Positive Surgical Margins After Radical Prostatectomy: A Systematic Review and Contemporary Update

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Abstract

Context: The clinical significance of positive surgical margins (PSMs) in radical prostatectomy (RP) specimens and the management of affected patients remain unclear. Objectives: To address pitfalls in the pathologic interpretation of margin status; provide an update on the incidence, predictors, and long-term oncologic implications of PSMs in the era of robot-assisted laparoscopic RP (RALRP); and suggest a practical evidence-based approach to patient management.

Evidence acquisition: A systematic review of the literature was performed in April 2013 using Medline/PubMed, Web of Science, and Scopus databases and the Cochrane Database of Systematic Reviews. Studies focusing on PSMs in RP pertinent to the objectives of this review were included. Particular attention was paid to publications within the last 5 yr and those concerning RALRP.

Evidence synthesis: A total of 74 publications were retrieved. Standardized measures to overcome variability in the pathologic interpretation of surgical margins have recently been established by the International Society of Urological Pathology. The average rate of PSMs in contemporary RALRP series is 15% (range: 6.5–32%), which is higher in men with a more advanced pathologic stage and equivalent to the rate reported in prior open and laparoscopic prostatectomy series. The likelihood of PSMs is strongly influenced by the surgeon’s experience irrespective of the surgical approach. Technical modifications using the robotic platform and the role of frozen-section analysis to reduce the margin positivity rate continue to evolve. Positive margins are associated with a twofold increased hazard of biochemical relapse, but their association with more robust clinical end points is controversial. Level 1 evidence suggests that adjuvant radiation therapy (RT) may favorably affect prostate-specific antigen recurrence rates, but whether the therapy also affects systemic progression, prostate cancer-specific mortality, and overall survival remains debatable.

Conclusions: Although positive margins in prostate cancer are considered an adverse oncologic outcome, their long-term impact on survival is highly variable and largely influenced by other risk modifiers. Adjuvant RT appears to be effective, but further study is required to determine whether early salvage RT is an equivalent alternative.

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1. Introduction

Positive surgical margins (PSMs) after radical prostatectomy (RP) are uniformly considered an adverse outcome associated with failure of the surgery to achieve cure of the prostate cancer (PCa). In 2009, we published a comprehensive review on the issue of positive margins that was based primarily on studies conducted in the late 1990s and early in the first decade of the 2000s [1]. Since then, there has been a dramatic worldwide shift in practice patterns from open to robotic surgery and a substantial increase in RP volume [2]. In addition, data from clinical trials and case series have matured, allowing for better appraisal of the true impact of PSMs on oncologic outcomes and the role of radiation therapy (RT) in this setting. We hence sought to present an update addressing the pitfalls in the pathologic interpretation of margin status and the incidence and long-term oncologic implications of PSMs in the current era of robot-assisted laparoscopic RP (RALRP). A practical evidence-based approach to the management of patients with PSMs is suggested.

2. Evidence acquisition

To update our previous review [1], we performed a systematic literature search in April 2013 using the Medline/PubMed, Scopus, and Web of Science databases and the Cochrane Database of Systematic Reviews, including both medical subject headings and free text protocols. The search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria for systematic reviews (http://www.prisma-statement.org) and was restricted to the term positive margins or surgical margins and one of the following: prostate cancer, prostate carcinoma, pathological, radical prostatectomy, robotic-assisted laparoscopic radical prostatectomy, surgical experience, prognosis, oncologic outcomes, survival, and radiation therapy. The following limits were used: humans; gender (male); English language; and publications dating from January 1, 2005 (Fig. 1).

Two authors (O.Y. and K.T.) independently reviewed the abstracts of the retrieved studies and selected the abstracts that were pertinent to the objectives of the present review. The corresponding full-length articles and their linked references were carefully assessed by all authors; particular attention was paid to publications that appeared within the last 5 yr and publications concerning RALRP. Studies published as abstracts or reports from meetings were excluded. When two or more papers reported on updated series of the same cohort, the most recent paper was considered. Only articles reporting complete data with clinical relevance for the present review were included in the final analysis.

