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Original Article

Comparison of two commonly used methods in measurement of cancer volume in prostate biopsy

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Abstract: Currently, cancer volume in prostate biopsy samples is commonly calculated as linear length of carcinoma divided by total core length and reported as percentage involvement. The measurement of the linear length of carcinoma can be problematic particularly when there are two or more separate foci of carcinoma in a single core. There are two most methods commonly used by practicing pathologists. One method is to measure the exact linear extent of each discrete carcinoma foci in millimeters and then add up the linear length (the exact method, E method). The other method is to measure the core length encompassing all carcinoma foci including the intervening benign prostate tissue (glands and/or stroma) (the scattered method, S method). In this study, we used digital pathology to compare the site-specific and overall cancer volumes measured with the E and S methods and analyzed their correlation with the cancer volume in the corresponding prostatectomy specimens. Our results showed that prostate-cancer volumes estimated with both E and S methods on biopsy samples positively correlate with cancer volume at radical prostatectomy. However, the cancer volumes measured with both E and S methods in the majority of biopsy samples were significantly larger than that in prostatectomy ($P<0.001$). The E method more closely predicts the cancer volume compared to the S method. The overall cancer volume is better than site-specific cancer volume at biopsy in predicting cancer volume at prostatectomy.

Keywords: Exact method, scattered method, prostate biopsy, cancer volume

Introduction

Prostate cancer (PCa) volume in biopsy cores is one of the important parameters for risk stratification and clinical management of patients [1]. Clinically, cancer volume >50% in a single core excludes a patient that meets all other criteria for active surveillance [2, 3]. Accurate assessment of tumor volume becomes critical in the clinical management of PCa patient and is demanded in pathology practice. In pathology practice, cancer volume is commonly reported as percentage of involvement, which is calculated by dividing linear length of carcinoma with total core length. Estimation of tumor volume can be particularly problematic when there are two or more foci of carcinoma in a single core. There are two commonly used methods in measuring PCa volume in biopsy samples. One method is to visually measure the percentage of each discrete foci of carcinoma in a single core and then sum up each percentage of cancer foci in linear length. The other method is to visually measure the core length encompassing all cancer foci in a single core including the intervening benign tissue (glands and stroma). However, there is no consensus among practicing pathologists how the PCa volume should be measured in biopsy samples [4]. Previous studies addressing this issue have had mixed results, where some authors found that measuring only the discrete foci of cancer while excluding the intervening benign stroma and glands is more accurate, while other authors propose that inclusion of the benign stroma and glands in discontinuous foci correlate better with surgical margin status [5], The heart of the issue lies with the interpretation of what discrete foci of tumor with intervening benign stromal tissue represent. Some pathologists view that it is the same tumor in the biopsy just in and out of the plane of section, while others believe that they represent multiple separate tumor foci. For those that

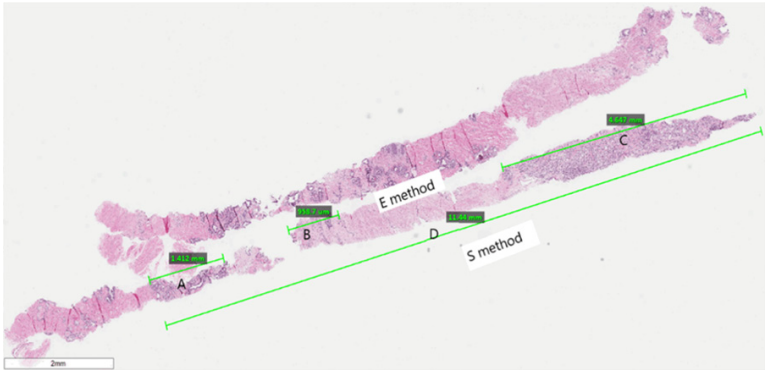

Figure 1. Illustration of E and S methods using Aperio ImageScope software. E method: Tumor volume (MIOSC) = (1.412+0.959+4.647)/14.44 = 48.6%. Total tumor volume = 24.3%. S method: Tumor volume (MIOSC) = 11.44/14.44 = 79.2%. Total tumor volume = 39.6%.

believe it is the same tumor in and out of the plane of section, they include the intervening stroma and benign glands in their estimation of tumor volume. These two methods can produce significantly different tumor volume estimation in core biopsy samples with separate tumor foci. Thus, an important parameter that determines whether some patient meets criteria for active surveillance depends on the pathologists' subjective interpretation regarding which method of tumor volume estimation they prefer. To provide more objective data on which method of estimating tumor volume is most accurate at the time of biopsy, especially when at least two foci of carcinoma are present, we compared the cancer volume measured with the two commonly used methods and analyzed their correlation with the cancer volume in the corresponding prostatectomy specimens using digital pathology in this study.

Materials and methods

Materials

This study is part of a study protocol by approved by the University of Wisconsin Health Science Institutional Review Board (2017-0670-CR001). The prostate biopsy cases selected in this study included primarily biopsy specimens of six-sites (right and left apex, mid and base) and two sites (right and left). For a two-site biopsy, each slide/site had 2-3 cores. For a six-site biopsy, each slide/site had 5-6 cores. A total of 128 prostate biopsy cases were randomly selected for this study from Pathology Archive at the University of Wisconsin-Madison. One representative biopsy slide/site with dominant volume was selected from each of the 78 of the 128 patients. Each selected slide/site had at least two separate foci of volume-dominant prostate cancer in a single core and had 2-6 cores per slide. The tumor foci were considered separate foci only when they were at least 0.5 mm apart. Cases with a tumor volume difference of equal or greater than 5% (equivalent to accumulative non-cancer spacing equal or greater than 0.5 mm between cancer foci) between the two methods were included for analysis. Fifty concordant cases (39%) (with a difference of tumor volume from 0 to <5%) were excluded for analysis.

Methods

Biopsy slides were scanned with Aperio CS2 (Leica Biosystem). Prostate cancer volume (%) was measured with the two methods commonly used by practicing pathologists using digital slides and Aperio ImageScope software: the S and E methods. The S method calculates the ratio of the core length (mm) encompassing all the tumor foci including the intervening uninvolved benign tissue to the total core length (mm). The E method calculates the ratio of the sum of each discrete cancer foci in length (mm) to the total core length (mm) (**Figure 1**). The total site-specific cancer volume and maximal involvement of a single core (MIOSC) by each method were compared and correlation of cancer volume in biopsy samples to that in corresponding prostatectomy specimens was analyzed. Normalized total cancer volume (overall cancer volume, case-specific) was also calculated by taking benign cores in other sites into consideration. A normalizing factor for each case was determined by cancer positive core number divided by total core number. At our institution, tumor volume of prostatectomy specimens was estimated manually by tumor area relative to tissue size per slide in all the slides submitted. We considered ±4% of cancer volume at prostatectomy as the margin of error.

