

CANCER PROGRESSION AND SURVIVAL RATES FOLLOWING ANATOMICAL RADICAL RETROPUBIC PROSTATECTOMY IN 3,478 CONSECUTIVE PATIENTS: LONG-TERM RESULTS

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ABSTRACT

Purpose: We updated a long-term cancer control outcome in a large anatomical radical retro-pubic prostatectomy (RRP) series. We also evaluated the perioperative parameters that predict cancer specific outcomes following surgery.

Materials and Methods: From May 1983 to February 2003, 1 surgeon (WJC) performed RRP in 3,478 consecutive men. Patients were followed with semiannual serum prostate specific antigen (PSA) tests and annual digital rectal examinations. We used Kaplan-Meier product limit estimates to calculate actuarial 10-year probabilities of biochemical progression-free survival, cancer specific survival and overall survival. Multivariate Cox proportional hazards models were used to determine independent perioperative predictors of cancer progression.

Results: At a mean followup of 65 months (range 0 to 233) actuarial 10-year biochemical progression-free, cancer specific and overall survival probabilities were 68%, 97% and 83%, respectively. On multivariate analysis biochemical progression-free survival probability was significantly associated with preoperative PSA, clinical tumor stage, Gleason sum, pathological stage and treatment era. Cancer specific survival and overall survival rates were also significantly associated with clinicopathological parameters.

Conclusions: RRP can be performed with excellent survival outcomes. Favorable clinicopathological parameters and treatment in the PSA era are associated with improved cancer control.

KEY WORDS: prostate, prostatectomy, prostatic neoplasms, outcome assessment (health care)

In 1982 Walsh and Donker introduced anatomical radical retro-pubic prostatectomy (RRP).¹ With the surgical modifications that preserve neurovascular bundles excellent cancer control can be achieved, while preserving erectile function and urinary continence in most appropriately selected patients.^{2,3} Since then, radical prostatectomy has become the most common treatment for clinically localized prostate cancer.⁴

We have previously reported 5 and 7-year results in a large RRP series.^{5,6} In this report we update the series with 10-year followup. We performed univariate analyses of known perioperative parameters for predicting progression-free survival following RRP. We then included a multivariate proportional hazards model to evaluate perioperative clinicopathological parameters and the treatment era for independently predicting treatment outcomes. Finally, we performed subset analysis comparing patient characteristics during the pre-prostate specific antigen (PSA) screening era (1983 to 1991) and the PSA screening era (1992 to 2003).

METHODS

Patients. Between May 1983 and February 2003 a single surgeon (WJC) performed staging bilateral pelvic lymphadenectomy and anatomical RRP in 3,478 consecutive men. Table 1 lists patient demographics and disease characteris-

tics. Briefly, mean age \pm SD at surgery was 61 \pm 7 years (range 36 to 80). The majority of patients (94%) identified themselves as of white descent, more than 60% had preoperative serum PSA between 4 and 10 ng/ml, approximately half had clinical stage T1c disease and more than 70% had Gleason sum 6 or 7 in the RRP specimen. The majority of patients (3,146 or 91%) underwent a bilateral nerve sparing procedure, while some who had clinically more advanced disease underwent unilateral or partial nerve sparing (157 or 5%) or nonnerve sparing (161 or 5%) procedures.

Tumor stage and grade. Tumor staging was performed as previously described.² Digital rectal examination was performed by a single surgeon (WJC) and clinical stage was determined according to 1992 American Joint Committee on Cancer staging guidelines.⁷ Pathological staging was performed as previously described.⁶ Organ confined disease (pT2 R0) was defined as cancer confined to the prostate with negative surgical margins. Pathologically advanced disease was defined as tumor with positive margins only (pT2 R1), confirmed extraprostatic tumor extension with or without cancerous surgical margins (pT3a/b R0/1), cancer involvement of the seminal vesicles (pT3c) and/or pelvic lymph node metastases (N1).

