Chapter 7
Oncologic Outcomes of Robotic-Assisted Radical Prostatectomy: The "Balancing Act" of Achieving Cancer Control and Minimizing Collateral Damage

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Defining Oncologic Outcomes After Radical Prostatectomy

To this day, prostate cancer remains the most common nondermatologic malignancy in Western men, with the vast majority of cases presenting with localized or locally advanced disease [1]. A standard treatment option for this is radical prostatectomy (RP), which was traditionally performed via the open approach, but more recently is typically conducted using robotic assistance (robotic-assisted radical prostatectomy; RARP). As localized/locally advanced prostate cancer has a long natural history, studies examining survival take many years to mature and thus often suffer from low power. Hence, intermediate markers of oncologic outcome have become abundant in the literature, the commonest being biochemical recurrence (BCR). This is defined as a rise in a prostate-specific but not cancer-specific protein called Prostate-Specific Antigen (PSA) released in the blood. While the exact rise that defines BCR is not universally agreed upon, most authorities use a PSA of 0.2 ng/ml or greater [2].

Due to competing causes of mortality in men with BCR post-RP, not all recurrences lead to death, but this measure is regarded as a fairly accurate predictor of

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prostate cancer-specific mortality and thus used to guide the need for salvage therapy [3]. The largest study examined 1997 men postprostatectomy from 1982 to 1997, of which 15 % developed BCR. Thirty-five percent of patients with BCR developed metastases after a median of 8 years, and 43 % died of prostate cancer, after a median of circa 5 years after metastases [4]. Hence the risk of death from prostate cancer in those with BCR was 15 %. A more recent study has quoted a 21 % risk of death in men with BCR post-RP, and clearly case-mix is responsible for some of these differences [5]. Regardless, lethal metastatic disease is almost always preceded by a rise in PSA that signifies BCR.

How Positive Surgical Margins Correlate with Oncologic Outcome

A positive surgical margin (PSM) may reflect residual cancer cells at the edge of the surgical resection, and this is a consistent predictor of BCR [6–10]; one study reported a BCR-free survival of 93.8 and 79.9 % after adjustment for covariates in those with negative and positive surgical margins, respectively [11]. However, studies directly comparing the effect of a PSM to metastasis-free survival and mortality are much less conclusive. A large registry study of 65,633 patients demonstrated a significant effect of PSM on cancer-specific mortality (HR:1.70 [1.32–2.18]) [10]. Criticism of this work has been directed at the absence of preoperative PSA data, and a recent audit which identified a significant rate of inaccurate coding in the database [12], although a second study has further supported the same conclusions from the SEER database, with PSM affecting mortality after multivariate modeling (HR:1.4 [1.0–1.9]; $p=0.036$) [7]. Nonetheless, some studies which have shown PSM to predict BCR have failed to demonstrate a significant relationship with mortality [6, 13, 14]. With such large differences in follow-up, inclusion criteria, and the accurate capture of covariates, it is unsurprising that the literature is conflicting as to whether PSM per se have a direct effect on prostate cancer mortality [15].

What we do know is that the vast majority of studies examining the relationship between PSM and oncologic outcome have done so after open RP. However, RARP has become the market leader in the United States and many other Western nations [16]. Hence, more recent work has sought to compare PSM rates across surgical approaches and to determine the impact on PSM in the RARP population. A meta-analysis based on 400 original articles used propensity score adjustments to demonstrate similar PSM rates for RARP and open RP [17], although a recent retrospective study of over 22,000 RP cases showed superior PSM rates in minimally invasive cases over open RP [18].

Multifocal Margins and Oncologic Outcome

If we accept some of the evidence cited earlier that PSM itself is associated with BCR, we might intuitively expect that multifocal tumors should be at greater risk for more residual tissue to be left behind and BCR to occur more quickly. To this

end, a study of 210 men with PSMs revealed a 2.19-fold greater risk of recurrence in those with two or more PSM compared to a unifocal margin [19]. Swanson et al. [20] described an overall crude (unadjusted) recurrence rate across seven recent large case series of 20 % vs. 70 % between unifocal and multifocal disease. However, this result has not been reproduced by larger studies [21, 22], where the additional negative prognostic effect of an additional PSM has not been realized [23]. In a recent review of studies from 2005 to 2011, Fontenot [24] identified three studies where multifocality was found to confer a greater risk of BCR compared to unifocality [25–27], and seven in which no such additive effect was seen [6, 28–30].

