Analysis of repeated 24-core saturation prostate biopsy: Inverse association between asymptomatic histological inflammation and prostate cancer detection

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Abstract. Saturation prostate biopsy protocols have been developed to improve the prostate cancer (PCa) detection rate, particularly in the setting of repeat biopsies. The present study attempted to clarify the association between PCa detection and various risk factors in repeat saturation biopsies. A retrospective analysis was conducted on 78 Japanese patients for whom findings had caused suspicion of PCa despite previous negative prostate biopsies, and who consecutively underwent a 24-core transperineal repeat biopsy at Toyama University Hospital (Toyama, Japan). PCa was confirmed histologically in 16 of the 78 patients (20.5%). A univariate analysis revealed that the prostate-specific antigen (PSA) level at repeat biopsy was higher (P<0.01), the fPSA/tPSA ratio was lower (P=0.04), the total prostate volume was smaller (P=0.01) and the PSA density was higher (P<0.01) in PCa patients than in patients with benign prostatic disease (BPD). Histological inflammation was more frequently observed in BPD patients than in PCa patients (P<0.01). A multivariate analysis revealed that histological inflammation was the only independent predictor of the presence of a malignant lesion on repeat biopsy (odds ratio, 0.027; P=0.01). It must be considered that inflammation may cause a PSA increase in some patients with a negative initial biopsy, leading to unnecessary repeat biopsy.

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Introduction

With the introduction of the serum prostate-specific antigen (PSA) assay in combination with digital rectal examination (DRE) to screen for prostate cancer (PCa), the number of patients undergoing subsequent transrectal ultrasonography (TRUS)-guided needle biopsy has markedly increased (1). In addition, the systematic sextant biopsy technique has become the standard method for prostate biopsy, which has resulted in a significant improvement in the accuracy of PCa diagnosis (2). However, a number of studies have suggested that sextant biopsy may underestimate the presence of malignancy (3,4). Thus, there has been increasing interest in defining more accurate prostate biopsy strategies in order to improve the PCa detection rate. The benefits of increasing the number of biopsy cores and/or expanding the number of regions sampled have been demonstrated previously (5,6); however, it has also been suggested that a 10- to 12-core initial biopsy may miss PCa in almost a third of cases (7,8). Saturation prostate biopsy, which consists of ≥20 cores, has been developed to improve the detection rate of PCa in the context of repeat biopsies, radically altering the general concept of prostate biopsy (9-12).

The decision to conduct a prostate biopsy predominantly depends on the PSA value, which often generates false positive results as this value may be increased by inflammation (13). Our group previously reported that histological prostatic inflammation significantly correlated with the serum PSA level and a negative initial biopsy result (14). Consequently, we hypothesized that asymptomatic prostatic inflammation may cause a persistent PSA increase in patients with a negative initial biopsy, leading to repeat biopsy.

The present study attempted to clarify the association between the risk factors for PCa and PCa detection in a repeat biopsy with a 24-core saturation protocol. Repeat biopsy specimens were evaluated for evidence of histological inflammation by examining the leukocytes as one of the risk factors for PCa.

Materials and methods

Patients. Commencing in December 2010, 24-core repeat biopsies were performed in patients for whom findings aroused

suspicion of PCa despite previous negative prostate biopsies. Such patients included those with any of the following indications for repeat biopsy: PSA >10 ng/ml; free-to-total PSA (fPSA/tPSA) ratio <15%; PSA velocity (PSAV) >0.75 ng/ml/year; abnormal findings on DRE, magnetic resonance imaging (MRI) or TRUS; or atypical small acinar proliferation (ASAP) in the initial biopsy specimens.

The analysis included 78 Japanese patients whose initial biopsy was negative and who consecutively underwent 24-core prostate transperineal needle biopsy as a repeat biopsy between December 2010 and November 2013 at Toyama University Hospital (Toyama, Japan). All patients underwent TRUS to calculate the whole prostate volume. Prostate volume (ml) was calculated using the prostate ellipsoid formula (width x length x height x 0.523). PSA density (PSAD) was calculated by dividing the total PSA (ng/ml) by the prostate volume. The data were retrospectively analyzed. The institutional review board of the University of Toyama (Toyama, Japan) approved the study (#26-34). Due to the retrospective nature of the study, written informed consent was waived. The study conformed to the principles outlined in the Declaration of Helsinki (15).