Fig. 1 – Systematic electronic search method.
3. Evidence synthesis

3.1. Assessment of margin status in radical prostatectomy specimens: the pathologist’s view

In 2009, the International Society of Urological Pathology (ISUP) published standardized measures on the handling, staging, and reporting of RP specimens [3]. Following the distribution of international online surveys to 255 ISUP members, the protocol was approved by a large consensus conference held in conjunction with the 2009 annual scientific meeting of the United States and Canadian Academy of Pathology. Several important criteria pertaining to PSMs were established as described in the following discussion.

Whether one partially or totally embeds the prostate is largely dependent on the capability of the institution to dissect and archive whole-mount specimens. Regardless of the approach, the most diagnostically sound and clinically useful method is the one that provides maximal information on grade, stage, and margin status. Surgical margins are deemed positive only if cancer cells touch the surface of the RP specimen (tumor on ink). The distance from tumor to ink is generally considered to have no effect on the risk of recurrence [4–7], although one study found conflicting evidence [8].

The location of the positive margin, determined predominantly by the volume and location of the tumor within the gland, should be specified in the pathology report and stratified as posterior, posterolateral, lateral, anterior, apical, and bladder neck. Although most studies have shown that the site of the positive margin does not affect the prognosis, distinguishing among the posterior, posterolateral, and lateral sites, for example, makes it possible for urologists to modify their technique in the regions of the neurovascular bundles. The apex is one of the most frequent sites of positive margins, yet when a tumor is found at the inked apical margin, the pathologic stage is classified as pT2x so long as the tumor is organ-confined elsewhere. This staging uncertainty reflects the vague boundaries at the apex of the prostate, where it cannot be determined whether a cancer with a positive margin is intraprostatic or extraprostatic (Fig. 2A). Adjunctive immunohistochemistry is occasionally required to confirm the presence of an apical positive margin (Fig. 2B).

The proximal margin in RP specimens consists of the bladder neck, which is composed of thick muscle bundles. Positive proximal margins usually correlate with extensive tumor at the base of the prostate, although that finding by itself lacks prognostic significance [9,10]. The anterior margin may be involved in a larger percentage of prostatectomies performed for stage T1a/b disease, as patients diagnosed with PCa during transurethral prostatectomy are more likely to harbor large transitional zone tumors.

The amount of tumor at the inked margin should be measured in millimeters and recorded. Most studies show a clear association between the linear extent of margin positivity and risk of disease recurrence [11–17].

Positive margins may also be a consequence of surgical transection into an intraprostatic tumor. This is often referred to as capsular incision, although the term is

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Fig. 2 – Prostate apex examined with the cone method. (A) The arrow indicates an area of the inked surface suspicious for positive surgical margin in the hematoxylin and eosin–stained section. (B) The cytokeratin (CAM 5.2)–immunostained section (see arrow) shows individual neoplastic cells touching the apical surgical margin. This is an example of a focal positive surgical margin determined after applying immunohistochemistry.
erroneous because there is no prostatic capsule. Intraprostatic incision often occurs in the regions of the neurovascular bundles, where urologists may inadvertently cut into the prostate in an attempt to preserve erectile function. The reported incidence of intraprostatic incision varies widely, from 1.3% to 71% [18], mainly because of the inherent difficulty in recognizing an underlying extraprostatic extension. For instance, if an extraprostatic tumor is associated with a desmoplastic stromal response at the margin of resection, the tumor may be misdiagnosed as organ-confined, and the positive margin will be misclassified as an intraprostatic incision. Therefore, to identify a positive margin because of intraprostatic incision, both the tumor and benign glands transected in the same area should be present at the inked margin (Fig. 3). Intraprostatic incision is associated with an increased risk of postoperative progression, equivalent to that seen with PSMs in an area of focal extraprostatic extension [15].

The clinical implications of benign positive margins remain controversial [19,20]. Typically, a finding of only a few benign glands at the surgical margin often goes unreported; however, significant intraprostatic incision across benign glands should be noted, as it may serve as a source of elevated prostate-specific antigen (PSA) postoperatively (Fig. 4). Currently, reporting the tumor grade at the site of margin positivity is not required, although the majority of studies have demonstrated its prognostic value [12–14,21].

