The Clinical Management of Patients With a Small Volume of Prostatic Cancer on Biopsy: What Are the Risks of Progression?

A Systematic Review and Meta-analysis

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Clinically localized prostate cancer is associated with a wide variation in biologic behavior, and men with the less aggressive form of the disease may never develop symptoms. There has been a rise in prostate cancer incidence in countries in which the blood test for prostatic-specific antigen (PSA) is common, and concerns have been expressed that this may be because of the increased detection of indolent disease, subjecting these men to unnecessary treatment and associated side effects. For the current review, the authors conducted a systematic evaluation of the literature regarding the outcomes of men who were diagnosed on the basis of a small volume of cancer in prostatic biopsies. The results indicated that, despite differences in study design and reporting, a significant proportion of patients with microfocal cancer, regardless of how it was defined, had adverse pathologic findings and a significant risk of PSA recurrence after undergoing radical prostatectomy. Biochemical and clinical recurrences also were observed after radiotherapy or watchful waiting. The authors concluded that patients with microfocal carcinoma on biopsy should be advised that their disease is not necessarily "insignificant" and should be counseled accordingly. ***Cancer* 2008; 112:971–81.** © *2008 American Cancer Society.*

KEYWORDS: prostate cancer, biopsy, microfocal disease, insignificant cancer, systematic review, meta-analysis.

Clinically localized prostate cancer is associated with a wide variation in biologic behavior,[1] and men with the less aggressive form of the disease may never develop symptoms. There has been a rise in prostate cancer incidence in countries in which the blood test for prostatic-specific antigen (PSA) is common, and concerns have been expressed that this may be because of the increased detection of indolent disease,[2] subjecting these men to unnecessary treatment and associated side-effects. It has been estimated that only 13% to 22% of men who have prostate cancer detected on the basis of the PSA test would benefit from treatment.[3] Current imaging modalities have a limited ability to observe the extent of prostate cancer within the gland[4] and, thus, cannot be used to monitor tumor behavior or the rate of growth. Histologic grading, in the form of the Gleason score,[5,6] is a well established prognostic factor in prostatic cancer but is most powerful at the extreme ends of the spectrum, with high scores from 8 to 10 associated with aggressive disease.[7] However, most patients present with intermediate Gleason

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scores of 6 or 7. The other commonly used prognostic factors in prostate cancer are clinical stage and the level of serum PSA at presentation, which are indicators of disease extent and/or tumor volume. Nevertheless, clinical staging often underestimates disease extent compared with findings at radical prostatectomy.[8] In addition, PSA is produced by both benign and malignant prostatic epithelial cells, so that serum levels increase in both benign prostatic hyperplasia and cancer, conditions that commonly coexist in older men.[9] Consequently, the combination of clinical stage, serum PSA level at presentation, and Gleason score, particularly in the common, low-to-moderate ranges, can provide only imprecise indications of the likely significance of the finding of prostate cancer for an individual patient. For instance, for a patient with nonpalpable disease, a serum PSA level of 6.5 ng/mL, and a biopsy Gleason score of 7, the chances of having cancer limited to the prostate gland (organ confined) or extraprostatic extension (EPE) appear to be split almost equally (estimated median probability of organ confinement, 54%; 95% confidence interval, 49%–59%).[10] Therefore, other prognostic factors are required, and it has been claimed that the measurement of the extent of carcinoma in diagnostic biopsies is useful to predict the natural course of the disease[1] and guide treatment decisions, although the evidence for this has not been reviewed systematically. If small-volume cancer in the biopsies equates with good outcomes, then this would be a strong argument in favor of watchful waiting for this group of patients. With the rise of PSA-detected prostate cancer in asymptomatic men, this is an increasingly common clinical situation that affects up to 29% of men.[11]

The objective of this review was to systematically evaluate the literature regarding the outcomes of men diagnosed on the basis of a small volume of cancer in prostatic biopsies. Biochemical or clinical recurrence or progression and prostate cancer-specific mortality clearly are the most relevant outcome measures. In addition, however, spread of carcinoma beyond the confines of the prostate (EPE),[12] a large tumor volume,[13] the presence of high Gleason grades, and positive margins[14] have been associated with an increased risk of progressive disease after radical prostatectomy. Indeed, some investigators believe that tumors that do not exhibit any of these features lack the ability to progress during a patient's lifespan and, thus, are "clinically insignificant."[11,15–26] A strong association between microfocal carcinoma on biopsy and "clinically insignificant" disease in the prostatectomy specimen would be a strong argument against actively treating these patients. Therefore, pathologic stage, the tumor volume, and surgical margin status also are valid outcome measures for patients undergoing radical prostatectomy.