TRUS-guided systematic biopsy. Biopsies were performed with the patient in a dorsal lithotomy position under spinal anesthesia. TRUS was performed using the Aloka Prosound Alpha 5 SV Ultrasound system and a 5.0/7.5 MHz biplanar probe (Hitachi Aloka Medical, Ltd., Tokyo, Japan). Transperineal biopsies of the prostate were obtained with an 18-gauge spring-loaded biopsy gun (Bard® Max-Core® Disposable Core Biopsy Instrument; C. R. Bard, Inc., Tempe, AZ, USA) under TRUS guidance. Biopsy cores were taken from 24 biopsy locations based on a standardized biopsy scheme (Fig. 1) described by Abdollah *et al* (9), with some modification. Biopsy cores of odd numbers were taken from the apex, whereas cores of even numbers were taken from the base of the prostate. Urethral catheters were routinely inserted following the procedures. In the majority of cases without severe adverse effects, the urethral catheters were removed on the first day and patients were discharged within three days subsequent to the procedure. All biopsy samples were evaluated by the Department of Pathology at Toyama University Hospital using the Gleason scoring system (16). These findings were morphologically evaluated on hematoxylin and eosin stained tissue sections. Histological inflammation of the prostate was defined as infiltration of prostatic biopsy specimens by inflammatory cells, lymphocytes, plasma cells and/or histiocytes (17).

Statistical analysis. Data are presented as the mean ± standard deviation (SD). Variables from the different groups were compared by the Mann-Whitney U-test or Student's *t*-test using StatView version 5 software (SAS Institute, Cary, NC, USA). $P<0.05$ was considered to indicate a statistically significant difference. Independent factors predicting a positive repeat biopsy were identified by a logistic regression analysis.

Results

Patient characteristics. Tables I and II list the characteristics of all 78 patients who underwent repeat prostate biopsies
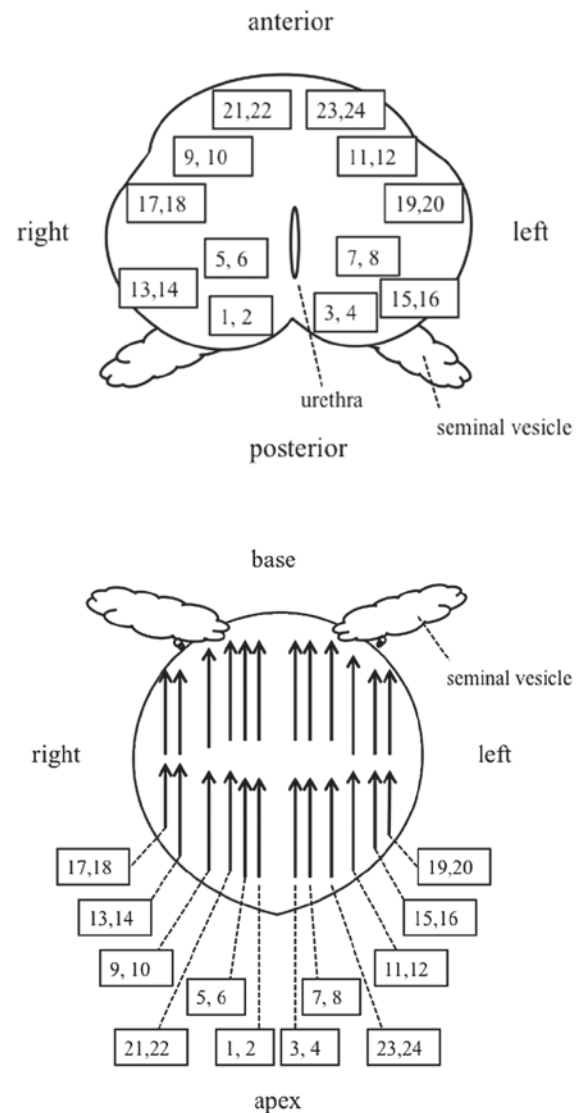

Figure 1. Biopsy cores were taken from 24 locations based on a standardized biopsy scheme (Abdollah *et al*) (9). The biopsy cores of odd numbers were taken from the apex, whereas cores of even numbers were taken from the base of the prostate.