To date, the vast majority of studies addressing PSMs have been largely deficient in defining and reporting one or more of the criteria set by the ISUP committee [11]. Thus, the true clinical impact of specific positive margin-associated variables remains uncertain.
3.2. Incidence and predictors of positive surgical margins in contemporary radical prostatectomy series

Comparative data indicate clearly that the incidence of positive margins is equivalent among the open, laparoscopic, and RALRP approaches [22,23]. In the most extensive literature review thus far, Novara et al. reported a 15% mean rate of PSMs in RALRP series published between 2008 and 2011 (each including >100 cases), with a range of 6.5–32% [24]. The stage-specific rates were 9% for pT2 (range: 4–23%), 37% for pT3 (range: 29–50%), and 50% for pT4 (range: 40–75%), supporting the notion that the more extensive the cancer, the higher the risk of positive margins.

Data on additional clinical and pathologic predictors of PSMs have been largely inconclusive. Most authors believe that factors that make surgery more difficult—namely, elevated body mass index [25], large prostate [26], previous surgery for prostatic hyperplasia [27], and prior abdominal surgery [28]—have a negligible impact. Distinctively, Patel and colleagues, in a large multi-institutional study comprising >8000 patients, found high body mass index and large prostate volume to be independent predictors of PSMs overall and in men with organ-confined tumors [29]. The influence of surgical experience and RALRP training on the risk of PSMs is discussed in greater detail in Section 3.4.1.

3.3. Oncologic implications of positive surgical margins on hard clinical end points

PSMs in RP specimens have been consistently associated with an increased risk of PSA relapse [1,3,24,30–34]. To date, owing mostly to restricted follow-up, most studies addressing the impact of PSMs on treatment efficacy have conveniently used biochemical recurrence (BCR) as an early end point. Although a rising PSA, left untreated, may predate overt clinical progression, the highly variable natural history of BCR limits its surrogacy for metastatic progression and PCa mortality. For many men, a slowly rising PSA may pose little threat to longevity or quality of life, particularly if managed properly with salvage therapy. An abnormal postoperative PSA may arise from the microscopic focus of PCa outside the pelvis (present at surgery), or a combination of both. Although cancer at the surgical margin is more likely to be associated with local tumor recurrence, it may also indicate distant relapse, particularly in men with additional high-risk features such as extensive extraprostatic extension or seminal vesicle involvement. Zealous attempts to preserve the bladder neck or neurovascular bundles may result in retained benign prostatic tissue elements, another potential source of measurable PSA irrespective of margin status [19,20]. With these considerations, predicting the actual influence of PSMs on the natural course of the disease in the individual patient poses a difficult challenge.

Table 1 summarizes the available evidence from five contemporary studies on the impact of PSMs on robust clinical end points [30–34]. All studies found PSMs to be associated with a higher risk of BCR. However, the data pertaining to metastatic progression and death were less consistent. Using the Surveillance Epidemiology and End Results cancer registry, comprising >65 000 patients followed for a median of 4.2 yr, Wright and colleagues noted a 1.7-fold increased risk of death from PCa among men with positive compared with negative surgical margins [34]. However, in a multivariate model adjusting for adverse pathologic features, these findings held true for only high-grade tumors or extraprostatic disease (pT3). Similarly, in a study of >4500 patients followed for a median of 10 yr, Chalfin et al. confirmed the detrimental impact of PSMs on survival, but that impact was fairly marginal relative to the impact of RP Gleason score and pathologic stage [31]. Other studies did not find PSMs to be an independent predictor of systemic progression or survival [30,32,33], leading to questioning of the influence of positive margins on long-term outcomes.

Why PSMs would affect the probability of BCR but not the more robust clinical end points remains perplexing. PSMs undoubtedly increase the risk of disease recurrence and, conceivably, the risk of dying from cancer. However, the range of risk and the time to event are very wide, depending mostly on the presence or absence of other risk modifiers [35]. Even if the risk is real, competing causes of mortality may obscure the predictive value of PSMs for death due to PCa. Mauermann and associates followed men

<table>
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<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>PSMs, no. (%)</th>
<th>Median follow-up, yr</th>
<th>HR for BCR (95% CI), p value</th>
<th>HR for MP (95% CI), p value</th>
<th>HR for PCSM (95% CI), p value</th>
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<td>Mauermann et al.</td>
<td>2012</td>
<td>1712</td>
<td>281 (16.4)</td>
<td>6.2</td>
<td>1.7 (1.2–2.3), 0.001</td>
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<td>2008</td>
<td>406</td>
<td>70 (17)</td>
<td>5.2</td>
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<td>2010</td>
<td>11729</td>
<td>3651 (31.1)</td>
<td>8.2</td>
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<td>6.6 (1.9–23), 0.003</td>
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<td>Chalfin et al.</td>
<td>2012</td>
<td>4461</td>
<td>462 (10.4)</td>
<td>10</td>
<td>5 (3.7–6.7), &lt;0.001</td>
<td>NR</td>
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* Study Year

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PSM = positive surgical margin; HR = hazard ratio; NR = not reported; NS = not significant; BCR = biochemical recurrence; MP = metastatic progression; PCSM = prostate cancer–specific mortality; CI = confidence interval.