Table 1. Case Information (n = 78)

Age (yrs)	Mean (Range)	61 (46-74)
Race (n)	CA	71
	AA	6
	AsA	1
Gleason Grade Group (n)	1	12
	2	42
	3	13
	4	7
	5	4

AA = African American, AsA = Asian American, CA = Caucasian American.

Table 2. Case frequency in three categories by E and S methods

Method	Under-estimated n (%)	Matched n (%)	Over-estimated n (%)
E-method	3 (4)	18 (23)	57 (73)
S-method	2 (3)	0 (0)	76 (97)
nE-method	13 (17)	30 (38)	35 (45)
nS-method	5 (6)	17 (22)	56 (72)

E: exact, S: scattered, n: normalized, Underestimate: biopsy cancer volume less than that of prostatectomy by more than 5%, Matched: biopsy cancer volume within ±4% of that of prostatectomy, Over-estimated: biopsy cancer volume more than 5% of that of prostatectomy.

Analysis

The Microsoft Excel and IBM SPSS Statistics (version 22) were used for the analysis. Student *t*-test and one-way ANOVA were used to compare the means. A *p*-value of less than 0.05 was considered significant. The correlation between the cancer volumes measured with E and S methods and estimated cancer volume at prostatectomy was analyzed with Spearman's correlation coefficient.

Results

The patient population consists of predominantly Caucasian men with a mean age of 61 at time of biopsy. The slides included PCa of different Gleason scores/Grade groups (**Table 1**).

We first divided the biopsy measurements with E and S methods in three categories: underestimated, matched and overestimated. Underestimated was defined as biopsy cancer volume less than that of prostatectomy by more than 5%, matched was defined as biopsy cancer volume within ±4% of that of prostatectomy, and overestimated was defined as biopsy cancer volume more than 5% of that of prostatectomy. We found that biopsy cancer volumes (dominant site-specific and overall) measured by both E and S methods tended to overestimate the true cancer volume in the prostate. Overall, E-method showed more matched and less overestimated cancer volume compared to S method in predicting cancer volume in prostatectomy (**Table 2**).

We then compared the E and S methods by dividing the 78 cases into two types of cases: average cases and outliers. The average cases were those with total cancer volume or normalized total (overall) cancer volume measured by both E and S method at biopsy equal or greater than that estimated at prostatectomy. Outliers were cases with total cancer volume or normalized total (overall) cancer volume measured by either E or S method at biopsy less than that estimated at prostatectomy. We compared the biopsy cancer volumes by E and S methods in each category.

1. Comparison of Site-Specific Cancer Volumes by E and S Methods: Among the 78 cases, 68 were average cases and 10 were outliers. Although the cancer volume (total and MIOSC) measured by both the E and S methods was positively correlated at prostatectomy, we found that both methods tended to overestimate cancer volume (**Figure 2A**, **2B**). The comparison of mean cancer volume (total and MIOSC) at biopsy by E and S methods for all 78 cases showed that there was significant difference (P<0.001) in cancer volume between the two methods (**Table 3**; **Figure 3A**). The cancer volume (total and MIOSC) measured by the E method correlated better than the S method with the cancer volume at prostatectomy for both average cases and the outliers (**Tables 4** and **5**; **Figure 3B** and **3C**). Within the 10 outlier cases, only 3 cases could be considered true outliers as the difference between the tumor volume at prostatectomy vs. biopsy exceeded greater than the margin of error (±4%) (Table S1).

We then further stratified the 68 average cases by the differences of cancer volume measurement between the two methods into 3 groups to examine the degree of overestimation of each of the two methods. Group 1 represented

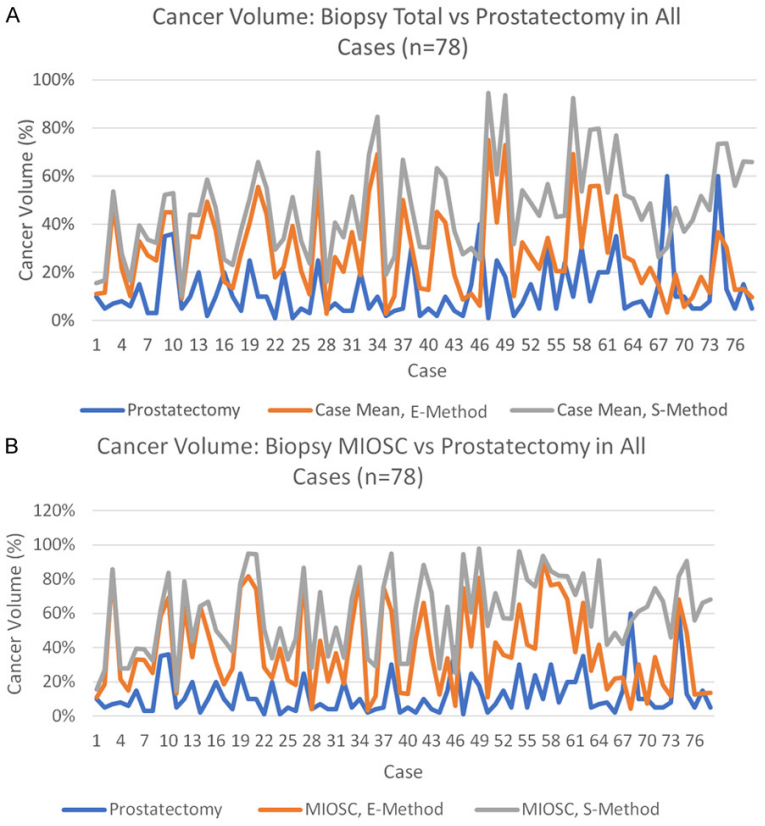

Figure 2. Estimation of PCa volume by E and S methods at biopsy vs. prostatectomy. Both methods positively correlate with PCa volume at prostatectomy, though both methods overestimate PCa volume in the biopsy, when evaluated by either total PCa volume in the biopsy (A) or MIOSC (B).

