Surgical margin status does not affect overall survival following radical prostatectomy: a single institution experience with expectant management

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Introduction: *The objective of this report is to describe the oncologic outcomes of men with margin-positive prostate cancer who were managed expectantly following radical prostatectomy.*

Materials and methods: *Between January 1992 and January 2011, 2166 men underwent an open radical prostatectomy by a single surgeon. Of these patients, 1592 (74%) had complete data and met the inclusion criteria of negative lymph nodes and no history of neoadjuvant or adjuvant therapy. This cohort was dichotomized by the presence or absence of at least one positive surgical margin. Groups were compared for differences in recurrence-free and overall survival.*

Results: *In total, 507 (32%) of 1592 patients had at least one positive surgical margin. Clinical and pathological characteristics of these patients indicated more aggressive disease. The median follow up for biochemical recurrence and overall survival was 3.4 years and 7.7 years, respectively. Of those patients with a positive margin, 147 (29%) recurred, with estimated 5 and 10 year biochemical recurrence rates of 31% and 47%, respectively. Multivariate analysis demonstrated that the presence of a positive margin was associated with a 2.45-fold increased hazard of recurrence ($p < 0.001$). Despite initial observation, surgical margin status was not associated with a decrease in overall survival on both uni- ($p = 0.684$) and multivariate analyses ($p = 0.177$).*

Conclusion: *Although a positive surgical margin is associated with an increased risk of biochemical recurrence, patients in our series were not at an increased risk of all-cause mortality.*

Key Words: biochemical recurrence, prostate cancer, adjuvant radiation therapy, positive margin, salvage radiation

Introduction

It is estimated that up to one third of men who undergo primary treatment for localized prostate cancer with radical prostatectomy (RP) will have at least one adverse pathological feature including extraprostatic extension (EPE), a positive surgical margin or seminal vesicle invasion (SVI).[1,2] The approach to managing these patients following RP is currently the subject of considerable controversy within the urological community. This is especially true of men whose only adverse feature is a positive surgical margin.[3]

To date, three prospective randomized clinical trials (SWOG 8794, EORTC 22911, and ARO 96-02/AUO AP 09/95) have demonstrated a significant benefit in biochemical recurrence (BCR)-free survival for patients with adverse pathological features who underwent adjuvant radiation therapy (A-RT) compared to initial observation.[4-6] Despite these reports, the use of A-RT has not increased.[7] This is likely the result of the unclear survival advantage of A-RT, as these trials have failed to uniformly demonstrate improved metastasis-free and overall survival with A-RT.[8,9]

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In light of these discordant data, it has been our philosophy to manage patients with a positive surgical margin expectantly. Among those patients who recur, salvage treatment is only offered after taking into account a variety of clinical parameters including age at the time of recurrence, performance status, and the presence of other adverse pathological features. The objective of this report is to detail the oncologic outcomes of this management strategy.

Materials and methods

Between January 1992 and January 2011, 2166 men underwent an open RP by a single surgeon. Data from all cases was entered into an Institutional Review Board approved database. Patients excluded from our analysis included those with positive lymph nodes (n = 13), a history of neoadjuvant (n = 318) or adjuvant (n = 80) therapy and incomplete data (n = 163). Exclusion of these patients resulted in a study population of 1592 men.

All patients underwent a RP with the modified Walsh technique.[10,11] Bilateral lymph node dissection and bladder neck preservation were performed in most instances. Surgical specimens were fixed, embedded and processed as described previously.[12] As part of routine clinical protocol, all specimens were evaluated by a dedicated genitourinary pathologist. A positive margin was defined as direct contact between the inked margin and prostate cancer. Specimens were not re-reviewed specifically for the purposes of this analysis.

Postoperatively, patients were typically evaluated every 3 months for the first 2 years and every 6 months thereafter. BCR was defined as a prostate specific antigen (PSA) level ≥ 0.2 ng/mL. The duration of follow up for BCR was calculated by subtracting the date of surgery from either the date of last PSA measurement or the date of recurrence. Patient mortality was ascertained by searching the Social Security Death Index (http://ssdi.rootsweb.ancestry.com/). The duration of follow up for overall survival was calculated by subtracting the date of surgery from either the date of death or the date when the Social Security Death Index was last referenced.

