Published in final edited form as:

J Urol. 2018 April ; 199(4): 961–968. doi:10.1016/j.juro.2017.10.010.

Biopsy Core Features are Poor Predictors of Adverse Pathology in Men with Grade Group 1 Prostate Cancer

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Abstract

Purpose—Active surveillance (AS) is often restricted to patients with low-risk prostate cancer (PCa) with three or fewer positive cores. We aimed to identify predictors of adverse pathology for low-risk PCa treated with radical prostatectomy (RP) and to determine if a threshold number of positive cores could help the decision process for AS.

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Materials and methods—A total of 3,359 men with low-risk PCa underwent RP between January 2000 and August 2016. We analyzed the relationship between biopsy core features and adverse pathology at RP, defined as grade group (GrdGrp) 3, seminal vesicle invasion (SVI), or lymph node involvement (LNI).

Results—Of the 171 (5.1%) patients with adverse pathology at RP, 144 (4.3%) were upgraded to GrdGrp 3, 31 (0.9%) had SVI, and 15 (0.4%) had LNI. Prostate-specific antigen and age were the only predictors of adverse pathology; there was no significant association with number of positive cores, total millimeters of cancer, or maximum percentage of cancer in any core. When we expanded the definition of adverse pathology to include GrdGrp 2 and extraprostatic extension, the association between core features and outcome, while statistically significant, was clinically weak, with no evidence of threshold effects.

Conclusions—There is little basis for excluding patients with otherwise low-risk PCa on biopsy from AS based on criteria such as the number of positive cores or maximum cancer involvement of biopsy cores.

Keywords

active surveillance; grade group; prostate cancer; radical prostatectomy; risk stratification

INTRODUCTION

Practice guidelines recommend that patients with low-risk prostate cancer (PCa) be managed by active surveillance (AS).^{1,2} The purpose of AS is to reduce overtreatment and attendant morbidity, without compromising the opportunity for cure of lethal disease. The exact criteria used to determine eligibility for AS vary importantly. For instance, in a systematic review on AS, Dall'Era et al. report that seven major AS series used eligibility criteria that differed for clinical stage, biopsy grade, prostate-specific antigen (PSA), and biopsy cores features.³

Of the criteria used for AS, the prognostic value of grade group (GrdGrp) and stage are unambiguous,^{4,5} and there has been considerable study of PSA level.⁶ To date, there has been little research on the prognostic value of biopsy cores.

The goal of our study was to determine the relationship between the number of positive biopsy cores and oncologic risk. In particular, we were interested in evaluating the widely used criteria that patients with more than three positive cores or more than 50% cancer involvement in any one core should be referred to immediate treatment.

MATERIALS AND METHODS

After obtaining institutional review board approval, we retrospectively collected data on 3,359 men who had GrdGrp 1 (Gleason score 3+3=6) disease on biopsy and a PSA level ≤ 10 ng/mL and underwent radical prostatectomy (RP) at Memorial Sloan Kettering Cancer Center (MSKCC) between January 2000 and August 2016. While 86% of pre-radical prostatectomy biopsies were done at outside institutions, pathology from these biopsies was reviewed at MSKCC prior to surgery.

We aimed to evaluate the relationship between the amount of cancer present on biopsy and the risk of adverse pathology at RP for low-risk PCa. Adverse pathology was defined as GrdGrp 3 (Gleason score 4+3=7), seminal vesicle invasion (SVI), or lymph node involvement (LNI). The amount of cancer was defined in three ways: number of positive biopsy cores, total millimeters of cancer on biopsy, and maximum percentage of cancer in any biopsy core. We excluded extraprostatic extension (EPE) and GrdGrp 2 (Gleason score 3+4=7) from our criteria for adverse pathology, as we previously demonstrated that oncologic outcome remained favorable for patients who had preoperatively low-risk PCa, but were upstaged to EPE or upgraded to GrdGrp 2 following RP.⁷

Using Wilcoxon rank sum and Fisher's exact tests, patient characteristics and the amount of cancer on biopsy were compared between those who presented with adverse pathology at RP and those who did not. To investigate whether the probability of adverse pathology increased significantly when there is a larger amount of cancer on biopsy, we plotted the probability of adverse pathology using locally-weighted scatterplot smoothing (LOWESS). As a sensitivity analysis, we repeated all analyses using an alternate definition of adverse pathology that included GrdGrp 2 and EPE. We also performed a sensitivity analysis limited to patients who underwent biopsy or had all biopsy cores reviewed at MSKCC. All analyses were conducted using Stata 13 (StataCorp, College Station, TX).

