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ORIGINAL ARTICLE

Detection rate of clinically insignificant prostate cancer increases with repeat prostate biopsies

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To analyze if clinically insignificant prostate cancer (CIPC) is more frequently detected with repeat prostate biopsies, we retrospectively analyzed the records of 2146 men diagnosed with prostate cancer after one or more prostate biopsies. The patients were divided into five groups according to the number of prostate biopsies obtained, e.g. group 1 had one biopsy, group 2 had two biopsies and group 3 had three biopsies. Of the 2146 patients diagnosed with prostate cancer, 1956 (91.1%), 142 (6.6%), 38 (1.8%), 9 (0.4%) and 1 (0.1%) men were in groups 1, 2, 3, 4 and 5, respectively. Groups 4 and 5 were excluded because of the small sample sizes. The remaining three groups (groups 1, 2 and 3) were statistically analyzed. There were no differences in age or prostate-specific antigen level among the three groups. CIPC was detected in 201 (10.3%), 28 (19.7%) and 9 (23.7%) patients in groups 1, 2 and 3, respectively ($P<0.001$). A multivariate analysis showed that the number of biopsies was an independent predictor to detect CIPC (OR=2.688 for group 2; OR=4.723 for group 3). In conclusion, patients undergoing multiple prostate biopsies are more likely to be diagnosed with CIPC than those who only undergo one biopsy. However, the risk still exists that the patient could have clinically significant prostate cancer. Therefore, when counseling patients with regard to serial repeat biopsies, the possibility of prostate cancer overdiagnosis and overtreatment must be balanced with the continued risk of clinically significant disease.
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INTRODUCTION

The widespread use of prostate-specific antigen (PSA) level as a screening tool for diagnosing prostate cancer (PCa) along with the improvements in prostate biopsy yield with extended and saturation techniques has led to improved detection of PCa at earlier stages.[1] However, a phenomenon called 'stage migration' has arisen, which has led to two clinical issues for urologists.

The first issue is the progressive emergence of clinically insignificant PCa (CIPC) over the last two decades. CIPC is a low-grade, small-volume, and organ-confined PCa that is unlikely to progress to clinical or biologic significance without treatment.[2] Thus, the diagnosis of CIPC is regarded as an overdiagnosis, defined as the diagnosis of cancers that would not be clinically diagnosed during normal life.[3] The overtreatment of CIPC is also debatable because the morbidity and decreased quality of life due to local treatment of PCa can have such a negative impact. Therefore, the possibility of overdiagnosis and overtreatment of CIPC needs to be considered in the clinical setting.

The second issue is the debate regarding serial prostate biopsy. There is no definitive guideline available on the management of patients with stable or rising PSA level after a negative prostate biopsy. The most salient question surrounding the debate of serial biopsy is whether 'missed' PCa truly impacts patient survival.

Therefore, it is important for urologists to minimize the detection of PCa that does not require treatment and to maximize the detection of clinically significant PCa (CSPC). We considered a possible association between the number of repeat prostate biopsies and detection rate of CIPC. A few studies have evaluated the association of repeat biopsy and the detection of CIPC.[4–7] However, those studies had limitations such as small sample size, unclear results, or merely showing a certain trend. We conducted the present study to determine the detection rate of CIPC with serial prostate biopsies.

MATERIALS AND METHODS

Data collection and study design

After receiving approval by the institutional review board of Samsung Medical Center (IRB File No. 2012-02-005), we retrospectively reviewed and analyzed the medical records of included patients. Between November 1994 and July 2011, a total of 8371 patients underwent transrectal ultrasound-guided prostate biopsy at our institution. The indications for prostate biopsy were an elevated PSA level and/or the presence of palpable nodules on digital rectal examination (DRE). The indications for repeat prostate biopsy were as follows: (i) persistently elevated PSA level; (ii) persistently palpable nodules on DRE; (iii) atypical small acinar proliferation on initial biopsy; and (iv)

