How Accurate is our Clinical Prediction of "Minimal Prostate Cancer"?*

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ABSTRACT: **Background:** Recommendations for active surveillance versus immediate treatment for low risk prostate cancer are based on biopsy and clinical data, assuming that a low volume of well-differentiated carcinoma will be associated with a low progression risk. However, the accuracy of clinical prediction of minimal prostate cancer (MPC) is unclear.

Objectives: To define preoperative predictors for MPC in prostatectomy specimens and to examine the accuracy of such prediction.

Methods: Data collected on 1526 consecutive radical prostatectomy patients operated in a single center between 2003 and 2008 included: age, body mass index, preoperative prostate-specific antigen level, biopsy Gleason score, clinical stage, percentage of positive biopsy cores, and maximal core length (MCL) involvement. MPC was defined as < 5% of prostate volume involvement with organ-confined Gleason score ≤ 6. Univariate and multivariate logistic regression analyses were used to define independent predictors of minimal disease. Classification and Regression Tree (CART) analysis was used to define cutoff values for the predictors and measure the accuracy of prediction.

Results: MPC was found in 241 patients (15.8%). Clinical stage, biopsy Gleason's score, percent of positive biopsy cores, and maximal involved core length were associated with minimal disease (OR 0.42, 0.1, 0.92, and 0.9, respectively). Independent predictors of MPC included: biopsy Gleason score, percent of positive cores and MCL (OR 0.21, 095 and 0.95, respectively). CART showed that when the MCL exceeded 11.5%, the likelihood of MPC was 3.8%. Conversely, when applying the most favorable preoperative conditions (Gleason ≤ 6, < 20% positive cores, MCL ≤ 11.5%) the chance of minimal disease was 41%.

Conclusions: Biopsy Gleason score, the percent of positive cores and MCL are independently associated with MPC. While preoperative prediction of significant prostate cancer was accurate, clinical prediction of MPC was incorrect 59% of the time. Caution is necessary when implementing clinical data as selection criteria for active surveillance.

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KEY WORDS: prostate cancer, active surveillance, minimal disease, patient selection, clinical prediction, Classification and Regression Tree (CART)

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Localized low risk prostate cancer is often a slowly progressing disease, with a 20 year cancer-related mortality under 20–25% [1,2]. Therefore, active surveillance is a reasonable management strategy for selected patients with low risk prostate cancer [3]. The ideal candidate for active surveillance often has a minimal burden of well-differentiated localized prostate cancer that may not progress to metastatic disease within the expected life span of the patient. Unfortunately, the clinical data used to select patients for active surveillance may underestimate the extent of cancer involvement and Gleason score [4-7]. In a previous study, 27% of patients who met the criteria for active surveillance on their initial biopsy had more significant cancers on repeat biopsy that rendered them ineligible for non-active management [8]. Additionally, Epstein's criteria were recently shown to better predict organ-confined disease that could be cured with aggressive therapy than "non-significant" disease where active surveillance would be an adequate approach [9].

More accurate outcome prediction is possible after radical prostatectomy when the clinical data are combined with the information gleaned from pathological examination of the surgical specimen [10]. However, in patients choosing active surveillance, the prostate specimen is not available for pathological examination, and as a result underestimation of cancer grade, stage and volume may lead to incorrect management decisions.

Although there is no perfect discriminator to define who should or should not receive active surveillance, for the purposes of this study we chose "minimal" prostate cancer as an endpoint. The purpose of our study was to assess whether clinical data can accurately predict minimal prostate cancer in prostatectomy specimens.

PATIENTS AND METHODS

Between 2003 and 2008 a total of 1526 consecutive patients with stage T1c-T2 prostate carcinoma underwent robotic-assisted laparoscopic radical prostatectomy and pelvic lymph node dissection in a single institution (The University of Chicago Medical Center). Prostate needle biopsies were all performed in multiple clinics referring to our center. All prostate needle biopsy specimens were reviewed in the same institution, as were all surgical specimens. All clinical and pathological data were collected prospectively under an institutional review board-approved protocol with informed patient consent.