following previous negative biopsies according to the indications described. The indications for biopsies were as follows: a PSA value >10 ng/ml in 43.6% of cases; a fPSA/tPSA ratio <15% in 51.3%; a PSAV >0.75 ng/ml/year in 53.8%; abnormal findings on DRE in 10.2%, TRUS in 26.9% or MRI in 44.1%; and ASAP in previous biopsy specimens in 18.4%. Of the included patients, 19 (24.4%) had a single indication, whilst the remaining 59 (75.6%) had multiple indications. The mean age at the time of repeat biopsy was 68.5±7.0 years and the mean PSA level prior to repeat biopsy was 12.4±10.7 ng/ml. The mean number of previous TRUS-guided needle biopsies was 1.6±1.0 (range, 1-6). Collectively, the 78 patients had experienced a total of 124 previous biopsies, with mean of 10.7±3.5 cores per patient (range, 6-24 cores), sampled via 82 transrectal (66.1%), 13 transperineal (10.4%) and 29 unknown (23.3%) routes.

Cancer detection. PCa was confirmed histologically in 16 of the 78 patients (20.5%), and benign prostatic disease (BPD) was diagnosed in the remaining 62 patients (79.5%) based

Table I. Characteristics of 78 patients who underwent repeat prostate biopsies following previous negative biopsies.

Parameter	n	mean ± SD
Age at diagnosis, years		68.5±7.0
50-59	8	
60-69	33	
70-79	33	
80+	4	
Number of previous negative biopsies		1.60±1.03
1	50	
2	17	
3	7	
≥4	4	
Serum PSA value at repeat biopsy, ng/ml		12.4±10.7
3.0-10.0	44	
10.1-20.0	24	
20.1-50.0	9	
50.1-100.0	1	
fPSA/tPSA ratio, %		15.6±9.3
5.0-15.0	40	
15.1-30.0	22	
30.1-50.0	4	
Not measured	12	
Prostate volume, ml		47.3±19.0
20.0-40.0	35	
40.1-60.0	27	
60.1-100.0	14	
>100.0	2	
PSA density, ng/ml/ml		0.32±0.41
0.050-0.150	23	
0.151-0.50	46	
>0.50	9	
PSA velocity, ng/ml/year		0.63±16.27
<0	11	
0-0.750	25	
0.751-5.000	28	
>5.000	14	
Abnormal findings on DRE		
Yes	8	
No	70	
Abnormal findings on TRUS		
Yes	21	
No	57	
Abnormal findings on MRI		
Yes	34	
No	43	
Not assessed	1	

Table I. Continued.

Parameter	n	mean ± SD
ASAP in initial biopsy specimens		
Yes	11	
No	67	

SD, standard deviation; PSA, prostate-specific antigen; fPSA/tPSA, free-to-total PSA; DRE, digital rectal examination; TRUS, transrectal ultrasonography; MRI, magnetic resonance imaging; ASAP, atypical small acinar proliferation.

on the repeat biopsies. Table II shows the clinical parameters of the PCa and BPD patients. A univariate analysis revealed that the PSA value at repeat biopsy, the fPSA/tPSA ratio, the prostate volume and the PSAD were significantly associated with the repeat biopsy outcome. PSA at repeat biopsy was higher (P<0.01), fPSA/tPSA ratio was lower (P=0.04), total prostate volume was smaller (P=0.01) and PSAD was higher (P<0.01) in patients with PCa compared with BPD patients. Furthermore, histological inflammation was more frequently observed in BPD patients than PCa patients (P<0.01). Unexpectedly, the differences between the PCa and BPD patients were not significant for abnormal findings on DRE, MRI or TRUS. The presence of ASAP in the initial biopsy specimens was also not associated with the outcome of the repeat biopsy.

Table III demonstrates results of the multivariate analysis of predictive variables for the presence of prostate cancer on repeat biopsy. The value of these factors as predictors of PCa detection on repeat biopsy was subsequently analyzed using a logistic regression analysis. The variables entered into the model were PSA at repeat biopsy, fPSA/tPSA ratio, prostate volume, PSAD and presence of histological inflammation. Among these factors, histological inflammation was the only independent predictor for the presence of a malignant lesion on repeat biopsy (odds ratio, 0.027; P=0.01).