Before 1992 the Gleason grading system was not routinely used at Washington University.² For the final analysis of Gleason score and biochemical progression-free survival well differentiated tumors prior to 1992 were considered Gleason sum 3, moderately differentiated tumors were considered Gleason sum 6 and poorly differentiated tumors were considered Gleason sum of 9. Since 1992, Gleason sums have been routinely assigned, as previously described.⁸

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TABLE 1. Patient characteristics overall and by era

	Pre-PSA Era (1983–1991)	PSA Era (1992–2003)	Overall (1983–2003)	p Value (Armitage chi-square or t test)
Mean age ± SD (range)	65 ± 7 (41–80)	60 ± 7 (36–78)	61 ± 7 (36–80)	0.0001
No. race (%):				0.001
White	637 (97)	2,630 (93)	3,267 (94)	
Black	14 (2)	88 (3)	102 (3)	
Other	5 (1)	104 (4)	109 (3)	
No. ng/ml preop PSA (%):				0.001
Less than 2.6	48 (10)	174 (7)	222 (7)	
2.6–4.0	35 (7)	358 (16)	393 (12)	
4.1–10.0	239 (48)	1,848 (65)	2,087 (63)	
Greater than 10.0	172 (35)	433 (15)	605 (20)	
No. clinical stage (%):				0.001
cT1a/b	74 (11)	38 (1)	112 (3)	
cT1c	42 (6)	1,732 (62)	1,774 (51)	
cT2a	222 (34)	353 (13)	575 (17)	
cT2b/c	311 (47)	664 (24)	975 (28)	
cT3	6 (1)	28 (1)	34 (1)	
No. pathological stage (%):				0.001
pT2	369 (61)	1,924 (69)	2,293 (68)	
pT3a/b, neg SMs	13 (2)	242 (9)	255 (8)	
pT3a/b, pos SMs	142 (23)	490 (18)	632 (19)	
pT3c/N1	83 (14)	119 (4)	202 (6)	
No. pathological Gleason sum (%):				0.001
2–4	172 (27)	54 (2)	226 (7)	
5	147 (23)	343 (11)	490 (14)	
6	144 (23)	1,301 (47)	1,445 (42)	
7	93 (15)	924 (33)	1,017 (30)	
8–10	79 (12)	158 (6)	237 (7)	

Because of adverse histopathological findings in the radical prostatectomy specimen (extraprostatic extension, positive surgical margins, seminal vesicle invasion or pelvic lymph node involvement), 217 men (6%) elected adjuvant radiotherapy. The mean radiotherapy dose was 63 Gy.

Followup evaluation. Postoperative followup evaluation included semiannual serum PSA measurements and yearly digital rectal examination. Cancer progression was defined as detectable serum PSA (greater than 0.2 ng/ml), as documented by repeat PSA measurements, local recurrence or distant metastases. The date and cause of death were obtained when available.

Statistical analysis. We used the Armitage chi-square test for linear trends to compare categorical clinical and pathological characteristics by era. We used the t test to compare continuous variables by era.

For univariate analyses we calculated actuarial 10-year biochemical progression-free probabilities using Kaplan-Meier product-limit estimates. Patients without progression were censored at the most recent followup. We used log rank statistics to determine whether clinicopathological variables and era were significant predictors of progression.

For multivariate analyses we used the Cox proportional hazards method to determine whether variables that were significantly associated with progression on univariate analyses remained independent predictors after adjustment for other variables in the model. We also performed subset analysis to evaluate the influence of adjuvant radiotherapy on cancer progression in men in whom advanced pathological findings suggested the need for adjuvant radiotherapy.

We calculated actuarial 10-year all-cause and cancer specific survival probabilities using Kaplan-Meier product limit estimates. For estimating all-cause survival we censored men known to be alive at the most recent followup. Similarly for estimating cancer specific survival we censored patients known to be alive at the most recent followup or those who had died of causes other than prostate cancer.

RESULTS

Mean followup was 65 ± 50 months (range 0 to 233). Of the patients 1,620 (47%) and 579 (17%) had 5 and 10-year followup information available, respectively. A total of 59 men (2%) were lost to followup.

Overall cancer progression. Of 3,478 men 631 (18%) experienced cancer progression following RRP. Kaplan-Meier analysis showed actuarial 5 and 10-year biochemical progression-free survival estimates of 80% (95% CI 79 to 82) and 68% (95% CI 66 to 71), respectively. Mean time to progression was 38 ± 34 months (median 28, range 1 to 189). Of 631 men with cancer progression 68 (11%) had received adjuvant radiotherapy for adverse pathological findings, of whom 39 subsequently received hormonal therapy.