Data were prospectively recorded, including patient age, prostate-specific antigen level, clinical stage, biopsy Gleason score, body mass index, the percentage of positive biopsy cores from all cores taken and the maximal percentage of core length involved with cancer. All operations were performed by A.L.S. and G.P.Z. using the same surgical technique [11]. The surgical specimen was processed according to the modified Stanford technique [12] with standard formalin fixation and staining.

DEFINITION OF MINIMAL PROSTATE CANCER

In this study minimal prostate cancer was defined as cancers confined to the prostate (pT2), ≤ 5% of prostate volume involved by cancer, Gleason score ≤ 6, and no intravascular or perineural invasion.

ENDPOINT ANALYSIS AND STATISTICS

Patients with minimal disease were compared with other patients in whom "significant" cancer was observed with regard to the aforementioned clinical parameters. Simple and multivariate logistic regressions were used to identify the independent preoperative predictors of minimal disease. Clinical data that were significantly associated with minimal disease ($P < 0.05$) were incorporated into the multivariate analysis. We then used Classification and Regression Tree analysis (CART Salford Systems, San Diego, CA, USA) [13] to define predictor cutoff values that would most accurately distinguish between minimal disease and significant prostate cancer for the individual patient. The CART analysis builds an algorithm for predicting a dependent variable (chance of minimal disease) from a set of predictor factors (parameters known to the clinician prior to surgery). The advantages of this analysis are: the simplicity of the result (with usually just a few logical "if-then conditions" specified), the absence of an implicit assumption of an underlying linear relationship between the predictors and the dependent variable, and the cross-validation performed during the construction of the decision tree performed many times over, with different randomly drawn samples from the data. The predictions of the CART analysis are generally more conservative than those generated by logistic regression. CART analysis was also used to generate a decision algorithm utilizing the selected predictors and best cutoff values to predict any specific endpoint of interest.

CART = Classification and Regression Tree

RESULTS

According to our definition of minimal prostate cancer, 241 patients (15.8%) met the criteria for "minimal" disease. When compared to patients with "significant" disease, patients with minimal disease had a slightly lower BMI, a higher proportion of low Gleason score and clinical T1c prostate cancers, fewer biopsy cores involved and a smaller extent of core length involvement [Table 1].

Simple logistic regression showed that clinical stage, biopsy Gleason score, maximal length of the involved core, and percent of positive cores were all associated with likelihood of finding minimal disease in the prostatectomy specimens (odds ratios 0.42, 0.1, 0.92, and 0.9, respectively; $P < 0.05$). Body mass index was marginally associated with minimal disease [Table 2].

Multivariate logistic regression showed that biopsy Gleason score, percent of positive cores and maximal percent of core length involved were independent predictors of minimal disease (OR 0.21, 0.95, and 0.95, respectively) [Table 3]. Patient

BMI = body mass index
OR = odds ratio

Table 1. Clinical features of patients with "minimal" versus "significant" disease

	Minimal disease	Significant disease	*P* value
No. (% total)	241 (16%)	1285 (84%)	–
Age (yr) Mean (range)	59.7 (42–73)	59.0 (40–78)	0.13
PSA (ng/ml) Mean (range)	5.9 (0.6–26.2)	6.3 (0.5–23.1)	0.18
BMI (kg/m²) Mean (range)	27.6 (19.1–59.5)	28.4 (14.5–50.5)	0.03
Biopsy Gleason score (n, %) ≤ 6 7 ≥ 8	 223 (92%) 17 (7%) 1 (1%)	 658 (51%) 515 (40%) 112 (9%)	< 0.0001
Clinical stage (n, %) cT1c cT2a cT2bc	 213 (88%) 24 (10%) 4 (2%)	 930 (72%) 251 (20%) 104 (8%)	< 0.0001
Maximal % of Ca in a core Mean (range)	7.8 (1–50)	29.8 (0.5–100)	< 0.0001
% positive biopsy cores Mean (range)	13.6 (3.3–100)	31.2 (2.5–100)	0.001
Median no. of biopsy cores (IQR)	12 (10–12)	12 (11–12)	0.18

PSA = prostate-specific antigen, BMI = body mass index, IQR = interquartile range

Table 2. Univariate analysis (simple logistic regression) of preoperative parameters to predict "minimal" disease in the prostatectomy specimen