Characteristics of prostate cancer patients diagnosed by repeat biopsies. Table IV lists the characteristics of all 16 patients diagnosed with PCa. Of these 16 patients, 14 (87.5%) had localized disease and 2 (12.5%) had metastasis. The clinical stages were T1c, T2a and T2b in 4 (25%), 10 (62.5%) and 2 (12.5%) patients, respectively. The Gleason scores were 3+3, 3+4 and ≥4+4 in 6 (37.5%), 3 (18.8%) and 7 (43.8%) patients, respectively.

Of the 16 cases, 2 were compatible with the widely used criteria for predicting clinically insignificant PCa, consisting of T1c, PSA ≤10 ng/ml, Gleason score ≤6 and <50% cancer involvement in any core (18). Of these, 1 patient was subsequently determined to have significant cancer. The PSA level, the clinical stage, and the Gleason score of this patient were 5.73 ng/ml, T1cN0M0, 3+3, respectively, and 3/24 cores were positive for cancer. When the patient was subsequently treated with radical retropubic prostatectomy (RRP), pT2c significant disease and a Gleason score of 4+5 in the prostatectomy specimen were determined. By contrast, the other patient was confirmed to have clinically insignificant cancer. The detailed

Table II. Clinical parameters of the PCa and BPD patients.

Parameters	All (n=78)	PCa (n=16)	BPD (n=62)	P-value
Age at diagnosis, years[a]	68.5±7.0	69.5±7.7	68.2±6.8	0.54
Number of previous biopsies[a]	1.60±1.03	1.62±1.31	1.59±0.96	0.92
Serum PSA value at repeat biopsy, ng/ml[a]	12.4±10.7	18.9±18.2	10.8±7.0	<0.01
fPSA/tPSA ratio, %[a]	15.6±9.3	11.1±5.2	16.8±9.9	0.04
Prostate volume, ml[a]	47.3±19.0	36.5±17.3	50.0±18.5	0.01
PSA density, ng/ml/ml[a]	0.32±0.41	0.62±0.71	0.24±0.23	<0.01
PSA velocity, ng/ml/year[a]	0.63±16.27	4.62±5.81	50.0±17.9	0.27
Abnormal findings on DRE[b]	10.2% (8/78)	12.5% (2/16)	9.6% (6/62)	0.76
Abnormal findings on TRUS[b]	26.9% (21/78)	31.2% (5/16)	25.8% (16/62)	0.66
Abnormal findings on MRI[b]	44.1% (34/77)	56.3% (9/16)	40.9% (25/61)	0.28
ASAP in initial biopsy specimens[b]	14.1% (11/76)	18.8% (3/16)	12.9% (8/62)	0.55
Histological inflammation[b]	47.4% (37/78)	6.3% (1/16)	58.0% (36/62)	<0.01

[a]Data presented as mean ± standard deviation; [b]data presented as % (n). PCa, prostate cancer; BPD, benign prostatic disease; PSA, prostate-specific antigen; fPSA/tPSA, free-to-total PSA; DRE, digital rectal examination; TRUS, transrectal ultrasonography; MRI, magnetic resonance imaging; ASAP, atypical small acinar proliferation.

Table III. Results of the multivariate analysis of predictive variables for the presence of prostate cancer on repeat biopsy.

Factor	P-value	Relative hazard ratio	95% confidence interval
Serum PSA value at repeat biopsy	0.64	0.87	0.50-1.51
fPSA/tPSA ratio	0.34	0.93	0.82-1.07
Prostate volume	0.80	0.98	0.86-1.12
PSA density	0.47	571	1.5×10^{-5}-2.1×10^{10}
Histological inflammation	0.01	0.027	0.001-0.54

PSA, prostate specific antigen; fPSA/tPSA, free-to-total PSA.

clinical findings of this patient were as follows: PSA at repeat biopsy, 4.48 ng/ml; clinical stage, T1cN0M0; Gleason score, 3+3; and 1/24 cores positive for cancer. This patient subsequently underwent RRP; however, the pathological stage was pT0.

Adverse effects. Major complications associated with biopsy that required subsequent inpatient intervention occurred in 3 patients (3.8%): 2 patients experienced urinary retention requiring temporary catheterization; the other patient experienced severe septicaemia with *Escherichia coli* that required intravenous antibiotic administration, and this patient made a full recovery two weeks after the procedure.