The Impact of Margin Length

The impact of margin length would follow similar arguments to the impact of multifocality on BCR outcomes. However, most studies on PSM and BCR in both the open and robotic literature do not report on PSM length and so we are limited to a few reports on which to draw our inferences. Furthermore, studies have generally reduced margin length into a categorical variable, often separating into <1/≥1 mm or <3/≥3 mm. Noting the aforementioned, there have been four recent studies [31–34] which found an increasing PSM length to increase the risk of BCR, while three studies failed to show any significant increase in BCR risk on multivariable analyses [29, 35, 36].

Shikanov and colleagues demonstrated a relationship between PSM length and risk of BCR in 1398 cases of RARP after a median follow-up of 1 year. They were unable to demonstrate an effect of PSM < 1 mm on BCR and postulate that these may represent false positive margins. However, an analysis of 294 RARPs with PSM, which reported margin length as a continuous variable, showed a correlation with BCR across all PSM lengths [31]. A more robust analysis of RARP patients with at least 5 years follow-up established the predictive capability of PSMs ≥3 mm/multifocal margins compared to those <3 mm/unifocal margins (HR:2.84 [1.76–4.59]), and this effect was even more substantial in lower risk cohorts [37].

The Impact of Margin Location

So if margin length is important in predicting oncologic outcome, the next question is whether the site of the PSM matters. If papers dealing with margin length were few and far between, this problem is even greater for the margin location literature, with most studies having insufficient power to pick up any association between margin location and BCR, especially after covariate adjustment or subgroup stratification. The subject is further complicated by inconsistent reporting methods of locations, with the International Society of Urologic Pathologists and the College of American Pathologists proposing different classifications of PSM locations [24]. In general, the following are considered by most investigators to be appropriate descriptors for PSM location [24]:

1. *Apex*: The most distal aspect of the prostate is the most surgically challenging to access especially as we try to maximize preserved urethral length. The prostatic apex passes adjacent to the dorsal venous complex and neurovascular bundles under the pubis [24]. It also presents difficulties during histopathologic analysis because of a sparse 'capsule' which complicates correctly labeling PSMs as organ-confined tumors with an intraprostatic incision (pT2 with PSM); or a margin positive extraprostatic tumor (pT3 with PSM), and risks incorrectly labeling organ-confined tumors (pT2 with negative margin, NSM). Hence, the PSM data at the apex is hugely subjected to the Will Rogers phenomenon in which both pT2 and PT3 PSM rates would be reduced if apical PSMs are reported as pT3 PSM cases due to a lack of a 'capsule' [38]. The apex is considered to be the most common location for PSM across the ORP literature [39]. Although some studies showed a significantly increased risk of BCR with apical PSM after multivariable analysis, others have shown no such relationship [24]; the problem is that prostate cancer that reaches the apex may be indicative of larger tumor volume which may then confound multivariable analyses [40].
2. *Posterolateral and posterior*: Posterolateral margins are the second most common [39] and most often a result of efforts to preserve the neurovascular bundles, as this broadly describes the region where intra-/interfascial dissection occurs for nerve sparing. Three recent reports describe a greater impact on BCR rates with a PSM in this area, while only one failed to demonstrate a significant relationship (of any location including posterolateral) after multivariable regression, likely due to the small sample size [41]. Prostate cancers can also invade posteriorly into Denonvilliers fascia necessitating resection of this posterior fascia. The association between PSM in this region and BCR has also been varied; Fontenot summarized three studies from the last decade which support both conclusions [24].
3. *Base and bladder neck*: The basal prostate refers to the cranial end of the prostate around the bladder neck, although PSM at these sites are often grouped together [34]. PSM here can result from surgical efforts to preserve the bladder neck in an attempt to improve urinary continence recovery. The finding of an isolated PSM at the bladder neck is a reasonably infrequent occurrence (compared to microscopic invasion of the bladder neck, pT3 disease which need not necessarily have an associated PSM). Controversy regarding the impact of PSMs at these sites also exists, particularly for those at the base. Hsu and colleagues reviewed 117 RP patients with positive margins and described a significant impact of bladder neck PSM on BCR (HR:1.29 [1.0–1.67]; $p=0.046$). In contrast, other studies refute the impact of a PSM at the bladder neck on BCR [28, 34, 42].
4. *Anterior*: This is generally considered as a fibromuscular stromal region which is less commonly associated with finding PSMs, with an incidence of 2–15 %. Anterior PSM may be associated with transitional zone tumors and those among the 'anterior horns,' which are at risk of iatrogenic cautery when controlling the surrounding vasculature. This again illustrates the inverse relationship between minimizing collateral damage and PSM rates. The study by Hsu and colleagues also revealed an effect of anterior PSM on BCR (HR:1.17 [1.02–1.33]; $p=0.027$),

possibly as a result of greater iatrogenic intraprostatic incision during vascular control. However, similar to other sites, there remains ambivalence regarding the effect a PSM at this site has on BCR [32, 34, 41, 43, 44].