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multifocal high-grade prostatic intraepithelial neoplasia on initial biopsy. A 10-core biopsy was performed before November 2009, and the biopsy protocol has been changed to standardized 12-core biopsy since November 2009. The conventional Gleason grading system was used before January 2006, and the modified Gleason grading system declared by the 2005. International Society of Urological Pathology Consensus Conference[8] has been used since January 2006. If abnormal lesions suspicious for malignancy were detected, additional targeted biopsies could be performed. Clinical T staging was conducted by DRE and/or prostate magnetic resonance imaging (MRI), and the metastatic status was assessed by chest X-ray and whole-body bone scans. Of the 8371 patients, 2225 (26.6%) had been diagnosed with prostate adenocarcinoma. Of the 2225 men with PCa, 79 had taken 5-alpha reductase inhibitors. Because many studies have reported that 5-alpha reductase inhibitors decreased PSA level and may affect Gleason grading,[9–12] the 79 men were excluded. Therefore, 2146 men were finally included in this study. Variables such as age, PSA level, prostate volume (PV) measured by transrectal ultrasound, clinical T stage, biopsy Gleason score, numbers of total and positive biopsy cores, and maximal tumor volume of one positive core were recorded. As researchers in our institution conducted most of the clinical T staging of PCa with MRI, we assessed the clinical T stage by MRI preferentially. In case a patient did not undergo prostatic MRI, we assessed the clinical T stage by DRE. All parameters were those measured at the time of the initial or repeat biopsies. We divided those 2146 cancer patients into five groups according to the number of biopsies that had been performed (e.g. group 1 were those who were diagnosed with PCa on initial biopsy, and group 3 were those who were diagnosed with cancer after three consecutive biopsies). The ratio of CIPC to CSPC and other clinical variables were analyzed and compared.

Definition of CIPC

The Epstein criteria, the most commonly used criteria for CIPC, were first defined in 1994 and updated in 2004.[13,14] The updated Epstein criteria consist of a PSA density (PSAD) $\leqslant 0.15$ ng ml^{-1} g^{-1}, a Gleason score $\leqslant 6$, fewer than three positive cores and $<50\%$ of cancer involvement in any core. However, multiple selection criteria or nomograms for CIPC have been reported, and many of them use PSA level as an additional factor to define CIPC.[15–17] The 2011 National Comprehensive Cancer Network practice guidelines for PCa also added PSA level to the conventional Epstein criteria as a very low risk group of localized PCa.[18] Thus, we defined CIPC in our study as follows: (i) PSA level <10 ng ml^{-1}; (ii) PSAD <0.15 ng ml^{-1} g^{-1}; (iii) biopsy Gleason score $\leqslant 6$; (iv) fewer than three positive biopsy cores; and (v) maximal tumor volume of each core $\leqslant 50\%$. The diagnosis of CIPC should meet all the above criteria.

Statistical analysis

The Kruskal–Wallis and Mann-Whitney *U* tests were performed to compare the interval variables. Chi-square and Fisher's exact tests were conducted to compare the nominal variables among the different groups. The Pearson's correlation test was performed to evaluate the correlation between the PV and the maximal tumor volume of each positive core. For the multivariate analysis, the binary logistic regression test was used to determine the independent predictors for detecting CIPC. All analyses were performed using SPSS v.19.0 (SPSS Inc., Chicago, IL, USA), and $P<0.05$ was considered statistically significant.

RESULTS

The 8371 patients had a variable number of prostate biopsies. The cancer detection rates were 27.2% in group 1 (one biopsy), 14.5% in group 2 (two biopies), 21.8% in group 3 (three biopies), 33.3% in group 4 (four biopies) and 33.3% in group 5 (five biopies) (**Table 1**). Of the 2146 patients with PCa, 1956 (91.1%), 142 (6.6%), 38 (1.8%), 9 (0.4%) and 1 (0.1%) men were in groups 1, 2, 3, 4 and 5, respectively.

Groups 4 and 5 were excluded from the following statistical analysis because of the small sample sizes. The remaining three groups (groups 1, 2 and 3) were further analyzed and compared statistically.