* There were 281 patients with a solitary positive margin and 310 patients with multiple positive margins.

** The p values were not reported; statistical significance was reached only in patients with high-grade tumors or extracapsular extension.
with PSMs for a median of 6.2 yr and found that the risk of dying from PCa was exceeded 15-fold by the risk of dying from other causes [32]. In the Southwest Oncology Group (SWOG) 8794 study, a median of 12.7 yr from surgery was required for the detrimental influence of PSMs on survival to become evident [36]. The Prostate Cancer Intervention Versus Observation Trial [37] and a subanalysis of the Scandinavian Prostate Cancer Group 4 study [38] both found RP to have no apparent survival benefit in men with low-risk cancer. These findings imply that the presence of positive margins in low-risk tumors may not matter if a similarly excellent outcome can be achieved without any treatment. Thus, when interpreting the results of retrospective series assessing the impact of PSMs on survival in patients with PCa, clinicians should carefully scrutinize the proportion of high-risk tumors in the cohort, the administration and timing of salvage therapies (early vs late intervention and the proportion of men treated), and most important, the extent of follow-up.

### 3.4. Reducing positive surgical margins rates

Regardless of their oncologic implications, PSMs are likely to generate anxiety among affected patients [39] 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.

#### 3.4.1. 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 [40], laparoscopic RP [41], and RALRP [42], attesting to the importance of surgeon experience in optimizing outcome. The incidence of PSMs is expected to be relatively high initially, but it generally plateaus 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 series [41] to 1000–1500 cases using the robotic approach [42].

While there is no definitive proof to support one surgical approach over the others with respect to the rate of PSMs [22,43,44], several studies have highlighted the variability in margin status among individual surgeons using the same modality (including highly experienced surgeons from the same institution) [40], suggesting that surgeon proficiency irrespective of the number of procedures performed might be the primary determinant of PSMs. The manner in which surgeons learn to improve their technique has been a matter of ongoing research, particularly given the intense shift observed in practice patterns from open RP to RALRP [2]. 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 [45].

#### 3.4.2. 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 [46,47].

##### 3.4.2.1. 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. For example, to prevent the dorsal venous complex or puboprostatic ligaments from obstructing the view, Tewary and colleagues used a 30° upward-facing lens combined with cephalad retraction of the prostate to approach the transition of the apex into the membranous urethra from the posterior undersurface of the gland rather than the conventional anterior view [48]. After sharp and blunt dissection, the layers of the Denonvilliers fascia were divided, followed by the entire urethral circumference, leaving the prostate tethered by the dorsal venous complex and anterior fibromuscular ligaments. The latter were then divided via the traditional anterior approach. This novel retroapical technique decreased the authors’ rate of PSMs from 4.4% to 1.4%. Other proposed modifications include the use of a lateral viewing camera through the assistant’s port [49] and upfront cold transection of the dorsal venous complex facilitated by increased pneumoperitoneum and its subsequent ligation [50,51].

##### 3.4.2.2. 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 [52] or failure to excise the extraprostatic...
extension of the prostate carcinoma. Because several planes of dissection can be entertained to ensure oncologic safety at the posterolateral site, nerve preservation 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 [53]. Patel and colleagues, assisted by the high-quality magnified image provided by the robotic camera, highlighted two anatomic elements that may help surgeons delineate the appropriate plane of dissection between the prostate and neurovascular bundles: a landmark artery running on the lateral border of the prostate and the pearly areolar plane that marks the natural separation between prostate and neurovascular tissue [47]. Tewari et al. recommended using the periprostatic veins as an anatomic landmark to discern among the various periprostatic fascial compartments [46]. Depending on how the extent of the tumor at base is appreciated, surgeons may choose the carry the dissection in an intrafascial 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). Secin et al. found that interfascial or extrafascial nerve sparing (in which an additional layer of fascia is left to cover the tumor) was associated with a higher rate of positive margins compared with intrafascial nerve sparing (in which no fascia is left to cover the tumor) [53]. 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).