Differences with the Robotic Approach

One might predict the operative differences of minimally invasive RP may result in a distinct pattern of PSM. A study of 538 patients described the most common PSM site to be in the apical region for ORP (54 %) compared to the posterolateral region (54 %) for laparoscopic RP [45]. Guillonneau [46] reported similar findings with 50 and 30 % at the apex and posterolateral regions, respectively, for their series of 1000 consecutive laparoscopic RP [46]. Similarly, Patel and colleagues reported on 1272 PSMs in 8095 RARP procedures, and in agreement with earlier studies [47] found the apex and posterolateral sites to be the most common PSM locations (36 and 29 %, respectively) [48]. The findings suggest unique technical challenges for intraoperative dissection which may reflect in differing locations of PSM for different surgical approaches.

Sooriakumaran et al. were unable to draw statistically significant conclusions regarding the effect of PSM location on BCR. Initial trends suggest PSM locations in RARP having different prognostic value when compared to ORP, where there is more widely (albeit not completely) accepted importance of posterolateral margins and relative equipoise regarding apical margins [37]. If the fourth arm superomedial traction applied in RARP during nerve sparing is responsible for significantly more intraprostatic incisions, which are considered to have less effect on BCR, then posterolateral margins in RARP should have less oncologic impact than in ORP series.

In order to investigate the impact of PSM parameters (length and location) on BCR after RARP, we conducted a tri-institutional, trans-Atlantic analysis on the topic [49]. Between January 2002 and May 2013 clinicopathologic data on RARP patients was prospectively collected across three participating centers (two US, one Europe). Patients who had received RARP for cT1-3 prostate cancer and did not meet any of the following exclusion criteria were included in this study: not received adjuvant hormonal or radiation therapy; PSA had been recorded for at least 3 years post-RP; and the margin status (presence or absence) of the histopathologic specimen had been recorded. In total, 4001 consecutive patients fulfilled these criteria and were included in this study.

Margin Positive Cases Have Worse Pathologic Stage, Grade, and Preoperative PSA

When comparing a PSM with negative margin cases, chi-squared differences revealed a higher preoperative PSA, smaller prostate volume, and higher stage and grade disease. Thirty-seven percent PSM cases went onto develop BCR compared with just 10 % of negative margin cases.

Posterolateral and Apical Margins Are the Most Common Site of Margin Positivity with RARP

Multifocal, posterolateral, and apical regions contributed to the greatest number of PSMs (27, 27, and 32%, respectively), and not unexpectedly the largest number of BCR among PSM cases. The highest level of BCR as a proportion was found at the base, with over half of all margins (19 of 35) producing BCR.

A Positive Margin Adversely Affects Outcome

On univariate binary logistic regression analysis, margin positivity at the base demonstrated a 10.2× greater risk of BCR, compared to the 3–4× odds ratio for the other locations. The effect however was lost on multivariate analysis, and similarly institution, BMI and age become nonsignificant when covariates are included. However, the odds for BCR with a PSM vs. NSM remained prominent: OR:3.1 c.f. OR:4.2 for stage ≥pT3b c.f. OR:1.3 for preoperative PSA.

A Positive Margin at Any Location Favors BCR

All margin locations had a significantly greater chance than negative margins of resulting in BCR, with a trend in odds ratios favoring anterior and apical margins as predictors of BCR compared to margins at the base or posterolaterally (odds ratios: 3.36, 3. 27, 3.01, and 2.97, respectively).

PSM and Margin Length ≥3 mm Has a Greater Effect on BCR in Lower Risk Cohorts

Multivariate cox regression identified an instantaneous hazard ratio of 1.85 for PSM vs. NSM leading to BCR. Stratification by pathologic stage (≤pT2 vs. ≥pT3) and Gleason grade (≤3+4 vs. ≥4+3) revealed a substantially greater impact of a PSM in lower risk cohorts: 3.06 vs. 1.58 and 2.35 vs. 1.67, respectively (all $p<0.001$). This holds true for margin length, with PSM ≥ 3 mm having almost double the effect of ≤3 mm on BCR in lower risk cohorts compared to all risk cohorts taken together.