Table 3. Comparison of cancer volume (%) between E and S methods and between biopsy and prostatectomy in all cases (n = 78)

			Mean ± SD (%)	T-test
Biopsy	Total Involvement	E-method	28±18	[a]P<0.001
		S-method	47±19	
	MIOSC	E-method	39±25	[b]P<0.001
		S-method	60±23	
Prostatectomy	Total Involvement	Estimate	12±12	[c]P<0.001

E = exact, S = scattered, MIOSC = maximal involvement of single core, SD = standard deviation, [a]P: E vs S (total involvement), [b]P: E vs S (MIOSC), [c]P: P vs E (total and MIOSC, respectively) and P vs S (total and MIOSC, respectively).

average cases with a difference of >5-10% prostate cancer volume (equivalent to the accumulative distances between cancer foci of 0.5 to 1 mm), group 2 represented average cases with a difference of >10-20% prostate cancer volume (equivalent to the accumulative distances between cancer foci of >1 to 2 mm), and group 3 represented average cases with a difference of >20% prostate cancer volume (equivalent to the accumulative distances between cancer foci of >2 mm). We found that the greater the accumulative distance between the cancer foci were, the more prominent the exaggeration of the cancer volume was by the S method compared to the E method (**Tables 6**, S1; **Figure 4**).

2. Comparison of Overall (normalized) Biopsy Cancer Volumes by E and S Methods: The overestimation trend remained but at lesser degree in the overall (normalized) cancer volumes measured by both E and S methods. There was still a significant difference in cancer volume measurements between E and S methods (P<0.001). Overall, E method was better in predicting the cancer volume at prostatectomy (**Table 7** and **Figure 5**). Similarly, when dividing the cases into average and outlier cases (Table S2), the E method was superior in predicting cancer volume at prostatectomy than S method in 53 average cases. However, S method was better at predicting cancer volume at prostatectomy in 25 outlier cases (**Table 8**; **Figure 6**).

Discussion

Though PSA, Gleason Grade, pathologic stage, including perineural invasion [6], extraprostatic extension [7], seminal vesicle involvement [8], and surgical margin status [5, 9] are known prognostic parameters with respect to prostate carcinoma at radical prostatectomy, tumor volume has yet to be determined to be a significant independent prognostic factor [10]. Some studies have shown modest correlations of prostate cancer volume to the outcomes previously mentioned [11, 12] while others concluded that cancer vol-

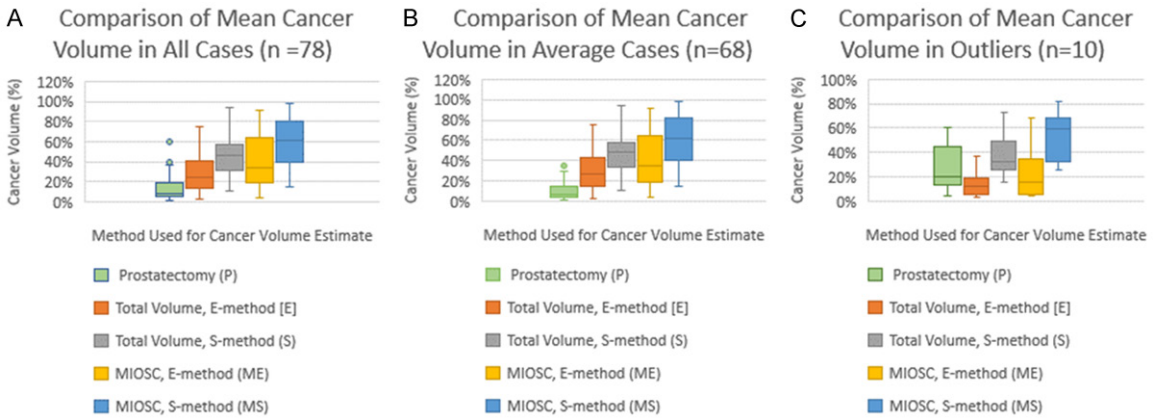

Figure 3. Comparison of the mean PCa volume measured via total volume and MIOSC using both the E and S methods. In all 78 cases, the mean PCa volume, measured by the E method via MIOSC and total volume, correlated better with prostatectomy than the S method (A). The same overall trend is observed in the average cases (B) and within the 10 outlier cases (C).

Table 4. Comparison of cancer volume between E and S methods and correlation between biopsy and prostatectomy in average cases (n = 68)

			Mean ± SD (%)	Pearson R-value (Biopsy vs Prostatectomy)	T-test
Biopsy	Total Involvement	E method	30±18	0.34*	[a]P<0.001
		S method	48±19	0.29*	
	MIOSC	E method	41±25	0.46*	[b]P<0.001
		S method	60±23	0.40*	
Prostatectomy	Total Involvement	Estimate	10±9		[c]P<0.001

E = exact, S = scattered, MIOSC = maximal involvement of single core, SD = standard deviation, [a]P: E vs S (total involvement), [b]P: E vs S (MIOSC), [c]P: P vs E (total and MIOSC, respectively) and P vs S (total and MIOSC, respectively), *P<0.05.

Table 5. Comparison of cancer volume between E and S methods and correlation between biopsy and prostatectomy in outliers (n = 10)

			Mean ± SD (%)	Pearson R-value (Biopsy vs Prostatectomy)	T-test
Biopsy	Total Involvement	E method	13±10	0.36*	[a]P<0.01
		S method	38±18	0.34*	
	MIOSC	E method	23±21	0.34*	[b]P<0.01
		S method	54±20	0.24*	
Prostatectomy	Total Involvement	Estimate	27±10		[c]P<0.01

E = exact, S = scattered, MIOSC = maximal involvement of single core, SD = standard deviation, [a]P: E vs S (total involvement), [b]P: E vs S (MIOSC), [c]P: P vs MIOSC, S-method (MS), *P<0.05.

ume is not an independent predictor following prostatectomy [13]. Nevertheless, consensus conferences such as the 2009 ISUP [14], the recent ICCR [15], and CAP guidelines and protocol recommend tumor quantitation on biopsy and radical prostatectomy specimens (Prostate Radical Prostatectomy 4.0.4.0, 2019). However, there is no consensus among pathologists regarding the measurement and subsequent reporting of estimated tumor volume (%) at radical prostatectomy or biopsy [16]. Various methods have been used for tumor quantitation in previous studies, including morphometric analysis [17], ocular micrometers, and simple visual estimation [18]. Of the methods available, the two most common methods

Table 6. Comparison of cancer volume between E and S methods and correlation between biopsy and prostatectomy in the three groups of average cases (n = 68)

			Group 1 (n = 19)		Group 2 (n = 24)		Group 3 (n = 25)	
			Mean ± SD	T-test	Mean ± SD	T-test	Mean ± SD	T-test
Biopsy	Total volume	E-method [E]	31±15	[a]P<0.001	32±20	[a]P<0.001	29±18	[a]P<0.001
		S-method (S)	38±16		47±20		56±17	
	MIOSC	E-method (ME)	42±25	[b]P<0.001	41±25	[b]P<0.001	41±24	[b]P<0.001
		S-method (MS)	51±25		59±24		70±18	
Prostatectomy		Prostatectomy (P)	12±10	[c]P<0.001	8±8	[c]P<0.001	12±9	[c]P<0.001

E = exact, S = scattered, MIOSC = maximal involvement of single core, SD = standard deviation, [a]P: E vs S (total involvement), [b]P: E vs S (MIOSC), [c]P: P vs E (total and MIOSC, respectively) and P vs S (total and MIOSC, respectively).