	P value	OR	95% CI
Age	0.14	0.98	0.96–1.0
BMI (kg/m²)	0.03	0.96	0.93–0.99
PSA (ng/ml)	0.18	0.97	0.94–1.0
Clinical stage			
cT1c	Reference	1.0	-
cT2a	< 0.0001	0.42	0.27–0.65
cT2bc	0.001	0.17	0.06–0.46
Biopsy Gleason score			
≤ 6	Reference	1.0	–
7	< 0.0001	0.1	0.06–0.17
≥ 8	< 0.0001	0.03	0.01–0.18
Maximal % of Ca in a core (%)	< 0.0001	0.92	0.90–0.93
% positive biopsy cores (%)	< 0.0001	0.9	0.88–0.92

BMI = body mass index, PSA = prostate-specific antigen, Ca = carcinoma

age and PSA were not independent predictors, while BMI had only marginal significance.

CART analysis found that the maximal percent of core length involved was the strongest predictor of "significant" prostate cancer. When more than 11.5% of a biopsy core length was involved with cancer the chance of that patient having minimal disease was 3.8% regardless of all other clinical parameters [Figure 1]. Conversely, even when applying the most favorable predictor combination (maximal involved core length ≤ 11.5%, Gleason score ≤ 6, and < 20% of biopsy cores involved with cancer) the chance for an endpoint of minimal disease in the prostate specimen was 41%.

This combination of the most favorable predictors was observed in 411 patients. Of them 243 patients (59.1%) were defined by the CART as having "significant" disease. Sixty per-

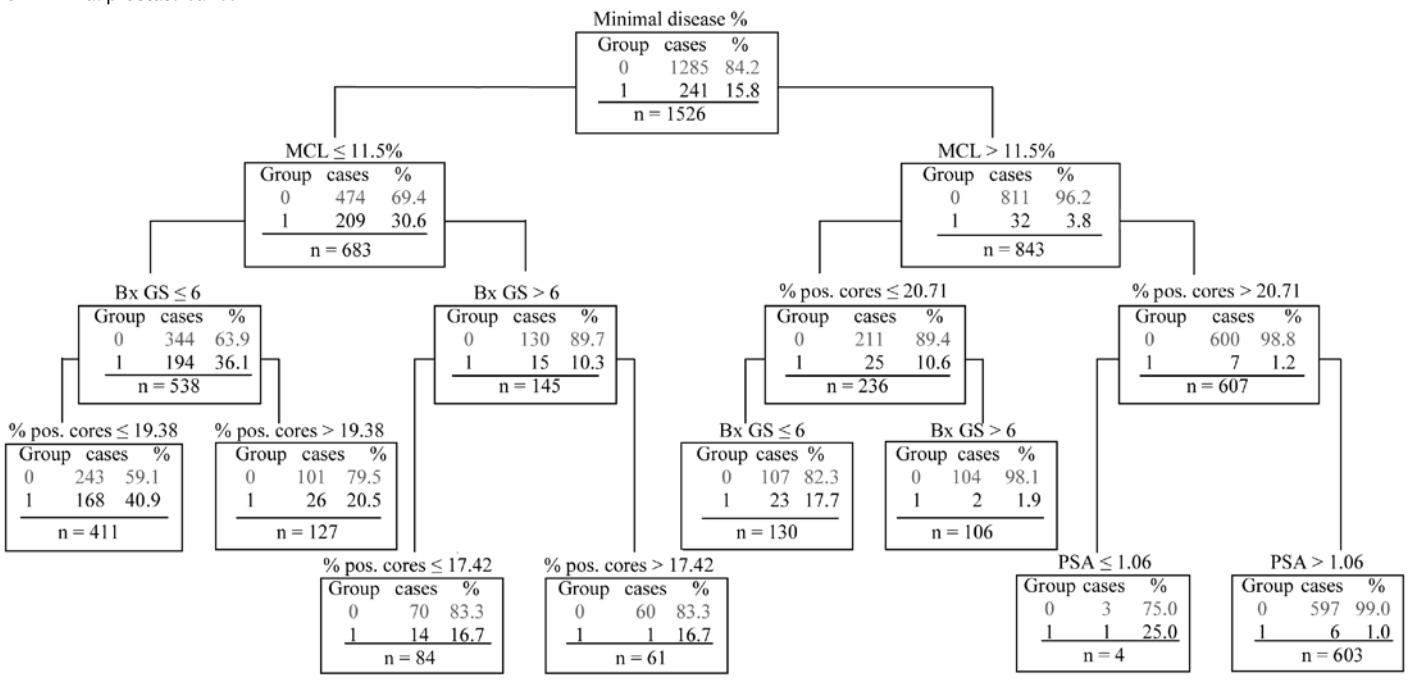
PSA = prostate-specific antigen

Table 3. Multivariate analysis showing independent predictors of "minimal" disease