RESULTS

Patient characteristics are presented in Table 1. Adverse pathology at RP was present in 171 (5.1%) of the 3,359 patients who had low-risk PCa on biopsy. Of these 171 patients, 144 (4.3%) were upgraded to GrdGrp 3, 31 (0.9%) had SVI, 15 (0.4%) had LNI, and 17 patients (0.5%) had 2 or more adverse features. Of note, 77% of the 3,359 patients underwent lymph node dissection, as we believe it improves the accuracy of PCa staging, even in low-risk patients. The 171 patients with adverse pathology at RP were significantly older than the rest of the cohort, age 62 (interquartile range [IQR]: 56–66) vs. age 59 (IQR: 54–63), respectively, $p < 0.0001$. These 171 patients had significantly higher PSA levels prior to RP than the rest of the cohort, 5.8ng/mL (IQR: 4.5–7.1) vs. 4.7ng/mL (IQR: 3.4–6.1), respectively, $p < 0.0001$. The median number of positive cores for the whole cohort was 2 (IQR: 1–3), and the number of positive cores was not significantly different between patients who had adverse pathology and those who did not ($p=0.7$).

We tested whether there was a significant association between the amount of cancer on biopsy and the risk of adverse pathology at RP. We found no evidence of an association between the number of positive cores ($p=0.7$), total millimeters of cancer in biopsy ($p=0.6$), or maximum percentage of cancer in any core ($p>0.9$, Table 2). Although we did not find any significant associations, we wanted to explore the possibility of nonlinearity or discontinuities that would suggest a threshold for AS eligibility. Fig. 1 shows the probability of adverse pathology among all patients over the number of positive cores (1A), total millimeters of cancer on biopsy (1B), and maximum percentage of cancer in any biopsy core (1C). There is no obvious evidence of a threshold effect.

For the sensitivity analysis, we repeated the analyses to include patients with GrdGrp 2 and EPE. Out of the 3,359 patients, 1,691 (50%) were found to have adverse pathology at RP based on this expanded definition. Number of positive biopsy cores, total millimeters of cancer in biopsy, maximum percentage of cancer in any core, GrdGrp 2, and EPE were significantly associated with the risk of having adverse pathology ($p < 0.0001$ for all, Table 3). Risk of adverse pathology plotted against core features is shown in Fig. 2. Similar to our analyses excluding GrdGrp 2 and EPE, there was no evidence to support commonly used thresholds such as 3 positive cores or maximum 50% core involvement and risk of adverse pathology. Furthermore, changes in risk were more moderate after these thresholds were reached.

We also performed the same analyses on patients who underwent biopsy or had all biopsy cores reviewed at MSKCC (N=1,721). Results were consistent with the main analysis and the corresponding figures looked similar, but with larger confidence intervals (See Supplementary Fig. 1 and 2).

DISCUSSION

AS is increasingly accepted as a safe approach to favorable-risk PCa. In our study, approximately 5% of patients with GrdGrp 1 on biopsy and a pretreatment PSA level 10ng/mL harbored adverse pathologic features after RP. Dall'Era et al. detailed the long-term follow-up of seven large series of AS and confirmed that AS could be confidently used to manage most indolent and non-lethal low-risk PCa.³ Of the seven series, the University of Toronto had the longest median follow-up time of 6.4 years from the first biopsy. Ten- and 15-year cancer-specific survival rates for this cohort were 98.1% and 94.3%, respectively.⁸ Of note, 25% of this cohort had intermediate-risk PCa according to the D'Amico criteria. The mortality rates in this study were much lower than those of patients with low-risk PCa managed with watchful waiting and no option for radical intervention.⁹ The ProtecT trial is the only randomized trial to compare AS, RP, and external beam-radiotherapy for the treatment of clinically localized PCa, and it demonstrated that disease progression and metastatic evolution occurred more frequently in the AS group.¹⁰ Therefore, long-term safety of AS depends on the ability to select appropriate patients for AS and to initiate treatment when needed.¹¹