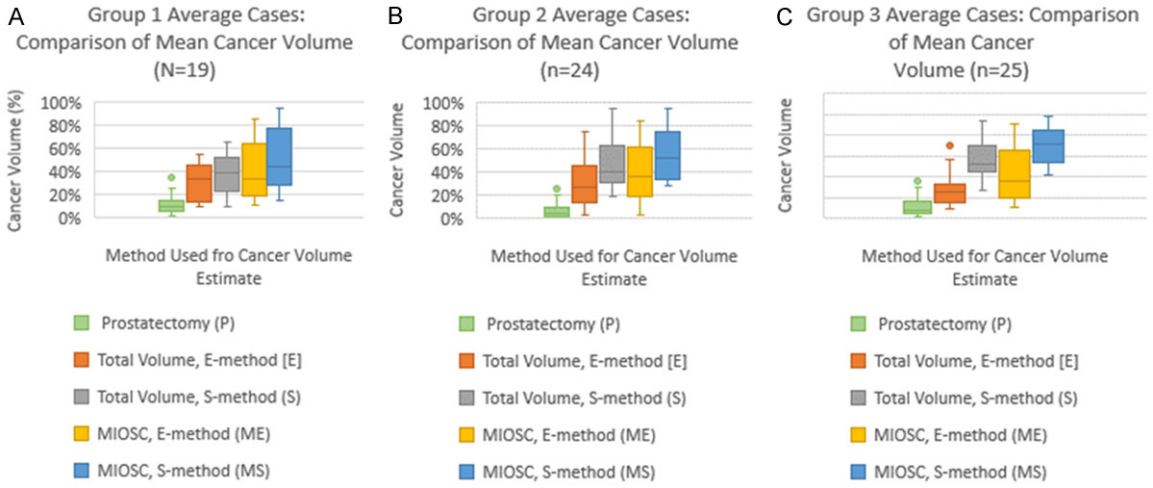

Figure 4. Comparison of the mean cancer volume following stratification of average cases into three groups based on differences of cancer volume measurement between the two methods. In all three groups, the mean cancer volume correlated better via the E method (A-C). However, the greater the average distance between the cancer foci, the greater the exaggeration of cancer volume was observed by the S method.

Table 7. Comparison of mean cancer volume (%) between biopsy (normalized) and prostatectomy and between nE and nS methods in all cases (n = 78)

	Method	Mean ± SD (%)	T-test
Biopsy	nE-method	17±15	[a]P<0.001
	nS-method	28±18	
Prostatectomy	Manual Estimate	12±12	[b]P = 0.02, [c]P<0.001

nE = normalized exact, nS = normalized scattered, SD = standard deviation, [a]P: nE vs nS, [b]P: P vs nE, [c]P: P vs nS.

used by practicing pathologists for cancer volume estimation at biopsy involve measuring the maximal tumor diameter. At biopsy, this is accomplished by measuring the linear extent of tumor in millimeters, either by including the intervening benign prostate (glands and/or stroma) between foci of tumor or by excluding the intervening benign prostate (glands and/or stroma) and measuring discrete foci of tumor and dividing by the total core length in millimeters. A survey to practicing pathologist found that both methods have robust favorability in responses for the two methods used by pathologists [4].

Within the literature, there are multiple studies where carcinoma was measured on prostate biopsies with correlations to outcomes such as pathological stage and/or biochemical recurrence [11, 12, 19]. However, different criteria for measurement were used, including maximum length in a single core, percentage of positive biopsies, greatest percentage of carcinoma in a single core, extent of carcinoma in millimeters, among

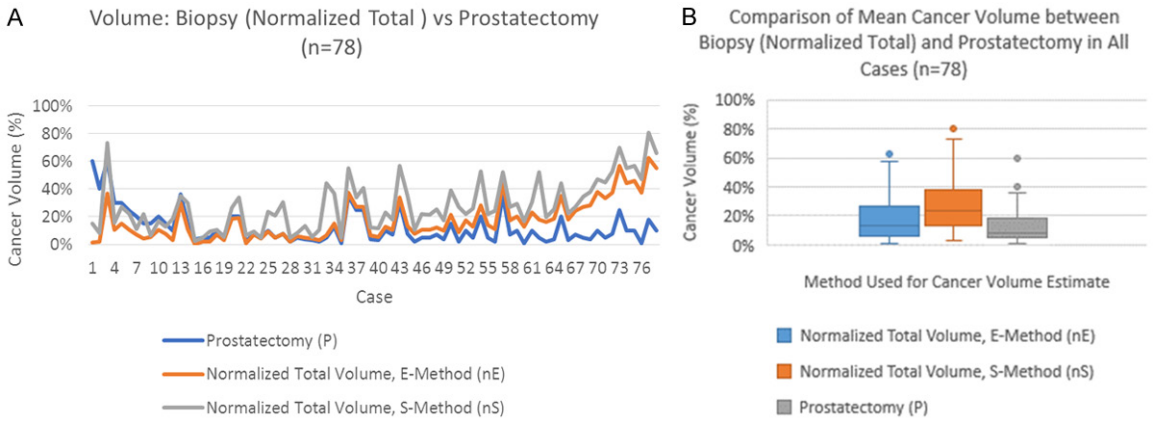

Figure 5. Though overestimation by both E and S methods remained when including benign prostatic tissue in the normalized cancer volume measurement, the E method better predicts cancer volume at prostatectomy: line graph (A) and boxplots (B).