Discussion

To date, PSA measurement has been the most valuable criterion upon which to base a diagnosis of PCa (19). The benefits of increasing the number of biopsy cores and/or expanding the number of regions sampled have been demonstrated in several studies. Pepe *et al* (5) compared 12-core with 18-core biopsies, and identified significant differences in the detection rates, which were determined to be 35 and 51%, respectively. Ficarra *et al* (6) demonstrated a correlation between a

detection rate and a core count. Initial biopsy protocols have been gradually extended to improve the detection rate through more representative sampling of all areas in the prostate (5,6).

Repeat saturation biopsies have also been developed in an effort to reduce the high false-negative rate of initial biopsies. Several studies introduced modified techniques for repeat biopsy involving an increased number of cores in order to sample the entire gland. Merrick *et al* (10) demonstrated a positive correlation between the detection rate and core count in a 50-core repeat biopsy series. In a study by Borboroglu *et al* (11), an average of 22.5 cores was obtained (depending on prostate size) in patients with previous negative sextant biopsies, and cancer was identified in 30% of patients. Similarly, Stewart *et al* (12) obtained an average of 23 cores throughout the whole prostate of patients who had previously had negative sextant biopsies, and cancer was detected in 34% of cases.

To date, there are no established procedures for repeat saturation biopsy. Abdollah *et al* (9) evaluated 332 patients who underwent a transrectal 24-core repeat biopsy compared with 140 who underwent a 24-core transperineal biopsy, and concluded that transperineal and transrectal saturation biopsies have a similar PCa detection rate in patients undergoing

Table IV. Characteristics of 16 patients diagnosed with prostate cancer by repeat biopsy.

Parameters	n
Serum PSA value at repeat biopsy, ng/ml	
>3-10	6
>10-20	5
>20-50	4
>50-100	1
Clinical T stage	
T1c	4
T2a	10
T2b	2
Clinical N/M stage	
N0M0	14
N1M0	1
N0M1	1
Gleason score	
3+3	6
3+4	3
>4+4	7
Number of positive cores	
1-2	6
3-4	6
5-10	2
10-15	2

PSA, prostate-specific antigen; T, tumor; N, node; M, metastasis.

a repeated saturation biopsy. On the other hand, a number of studies have demonstrated that tumors subsequently identified upon repeat biopsy are most frequently found in the anterior prostate and/or transition zone (20,21). In the present study, a transperineal route was used for repeat biopsy as the majority of the patients had undergone initial biopsies via the transrectal approach. Geometric considerations dictate that the apex and the anterior region of the prostate are better sampled via the transperineal route, while the base is better sampled via the transrectal approach. However, in the current study, the sites in which the cancer was detected were distributed uniformly, and there did not seem to be any trends in the sampling site (data not shown).

The detection of clinically insignificant PCa is an inevitable risk of repeat biopsy (14). The majority of patients in the current study were considered to have significant cancer. In particular, 2 patients (12.5%), whose cancer was not detected in the initial biopsy, had metastatic disease. Thus, the present saturation protocol has demonstrated generally favorable results. However, 1 patient (6.25%) was considered to have insignificant cancer in the current study. It is supposed that clinically insignificant disease is more likely to be detected with more extensive sampling, which is why extensive sampling remains controversial. A study by Zaytoun et al (22) suggested that almost a third of PCa detected in the repeat saturation biopsy was clinically insignificant. Conversely, a number of reports have demonstrated that saturation repeat biopsy may not increase the detection of clinically insignificant tumors (23,24).

Discriminating between PCa and BPD is difficult, particularly in patients with initial negative biopsies (25,26). The serum PSA level at repeat biopsy is one of the strongest predictors of a positive repeat biopsy (25,26). However, it is generally recognized that PSA lacks specificity for PCa detection (14). Several clinically available PSA-associated factors, including the free-to-total PSA ratio, PSAD and PSAV, have been examined in an attempt to improve the efficiency of repeat biopsies; however, the value of these parameters remains the subject of considerable debate.