Table 2 shows the clinicopathological characteristics among the three groups. The age and PSA level were not different among the three groups. The mean biopsy interval was 25.2 (range: 0.4–149.3) months between group 1 and group 2, and 20 (range: 0.7–49.9) months between group 2 and group 3. There was no significant difference between the two biopsy intervals ($P=0.771$). As we serially diagnosed PCa from group 1 to group 3, various characteristics showed certain trends. Increasing PV was observed, but parameters including PSAD, biopsy Gleason score, number of positive cores and maximal tumor volume of each positive core decreased. There was a statistically significant trend toward increasing lower clinical T stage and decreasing higher clinical T stage with serial biopsies ($P=0.001$). Lastly, the detection rate of CIPC significantly increased with diagnosis of PCa from group 1 to group 3 ($P<0.001$). To evaluate a difference of outcomes between the 10- and 12-core biopsies, we conducted comparative statistical tests as a subgroup analysis with those who had 10- and 12-core biopsies. The result showed that more CIPC was detected in 12-core groups than 10-core groups ($P<0.001$) (**Table 3**). Simultaneously, the 12-core group had significantly lower PSA level ($P<0.001$), PSAD ($P<0.001$) and biopsy Gleason grading ($P=0.047$).

Using the univariate and multivariate analysis, we determined that there were independent predictors to detect CIPC. Age, PSA level and PV were each significant predictors to detect CIPC in the multivariate analysis (**Table 4**). Simultaneously, the number of biopsies was also an independent predictor for CIPC ($P<0.001$) with an odds ratio (OR) of 2.688 (95%CI: 1.506–4.797) for group 2 and 4.723 (95% CI: 1.673–13.329) for group 3. The biopsy interval was not a predictive factor to diagnose CIPC in univariate analysis (OR=0.998, 95% CI: 0.982–1.014). Because group 1 had no data for biopsy intervals, the multivariate analysis failed to show the influence of biopsy interval on predicting CIPC. Therefore, we performed the univariate and multivariate analyses among the groups 2 and 3, and the result showed that

Table 1 Distribution of prostate biopsies and their cancer detection rates

	Group 1	*Group 2*	*Group 3*	*Group 4*	*Group 5*
Total number of patients, *n*	7191	976	174	27	3
Cancer detection, *n* (%)	1956 (27.2)	142 (14.5)	38 (21.8)	9 (33.3)	1 (33.3)
CSPC, *n* (%)	1755 (89.7)	114 (80.3)	29 (76.3)	9 (100)	1 (100)
CIPC, *n* (%)	201 (10.3)	28 (19.7)	9 (23.7)	0 (0)	0 (0)

Abbreviations: CIPC, clinically insignificant prostate cancer; CSPC, clinically significant prostate cancer.

Table 2 Clinicopathological characteristics among the three positive biopsy groups

	Group 1 (n=*1956*)	*Group 2* (n=*142*)	*Group 3* (n=*38*)	P
Age, year (range)[a]	67.0 (37–91)	66.5 (49–84)	68.0 (51–86)	0.144[d]
PSA, ng ml^{-1} (range)[a,b]	8.21 (0.16–8400.93)	7.30 (1.43–104.91)	8.06 (0.72–103.73)	0.149[d]
Prostate volume, g (range)[a]	30.5 (10–380)	34.0 (16–137)	37.6 (16–153)	<0.001[d]
PSA density, ng ml^{-1} g^{-1} (range)[a]	0.30 (0.01–394.29)	0.24 (0.03–1.86)	0.23 (0.03–2.41)	<0.001[d]
Clinical T stage, *n* (%)				0.001[e]
cT_1	284 (14.5)	15 (10.6)	7 (18.4)	
cT_2	987 (50.5)	92 (64.8)	28 (73.7)	
cT_3	576 (29.4)	31 (21.8)	2 (5.3)	
cT_4	109 (5.6)	4 (2.8)	1 (2.6)	
Biopsy Gleason score, *n* (%)				<0.001[e]
⩽6	697 (35.6)	72 (50.7)	24 (63.2)	<0.001[e]
=7	568 (29.0)	50 (35.2)	9 (23.7)	0.220[e]
⩾8	691 (35.3)	20 (14.1)	5 (13.2)	<0.001[e]
No. of total biopsy cores (range)[a]	10 (1–15)	10 (7–13)	10 (6–14)	0.016[d]
No. of positive biopsy cores (range)[a]	4 (1–12)	2 (1–12)	1.5 (1–9)	<0.001[d]
Maximal tumor volume of each positive core, % (range)[a]	50 (0.5–100)	27.5 (2.5–100)	20 (2.5–90)	<0.001[d]
Interval from prior biopsy, month (range)[c]	NA	25.2 (0.4–149.3)	20.0 (0.7–49.9)	0.771[f]
CIPC, *n* (%)	201 (10.3)	28 (19.7)	9 (23.7)	<0.001[e]