Table 8. Comparison of mean cancer volume (%) between biopsy (normalized) and prostatectomy and between nE and nS methods in average (n = 53) and outlier cases (n = 25)

		Method	PCa Volume Mean ± SD (%)	T-test
Biopsy	Average Case	nE-method	21±15	[a]P<0.001
		nS-method	32±18	
	Outliers	nE-method	9±9	[b]P<0.01
		nS-method	18±15	
Prostatectomy (Pr)	Average Cases	Manual Estimate	9±9	[e-pr]P<0.001, [s-pr]P<0.001
	Outliers		19±16	[e-pr]P<0.01, [s-pr]P = 0.38

nE = normalized exact, nS = normalized scattered, SD = standard deviation. PCa volume comparison between methods: [a]P: nE vs nS in average cases, [b]P: nE vs nS in outliers, [e-pr]P: nE vs Pr, [s-pr]P: nS vs Pr.

others [9, 11, 19-22]. In the studies that measured the linear extent of carcinoma, some measured the linear extent of carcinoma in millimeters, without specifying how discontinuous foci of cancer were accounted for [21]. Other studies considered discontinuous foci as a single focus of carcinoma and included the intervening benign glands and/or stromal tissue [11, 12, 22]. The lack of consensus in measuring tumor extent in the biopsy in multiple studies evaluating tumor volume may have contributed to the discordant results regarding tumor volume in the literature. Some calculated the linear extent of carcinoma using a micrometer and were able to exclude minute areas of benign stroma, as small as 0.1 mm [11, 22]. Lewis et al. concluded that total tumor length was most closely associated with tumor volume [22]. Bismar et al. found strong significance for the prediction of pathologic stage by the tumor extent in core biopsy [11]. However, in both studies, there is no mention of how large areas of discontinuous foci are measured and whether the types of measurements performed would yield the same results in cases with large areas of discontinuous foci. In contrast, Kajikawa et al. found that the length of cancer in the core, measured by summing the individual foci of cancer and excluding the intervening benign stroma, was the best discriminator of small volume carcinoma among other measurements of tumor extent, such as the positive core number, greatest percentage of cancer in a single core, and greatest length of cancer in cores [23]. The previous cases highlight the variability of methods used to address discontinuous foci of cancer in biopsy specimens, though none of them compare which method is superior.

Of the few studies addressing the issue of discontinuous foci, Arias-Stella III et al., found that discontinuous tumor foci in needle core biopsies result from a single large tumor focus inter-

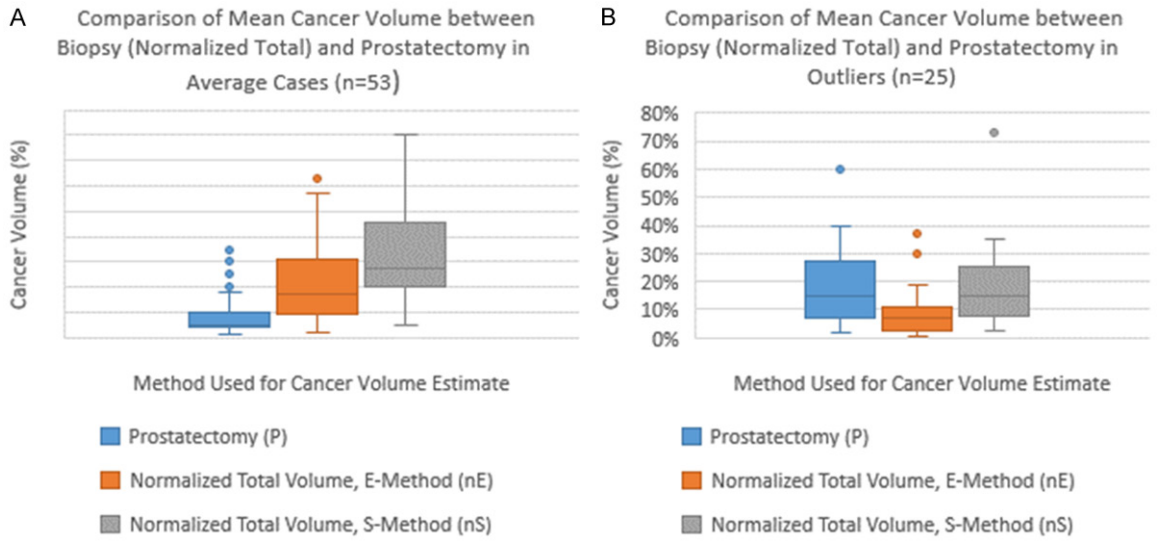

Figure 6. Comparison of normalized total mean cancer volume at biopsy vs. prostatectomy via E and S methods after stratification into average (n = 53) and outlier cases (n = 25). When including the benign prostatic tissue in the normalized cancer volume, the E method was superior in the average cases (A). However, in the outlier cases, the S method better predicted the cancer volume at prostatectomy (B).

sected in two areas of the corresponding region of the prostate gland, and they found that including the intervening stroma correlated with surgical margin status [24]. Similarly, Shchultz et al. and Karram et al. found that discontinuous foci of carcinoma correlated with surgical margin status when the total linear extent of tumor was measured [25, 26]. Additionally, Bsirini et al. also concluded that linear extent of tumor correlates with surgical status margin when they examined sextant biopsies where a single core was involved by prostate cancer [27]. Though the previous studies report correlation between the prostate volume at biopsy and prostatectomy, as expected, they fall short of evaluating which method best correlates with tumor volume, an important factor, whose significance is still in debate.

In this study, we chose to compare the two commonly used methods for tumor volume estimation at biopsy by practicing pathologists to determine which method more closely predicts the prostate volume expected at the time of radical prostatectomy. Biopsies with at least two discontinuous foci of carcinoma were included to specifically address the issue of discontinuous foci. With digital pathology, outlining each focus of tumor, no matter how small or large, is accomplished relatively quickly and accurately. When repeating the measurement to include the intervening benign stroma, there is a significant difference in the resulting tumor volume between the two methods. Thus, the tumor volume reported by the pathologist can dramatically influence clinical management in certain clinical scenarios. For example, in active surveillance protocols for patients with low volume cancer, tumor extent measurements are necessary for patient selection, such that greater than 50% involvement in a single core excludes the patient from the protocol. When comparing both the E and S methods on the same core, different tumor volumes are obtained, based on the definition of linear extent of tumor. Therefore, the same biopsy can result in a tumor volume in a single core that is less than 50% by one method, and greater than 50% by the contrasting method. In this scenario, the pathologists' judgement determines whether the patient will be selected for active surveillance [3]. As active surveillance protocols are increasingly popular, the definition of clinically significant prostate cancer and the criteria for active surveillance have become more concrete [28]. To better serve the patients, it would be imperative for pathologists to agree on a single method for measuring tumor volume on biopsy specimens. Having a consistent measuring method will not only facilitate appropriate patient stratification for clinical management, but also allow for standard-

ization of the tumor measurement in future studies to re-evaluate whether tumor volume is indeed a significant independent prognostic factor. The results of this study show that the E method has a stronger correlation than the S method, and more closely predicts the tumor volume present at radical prostatectomy.