Statistical analysis

Comparisons of categorical variables were performed with the Pearson chi-squared test. The normal distribution of continuous variables was verified using the Shapiro-Wilk W test. Comparisons were performed with the Mann-Whitney U test or the Student's t test as appropriate. Variables associated with a positive surgical margin on univariate analysis were included in a multivariate logistic regression analysis. BCR-free and overall survival of men with and without a positive surgical margin were performed using the Kaplan-Meier method and results were compared with the univariate log-rank test. A Cox proportional hazards model was used to determine independent predictors of survival. All tests were two-sided with a p value of < 0.05 considered significant. Stata version 11.0 (College Station, Texas, USA) was used for all data analysis.

Results

Table 1 lists the demographic, clinical, and pathological characteristics of patients with (n = 507) and without (n = 1085) a positive surgical margin. The median follow up for BCR was 3.4 years, with 544 (34%) patients followed for 5 or more years. In terms of overall survival, the median follow up was 7.7 years.

Among those with a positive surgical margin, 147 (29%) recurred, with estimated 5 and 10 year BCR rates of 31% and 47%, respectively. Compared to patients with a negative surgical margin, this group was at an increased risk of BCR, Figure 1, $p < 0.001$. Patients with

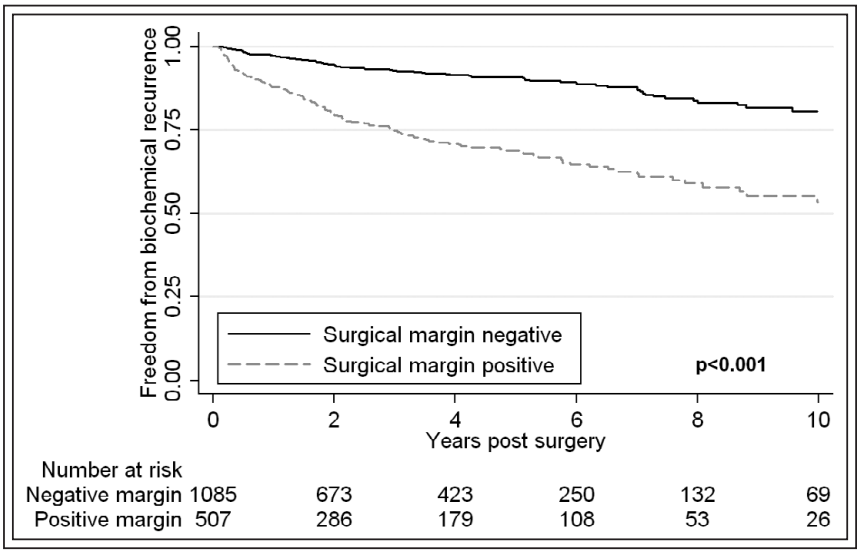

Figure 1. Comparison of recurrence-free survival between patients with and without a positive surgical margin.