Abbreviations: CIPC, clinically insignificant prostate cancer; NA, not applicable; PSA, prostate-specific antigen.
[a] Median values;
[b] The PSA level described above was that measured at the time of the initial or repeat biopsies;
[c] Mean value.
[d] Kruskal–Wallis test.
[e] Chi-square and Fisher's exact test.
[f] Mann–Whitney *U* test.

biopsy interval was not an independent predictor for detecting CIPC (OR=0.989, 95% CI: 0.962–1.016) (**Table 5**).

DISCUSSION

There have been a few studies reporting the association of repeat prostate biopsy and the detection of CIPC.[4–7] Lujan *et al.*[4] reported a non-significant trend toward an increased rate of clinically localized tumors with repeat prostate biopsies. Although Tan and colleagues[6] failed to reveal a significant association between detection of CIPC and number of repeat biopsies, they concluded that PCa diagnosed with a repeat biopsy had smaller tumor volume. More recently, Resnick *et al.*[7] showed a significantly increased detection rate of CIPC with repeat biopsies after analyzing patients who underwent radical prostatectomy (RP). However, this study needs further investigation due to a potential selection bias since it included only RP cases.

In our series, the proportion of CIPC to the total PCa cases was 10.3%, 19.7% and 23.7% in group 1, 2 and 3, respectively. This increasing trend in the detection rate of CIPC was statistically significant. On our multivariate analysis, age, PSA level and PV were significant predictors to detect CIPC. Of these variables, PSA level was a reasonable

Table 3 A subgroup analysis to compare between 10- versus 12-core prostate biopsies

	10-core (n=*940*)	*12-core* (n=*562*)	P *value*
Groups, *n* (%)			0.013[d]
Group 1	885 (94.1)	514 (91.4)	
Group 2	42 (4.5)	44 (7.8)	
Group 3	13 (1.4)	4 (0.7)	
Age, year (range)[a]	67.0 (38–91)	67.0 (37–91)	0.721[c]
PSA, ng ml^{-1} (range)[a,b]	8.11 (1.02–7750.00)	5.85 (0.16–7255.00)	<0.001[c]
Prostate volume, g (range)[a]	29.9 (11–208)	31.4 (10–316)	0.056[c]
PSA density, ng ml^{-1} g^{-1} (range)[a]	0.30 (0.04–192.79)	0.20 (0.005–394.29)	<0.001[c]
Biopsy Gleason score, *n* (%)			0.047[d]
⩽6	364 (38.7)	234 (41.6)	0.276[d]
=7	287 (30.5)	177 (31.5)	0.729[d]
⩾8	289 (30.7)	151 (26.9)	0.114[d]
No. of positive biopsy cores (range)	3 (1–10)	3 (1–12)	0.772[c]
Maximal tumor volume of each positive core, % (range)	50.0 (0.5–100)	47.5 (1–100)	0.482[c]
CIPC, *n* (%)	95 (10.1)	102 (18.1)	<0.001[d]

Abbreviations: CIPC, clinically insignificant prostate cancer; PSA, prostate-specific antigen.
[a] Median values.
[b] The PSA level described above was that measured at the time of the initial or repeat biopsies.
[c] Mann–Whitney *U* test.
[d] Chi-square and Fisher's exact test.