The significance of the prostate volume for the detection of PCa is thought to differ between the initial and repeat biopsies (27-29). For initial biopsies, previous studies have reported a decreasing probability of detecting cancer when the same number of biopsy cores is taken from glands of increasing size, indicating a potential benefit of increasing the number of core samples in larger glands (27). In addition, several studies have demonstrated an inverse correlation between the PCa detection rate in repeat saturation biopsies and the prostate volume; that is, there was a lower PCa detection rate in large prostates compared with smaller glands (28,29).

Consistent with previous reports (9,11,22,26,28,30), the current study demonstrated that a higher PSA level at repeat biopsy, lower prostate volume and elevated PSAD, were associated with a higher rate of PCa detection. In the context of repeat biopsy, intensive saturation biopsies should be recommended in patients with a smaller prostate volume or increased PSAD.

DRE is indispensable for PCa screening, and is a meaningful indication for an initial biopsy (14). Abnormal findings on MRI and TRUS are also significant predictors of PCa, particularly in the initial biopsy setting (31). By contrast, in the repeat biopsy setting, the present study demonstrated that the incidence of abnormal findings on DRE, TRUS and/or MRI in patients with PCa was not significantly higher than that in patients with no evidence of cancer. We hypothesize that this was due to a selection bias, i.e. patients with well-visualized cancers had already been diagnosed in the initial biopsies, and a biased population therefore remained in the repeat biopsy setting.

Previously, the presence of high-grade prostatic intraepithelial neoplasia (HGPIN) and/or ASAP was demonstrated to be a useful predictor of the repeat biopsy outcome (28,32). The role of HGPIN as a precursor of PCa remains controversial. According to recent guidelines, a HGPIN diagnosis no longer represents an indication for immediate repeat biopsy (33). By contrast, ASAP indicates the presence of suspicious glands with insufficient cytological or architectural atypia for a definitive diagnosis of prostatic adenocarcinoma (30). In the present study, the incidence of PCa was not significantly higher in patients with ASAP. This may have been due to the limited number of patients with ASAP in this cohort, and so these findings are not conclusive. Further studies are required to clarify the prognostic value of the presence of ASAP.

Serum PSA levels may be increased not only in patients with PCa, but also in those with non-malignant conditions, including benign prostatic hyperplasia, prostatic manipulation and even asymptomatic and chronic prostatitis (19,34).

Prostatic inflammation is detected in some biopsy specimens, and subclinical prostatitis is known to cause increases in the serum PSA level (35-37). Morote *et al* (13) retrospectively studied 284 patients with no evidence of cancer on sextant ultrasound-guided biopsies. Benign tissue without inflammation was detected in 23.2% of the patients, whilst 68.3% had chronic prostatitis and 8.4% had acute prostatitis, suggesting that prostatic inflammation is common in specimens of BPD. Our group previously reported that histological prostatic inflammation was significantly correlated with the serum PSA level and a negative biopsy result (14). Similarly, Terakawa *et al* (38) reported that histological inflammation in initial biopsy specimens was associated with a negative initial biopsy outcome in men with a serum PSA level of 10-50 ng/ml.

In the current study, histological inflammation was found to be independently associated with a lower risk of PCa, even on repeat biopsy. Asymptomatic inflammation may cause increased PSA in some men, leading to repeat prostate biopsy (14). A more selective repeat biopsy strategy would help avoid unnecessary repeat biopsies in men with an increased PSA level.

The limitations of this study include its retrospective design, its being performed at a single center using a single arm, and the relatively small number of patients. The results may have been biased by the patient selection for repeat biopsy. The probability of detecting clinically insignificant PCa is still uncertain based on this study due to the limited number of patients; further prospective studies with large populations are necessary in order to clarify this issue. Nevertheless, even with these limitations, the current results suggest that saturation repeat biopsy may be effective in patients for whom PCa is persistently suspected despite a negative initial biopsy.

Although numerous trials have been published, the number and most appropriate location of the cores, in addition to the timing and the criteria to perform repeat biopsy, remains matters of debate. However, saturation biopsy appears to be effective in patients with a persistent suspicion of PCa following a negative initial biopsy. A relatively small prostate volume in a patient with an elevated PSA level (i.e. a high PSAD) may be a useful indicator of the results of a repeat saturation biopsy. Furthermore, patients with asymptomatic inflammation appear to have a lower risk of PCa. It should be considered that inflammation may cause persistent elevated PSA in patients with a negative initial biopsy, leading to unnecessary repeat biopsy.

Acknowledgements

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