Apical Margins Are More Hazardous Than Posterolateral Margins

Propensity adjusted cox regression analysis revealed significant hazard ratios across all margin locations. Although the magnitude of the instantaneous risk of BCR differs between statistical models, the trend for apical locations to show *greater* effects across these multivariable models was noteworthy, particularly when compared to posterolateral margins: 3.54 vs. 2.837 (on propensity adjusted Cox regression); 2.334

vs. 1.685 (on multivariate Cox regression); 3.272 vs. 2.966 (on binary logistic model). Hence apical margins appeared to have a greater hazard of BCR than posterolateral margins, after statistical analysis based on a common reference (NSM).

Discussion

Our study found that PSM are associated with a greater risk of BCR after RARP compared to negative margins. This concurs with growing evidence across open series, and recent minimally invasive series [28, 48]. It is perhaps not surprising that some of this effect is by association, and we see PSM associated with other risk factors for BCR such as tumor grade and stage.

We demonstrated the greater impact PSM carries on lower risk (pT2 or Gleason $\leq 3+4$ or both) prostate cancers after subgroup analysis. This probably reflects a relative balance with other more influential factors. Gleason grade and tumor stage probably have the largest impact on risk of BCR [48, 50, 51], although PSM remains the most important 'surgically controllable' predictor of BCR. Indeed, the presence of a PSM is itself dependent on some of these factors, most notably pathologic stage; incidence of PSM has been reported as 9 % for pT2, 37 % for pT3, and 50 % for pT4 [52]. So this is the crux of the issue: with high grade and stage tumors, the biology of the disease drives the risk of BCR with margin status having little independent predictive value over and beyond the biologic variables. However, with low risk tumors in which biology is unlikely to lead to BCR, the relative increased risk of relapse with a PSM compared with a negative margin is much greater. A report on nearly 1000 cases from the Karolinska University Hospital (Stockholm, Sweden) on men with at least 5 years of follow-up post-RARP confirms these findings [53].

The counterpoint of this argument is that the absolute risk of BCR is much higher for high grade and stage tumors than for low ones, and thus any increased risk of relapse may be considered to be more important for the former cases. From the oncologic perspective, it might thus be more imperative for the surgeon to attempt to get a negative margin at the cost of increasing collateral damage in these high-risk cases and be less concerned with getting negative margins in cases of low Gleason grade or stage. Here, the surgeon might choose to accept higher PSM for minimizing collateral damage and thus optimizing the functional outcomes of urinary continence recovery and erectile function. This is the balancing act that becomes the surgeon's edict. With nerve sparing during RARP most likely to lead to PSM in the posterolateral region, and our work described herein that suggests this has minimal impact on BCR, surgeons should not shy away from aggressive nerve sparing for low-risk RARP cases. This is even more important given recent data that the more aggressive the nerve sparing, the better the continence as well as erectile outcomes are [54].

Hazard ratios from our statistical modeling appear to suggest a weaker impact of posterolateral margins on BCR compared to other sites, and this is particularly surprising when compared to evidence from open RP, where the impact of posterolateral PSM on BCR is well established [39]. Indeed, Vickers and colleagues have

described posterolateral PSM in pT2 disease as an adverse factor on outcome, and related to inadequate surgical technique [55].

The lack of tactile feedback which results from operating with a robotic platform has long been cited as a potential reason for greater iatrogenic PSM. However, many have reported the use of visual cues to offset any loss in tactile feedback and comparing crude PSM rates between studies seems to suggest fewer may be caused by robotic compared to open operations [56, 57]. That said, one hypothesis regarding posterolateral margins is the fourth arm robotic traction places on the prostatic 'capsule' and surrounding structures, particularly during craniomedial elevation of the vasa/seminal vesicles during posterolateral dissection. The sustained tension resulting from hitching up the prostate, particularly during prolonged periods when performing nerve sparing, is likely to facilitate easier dissection but perhaps also causes iatrogenic intraprostatic incisions. Secin and colleagues found a counterintuitive relationship between PSM and extrafascial nerve-sparing procedure, possibly resulting from a technical error forcing false planes and producing capsular flaps [15], although we did not have the 'nerve-sparing' status as a variable for our analysis.

In a study of 2442 patients, Eastham and colleagues describe a significant impact of posterolateral margin status on BCR (HR: 2.8 [1.76-4.44]), but failed to demonstrate an effect of apical margins (HR0.94 [0.59–1.51]). Eastham comments on a higher risk of BCR in open RP series with posterolateral margins, as the area least likely to receive iatrogenic trauma as well as its proximity to nerves which permits perineural invasion [3]. They instead suggest the apex is under greater traction with false positive margins, less supporting tissue at the apex providing less vascular support for metastatic spread [3]. While this cannot be discounted, this likely reflects the open surgical technique. Clearly, targeted traction of the robotic instruments around the prostate to facilitate nerve sparing can still cause iatrogenic damage while sparing the neurovasculature from direct injury.