TABLE 1. **Patient characteristics according to surgical margin status**

Variable	Overall	Margin negative	Margin positive	p value
No. of patients	1592	1085	507	–
Median age at surgery, years (IQR)	61.3 (55.6-66.3)	61.4 (55.8-66.1)	61.3 (55.4-67.0)	0.729
Median preoperative PSA, ng/mL (IQR)[1]	5.7 (4.5-8.0)	5.4 (4.3-7.4)	6.8 (4.9-9.4)	< 0.001
No. biopsy Gleason score (%)				< 0.001
2-6	986 (61.9)	708 (65.3)	278 (54.8)	
7 (3 + 4)	353 (22.2)	230 (21.2)	123 (24.3)	
7 (4 + 3)	123 (7.7)	81 (7.5)	42 (8.3)	
8-10	130 (8.2)	66 (6.1)	64 (12.6)	
No. clinical stage (%)				0.003
T1	1060 (66.6)	747 (68.8)	313 (61.7)	
T2	491 (30.8)	308 (28.4)	183 (36.1)	
T3	41 (2.6)	30 (2.8)	11 (2.2)	
No. pathological Gleason score (%)				< 0.001
2-6	700 (44.0)	531 (48.9)	169 (33.3)	
7 (3 + 4)	522 (32.9)	348 (32.1)	174 (34.3)	
7 (4 + 3)	204 (12.8)	121 (11.2)	83 (16.4)	
8-10	166 (10.4)	85 (7.8)	81 (16.0)	
No. EPE (%)	226 (14.2)	106 (9.8)	120 (23.7)	< 0.001
No. SVI (%)	106 (6.7)	47 (4.3)	59 (11.6)	< 0.001
No. BNI (%)	52 (3.3)	20 (1.8)	32 (6.3)	< 0.001
Median visually estimated percent of carcinoma, % (IQR)[2]	8 (3-15)	6 (2-12)	13 (7-22)	< 0.001
Median prostate weight, g (IQR)	42 (34-54)	44 (34-56)	42 (32-52)	0.691
No. nerve-sparing procedure (%)	1206 (75.8)	839 (77.3)	367 (72.4)	< 0.001
Median follow up for recurrence, years (IQR)	3.4 (1.3-6.3)	3.2 (1.3-6.1)	3.8 (1.4-6.7)	0.084

[1]not available for two patients; [2]not available for 48 patients
BNI = bladder neck involvement; IQR = interquartile range; EPE = extraprostatic extension; LNI = lymph node involvement; PSA = prostate-specific antigen; SVI = seminal vesicle invasion

a positive margin and a predominantly high grade Gleason sum had a 43% risk of BCR at 3 year follow up and 56% risk at 5 year follow up, Figure 2. After controlling for other pathological features known to confer a risk of recurrence, men with a positive surgical margin were at a 2.45-fold increased risk of BCR, Table 2; 95% CI 1.84-3.26, p < 0.001. Table 3 details the treatment modalities used to manage patients with BCR. Of note, patients with a positive margin who recurred were less likely to be managed with continued observation (p = 0.022).

Overall survival was not associated with surgical margin status in both univariate, Figure 3, p = 0.684) and multivariate analyses, Table 4; HR 0.68, 95% CI 0.39-1.18, p = 0.177). The 5 and 10 year overall survival rates were 98% and 96% for patients with a positive margin. In comparison, these rates were 98% and 95% for patients with a negative margin, respectively.

Discussion

The presence of a positive surgical margin is predictive for BCR following RP.[3,13-16] In a multi-institutional analysis of 5831 patients, Karakiewicz and coworkers[13] demonstrated a 3.7-fold increased independent risk of BCR associated with this pathological feature. Management options for patients with a positive margin include A-RT, initial observation with S-RT, androgen deprivation, or continued surveillance. The decision to institute treatment may depend on the patient's age,