3.4.3. 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 [54], 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 [55–58]. More recently, however, a systematic approach was introduced involving the assessment of the entire gland circumference. Schlomm and colleagues, in a study of 5392 patients, submitted the entire neurovascular-adjacent prostatic tissue for intraoperative assessment by dedicated genitourinary pathologists [59]. PSMs were detected in 1368 patients (25%), leading to secondary resection of the involved neurovascular tissue and conversion to definitive negative margins in 1180 patients (86%). The authors 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. Similar findings were reported by von Bodman et al., who found positive margins in 22% of patients and converted 92% of them to negative margins using systematic frozen-specimen analysis [60]. 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 (see Section 3.5).

3.5. Treatment of patients with positive margins: a practical evidence-based approach

Based on the notion that a PSM might represent retained cancer cells at the margin of resection, the rationale for offering additional local therapy to men with positive margins is clear. RT, the only effective form of treatment in this setting, can be offered to all men with PSMs immediately after surgery (adjuvant RT) or selectively to men with BCR as an early indicator of clinical relapse (salvage RT). Proponents of adjuvant RT argue that its optimal efficacy is attained with the smallest tumor burden and timely eradication of localized disease that has the potential to escape the irradiation portals and metastasize if left untreated. Opponents argue that the PSA test has high sensitivity and reliability to detect failure at an early stage so that with careful monitoring, RT can be delayed until the marker is detectable. Selecting the optimal strategy in these cases remains contentious, as do the radiation dose and the role of combined androgen-deprivation therapy.

Recent evidence indicates that RT delivered to the prostatic bed immediately after surgery may alter the natural course of the disease in men with PSMs. The SWOG 8794, European Organization for Research and Treatment of Cancer (EORTC) 20911, and German Cancer Society (ARO 96–02) studies all convincingly demonstrated that adjuvant RT may lead to a 50–60% reduction in the risk of PSA progression in men with pathologically advanced PCa [61–63]. With longer follow-up (median: >10 yr), SWOG 8794 (but not EORTC 20911) updated that this benefit translated into a lower risk of metastatic progression (hazard ratio: 0.7; p = 0.016) and improved overall survival [36,64]. The latter outcome, however, should be interpreted with caution, as the cause of death was not ascertained in that study, and patients in the observation arm were twice more likely to be diagnosed with a Gleason score 8–10 cancer compared with patients in the treatment arm. Nonetheless, patients with positive margins, including patients with poorly differentiated cancers and seminal
vesicle invasion, appeared to derive the greatest benefit from adjuvant RT [65], supporting the claim that the adjuvant approach should, at a minimum, be discussed with all men diagnosed with PSMs.

At the same time, several concerns have discouraged the endorsement of routine administration of adjuvant RT to all candidates with PSMs. First and most important, not all men with PSMs are destined to fail [66]. Although numerous studies have found positive margins to be an adverse prognostic feature associated with a relative twofold increased risk of PSA relapse, the majority of men with isolated PSMs, with or without extraprostatic extension, are cured after RP alone [66,67]. Given that delivery of adjuvant RT might have a detrimental impact on recovery of urinary continence after surgery [68], a universal policy would likely expose many men to unnecessary morbidity.

Second, PSMs increase the risk of BCR, but whether they are also associated with a higher probability of clinical progression and prostate cancer–specific mortality remains questionable [30,32,34]. A recent multi-institutional observational study including >23,000 men undergoing RP reported an exceedingly low long-term mortality risk in men with pathologically non–organ-confined disease. Neither extraprostatic extension nor PSMs was associated with death from PCa after adjusting for other adverse pathologic features [67]. Men with Gleason score 6, for example, had a negligible 15- to 20-yr mortality risk of \( \leq 1.2\% \). Thus, a uniform policy of adjuvant RT in an elderly population with competing risks of mortality would mean that an exceedingly large number of patients with PSMs and otherwise low-risk tumors would need treatment to improve survival. This idea is very similar to the reported long-term outcomes of the EORTC 22911 study, which showed that adjuvant RT offered to men aged \( \geq 70 \) yr effectively reduced the risk of PSA relapse but was likely to have no, or a possibly negative, impact on survival [64].