In the literature, the probability of discontinuing AS for active treatment varied from 11% to 32% and was dependent on regular PSA control, physical examination, and re-biopsy.³ The majority of patients discontinued AS within the first three years, probably because the grade and extent of their disease was initially underestimated. Among patients who are recommended for AS, 20 to 40% of men are shown to have higher GrdGrp or cancer volume after enrolling in AS.^{12,13} Several investigators have extensively examined the rates of upgrading and upstaging at RP. For example, Filippou et al. reported a 46% rate of adverse pathology after delayed RP, including upstaging, positive surgical margins, or upgrading.¹⁴ Ploussard et al. found that even with a stringent 21-core biopsy protocol, the rate of upgrading after RP in men eligible for AS was as high as 48%.¹⁵ These results are concordant with the 50% of adverse pathology we found after RP when expanding the definition of adverse pathology to include GrdGrp 2 and EPE.

Several studies have demonstrated how adverse pathologic features influence the risk of biochemical recurrence (BCR), including randomized trials demonstrating the benefit of adjuvant radiotherapy in men with adverse pathologic features at RP.^{16,17} However, these trials included a heterogeneous cohort of patients without clear delineation of risk groups. We previously demonstrated that adverse pathologic features did not have the same clinical relevance, depending on the preoperative risk.⁷ For example, 5-year BCR risk in patients with low-risk PCa at initial evaluation but with EPE at RP was 15%, compared to 43% in the overall population of patients with EPE. The risk of BCR is not only influenced by adverse pathologic features, but also substantially by pretreatment factors. When counselling a patient who is considering AS, the risk of having adverse pathologic features should be balanced by the oncologic risk in the specific context of clinically low-risk PCa.

Unlike GrdGrp 2 or EPE, the risk of BCR in this prior study was not significantly different among the low-, intermediate-, and high-risk groups when LNI or SVI was diagnosed at RP.⁷ Cases with EPE encompass a heterogeneous group of patients and some investigators believe that tumors with capsular invasion and tumors with capsular penetration should be distinguished.¹⁸ The level/extent of EPE is also highly correlated to PCa grade.¹⁹ Similarly, simply assigning a Gleason score 7 may not reflect the aggressiveness of the disease. With the advent of the GrdGrp system, which is based on the Gleason system, but more clearly delineates GrdGrp 2 from GrdGrp 3, prognosis was significantly worse for GrdGrp 3 compared to GrdGrp 2, which shows a recurrence-free progression after RP closer to GrdGrp 1.²⁰ Due to these reasons, we only initially considered GrdGrp 3, SVI, and LVI as clinical endpoints to assess the aggressive nature of the disease.

In our current study, only age and PSA were significantly associated with the probability of adverse pathology. Neither the number of positive cores, total number of biopsy cores, total length of cancer on biopsy, nor the maximum percentage of cancer in any core were predictive of adverse pathology at RP, although most AS protocols take these criteria into account for inclusion. After expanding the definition of adverse pathology to include GrdGrp 2 and EPE, we found no evidence to support commonly used thresholds such as 3 positive cores or maximum 50% core involvement. Moreover, changes in risk were more moderate after these thresholds were reached, making them less clinically relevant. In the PRIAS study, more than 2 positive cores at surveillance biopsy used as criteria to switch to active treatment was not predictive of unfavorable pathologic outcome at RP.²¹ In men who underwent RP due to more than 2 positive cores (as the sole factor in “progression”), the rate of adverse pathology defined as GrdGrp 3 or pT3 or higher, was close to 50%, and half of these patients could have remained under AS.

Pathologic features of positive cores have long been part of the criteria for many AS protocols. In the John Hopkins protocol, for instance, men are eligible for AS only if they are clinically low-risk (PSA density < 0.15 ng/mL, cT1c, and GrdGrp 1) and have fewer than 3 positive cores with no more than 50% cancer involvement in any core.¹³ A similar approach was taken by the PRIAS study, although a PSA level <10 ng/mL was used in place of PSA density with no criterion of single core percentage involvement.²² We have not been able to find studies clearly supporting the finding that a threshold number of cores or cancer involvement importantly increases oncologic risk for GrdGrp 1 disease. Epstein criteria