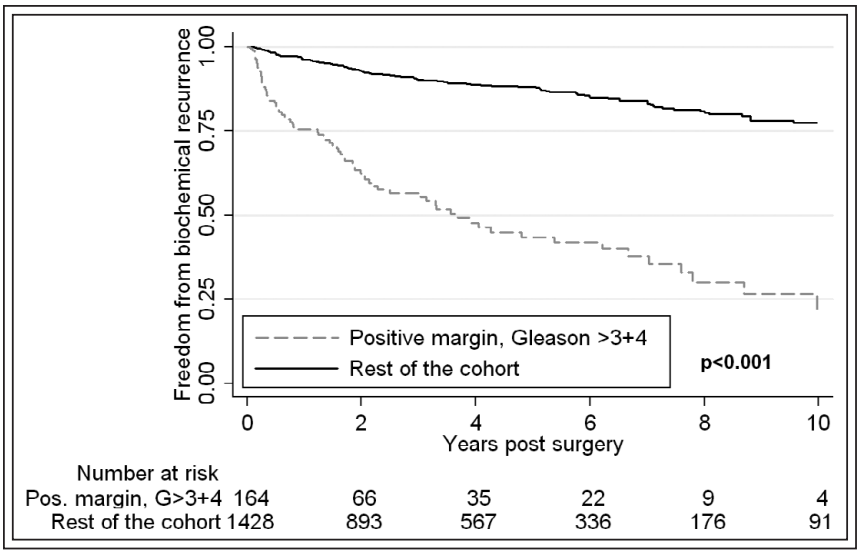

Figure 2. Predominance of a high grade cancer predicts recurrence among patients with a positive surgical margin.

presence of other adverse pathological features, as well as the number and/or extent of positive margins.

To date, three randomized trials (SWOG 8794, EORTC 22911, and ARO 96-02/AUO AP 09/95) have shown an improvement in BCR-free survival among patients with adverse pathological features who underwent A-RT after RP.[4-6] Patients in these trials had one or more adverse pathological feature including EPE, SVI, and/or a positive surgical margin. These trials enrolled 285 (67%), 629 (63%), and 260 (68%) men with a positive margin, respectively.

In the SWOG study, patients were randomized to receive either adjuvant external beam radiation therapy or initial observation. At a median follow up of 10.6 years, the authors observed an improvement in median recurrence-free survival with A-RT (13.8 years with A-RT versus 9.9 years with observation; HR 0.62, 95% CI 0.46-0.82, p = 0.001).[4] In the EORTC trial, the authors estimated 5 year BCR-free survival rates of 74% for men treated with A-RT as compared to 53% for men managed with observation (HR 0.48, 95% CI 0.37-0.62, p < 0.0001).[5] The German ARO 96-02/AUO AP 09/95 trial found similar 5 year BCR-free results (54% with A-RT versus 72% with observation; HR 0.53, 95% CI 0.37-0.79, p = .0015).[6] In summary, among these three

TABLE 2. **Association of variables with biochemical recurrence in a multivariate Cox proportional hazards model**

Variable	Hazard ratio (95% CI)	p value
Age, years (continuous)	0.99 (0.98-1.02)	0.913
PSA, ng/mL (continuous)	1.02 (1.01-1.03)	< 0.001
Margin status		
Negative	1	
Positive	2.45 (1.84-3.26)	< 0.001
Pathological Gleason score		
2-6	1	
7 (3 + 4)	2.05 (1.37-3.07)	< 0.001
7 (4 + 3)	3.09 (1.96-4.87)	< 0.001
8-10	4.92 (3.16-7.64)	< 0.001
EPE	1.42 (1.04-1.92)	0.026
SVI	2.11 (1.49-3.01)	< 0.001
BNI	1.33 (0.79-2.26)	0.283
Visually estimated percent of carcinoma		
0-9	1	
9.1-20	1.47 (1.05-2.07)	0.024
> 20	1.48 (0.98-2.23)	0.059

BNI = bladder neck involvement; EPE = extraprostatic; PSA = prostate-specific antigen; extension; SVI = seminal vesicle invasion