Table 4 Univariate and multivariate analysis of variables to predict clinically insignificant prostate cancer among the three positive biopsy groups

Variable	*Univariate*		*Multivariate*	
	OR (95% CI)	P[a]	*OR (95% CI)*	P[a]
Biopsy number	—	<0.001	—	<0.001
One biopsy	1	—	1	—
Two biopsies	2.145 (1.383–3.325)	0.001	2.688 (1.506–4.797)	0.001
Three biopsies	2.710 (1.265–5.806)	0.010	4.723 (1.673–13.329)	0.003
Biopsy interval	0.998 (0.982–1.014)	0.766	NA[b]	—
Total biopsy core	1.329 (1.218–1.450)	<0.001	1.019 (0.913–1.137)	0.734
Age	0.963 (0.948–0.979)	<0.001	0.975 (0.953–0.998)	0.033
PSA	0.615 (0.565–0.670)	<0.001	0.442 (0.390–0.500)	<0.001
Prostate volume	1.012 (1.006–1.018)	<0.001	1.082 (1.069–1.095)	<0.001

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; PSA, prostate-specific antigen.
[a] Binary logistic regression analysis.
[b] Not applicable because one biopsy group had no biopsy interval data.

factor because it was one of the components of the definition of CIPC in our study design. PV significantly increased with repeat biopsies. Because the PSA level did not change significantly with serial repeat biopsies, the increasing trend of PV might lead to the decreasing trend of PSAD and the number of positive cores. The trend toward increasing PV with serial biopsies could also explain why these patients had higher than normal PSA levels even if cancer was minimal. Many studies have reported that patients with repeat biopsies had high total PV.[7,19–21] A study by Raventós *et al.*[22] also revealed that PV was an independent predictor for diagnosing CIPC, as in our study. Therefore, it is suggested that the PV definitively affected the detection of CIPC. However, in our multivariate analysis, the number of biopsy sessions itself was also an independent predictor for CIPC. Thus, the number of repeat biopsy might have affected the detection of CIPC regardless of PV. To evaluate if the trend toward decreasing maximal tumor volume of each positive core with serial biopsies was affected by the increasing trend of PV, we conducted the Pearson's correlation test. The result showed a significant, but nearly negligible correlation between the two variables (P=0.017, r=0.051) (data not shown).

Biopsy protocol/design is also an important factor. The impact of total biopsy core on CIPC diagnosis is controversial. Singh and associates[23] reported that the risk of CIPC increased by increasing the number of cores from 6 to 12. On the other hand, Meng *et al.*[5] reported that taking more cores did not appear to increase the risk of detecting CIPC. In our subgroup analysis, patients with 12-core biopsy had significantly more CIPC compared to those with 10-core biopsy. The 12-core group had also significantly lower PSA level and biopsy Gleason grading. Thus, there is a possibility that lower PSA and Gleason score in 12-core group could have resulted in more significant detection of CIPC. In the logistic regression model, the total biopsy core was a significant predictor for CIPC in univariate analysis (P<0.001), but not in multivariate analysis (P=0.734). Considering that PV might have affected this result, we performed the multivariate analysis after removing the PV covariate, and the result showed that the total biopsy core still did not significantly predict CIPC (OR=1.074, 95% CI: 0.976–1.183, P=0.145) (data not shown).

It is noteworthy that the number of biopsies alone was an independent predictor for detecting CIPC. The risk of CIPC diagnosis increased with increasing number of biopsies. We believe that this result solidifies the association of repeat biopsies and detection of CIPC.