	P value	OR	95% CI
BMI	0.22	0.98	0.94-1.0
Clinical stage			
cT1c	Reference	1.0	–
cT2a	0.41	1.24	0.72–2.16
cT2bc	0.17	1.34	0.40–4.69
Biopsy Gleason score			
≤ 6	Reference	1.0	–
7	< 0.0001	0.21	0.12–0.38
≥ 8	0.02	0.08	0.01–0.62
Maximal % of Ca in a core (%)	< 0.0001	0.95	0.93–0.97
% positive biopsy cores (%)	< 0.0001	0.95	0.88–0.92

BMI = body mass index, Ca = carcinoma

Figure 1. Classification and Regression Tree analysis shows how the different predictors interplay under any given set of variables to provide the likelihood of minimal prostate cancer



CART = Classification & Regression Tree analysis, MPC = minimal prostate cancer, MCL = maximal core length, Bx GS = biopsy Gleason score, PSA = preoperative serum prostate-specific antigen

cent of these patients had at least one adverse feature in their prostatectomy specimens including perineural invasion with cancer in 146 patients (60%), Gleason score ≥ 7 in 94 patients (39%), and extracapsular cancer in 24 patients (9.9%).

DISCUSSION

In this study we show that biopsy Gleason score ≤ 6, the percent of positive biopsy cores < 21%, and the maximal percent of core length involvement < 11.5% are independent clinical predictors of minimal prostate cancer in the radical prostatectomy specimen. In addition, CART analysis provided the best cutoff values for the independent predictors of minimal disease and an algorithm with which the actual likelihood of any given patient to have minimal disease can be calculated. According to this algorithm the percentage of biopsy core length involvement with cancer was the strongest predictor of minimal disease versus significant prostate cancer. Although pathologists typically do not provide such accurate measurements of biopsy core length involvement, this cutoff value may be clinically useful. If the given percentage of core involvement is 10%, minimal disease may be anticipated along with other predictors; however, if ≥ 15% is reported, the likelihood of minimal disease is small. Therefore, our data show that clinically significant prostate cancer may be predicted accurately before surgery. Conversely, the accuracy of preoperative prediction of minimal disease was insufficient, and even under the most favorable patient conditions significant prostate cancer would be present in the prostatectomy specimens in 59% of the cases.

Therefore, relying on clinical and biopsy data as selection criteria for active surveillance may result in submitting patients with a significant disease burden to expectant management rather than to active therapy. Such patients have been shown to fare better with active therapy as compared to active surveillance [14]. Making the distinction between patients with low risk cancer who would follow a mild and indolent course and for whom active surveillance may be implemented, and others who are bound to progress and need timely aggressive therapy, remains a major challenge.

Preoperative measurement of the cancer burden within the prostate is difficult. This and previous studies have shown that clinical parameters are unreliable for making this prediction. Imaging studies including endorectal magnetic resonance may provide data on the volume of cancer in some patients. However, not all prostate cancers are measurable on MRI, and the accuracy of predicting minimal disease by MRI has not been evaluated. This has not yet become a routine procedure for candidates for active surveillance.