Though various technology is available for more accurate measurements, such as morphometric analysis, the use of an ocular micrometer; digital pathology or artificial intelligence-enabled software, these methods require significant resources to implement readily into daily practice. As such, visual inspection is probably the most practical means of estimation in current practice and each microscope has its set specifics at present. For example, the diameter of a 2× field of Olympus BX41 microscope is 10 mm; a 4× field, 5 mm; a 10× field, 2 mm; a 20× field, 1 mm and a 40× field, 0.5 mm. With a little effort, visual estimation of cancer foci can be done easily once field sizes of the microscope are calibrated. Of course, with the development and increased application of digital pathology and artificial intelligence, cancer measurement at biopsy and prostatectomy will be more precise and accurate in the near future.

Despite of the solid findings, we are aware of the limitations of this study. The cancer volume in prostatectomy specimens was estimated manually by different pathologists on the glass slides, which might not be as accurate and precise as measured with ImageScope on digital slides. However, since that is how it has been done in most pathology practice currently and we used it as a common denominator for comparing E and S method, the subjective nature of the estimated cancer volume in the prostatectomy specimens would not undermine the essence of this study. We noticed that the estimated cancer volume in biopsy samples by both E and S methods were significantly higher than that in prostatectomy specimens. We attribute this phenomenon mainly to one factor: biopsy sampling bias.

A caveat is the scenario of fragmented cores, which applies to any cores less than 1 cm in length. We believe that it is best to report by giving the tumor length measurements and core length measurement, e.g. 0.5 cm core, 0.4 cm length of tumor instead of giving tumor percentage as this may not represent true tumor percentage presence. This is another issue that pathologists need to come up with a consensus on how to report.

As we know, prostate biopsy is done under ultrasound guidance, more recently under MRI/ultrasound fusion-imaging guidance [29, 30], not surprisingly, the cancer tends to be enriched in biopsy samples in general.

At our institution, the prostate biopsy samples have been submitted as a mixed bag of 2 sites (right and left), six sites (right and left apex, mid and base) and more recently up to 10 sites (nodules and right and left apex, mid and base). There is at least 1, up to 6 cores per site (1 to 6 cores per slide). In this study, we selected cases with at least two separate foci of volume-dominant prostate cancer in a single core for cancer volume measurement. Currently, estimation of maximal involvement of a single core and total sample involvement per biopsy site is a standard practice. Although not perfect, our experiment design was, in fact, in keeping with the standard practice.

In conclusion, the E method, calculating the ratio of the sum of each discrete cancer foci in length (mm) to the total core length (mm), was better in the prediction of prostate cancer volume than S method, calculating the ratio of the core length (mm) encompassing all the tumor foci including the intervening uninvolved benign tissue to the total core length (mm), at the time of biopsy. Based on our findings, we believe that consistent use of the E method in practice will generate better data for future studies evaluating tumor volume and facilitate appropriate stratification of patients eligible for active surveillance protocols. Overall (normalized) cancer volume is better than site-specific cancer volume in predicting cancer volume at prostatectomy.

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Disclosure of conflict of interest

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Table S1. Patient Information and Cancer volume (%) Measurement at Biopsy (by E/S Methods) and at Prostatectomy

Case Type		Case Code	Age (y)	Race	Prostatectomy (P)	Case Mean, E-Method (E)	Case Mean, S-Method (S)	Difference			MIOSC, E-Method (ME)	MIOSC, S-Method (MS)	Difference	
								E-S	E-P	S-P			ME-P	MS-P
Outlier cases	True	D0460	53	CA	60%	3%	30%	27%	-57%	-30%	4%	55%	-56%	-5%
		D0228	68	CA	40%	6%	25%	19%	-34%	-15%	6%	25%	-34%	-15%
		D0071	70	CA	60%	37%	73%	37%	-23%	13%	68%	82%	8%	22%
	Marginal	D0529	57	AA	10%	6%	37%	31%	-4%	27%	7%	64%	-3%	54%
		D0524	60	CA	15%	11%	30%	19%	-4%	15%	34%	64%	19%	49%
		D0232	54	AA	20%	16%	25%	9%	-4%	5%	31%	50%	11%	30%
		D0072	56	CA	24%	21%	44%	23%	-3%	20%	39%	76%	15%	52%
		D0089	67	CA	15%	13%	66%	53%	-2%	51%	13%	66%	-2%	51%
		D0570	59	CA	4%	3%	16%	13%	-1%	12%	4%	28%	0%	24%
		D0293	64	CA	20%	19%	34%	15%	-1%	14%	19%	34%	-1%	14%
Average cases	Group 1	D0223	67	CA	10%	11%	16%	5%	1%	6%	11%	16%	1%	6%
		D0547	62	CA	5%	12%	17%	5%	7%	12%	19%	27%	14%	22%
		D0296	65	CA	7%	49%	54%	5%	42%	47%	86%	86%	79%	79%
		D0465	50	CA	8%	22%	28%	6%	14%	20%	22%	28%	14%	20%
		D0146	65	CA	6%	10%	17%	6%	4%	11%	15%	28%	9%	22%
		D0302	74	CA	15%	33%	39%	6%	18%	24%	33%	39%	18%	24%
		D0590	63	CA	3%	27%	34%	7%	24%	31%	33%	39%	30%	36%
		D0226	68	CA	3%	25%	32%	7%	22%	29%	25%	32%	22%	29%
		D0239	57	CA	35%	45%	52%	7%	10%	17%	58%	62%	23%	27%
		D0065	59	CA	36%	45%	53%	8%	9%	17%	69%	84%	33%	48%
		D0197	66	CA	5%	9%	10%	9%	4%	5%	13%	15%	8%	10%
		D0301	52	CA	10%	35%	44%	9%	25%	34%	64%	79%	54%	69%
		D0250	46	AA	20%	35%	44%	9%	15%	24%	35%	44%	15%	24%
		D0133	67	CA	2%	49%	59%	9%	47%	57%	64%	64%	62%	62%
		D0097	65	CA	10%	38%	47%	9%	28%	37%	48%	67%	38%	57%
		D0277	69	CA	10%	13%	23%	10%	3%	13%	19%	44%	9%	34%
		D0497	58	CA	4%	28%	38%	10%	24%	34%	28%	38%	24%	34%
		D0026	57	CA	25%	41%	51%	10%	16%	26%	75%	78%	50%	53%
		D0238	68	CA	10%	55%	66%	10%	45%	56%	82%	95%	72%	85%
	Group 2	D0290	62	CA	10%	44%	55%	11%	34%	45%	74%	95%	64%	85%
		D0400	72	CA	1%	18%	29%	12%	17%	28%	28%	51%	27%	50%
		D0408	57	CA	20%	22%	34%	12%	2%	14%	22%	34%	2%	14%