In our study, there was a statistically significant trend toward increasing lower and decreasing higher clinical T stages with serial biopsies, and the result was similar to other relevant studies.[4,5,7,21,24] Also, there was a trend toward increasing lower and decreasing higher Gleason grade with repeat biopsies. In the literature, there is a controversy on the association of the Gleason grade and the number of repeat biopsies. Studies have reported that Gleason grades were becoming more favorable with repeat biopsies as in our study,[7,21,24] while there were studies which have reported no differences of Gleason grades with repeat biopsies.[4,5,25] However, the results that all these studies reported were merely observational, and there were no clear explanations on the association of either clinical T stage or Gleason grades and repeat biopsies. It is thought that this trend might be one of the reasons to explain the association of CIPC detection and repeat biopsies. However, this needs to be validated with well-designed prospective trials.

Table 5 Univariate and multivariate analysis of variables to predict clinically insignificant prostate cancer among positive repeat biopsy groups

Variable	*Univariate*		*Multivariate*	
	OR (95% CI)	P[a]	*OR (95% CI)*	P[a]
Biopsy number	—	0.592	—	0.803
Two biopsies	1	—	1	—
Three biopsies	1.264 (0.538–2.970)	0.592	1.177 (0.326–4.249)	0.803
Biopsy interval	0.998 (0.982–1.014)	0.773	0.989 (0.962–1.016)	0.404
Total biopsy core	1.421 (1.113–1.813)	0.005	1.242 (0.873–1.768)	0.229
Age	1.010 (0.958–1.064)	0.721	1.029 (0.953–1.111)	0.472
PSA	0.648 (0.535–0.786)	<0.001	0.410 (0.284–0.592)	<0.001
Prostate volume	1.029 (1.009–1.049)	0.004	1.100 (1.059–1.143)	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio; PSA, prostate-specific antigen.
[a] Binary logistic regression analysis.

Bastian *et al.*[26] postulated that most patients with CIPC do not die of PCa, with reporting about 2%–6% of patients with CIPC dying of the disease. Therefore, the diagnosis and treatment of CIPC can be considered to be exaggerated. In terms of overdiagnosis, the possible morbidity associated with prostate biopsy should be considered. A recent study revealed that the hospitalization rate was 6.9% within 30 days of prostate biopsy, and this was substantially higher than the 2.7% in the control population.[27] In terms of overtreatment, the quality of life of patients undergoing RP is to be considered. Recently, a Swedish group[28] reported that those who underwent RP more frequently reported distress compared to the men assigned to watchful waiting.

One important point is that CSPC was diagnosed in 76.9% of patients after the third positive biopsy in our study. This indicates that serial repeat prostate biopsies still detect more CSPCs than CIPCs. Therefore, the possibility of CIPC overdiagnosis and overtreatment must be balanced with the risk of a CSPC when counseling patients about repeat biopsies.

Our study has several limitations including its retrospective design and performance at a single institution. There is the possibility of selection bias associated with the referral patterns to a tertiary medical center. The most significant limitation is that our study excluded the group 4 and 5 because of small sample sizes. However, **Table 1** shows that, although those cases were limited, the groups having four or five positive biopsies diagnosed CSPCs in all of the patients. We admit that this finding could call into question our conclusion in the present study. However, a certain trend toward increasing CIPC diagnosis from group 1 to group 3 was clearly significant. Therefore, we think that this could suggest a possible association with CIPC detection rate and serial prostate biopsies.

In conclusion, patients undergoing multiple repeat prostate biopsies are more likely to be diagnosed with CIPC than those who only undergo one biopsy. However, the risk still exists that the patient could have CSPC. Therefore, when counseling patients with regard to serial repeat biopsies, the possibility of PCa overdiagnosis and overtreatment must be balanced with the continued risk of CSPC. Further investigation with a prospective design is required to elucidate the association of CIPC and repeat prostate biopsies.

AUTHOR CONTRIBUTIONS

SSJ conceived and designed the study. SHJ, BCJ, SIS, SSJ, HML and HYC collected the data. BP and SHJ performed the studies. BP did the statistical analyses and wrote the manuscript with input from all co-authors. All authors revised the manuscript for intellectual content and approved the final version.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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