaves all or part of Denonvilliers’ fascia on the rectum rather than the prostate, thus increasing the likelihood of a posterior PSM. The risk of a PSM will be greatly reduced if this layer of fascia is excised with the specimen. However, recognizing that some of the nerve fibers constituting the NVB may be running between the anterior rectal wall and the prostate [50], one may consider sparing part or all of this fascia (ie, posterior intrafascial dissection) in low-volume, low-risk cancers. In contrast, in high-risk cancers located posteriorly, the dissection beneath Denonvilliers’ fascia can be further deepened to keep the perirectal fat on the prostate, acknowledging that even in the most aggressive tumors, rectal wall invasion is extremely uncommon [49].

3.1.5. The bladder neck margins
Bladder neck sparing was developed in an attempt to expedite the return of urinary continence and reduce the incidence of bladder neck strictures [51]. Concern has been raised, however, with regard to increasing the rate of PSM at the bladder neck site, thus compromising the primary goal of cancer control. PSM at the bladder neck are reported in 9% of procedures: 25% to a more aggressive approach (ie, initially scheduled for nerve resection) and 25% to a more conservative approach (ie, initially scheduled for nerve sparing). The impact of eMRI findings suggested changing the surgical plan in 39% of procedures: 14% to a more conservative plan (ie, initially scheduled for nerve resection) and 25% to a more aggressive approach (ie, initially scheduled for nerve sparing). The impact of eMRI was more pronounced in men with a high probability of extracapsular extension (>75% by Partin’s tables), with 78% requiring a change in surgical planning. The study highlighted two important management benefits of eMRI before RP: improved surgical planning in high-risk patients and appropriate reassurance for preserving the NVB without compromising the surgical margins in low-risk and intermediate-risk patients. The authors rightfully concluded that preoperative eMRI can provide critical information for tailoring surgery to an optimal patient-specific therapy.

In another noteworthy endeavor, investigators from Cleveland Clinic evaluated whether real-time...
TRUS during laparoscopic RP can delineate suspected areas of extracapsular extension, thereby allowing a calibrated dissection and decreasing the incidence of PSM [46]. With the introduction of this novel approach, the authors were able to demonstrate an overall reduction in the rate of PSM from 29% to 9% and from 57% to 18% in those patients with pT3a tumors. Based on this initial experience, it is plausible that rectum-based, intraoperative, real-time navigation will facilitate more sophisticated and accurate performance of RPs in the future.

3.3. Frozen section analysis

The difficulty in reliably determining the location and extent of a tumor within the prostate preoperatively has prompted efforts to explore the utility of frozen section analysis during RP, particularly in the setting of a palpable abnormality [58,59]. The underlying rationale is to monitor the site of PSM during the operation so that additional tissue at risk of harboring malignant cells can be removed. For instance, a positive posterolateral margin identified during surgery would allow real-time adaptation of the surgical strategy to resect rather than preserve the involved NVB. Using this approach, Eichelberg et al were able to “protect” the ipsilateral nerve in 52% of their patients with palpable lesions and negative finding on frozen section, whereas in 42% of their patients, the NVB was sacrificed based on positive frozen section assessment [58]. The latter resulted in a significant reduction in the overall rate of PSM, although on permanent section analysis, carcinoma could be found in only 14% of the resected bundles.

The findings of Tsuboi et al assessing the accuracy and efficiency of frozen section analysis to detect PSM were less encouraging [59]. Nearly half of all PSM in that series were in patients who did not have a sample taken for frozen section analysis by virtue of normal preoperative and intraoperative assessment. Moreover, the sensitivity of frozen section examination was deemed fairly low: 42% in those who had a frozen section taken and 22% for the entire study population undergoing RP. Thus, further evidence is needed before endorsing a policy of routine frozen section analysis to reduce the rate of PSM during RP.

3.4. Counseling the patient with positive margins: an evidence-based approach

A better understanding of the intricate periprostatic and pelvic anatomy, refinements in surgical technique, accumulating surgeons’ experience, and a downward stage migration during the PSA era have collectively contributed to declining rates of PSM in contemporary RP series [9,12,15,16]. Despite this, the incidence of PSM remains relatively stable, particularly in high-risk tumors [15], placing patients at an increased risk for biochemical and clinical disease progression. Based on the notion that residual cancer cells might be present at the margin of resection, the rationale for offering additional local therapy is evident. Radiotherapy (RT) is the only available form of curative treatment in these cases, and it can be delivered in an adjuvant or salvage setting. Unlike salvage therapy given to patients with PSA relapse or biopsy-proven local recurrence, adjuvant RT is administered to men without clinical evidence of disease in whom the PSA was rendered undetectable shortly after surgery. Proponents of therapy in an adjuvant setting argue that the optimal efficacy of RT is attained with the smallest tumor burden and timely eradication of localized disease that has the potential to metastasize and escape the radiation portals if left untreated [60]. Opponents highlight the sensitivity and reliability of the PSA test to detect failure at an early stage and argue that by monitoring postoperative PSA, RT can be delayed until the marker is detectable. Hence, unnecessary treatment-related morbidity in those who were cured by surgery alone can be prevented.