(PSA density < 0.15 ng/mL, GrdGrp = 1 and 2 positive cores with cancer < 3mm on one core sample) were initially defined to predict insignificant cancer (GrdGrp 1, < 0.2cm³) on RP specimen.²³ In a cohort of 472 men with screen-detected PCa from the Göteborg screening trial, the 15-year PCa specific survival was 100% in very low-risk (according to Epstein criteria) vs. 94% in low-risk prostate cancer, suggesting the predictive value of cores. However, there was no statistical comparison and one of the two patients who died in the low-risk group had what would currently have been graded as 3+4 disease.²⁴ We believe that criteria for AS were chosen conservatively based on educated guesswork when AS programs were first developing, and clinicians were understandably wary of including higher-risk patients. Komisarenko et al. showed, by exploring the performance of various criteria used to identify men with low-risk disease in AS protocols, that selective criteria do not significantly improve short-term outcomes.²⁵ Consequently, the criteria used by many institutions might be too restrictive and exclude many men who could benefit from AS.

Risk classification is clinically important to better select candidates for AS and to adjust subsequent monitoring. There is still room for improvement in PCa staging and new techniques to increase the accuracy of initial evaluation are being investigated. Although GrdGrp from prostate biopsy is upgraded after RP in up to 50% of men, magnetic resonance imaging (MRI) seems to be an effective method to exclude the presence of higher GrdGrp.²⁶ The definitive results of the ASIST trial (NCT01354171), investigating whether multiparametric MRI can improve selection of patients for AS at the time of confirmatory biopsy, will provide more information. Other approaches evaluate new biomarkers that include gene modification such as TMPRSS2:ERG fusion transcript in prostatic tissue or urine,²⁷ PCA3 in urine,²⁸ and microRNAs.²⁹ The role of these markers is still under investigation.

A limitation of our retrospective study is that all specimens did not undergo specific research review for this study. Another limitation was that biopsies were not performed according to a uniform protocol. While all patients have their biopsy slides (in house or outside) reviewed by pathology, the majority of biopsies were performed at outside institutions and may not have followed a uniform biopsy scheme; furthermore, not all cores were submitted for review on each case. Other limitations include the absence of imaging and the selection of patients who were candidates for RP. These patients may not be representative of the overall population, but fewer alternative therapies were available at the time of the study. Adverse pathology after RP is not a perfect surrogate for oncologic outcomes. However, it is an important predictive factor for BCR, progression to metastatic disease and death, independent of pretreatment risk status,³⁰ and we believe it should be taken into account for the prospective evaluation of AS protocols.

CONCLUSION

In this large single-center cohort, approximately 5% of patients with low-risk prostate cancer harbored clinically relevant adverse pathology after RP. The association between core features and the probability of adverse pathology at RP is sensitive to the definition of adverse pathology. However, even with the expanded definition, there is no evidence of a clinically important increase in risk at widely used criteria for AS. There is little basis for

excluding patients from AS based on threshold criteria such as the number of positive cores or maximum cancer involvement.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by David H. Koch provided through the Prostate Cancer Foundation; the Sidney Kimmel Center for Prostate and Urologic Cancers; SPORE grant from the National Cancer Institute to Dr. H. Scher (grant number P50-CA92629); and a National Institutes of Health/National Cancer Institute Cancer Center Support Grant to MSKCC (grant number P30-CA008748).

Key of definitions for abbreviations

AS	active surveillance
PCa	prostate cancer
PSA	prostate specific antigen
RP	radical prostatectomy
GrdGrp	grade group
SVI	seminal vesicle invasion
LNI	lymph node involvement
EPE	extraprostatic extension
BCR	biochemical recurrence
MRI	magnetic resonance imaging

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Figure 1.

Risk of adverse pathology (solid line) with 95% confidence interval (dashed lines) in patients with low-risk prostate cancer:

A: By number of positive biopsy cores. The histogram represents the distribution of the number of positive biopsy cores.

B: By total millimeters of cancer on biopsy. The histogram represents the distribution of total millimeters of cancer on biopsy.

C: By maximum percentage of cancer in any biopsy core. The histogram represents the distribution of maximum percentage of cancer in any biopsy core.

Figure 2.

Risk of adverse pathology including grade group 2 and extraprostatic extension (solid line) with 95% confidence interval (dashed lines) in patients with low-risk prostate cancer:

A: By number of positive biopsy cores. The histogram represents the distribution of number of positive biopsy cores.

B: By total millimeters of cancer on biopsy. The histogram represents the distribution of total millimeters of cancer on biopsy.