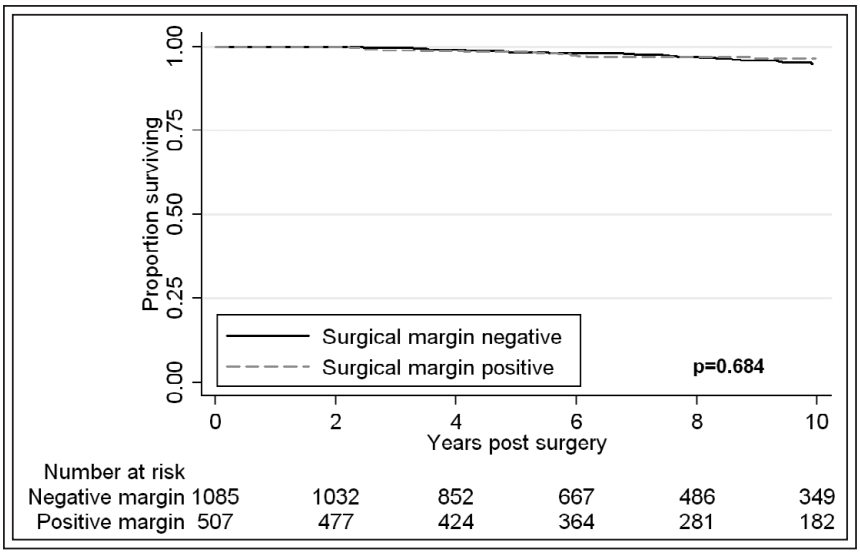

Figure 3. Comparison of overall survival between patients with and without a positive surgical margin.

trials, the reduction in risk of BCR associated with A-RT ranged from 18% to 22%.

While similar in terms of their findings on BCR, these trials differ in their findings regarding metastasis-free and overall survival.[8,9] Of note, ARO 96-02/AUO AP 09/95 did not report results for these endpoints. A recent update to the SWOG trial demonstrated a benefit in metastasis-free (HR 0.71, 95% CI 0.54-0.94; p = 0.016) and overall survival (HR 0.72; 95% CI 0.55-0.96; p = 0.023) with A-RT.[8] In contrast, the EORTC trial failed to show this same benefit. At the 2011 European Association of Urology Congress, the authors reported that an updated analysis failed to demonstrate a difference in 10 year rates of metastasis-free (10% with A-RT versus 11% with observation, p > 0.1) and overall survival (81% with A-RT versus 77% with observation, p > 0.1).[9] These authors emphasized that patients enrolled in the SWOG trial had more adverse pathological features and thus were at a higher risk of death from prostate cancer.

Several other important characteristics of the SWOG study deserve mention. First, most of the patients included in this trial were diagnosed in the early PSA-era (late 1980s to the first half of the 1990s). Therefore, the disease characteristics of this cohort may differ from those of contemporary prostate cancer patients. Second, in more than 10% of the patients studied, the PSA level after surgery was unknown or failed to nadir at zero. In these patients, radiation may not have truly been "adjuvant." Finally, only 55% of the patients randomized to observation received S-RT, many of whom only received RT in response to clinical recurrence and not BCR. In light of these observations, the applicability of the findings of the SWOG trial to contemporary patients with a positive surgical positive margin is somewhat limited.

Given the significant side effects associated with radiation therapy[17,18] and the controversy about the long term benefits in overall survival, most physicians in the United States still recommend initial observation in place of A-RT for patients with aggressive pathological features, such as a positive surgical margin. In a recent study of the SEER database, Hoffman and coworkers[7] found that less than 15% of men receive A-RT. These authors also found that the use of A-RT did not increase following the publication of these randomized trials.

One alternative to A-RT is initial observation followed by S-RT. Several studies have shown the efficacy of this management approach. Buskirk et al[19] found that 45% of men with positive surgical margin were relapse free at 5 years following S-RT. Similarly, Stephenson and coworkers[20] found that nearly half

TABLE 3. **Management of biochemical recurrence by surgical margin status**

Treatment type	Margin positive (n = 147)	Margin negative (n = 97)	p value
No. radiation only (%)	50 (34.0)	22 (22.7)	0.063
No. hormonal therapy only (%)	48 (32.7)	32 (33.0)	0.990
No. radiation and hormonal therapy (%)	19 (12.9)	7 (7.2)	0.204
No. continue monitoring (%)	22 (15.0)	27 (27.8)	0.022
No. unknown (%)	8 (5.4)	9 (9.3)	0.306

TABLE 4. **Association of variables with overall survival in a multivariate Cox proportional hazards model**