	D0092	66	CA	1%	39%	51%	12%	38%	50%	39%	51%	38%	50%
	D0599	55	CA	5%	21%	33%	12%	16%	28%	21%	33%	16%	28%
	D0147	65	Asa	3%	11%	24%	13%	8%	21%	18%	45%	15%	42%
	D0217	63	CA	25%	57%	70%	13%	32%	45%	85%	87%	60%	62%
	D0404	63	CA	7%	26%	41%	14%	19%	34%	44%	72%	37%	65%
	D0312	49	CA	4%	20%	35%	14%	16%	31%	20%	35%	16%	31%
	D0070	55	CA	4%	37%	51%	15%	33%	47%	37%	51%	33%	47%
	D0242	69	CA	5%	54%	69%	15%	49%	64%	54%	69%	49%	64%
	D0105	69	AA	10%	69%	85%	15%	59%	75%	82%	87%	72%	77%
	D0073	61	CA	2%	3%	19%	16%	1%	17%	3%	33%	1%	31%
	D0288	57	AA	4%	10%	27%	16%	6%	23%	12%	29%	8%	25%
	D0018	47	CA	5%	50%	67%	17%	45%	62%	75%	75%	70%	70%
	D0191	68	CA	30%	31%	48%	17%	1%	18%	62%	95%	32%	65%
	D0514	68	CA	2%	13%	31%	17%	11%	29%	13%	31%	11%	29%
	D0495	62	CA	5%	13%	30%	18%	8%	25%	13%	30%	8%	25%
	D0490	67	CA	2%	45%	63%	18%	43%	61%	45%	63%	43%	61%
	D0297	57	CA	10%	41%	59%	18%	31%	49%	66%	88%	56%	78%
	D0145	62	CA	4%	19%	37%	18%	15%	33%	35%	72%	31%	68%
	D0579	68	CA	2%	9%	27%	19%	7%	25%	13%	28%	11%	26%
	D0503	58	CA	1%	75%	94%	20%	74%	93%	75%	94%	74%	93%
	D0211	65	CA	25%	41%	61%	20%	16%	36%	41%	61%	16%	36%
Group 3	D0025	69	CA	18%	73%	94%	21%	55%	76%	81%	98%	63%	80%
	D0143	57	CA	2%	10%	32%	22%	8%	30%	11%	53%	9%	51%
	D0258	66	CA	7%	32%	54%	22%	25%	47%	43%	72%	36%	65%
	D0274	57	CA	15%	27%	49%	22%	12%	34%	36%	57%	21%	42%
	D0261	71	CA	5%	21%	44%	22%	16%	39%	34%	57%	29%	52%
	D0024	49	CA	30%	34%	57%	22%	4%	27%	65%	96%	35%	66%
	D0283	55	CA	5%	21%	43%	22%	16%	38%	42%	80%	37%	75%
	D0140	54	CA	10%	69%	92%	23%	59%	82%	91%	94%	81%	84%
	D0035	59	CA	30%	30%	54%	23%	0%	24%	76%	85%	46%	55%
	D0236	55	CA	8%	56%	79%	24%	48%	71%	77%	82%	69%	74%
	D0098	59	CA	20%	56%	80%	24%	36%	60%	68%	82%	48%	62%
	D0426	67	CA	20%	28%	53%	25%	8%	33%	37%	71%	17%	51%
	D0292	65	CA	35%	52%	77%	25%	17%	42%	66%	83%	31%	48%
	D0478	63	CA	5%	26%	52%	26%	21%	47%	26%	52%	21%	47%

D0134	70	CA	7%	25%	51%	26%	18%	44%	42%	91%	35%	84%
D0596	63	CA	8%	16%	42%	26%	8%	34%	16%	42%	8%	34%
D0528	56	CA	2%	22%	49%	27%	20%	47%	22%	49%	20%	47%
D0198	60	CA	15%	15%	26%	27%	0%	11%	23%	42%	8%	27%
D0031	47	AA	10%	19%	47%	28%	9%	37%	30%	61%	20%	51%
D0257	47	CA	5%	10%	42%	32%	5%	37%	34%	75%	29%	70%
D0578	68	CA	5%	18%	52%	34%	13%	47%	18%	67%	13%	62%
D0594	61	CA	8%	12%	46%	34%	4%	38%	12%	46%	4%	38%
D0195	69	CA	13%	30%	74%	43%	17%	61%	49%	91%	36%	78%
D0498	54	CA	5%	13%	56%	43%	8%	51%	13%	56%	8%	51%
D0038	57	CA	5%	10%	66%	56%	5%	61%	14%	68%	9%	63%

AA: African American, AsA: Asian American, CC: Caucasian American, E: cancer volume by E-method at biopsy, MIOSC: maximal involvement of a single core, M: MIOSC, P: cancer volume at Prostatectomy, S: Cancer volume by S-method at biopsy.

Table S2. Normalized cancer volume (%) measurement at biopsy (by E/S methods) and at prostatectomy

Case Type		Case Code	E-case Mean	S-case Mean	Factor for Normalization	Prostatectomy (P)	Normalized Total Volume, E-Method (nE)	Normalized Total Volume, S-Method (nS)	Difference		
									nE-nS	nE-P	nS-P
Outlier cases	True	D0460	3%	30%	0.50	60%	2%	15%	14%	-58.5%	-45.0%
		D0228	6%	25%	0.33	40%	2%	8%	6%	-38.0%	-31.7%
		D0071	37%	73%	1.00	60%	37%	73%	36%	-23.0%	13.0%
		D0191	31%	48%	0.33	30%	10%	16%	6%	-19.7%	-14.0%
		D0035	30%	54%	0.50	30%	15%	27%	12%	-15.0%	-3.0%
		D0072	21%	44%	0.50	24%	11%	22%	12%	-13.5%	-2.0%
		D0408	22%	34%	0.33	20%	7%	11%	4%	-12.7%	-8.7%
		D0089	13%	66%	0.33	15%	4%	22%	18%	-10.7%	7.0%
		D0302	33%	39%	0.17	15%	6%	7%	1%	-9.5%	-8.5%
		D0232	16%	25%	0.67	20%	11%	17%	6%	-9.3%	-3.3%
		D0198	15%	26%	0.50	15%	8%	13%	6%	-7.5%	-2.0%
		D0529	6%	37%	0.50	10%	3%	19%	16%	-7.0%	8.5%
		D0065	45%	53%	0.67	36%	30%	35%	5%	-6.0%	-0.7%
	Marginal	D0524	11%	30%	1.00	15%	11%	30%	19%	-4.0%	15.0%
		D0570	3%	16%	0.17	4%	1%	3%	2%	-3.5%	-1.3%
		D0495	13%	30%	0.17	5%	2%	5%	3%	-2.8%	0.0%
		D0498	13%	56%	0.17	5%	2%	9%	7%	-2.8%	4.3%