Pettus and Pfitzenmaier have described a significant impact of apical PSM on BCR [9, 23], although Pettus's analysis fails on multivariate analysis; several other earlier studies including one of 172 patients over 3½ years follow-up also failed to demonstrate an association between apical PSMs and clinical progression [58, 59].

The findings of our study suggest apical margins are more hazardous than posterolateral ones in RARP and support a trend seen in one recent study [37]. While the apex has been shown to impact BCR in some studies from ORP series, this effect is often less than a PSM elsewhere. While our study did not directly compare ORP and RARP cases, the dominance of apical margin positivity associated with BCR has not been seen before in RARP series, and technical differences between the two surgical approaches must be considered at least partially responsible. Intraoperative differences in terms of approach, traction, and risk of iatrogenic capsular incisions are likely to be responsible for these differences.

Two of the three institutions involved in our multi-institutional study have made specific efforts toward altering their control of the dorsal venous complex prior to attempting apical dissection. Theories as to why the order of these two operative steps may affect apical PSM rates include the possible effect of bunching up tissue around the apex and distorting apical anatomy. Alternative methods (supported by

the third institution of our study) advocate division of these vessels prior to apical dissection which would encourage more inferior incisions in an effort to avoid the dorsal veins and blood loss, which might inadvertently lead to an intraprostatic incision [37, 60, 61]. The apex is a technically challenging region to operate in, particularly with variations in shape. Technical modifications however continue to improve PSM rates, particularly at the apex, with variations in the RARP technique, e.g., retroapical approach [56], allowing better circumferential visualization of the apex and membranous urethra, leading to a total decrease as well as proportionally fewer apical margins as a percentage of total PSM burden. Because of these efforts it should therefore follow that the PSMs that will remain at the apex are biologically rather than surgically attributable PSM (i.e., fewer false positives) which would thus carry a worse prognosis.

Ergo, there are fewer apical margins evident with this technique, due to less false negative iatrogenic damage to the apex. Although there were 27.5 % margins classified as apical in our study, we do not have an open RP arm to compare with, and comparisons in the context of such a wide range of values in the literature are unhelpful. However, it remains possible that this reflects an increasingly smaller percentage of false positive margins as a result of improved technical dissection using the robotic platform.

A failure to identify capsular incisions from pT3 PSM at the apex would falsely upstage the disease (Will Rogers phenomenon) and also lead to lower than expected impact of the apical margin location when taking into account other variables in multivariable models. If carcinoma extends to the inked margin adjacent to benign prostatic glands, and in the absence of adipocytes, this can be used to differentiate PSM at the apex with associated extraprostatic extension (EPE). However, there is no consensus as to a reliable method to make this distinction and many authors do not routinely diagnose EPE at the apex for this reason [62].

Understaging can also result from a phenomenon of fibrotic desmoplastic reaction following extraprostatic extension, and can confuse any assessment of margin status, and this may lead to ascribing more importance to apical margins; although suggestions have been made that this occurs in the posterolateral region, which would further strengthen our findings of a difference between these locations [39].

We generally found higher hazard ratios associated with anterior and apical margins compared to posterolateral and basal ones, although the numbers involved at these sites were smaller. The anterior prostate is predominantly fibromuscular stroma and a PSM here may reflect inherent aggressiveness of any tumor able to migrate into it (rather than necessarily reflecting a site of origin which is innately aggressive—see earlier). It is also possible the close proximity to vasculature provides a more favorable location for distant spread.

Suggestions for future approaches to prevent PSM, beyond technical modifications, have included routine intraoperative frozen sections to permit secondary resection intraoperatively; 25 % of cases are found to detect residual cancer on attempts at removing further tissue, implying a PSM may not always reflect residual cancer in the prostatic bed [63]. Follow-up data is lacking regarding the effect on outcomes such as BCR rates in those treated using this method.

Conclusions

PSMs remain a critical finding to identify and better understand, given its profound patient implications in terms of prognosis and further treatment. All PSMs resulting from RARP are not equivalent; longer margins suggest a higher risk of recurrence and the influence is especially prominent in lower risk patients. The apex is a significant contributor to BCR and appears to have the strongest impact of all the margin locations in RARP patients. In contrast, the posterolateral region appears to carry a smaller effect on BCR, probably reflecting greater iatrogenic injury to the prostate in this region. Hence, RARP surgeons might choose to accept the increased risk of posterolateral margins during nerve sparing in lower grade and stage prostate cancer patients, but rather make a wider dissection in the higher risk cases sacrificing functional outcomes for lower PSM in these men.

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