Variable	Hazard ratio (95% CI)	p value
Age, years (continuous)	1.10 (1.05-1.15)	< 0.001
PSA, ng/mL (continuous)	1.02 (1.01-1.05)	0.031
Margin status		
Negative	1	
Positive	0.68 (0.39-1.18)	0.177
Pathological Gleason score		
2-6	1	
7 (3 + 4)	1.37 (0.68-2.77)	0.375
7 (4 + 3)	1.17 (0.47-2.90)	0.735
8-10	1.84 (0.75-4.50)	0.180
EPE	1.93 (1.02-3.64)	0.043
SVI	0.72 (0.29-1.83)	0.494
BNI	2.12 (0.71-6.30)	0.177
Visually estimated percent of carcinoma		
0-9	1	
9.1-20	0.98 (0.51-1.86)	0.947
> 20	1.55 (0.68-3.52)	0.299
Treatment for biochemical recurrence		
Radiation only	0.64 (0.15-2.77)	0.550
Hormonal therapy only	2.08 (0.93-4.64)	0.073
Radiation and hormonal therapy	0.88 (0.21-3.91)	0.632
Continue monitoring	0.43 (0.06-3.28)	0.418

BNI = bladder neck involvement; EPE = extraprostatic; PSA = prostate-specific antigen; extension; SVI = seminal vesicle invasion

of men treated with S-RT for a PSA ≤ 0.5 ng/dL were cured. Moreover, Trock et al[21] found that S-RT improved disease-specific survival by three-fold.

The data in our study also supports the use of initial observation for men with a positive surgical margin. While our findings are in agreement with others who have reported that men with one or more positive margins are at an increased risk of BCR, we did not observe any difference in the overall-survival of these patients. On multivariate analysis, the risk of all-cause mortality at a median follow up of 7.7 years was similar between men with and without a positive surgical margin, Figure 3 and Table 4. In light of these data, we believe that the decision to treat a patient with a positive surgical margin must take into account other factors such as SVI, primary Gleason score, rise of PSA on serial assays and multifocality of margins. Of note, Gleason score may be a particularly important factor in this regard. In our experience, we observed that patients with predominantly high grade cancer and a positive margin were at particularly high risk of BCR, Figure 2. In our opinion, this resulted from the increased risk of leaving behind more aggressive high grade tumor. In support of this, a recent report demonstrated that the Gleason score at a positive margin was predictive of BCR-free survival.[22] Better understanding of this association may aid in defining the group of patients for whom S-RT versus A-RT is most beneficial.

We would like to emphasize that our findings do not, and cannot, contradict the outcomes of randomized studies. It is clear that A-RT provides a substantial benefit in terms of BCR. It is, however, not clear how well this translates into a survival benefit. This is especially true for contemporary prostate cancer patients. This question can only be answered by future randomized studies directly comparing A-RT with S-RT.

A recent comprehensive review of currently available data by Fleshner et al[3] argues that men with organ confined cancer (pT2) and a positive margin should be managed with initial observation followed by S-RT only when necessary. In addition, patients with low to intermediate grade pT3a cancer and a positive margin should be managed in a similar fashion. In contrast, adjuvant treatment should be reserved for patients with pT3b tumors as well as those with high grade pT3a cancer and/or multiple positive

margins. In light of the findings of our study, we share the conclusions of these authors.

Our study is not without limitations. Most noteworthy is its retrospective design and the associated issues of selection and information bias. A second limitation is the relatively short follow up period for BCR of 3.4 years. We do, however, present mortality data with a median follow up of 7.7 years. This is possible because patients were tracked beyond their last clinic visit using the publicly available Social Security Death Index. Another limitation of this study is that our analysis did not incorporate the location, length and Gleason score of positive margins. These parameters have previously been shown to be independently associated with treatment outcomes.[22-24] Thus, our findings may not be applicable to certain types of positive surgical margins, e.g. extensive posteriolateral margins in patients with high Gleason sum. Finally, one last limitation is that we do not have consistent information about the cause of death and therefore were unable to analyze disease-specific survival.

Conclusions

Although a positive surgical margin at the time RP is associated with an increased risk of BCR, patients may not be at an increased risk of all-cause mortality. Hence, expectant management with regular PSA testing appears to be a safe management option for most men with a positive margin. This is especially true of men with organ-confined low grade cancer. □

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