	D0223	11%	16%	0.67	10%	7%	11%	3%	-2.7%	0.7%
	D0146	10%	17%	0.33	6%	3%	6%	2%	-2.7%	-0.3%
	D0098	56%	80%	0.33	20%	19%	27%	8%	-1.3%	6.7%
	D0293	19%	34%	1.00	20%	19%	34%	15%	-1.0%	14.0%
	D0073	3%	19%	0.33	2%	1%	6%	5%	-1.0%	4.3%
	D0465	22%	28%	0.33	8%	7%	9%	2%	-0.7%	1.3%
	D0197	9%	10%	0.50	5%	5%	5%	1%	-0.5%	0.0%
	D0031	19%	47%	0.50	10%	10%	24%	14%	-0.5%	13.5%
Average cases	D0257	10%	42%	0.50	5%	5%	21%	16%	0.0%	16.0%
	D0594	12%	46%	0.67	8%	8%	31%	23%	0.0%	22.7%
	D0514	13%	31%	0.17	2%	2%	5%	3%	0.2%	3.2%
	D0547	12%	17%	0.50	5%	6%	9%	3%	1.0%	3.5%
	D0288	10%	27%	0.50	4%	5%	14%	9%	1.0%	9.5%
	D0226	25%	32%	0.17	3%	4%	5%	1%	1.2%	2.3%
	D0143	10%	32%	0.33	2%	3%	11%	7%	1.3%	8.7%
	D0038	10%	66%	0.67	5%	7%	44%	37%	1.7%	39.0%
	D0195	30%	74%	0.50	13%	15%	37%	22%	2.0%	24.0%
	D0400	18%	29%	0.17	1%	3%	5%	2%	2.0%	3.8%
	D0292	52%	77%	0.71	35%	37%	55%	18%	2.1%	20.0%
	D0026	41%	51%	0.67	25%	27%	34%	7%	2.3%	9.0%
	D0211	41%	61%	0.67	25%	27%	41%	13%	2.3%	15.7%
	D0145	19%	37%	0.33	4%	6%	12%	6%	2.3%	8.3%
	D0147	11%	24%	0.50	3%	6%	12%	7%	2.5%	9.0%
	D0277	13%	23%	1.00	10%	13%	23%	10%	3.0%	13.0%
	D0258	32%	54%	0.33	7%	11%	18%	7%	3.7%	11.0%
	D0024	34%	57%	1.00	30%	34%	57%	23%	4.0%	27.0%
	D0596	16%	42%	0.83	8%	13%	35%	22%	5.3%	27.0%
	D0490	45%	63%	0.17	2%	8%	11%	3%	5.5%	8.5%
	D0261	21%	44%	0.50	5%	11%	22%	12%	5.5%	17.0%
	D0283	21%	43%	0.50	5%	11%	22%	11%	5.5%	16.5%
	D0134	25%	51%	0.50	7%	13%	26%	13%	5.5%	18.5%
	D0312	20%	35%	0.50	4%	10%	18%	8%	6.0%	13.5%
	D0274	27%	49%	0.80	15%	22%	39%	18%	6.6%	24.2%
	D0579	9%	27%	1.00	2%	9%	27%	18%	7.0%	25.0%
	D0301	35%	44%	0.50	10%	18%	22%	5%	7.5%	12.0%
	D0478	26%	52%	0.50	5%	13%	26%	13%	8.0%	21.0%

D0426	28%	53%	1.00	20%	28%	53%	25%	8.0%	33.0%
D0599	21%	33%	0.67	5%	14%	22%	8%	9.0%	17.0%
D0528	22%	49%	0.50	2%	11%	25%	14%	9.0%	22.5%
D0239	45%	52%	1.00	35%	45%	52%	7%	10.0%	17.0%
D0404	26%	41%	0.67	7%	17%	27%	10%	10.3%	20.3%
D0297	41%	59%	0.50	10%	21%	30%	9%	10.5%	19.5%
D0092	39%	51%	0.33	1%	13%	17%	4%	12.0%	16.0%
D0140	69%	92%	0.33	10%	23%	31%	8%	13.0%	20.7%
D0578	18%	52%	1.00	5%	18%	52%	34%	13.0%	47.0%
D0133	49%	59%	0.33	2%	16%	20%	3%	14.3%	17.7%
D0070	37%	51%	0.50	4%	19%	26%	7%	14.5%	21.5%
D0250	35%	44%	1.00	20%	35%	44%	9%	15.0%	24.0%
D0590	27%	34%	0.67	3%	18%	23%	5%	15.0%	19.7%
D0296	49%	54%	0.50	7%	25%	27%	3%	17.5%	20.0%
D0242	54%	69%	0.50	5%	27%	35%	8%	22.0%	29.5%
D0497	28%	38%	1.00	4%	28%	38%	10%	24.0%	34.0%
D0097	38%	47%	1.00	10%	38%	47%	9%	28.0%	37.0%
D0018	50%	67%	0.67	5%	33%	45%	11%	28.3%	39.7%
D0236	56%	79%	0.67	8%	37%	53%	15%	29.3%	44.7%
D0217	57%	70%	1.00	25%	57%	70%	13%	32.0%	45.0%
D0290	44%	55%	1.00	10%	44%	55%	11%	34.0%	45.0%
D0105	69%	85%	0.67	10%	46%	57%	11%	36.0%	46.7%
D0503	75%	94%	0.50	1%	38%	47%	10%	36.5%	46.0%
D0025	73%	94%	0.86	18%	63%	81%	18%	44.6%	62.6%
D0238	55%	66%	1.00	10%	55%	66%	11%	45.0%	56.0%