As the debate over the optimal timing of RT persists, two large randomized studies have now demonstrated persuasive evidence supporting adjuvant RT in men with high-risk disease after RP. The Southwest Oncology Group (SWOG) 8794 study and the European Organization for Research and Treatment of Cancer (EORTC) 22911 trial randomly assigned patients with high-risk features to either immediate RT to the prostate bed or no further treatment after RP [61,62]. Similar enrollment criteria were applied in both studies and included patients with node-negative disease and at least one of the following: extraprostatic tumor extension, SVI, or PSM in otherwise organ-confined cancers. Both studies showed that adjuvant RT effectively reduced the biochemical treatment failure rates. The SWOG 8794 study found that the actuarial probability of remaining free from PSA progression 10 yr after surgery was 47% in the treatment arm versus 23% in the observation arm [61]. With a median follow-up of 10.2 yr, a 25% reduction in the risk of developing metastatic disease among patients assigned to RT was observed. Although this difference did not meet criteria for statistical significance in the original report (p = 0.063), a recently presented update at the American Urological Association’s (AUA) annual meeting revealed...
that with longer follow-up, the 15-yr metastasis-free survival was 49% in the treated group versus 40% in the untreated group ($p = 0.021$). Furthermore, at 15 yr, a statistically significant survival advantage was evident for radiation-treated patients compared to men in the untreated group (50% vs 39%, $p = 0.031$).

In a larger clinical trial with shorter follow-up (median: 5 yr), the EORTC randomized 1005 men to adjuvant RT ($n = 502$) versus no immediate treatment ($n = 503$) [62]. As in the SWOG trial, RT improved the 5-yr biochemical progression-free survival from 53% to 74%, the local progression-free survival from 85% to 95%, and the clinical progression-free survival (ie, no evidence of clinical, sonographic, or radiographic recurrence) from 78% to 85%. Limited by the short follow-up time, metastasis-free survival, disease-specific survival, and overall survival (OS) were not altered by the intervention. Because the observed benefit of immediate RT appeared to be more prominent in the subset of patients with PSM compared to those without [63] and a substantial discordance was noted between the original pathology report and an expert review of the surgical margin status [3,64], the authors explored the relationship between adverse pathologic features and response to adjuvant RT, applying a central pathology review to 552 of the 1005 RP specimens [65]. Intriguingly, in this revised analysis, a PSM was the most powerful predictor of a durable response to adjuvant RT 5 yr after treatment: For every 1000 patients with positive margins, immediate postoperative RT was predicted to prevent BCR in 291. Moreover, those with negative margins did not seem to benefit from RT (irrespective of other adverse pathologic features), suggesting that PSM might be the primary predictor of a durable response to salvage RT administered at the earliest onset of PSA recurrence [67,68], and the potential for morbidity resulting from RT argue against its indiscriminate use. Although highlighting the advantages of adjuvant RT, the EORTC data clearly indicated that approximately three patients with positive margins need to be treated to prevent one biochemical relapse [65]. Taking into account that in the SWOG trial, adjuvant RT was associated with a 2.3-fold increased risk of total urinary incontinence, a 1.9-fold increased probability of urethral stricture, and a higher prevalence of proctitis and rectal bleeding, the reluctance to recommend RT in an adjuvant setting to men who were, in fact, cured by their surgery is understandable. Pathologic artifacts during specimen processing that could render the margins falsely positive likewise provide an argument against categorically offering adjuvant RT to all men with PSM. Unfortunately, SWOG 8794 combined extraprostatic extension, SVI, and PSM into a single high-risk category, making the application of its findings to the subgroup of patients with only PSM rather inaccurate.

Altogether, available data do not provide definite guidance on how to optimally manage patients with PSM. Although subgroup analyses of the SWOG trial suggest that salvage RT may not be as effective as radiation in the adjuvant setting [69,70], no definitive evidence exists to either support or refute one intervention as undeniably superior over the other. In the absence of randomized trials comparing adjuvant RT with early salvage RT in men with PSM, it seems prudent to discuss adjuvant RT with patients who have multiple positive margins—particularly if the margins are located posteriorly or posterolaterally—or with patients who have PSM associated with additional high-risk features [71]. Patients should be clearly informed of the potential urinary and rectal morbidity associated with RT and allowed the opportunity to consider early salvage RT as an alternative. It should also be acknowledged that salvage RT is supported by eminent retrospective data but must also be proved effective by future randomized trials.

4. Conclusions

PSM in RP specimens are uniformly acknowledged as an adverse outcome indicator associated with an increased hazard of BCR and local disease recurrence as well as the need for secondary cancer treatment. Tumor biology (volume, distribution, and aggressiveness) and surgical factors (type of procedure, technique, and experience) are the primary determinants of margin status. 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. Randomized controlled trials clearly indicate that adjuvant RT in these men improves BCR rates, reduces clinical progression, and possibly improves OS. However, before definite recommendations can be made, a randomized trial comparing adjuvant RT immediately after surgery to salvage RT at the earliest onset of PSA relapse is critically needed.

**Author contributions:** Ofer Yossepowitch had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Statistical analysis:** None.

**Administrative, technical, or material support:** None.

**Supervision:** Montorsi.

**Other (specify):** None.

**Financial disclosures:** I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter of materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

**Funding/Support and role of the sponsor:** None.

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