Cancer progression as a function of clinical characteristics. Figure 1 shows biochemical progression-free survival functions by PSA strata. Actuarial 10-year biochemical progression-free probabilities were 91% (95% CI 83 to 95) for PSA less than 2.6 ng/ml, 78% (95% CI 67 to 86) for PSA between 2.6 and 4.0 ng/ml, 74% (95% CI 70 to 77) for PSA between 4.1 and 10 ng/ml, and 49% (95% CI 44 to 54) for PSA greater than 10.0 ng/ml. We excluded 171 men (5%) from survival analysis because they underwent surgery before PSA testing became available. The log rank test comparing biochemical progression-free survival probabilities across the preoperative PSA strata was significant (p < 0.0001).

Biochemical progression-free survival was also significantly associated with patient age at surgery. Actuarial 10-

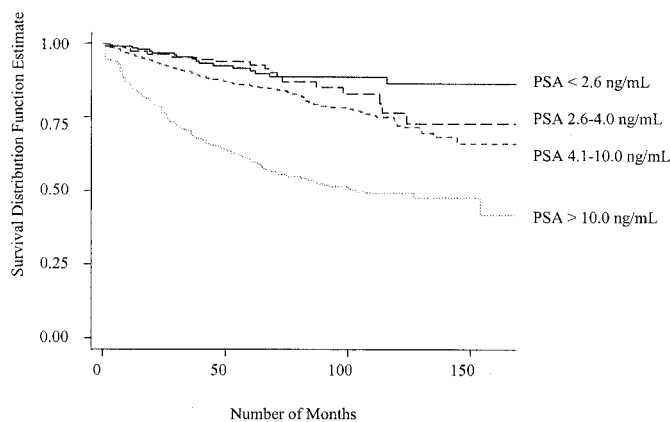


FIG. 1. Probability of nonprogression survival following RRP stratified by preoperative serum PSA (p < 0.0001).

year biochemical progression-free survival probabilities were 76% (95% CI 63 to 85) in men 41 to 50 years old, 71% (95% CI 66 to 76) in men 51 to 60 years old, 66% (95% CI 63 to 70) in men 61 to 70 years old and 63% (95% CI 57 to 69) in men older than 70 years ($p = 0.0001$).

Figure 2 shows biochemical progression-free survival functions for clinical stage. Actuarial 10-year biochemical progression-free survival probabilities were 75% (95% CI 65 to 83) for cT1a/b, 77% (95% CI 71 to 83) for cT1c, 69% (95% CI 64 to 74) for cT2a, 59% (95% CI 55 to 63) for cT2b/c and 15% (95% CI 3 to 35) for cT3 disease. The log rank test comparing survival functions across the clinical stage strata was significant ($p < 0.0001$).

Cancer progression as a function of pathological characteristics. Figure 3 shows biochemical progression-free survival functions by RRP Gleason sum. Actuarial 10-year biochemical progression-free survival probabilities were 77% (95% CI 74 to 79) for Gleason sums 2 to 6, 64% (95% CI 56 to 71) for Gleason sum 3 + 4, 50% (95% CI 39 to 60) for Gleason sum 4 + 3 and 32% (95% CI 25 to 40) for Gleason sums 8 to 10 disease. The log rank test comparing survival functions across Gleason sums was significant ($p < 0.0001$).

Figure 4 shows biochemical progression-free survival probabilities by pathological stage. Actuarial 10-year biochemical progression-free survival probabilities were 79% (95% CI 76 to 82) for organ confined disease, 62% (95% CI 51 to 72) for disease with extraprostatic extension without cancerous surgical margins, 53% (95% CI 47 to 59) for disease with extraprostatic extension and cancerous surgical margins, 26% (95% CI 18 to 35) for disease with seminal vesicle involvement and 12% (95% CI 3 to 27) for disease with lymph node metastases. The log rank test across pathological stages was significant ($p < 0.0001$).

Multivariate models for predicting cancer progression. The multivariate Cox proportional hazards model indicated that PSA, clinical stage, Gleason sum, pathological stage and era were each uniquely associated with cancer progression (table 2). However, age and race were not independently associated with cancer progression following surgery.