Our definition of minimal disease aimed at including only patients with a small burden of well-differentiated prostate cancer. Surgical margin status was not included in our definition because in the presence of a small and well-differentiated cancer, a positive margin probably reflects a technical problem rather than aggressive biological behavior. Using the above definition, the estimated 10 year progression-free survival in the post-prostatectomy nomogram is 97% [10]. There is previous evidence to support a cutoff volume of well-differentiated cancer of ≤ 0.5 ml as minimal [12]. Our aim was to select the smallest percentage of cancer involvement as the cutoff value. Choosing a 10% cutoff would have resulted in 458 (30%) of the patients being included in the minimal disease group. A 1% cutoff, on the other hand, would have resulted in 119 patients (7.7%) being included. We ran the CART analysis for both cutoff values of 1%, 5% and 10% and no difference in the model or cutoff values appeared. Since only rarely is cancer involvement < 5% of the prostate reported, we chose to use 5% as our cutoff. Because the specimen processing in our center is the modified Stanford technique we could not measure the actual tumor volume in the specimens and thus could not adhere to the 0.5 ml threshold for "minimal disease." Our data support those of previous studies showing that the current prediction accuracy for MPC is insufficient. Using PSA density in conjunction with favorable needle biopsy features to predict "insignificant" prostate cancer in the prostatectomy specimens, Loeb et al. [15] found that their definition of "insignificant" disease with a prediction model sensitivity of 57% and specificity of 76% applied to only 2.6% of their 274 patients. In a larger series of 1132 patients, 5.7% were defined as having minimal disease based on their prostatectomy specimens. However, 63% of the patients who were predicted to harbor minimal disease according to preoperative parameters were found to have aggressive cancer in the prostatectomy specimens [16]. Likewise, Lee and co-authors [17] reported that only 7% of men who had a single biopsy core involvement with ≤ 5% prostate cancer had "insignificant cancer" in the radical prostatectomy specimen.

Our results do not undermine the role of active surveillance, and since this approach is a continuous process of risk assessment, it appears that patients meeting definitions of disease progression while on active surveillance can be safely redirected to active therapy without compromising their chance for cure [18]. We also acknowledge that the pathology criteria for minimal disease are but a proxy to cancer indolence, which is largely a clinical endpoint.

The strengths of the current study are a large and contemporary cohort of patients who were all diagnosed and treated in the same manner. This makes the inference to the general population more appropriate. The use of CART analysis in this study pointed out the shortcomings of clinical prediction of minimal prostate cancer. This provides the clinician with a realistic grasp of the shortcomings of clinical prediction for the endpoint of minimal disease preoperatively. Consequently, this inaccuracy must be accounted for when consulting patients on active surveillance.

In the absence of better prognostic factors to predict minimal disease, selecting patients for active surveillance needs to rely more on host factors including age and co-morbidity. Further study is needed to establish additional biological and imaging-based predictors of cancer indolence. However, until such genetic predictors are determined the current selection criteria for active surveillance remain clinical.

Our work has several important limitations. Using an arbitrary 5% volume cutoff of prostate cancer, we found the proportion of patients with minimal disease to be 16%. Depending on the prostate volume 5% may be significantly more than the accepted 0.5 ml [19]. Performing whole-mount examination of the entire specimen rather than the sampling-based Stanford method would have provided us with actual cancer volumes and, consequently, with a more uniform definition of minimal disease. Nonetheless, others found that the percent of tumor involved is a predictor of tumor burden and outcome [20]. Additionally, since less than 5% tumor involvement is rarely reported, this was the smallest practical cutoff. Furthermore, using the Kattan nomogram our definition of minimal disease was associated with a 10 year progression-free survival rate of 97% [10]. We also acknowledge that minimal prostate cancer is but a surrogate marker for "indolent" prostate cancer that would be best managed by active surveillance. Consequently, although active surveillance remains a valid management option for many patients with low risk cancer, we emphasize the lack of accuracy of patient selection based on clinical data. Data on prostate volume were unavailable. As a result, we could not control our predictors for prostate volume which may be variable between patients. Finally, our work could have been biased if biopsy core fragmentation occurred, making the total core length shorter and the percent with cancer larger.

CONCLUSIONS

"Minimal" prostate cancer can be found in up to 16% of patients undergoing radical prostatectomy. Needle biopsy Gleason score, the percent of positive cores and the maximal length of core involved with cancer are all independent predictors of minimal disease, with the maximal involved core length being the strongest predictor. When more than 11.5% of a biopsy core is involved, the likelihood of minimal prostate cancer in the prostatectomy specimen is only 3.8%. Under the most favorable conditions, only 41% of the patients predicted to have minimal disease will actually have minimal disease in the prostatectomy specimen. Therefore, our ability to accurately predict minimal disease and thus select patients for active surveillance is limited. As such, caution is necessary when implementing clinical data as selection criteria for this approach versus active therapy.

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