Third, while data from randomized controlled trials are lacking, evidence from retrospective observational series indicates that RT delivered at the earliest onset of PSA relapse (detected by modern ultrasensitive assays) is a reasonable alternative to immediate adjuvant therapy [69–71]. Salvage RT has been found to effectively control local recurrence and reduce the risk of clinical progression and PCa mortality. Indeed, the durable response following early salvage RT (when PSA is \( \leq 0.5 \) ng/ml) seen in 50% of patients is comparable to the 50% relative reduction in BCR associated with adjuvant RT in randomized trials.

Because there is no conclusive evidence to support one of the irradiation strategies as undeniably superior over the other, it is incumbent on urologists to guide their patients using all available information. The trials of adjuvant RT cannot be used as definitive proof of the superiority of this approach, given that the indication for salvage radiation in the observation arm of these studies was a median PSA of 1.0 ng/ml or palpable local recurrence, both considered to occur fairly late in the course of relapse. In addition, retrospective matched control analyses comparing adjuvant and salvage RT regimens provide conflicting evidence. A benefit in favor of adjuvant RT was demonstrated by Trabulsi and colleagues, who showed that early RT increased the 5-yr BCR-free rate from 50% (after salvage RT) to 75% (after adjuvant RT) [72]. Nevertheless, the only predictor of metastatic progression on multivariate analysis was Gleason score \( \geq 8 \); neither the mode of irradiation nor the surgical margin status had an apparent impact. Similar findings were reported by Budiharto et al. [73] and Ost et al. [74], who highlighted the incremental benefit of adjuvant over salvage RT in improving the BCR-free rate in men with PSMs, with or without lymph node involvement.

However, the perceived advantage of adjuvant RT in these studies may be trumped by several factors: the unknown proportion of men with PSMs in the salvage arm who were followed after RP and never had recurrences; the long interval allowed between surgery and RT in the adjuvant arm (men with persistently undetectable PSA are less likely to have recurrence overtime); and the relatively high PSA cut-off used to trigger the intervention in the salvage arm, which places the validity of RT into question compared with contemporary standards. To overcome these caveats, Briganti and colleagues conducted a propensity-matched analysis of adjuvant RT compared with early salvage RT in men with pT3N0 tumors with or without involvement of the surgical margin, confirming that salvage therapy was delivered at a PSA \( \leq 0.5 \) ng/ml and that adjuvant RT was delivered within the first 6 mo after surgery [71]. There was no difference in BCR-free rates between the two irradiation modalities in patients with PSMs.

So how can urologists apply the available evidence to reconcile the optimal timing of RT in men with positive margins? There are two ongoing prospective phase 3 randomized studies seeking proof of the clinical benefit of adjuvant RT compared with early salvage RT in high-risk patients: The Radiotherapy and Androgen Deprivation in Combination After Local Surgery trial, conducted by the Medical Research Council, and the Radiotherapy–Adjuvant Versus Early Salvage (RAVES) trial, conducted by the Trans-Tasman Radiation Oncology Group. Until the results from these trials are made available, it is unlikely that this clinical dilemma will be resolved.

In the interim, we advocate a multidisciplinary approach in which the risk of clinical relapse is calculated by validated tools [67,70] and used to advise patients about the purported benefits and disadvantages of each treatment modality. Young men with several risk factors (high Gleason score, multiple positive margins) should be informed about the beneficial impact of adjuvant RT on the risk of clinical failure and death from PCa [21,36]. For patients with an isolated focal positive margin and otherwise low-risk organ-confined tumor, it may be prudent to recommend close monitoring with serial PSAs, advocating that RT may never be required and reassuring patients that intervention at the earliest sign of recurring disease will likely provide a similar outcome [71].

4. Conclusions

PSMs in PCa are uniformly considered an adverse oncologic outcome. However, their long-term impact on clinical
progression and cancer-specific survival is highly variable and largely dependent on additional risk modifiers, as well as patient life expectancy. The likelihood of positive margins is influenced by surgical experience irrespective of approach. Technical modifications using the robotic platform and the role of frozen-section analysis to reduce margin positivity rates continue to evolve. Adjuvant RT appears to be effective in this setting; however, further study is required to determine whether early salvage RT is an equivalent alternative.

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**Acquisition of data:** Yossepowitch.

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