Subset analysis was performed in 834 men in whom pathological findings suggested the need for adjuvant radiotherapy (cancerous surgical margins, pT3 or N1 disease). The multivariate model indicated that adjuvant radiotherapy was associated with a lower probability of cancer recurrence after controlling for PSA, era, age, race, tumor grade and stage (HR 0.72, $p = 0.029$, table 3).

All-cause survival. A total of 297 men (9%) died of any cause, yielding an actuarial 10-year overall survival rate of 83% (95% CI 81 to 85). Overall survival was significantly associated with Gleason sum (HR 1.22, $p = 0.001$), age (HR 1.8, $p < 0.001$) and pathological stage (HR 1.3, $p = 0.004$).

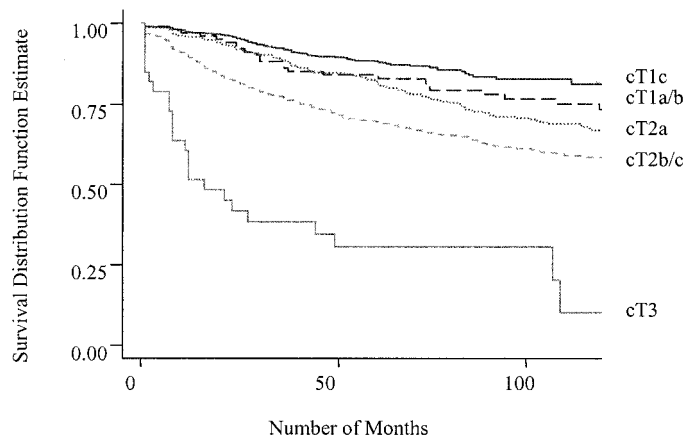


FIG. 2. Probability of nonprogression survival following RRP stratified by clinical stage ($p < 0.0001$).

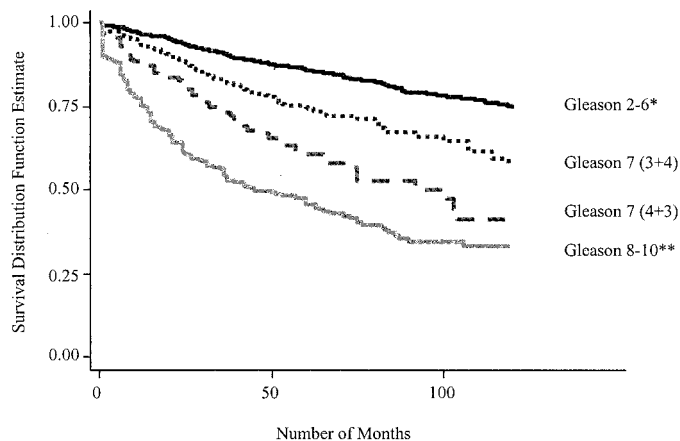


FIG. 3. Probability of nonprogression survival following RRP stratified by Gleason sum ($p < 0.0001$). Single asterisk indicates inclusion of well and moderately differentiated tumors prior to Gleason scoring system use. Double asterisks indicate inclusion of poorly differentiated tumors prior to Gleason scoring system use.

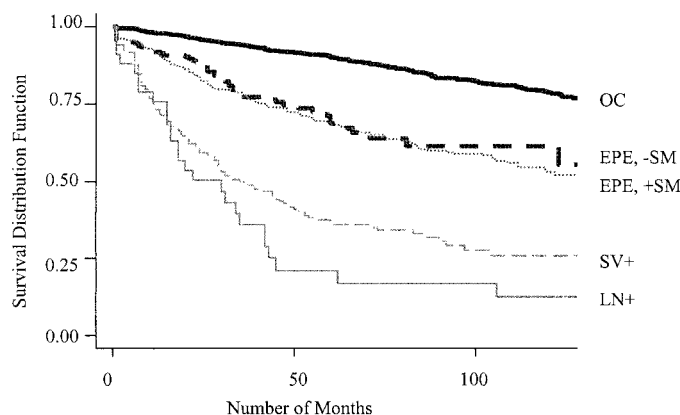


FIG. 4. Probability of nonprogression survival following RRP stratified by pathological stage ($p < 0.0001$). OC, organ confined. EPE, -SM, extraprostatic tumor extension, negative SMs. EPE, +SM, extraprostatic tumor extension, positive SMs. SV+, seminal vesicle tumor involvement. LN+, pelvic lymph node tumor involvement.