C: By maximum percentage of cancer in any biopsy core. The histogram represents the distribution of maximum percentage of cancer in any biopsy core.

Table 1

Patient characteristics. Data are presented as median (interquartile range) or frequency (%).

Variables	N=3,359
Age at biopsy	59 (54, 63)
Pre-RP PSA	4.7 (3.4, 6.2)
PSA density (N=2,269)	0.13 (0.09, 0.18)
<i>DRE Result:</i>	
Normal	2131 (63%)
Abnormal	537 (16%)
Unknown	691 (21%)
Prostate volume (mL) (N=2,269)	34 (26, 47)
Number of biopsy cores (N=3,351)	12 (8, 14)
Number of positive biopsy cores (N=3,356)	2 (1, 3)
Percent positive cores (N=3,351)	17 (11, 33)
Total mm of cancer in biopsy (N=2,254)	3.3 (1.4, 8.0)
Maximum percent cancer in any core (N=3,310)	15 (5, 30)
<i>Type of surgery:</i>	
RP	1856 (55%)
Laparoscopic RP	823 (25%)
Robotic-assisted RP	680 (20%)
<i>Adverse pathology:</i>	
Grade group 3	144 (4.3%)
Seminal vesicle invasion	31 (0.9%)
Lymph node invasion	15 (0.4%)

Abbreviations: RP = radical prostatectomy, PSA = prostate-specific antigen

Table 2

Univariate comparison between patients with and without adverse pathology at radical prostatectomy.

	No adverse pathology (N=3,188)	Adverse pathology (N=171)	p-value
Age at biopsy	59 (54, 63)	62 (56, 66)	<0.0001
Pre-RP PSA	4.7 (3.4, 6.1)	5.8 (4.5, 7.1)	<0.0001
PSA density	0.12 (0.08, 0.18)	0.17 (0.12, 0.23)	<0.0001
Abnormal DRE	503 (20%)	34 (25%)	0.12
Prostate volume (mL)	34 (26, 47)	34 (25, 46)	0.4
Number of biopsy cores	12 (8, 14)	12 (8, 14)	0.8
Number of positive biopsy cores	2 (1, 3)	2 (1, 3)	0.7
Percent positive cores	16.7 (11.1, 33.3)	18.2 (12.5, 33.3)	0.7
Total mm of cancer in biopsy	3.3 (1.4, 8.0)	3.1 (1.3, 7.0)	0.6
Maximum percent cancer in any core	15 (5, 30)	15 (5, 35)	>0.9
Type of surgery:			
RP	1758 (55%)	98 (57%)	0.9
Laparoscopic RP	782 (25%)	41 (24%)	
Robotic-assisted RP	648 (20%)	32 (19%)	

Abbreviations: RP = radical prostatectomy, PSA = prostate-specific antigen, DRE = digital rectal exam

Table 3

Univariate comparison between patients with and without adverse pathology (including grade group 2 and extraprostatic extension) at radical prostatectomy.

	No adverse pathology (N=1,668)	Adverse pathology (N=1,691)	p value
Age at biopsy	58 (53, 62)	59 (54, 64)	<0.0001
Pre-RP PSA	4.4 (3.0, 5.9)	5.0 (3.9, 6.5)	<0.0001
PSA density	0.11 (0.07, 0.16)	0.14 (0.10, 0.21)	<0.0001
Abnormal DRE	263 (20%)	274 (20%)	0.8
Prostate volume (mL)	36 (26, 50)	33 (25, 44)	<0.0001
Number of biopsy cores	12 (8, 14)	12 (8, 14)	<0.0001
Number of positive biopsy cores	2 (1, 3)	2 (1, 4)	<0.0001
Percent positive cores	16.7 (10.0, 33.3)	20.0 (12.5, 35.0)	<0.0001
Total mm of cancer in biopsy	2.5 (1.0, 6.5)	4.1 (1.8, 9.0)	<0.0001
Maximum percent cancer in any core	10.0 (5.0, 25.0)	20.0 (8.0, 40.0)	<0.0001
Type of surgery:			
RP	1030 (62%)	826 (49%)	<0.0001
Laparoscopic RP	364 (22%)	459 (27%)	
Robotic-assisted RP	274 (16%)	406 (24%)	

Abbreviations: RP = radical prostatectomy, PSA = prostate-specific antigen