TABLE 2. Cox proportional hazards model for predicting cancer progression

Variables	HR*	z	p	95% CI
PSA	1.77	8.41	0	1.55–2.03
Clinical stage	1.27	4.94	0	1.15–1.39
Gleason sum	1.36	6.92	0	1.24–1.48
Pathological stage	1.86	11.58	0	1.68–2.07
Era	0.76	-2.67	0.01	0.62–0.93
Age	1.05	0.88	0.38	0.94–1.18
Race	1.14	0.97	0.33	0.88–1.48

* Variables were used as categorical, as in table 1, except age was categorized in decades.

Prostate cancer specific survival. A total of 49 men (2%) died of prostate cancer, yielding an actuarial 10-year cancer specific survival rate of 97% (95% CI 96 to 98). Cancer specific survival was significantly associated with pathological stage (HR 2.24, $p < 0.001$), Gleason sum (HR 1.75, $p = 0.004$) and era (HR 0.45, $p = 0.04$).

DISCUSSION

For the last 2 decades the management of prostate cancer has undergone significant changes. With increasing use of PSA testing men are being diagnosed with earlier stage prostate cancer and at a younger age. As a result, in the PSA

TABLE 3. Cox proportional hazards model for predicting cancer progression in 834 men treated with radical prostatectomy with pathological stage pT3a/b and positive margins, pT3c or N1

Variable	HR*	z	p	95% CI
Age	0.96	-0.56	0.58	0.82-1.12
Clinical stage	1.46	3.77	0	1.20-1.79
Gleason sum	1.39	5.15	0	1.23-1.57
Pathological stage	1.25	3.53	0	1.10-1.41
PSA	1.74	5.78	0	1.44-2.10
Race	1.07	0.3	0.76	0.70-1.61
Adjuvant radiotherapy	0.72	-2.18	0.03	0.53-0.97

* Variables were used as categorical, as in table 1, except age was categorized in decades.

era more men are candidates for curative therapy. Coinciding with widespread prostate cancer screening, new anatomical discoveries and surgical modifications have allowed surgeons to perform RRP with substantially less morbidity.¹ We have previously reported our early and intermediate term results in a large cohort of men treated with RRP in the PSA era.^{5,6} In this article we updated our series and reported actuarial 10-year results.

Overall our cancer control outcomes are more favorable than those reported in the pre-PSA screening era.^{9,10} On the other hand, our results extend our initial findings and generally support those reported in other, similar, large contemporary RRP series.^{5,6} For example, the Johns Hopkins group reported on almost 2,000 men who underwent RRP between 1982 and 1997.¹¹ Mean followup was 64 months and the actuarial 10-year recurrence-free rate was 68%. Subsequently they updated their series with a followup analysis of 2,404 men.³ They excluded 90 men (4%) with adverse prognostic features in that analysis. Mean followup was 75.6 months and 621 men (26%) were followed at least 10 years. Actuarial 10 and 15-year biochemical progression-free survival estimates were 74% and 66%, respectively. In addition, actuarial 10 and 15-year cancer specific survival estimates were 96% and 90%, respectively. They also found significant downward stage migration and a significantly higher recurrence-free survival rate in men treated between 1982 and 1988 compared with those treated between 1989 and 1998.¹²

In the analysis of another large RRP series Hull et al reported the actuarial 10-year cancer recurrence-free survival outcome in 1,000 patients.¹³ They excluded men who received prior radiotherapy, cryotherapy or neoadjuvant hormonal therapy and those with clinical stage T3 disease but included patients in whom prostatectomy was abandoned because of lymph node metastases. However, in the latter group of patients progression was not declared until the initiation of adjuvant therapy or proven distant metastases. Mean followup was 4.3 years and 5.6% of patients were followed at least 10 years. Actuarial 5 and 10-year biochemical progression-free survival estimates were 78% and 75%, respectively. The actuarial 10-year cancer-specific survival rate was 97.6%.

There are many similarities between our series and 2 other large RRP series.^{3,13} All 3 series included a large number of men who underwent RRP for clinically localized prostate cancer. All 3 series demonstrated excellent cancer specific outcomes following RRP. Cancer progression was associated with multiple adverse prognostic factors in all 3 series. Also, many patients in these series underwent surgery during a transition period of improved prostate cancer screening with PSA testing.

However, there are notable differences between our series and the other series of Han³ and Hull¹³ et al. 1) There is a difference in inclusion criteria in the analysis. Han et al excluded patients who received immediate adjuvant radiotherapy, immediate postoperative hormonal therapy, preoperative radiotherapy or neoadjuvant hormonal therapy and

those who had stage D0/D2 disease.³ Hull et al also excluded men with adverse features from survival analysis.¹³

2) There is a difference in patient selection criteria and the followup interval. The patient cohort in the study of Han et al was younger.³ Followup frequency and duration were different in these series. The series of Han et al had the longest followup with 26% of patients having 10-year followup information available, while the current series and that of Hull et al¹³ had 16% and 5.6%, respectively, eligible for 10-year followup.

3) There is a difference in the definition of cancer progression. In our series and that of Han et al³ PSA greater than 0.2 ng/ml was considered evidence of progression, whereas a PSA cutoff of 0.4 ng/ml was used to define progression in the series of Hull et al.¹³

4) We included all patients with adverse clinical and pathological features in our analysis. However, 217 of our patients (6%) received adjuvant radiotherapy. A substantial but unquantified (not recorded in our database) proportion of our patients also received preoperative hormonal therapy because of adverse prognostic parameters. Therefore, it is likely that, if these patients were excluded from analysis, our biochemical progression-free survival rates would be higher.

Most importantly because more men were diagnosed with prostate cancer in the PSA screening era, the surgical outcome should continue to improve as more men undergo treatment for lower stage and grade disease. For example, in the series from Johns Hopkins actuarial 10-year biochemical recurrence-free survival rate improved from 68% to 74% as mean followup increased from 64 to 76 months and the proportion of men with T1c disease increased from 38% to 43%.^{3,11}

The current RRP series spans 2 decades, during which innovations in PSA screening and biopsy techniques have caused a dramatic, favorable shift in prognostic parameters. We included patients with adverse prognostic factors in the analysis. The likelihood of cancer progression was associated with known adverse prognostic parameters, such as serum PSA, clinical stage, Gleason sum, pathological stage and era. Our RRP series is still not sufficiently mature to evaluate effectively cancer specific survival trends. Our preliminary results show that cancer specific survival following RRP is favorable. Only 2% of the men died of prostate cancer, yielding an actuarial 10-year cancer-specific survival rate of 97%.

As subset analysis, we compared clinicopathological parameters according to whether patients were treated in the pre-PSA screening era (1983 to 1991) or in the PSA screening era (1992 to 2003). Similar to the study of Han et al,¹² we found a significant shift of prognostic parameters and more favorable treatment outcomes in the PSA screening era. The era of treatment was independently associated with biochemical progression-free survival on multivariate analysis. The favorable era effect is likely due to earlier detection, more effective treatment, lead-time and possibly length-time bias, and shorter followup during the PSA screening era.

In our previous analysis we found that adjuvant radiotherapy was associated with a lower probability of cancer recurrence.¹⁴ We investigated the influence of adjuvant radiotherapy in 834 men, of whom 217 (26%) received adjuvant radiotherapy, with pathological stage with positive surgical margins, extraprostatic extension, seminal vesicle invasion and/or lymph node metastasis. On the multivariate model that corrected for other prognostic parameters adjuvant radiotherapy was shown to be independently associated with improved biochemical progression-free survival (table 3). However, our study was not designed to evaluate accurately adjuvant radiotherapy. In fact, patients with more adverse pathological features were urged to undergo adjuvant radiotherapy, while those with less adverse features were encouraged to wait and monitor PSA. This policy may have introduced a bias against adjuvant radiotherapy.

CONCLUSIONS

Anatomical RRP provides excellent cancer control. Traditional clinicopathological parameters correlate with treatment results. Widespread screening for prostate cancer caused a favorable migration of these parameters and improved biochemical progression-free survival rates during the last 2 decades. In addition to known perioperative predictors of cancer recurrence, patient selection and the duration of followup monitoring are critical determinants of outcomes. Adjuvant radiotherapy appears to be of modest benefit for preventing cancer progression in a select group of men. Treatment results following radical prostatectomy will most likely continue to improve in the future as early detection is more widely practiced.

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