MATERIALS AND METHODS

The previously described,[27] overarching, comprehensive search strategy to identify all articles relevant to prostate cancer and pathology was updated to the end of March 2007 and was extended to include Scopus in addition to MEDLINE, Embase, and the Web of Knowledge. To search for additional studies, hand searching of relevant journals was undertaken, and the reference lists of retrieved articles were scrutinized. There were no language restrictions. The resulting bibliographic database (Endnote, version 7) was searched for articles that dealt with tumor extent on biopsy, yielding 238 articles for close reading. Thirty-four articles[11,15–26,28–48] addressed the specific question of the correlation between small-volume ("microfocal") cancer on biopsy and pathologic findings, biochemical or clinical progression, or mortality, and 32 of those articles provided original data.[11,15–26,28–48] Three of those articles were unique: One referred to the number of positive biopsy sites rather than cores,[42] another examined the relation between the number of positive cores on each side (right or left) and the incidence of extraprostatic spread on that side,[48] and the final article took into account both biopsy cancer volume and presenting PSA density in the presentation of results.[46] Those 3 articles were not considered further, because they did not provide data that were comparable with data from the other 29 articles.

Structured data extraction was performed as described previously to define the study design and outcomes reporting[27] that allowed comparison between studies. Data specific to the question under scrutiny included the definition of microfocal carcinoma and the number of biopsy cores obtained, because the diagnosis of microfocal carcinoma may have different implications, depending on how extensively the prostate was sampled.

Data were extracted and checked by 2 reviewers, and any differences were settled through discussion. Authors were contacted for clarification in case of doubt or language restrictions. However, only limited data could be extracted from 3 articles[25,43,45] because of these restrictions.

Where possible, outcome data were pooled to estimate the overall risk associated with small-volume cancer at biopsy (Comprehensive Meta-analysis, Biostat Inc.). A fixed-effect model was used if there was no evidence of heterogeneity at a significance

TABLE 1
Details of the Origin and Characteristics of Patients With Microfocal Carcinoma

Reference	Origin and dates	Age: Median [Mean/Range], y	Clinical stage: No. of patients (%)	PSA: Median [Mean/Range], ng/mL
Allan, 2003[22]	Baltimore, Md: 1999–2000	ND [58/47–70]	Abnormal DRE, 10/54 (18.5)	ND [6.3/0.8–16]
Barthelemy, 1996[15]	Creteil, France: 1989–1994	ND [65.5/50–74]	T1c, 6 (22); T2, 20 (74); T3a, 1 (4)	ND [12.85/1.6–39]
Boccon-Gibod, 2005[20]	Paris, France: 1988–2004	63.8 [ND/44–75]	T1c, 42 (75); T2, 14 (25)	8.5 [ND/11–35]
Bruce, 1996[28]	Lexington, Ky: 1990–94	ND [66.1/45–80]	T1c, 16 (33); T2, 30 (61); T3a, 3 (6); M1, 3 (6)	ND [6.8/0.3–139]
Cupp, 1995[35]	Rochester, NY: ND	ND	T1c or T2	ND
D'Amico, 2000[16]	Boston, Mass: 1988–1998	ND	T1c, 52 (79); T2, 14 (21)	ND [ND/ND-20]
Dietrick, 1995[36]	Stanford, Calif: 1987–1990	ND	ND	ND
Egevad, 1998[29]	Uppsala, Sweden: 1993–1997	ND	ND	ND
Furuya, 2002[30]	Toyama, Japan: ND	ND [66.9/ND]	Clinically localized	ND [8.1/ND]
Gardner, 1998[17]	New York, NY: 1990–1995	ND	ND	ND
Guzzo, 2005[41]	Philadelphia, Pa: 1991–2000	ND	T1c, 52 (51); T2, 50 (49)	ND [ND/0.8–46]
Hoedemaeker, 2003[21]	Rotterdam, the Netherlands: 1994–1997	ND	ND	ND
Huber, 2006[45]	Ried im Innkreis, Germany: 2003–2004	ND	ND	ND
Kakehi, 2000[18]	Nine institutions, Japan: 1990–1998	ND for overall group	T1c	ND for overall group
Kakehi, 2002[31]	Eight institutions, Japan: ND-1997	ND [ND/49–91]	T1c, 47 (60); T2, 27 (35); T3, 4 (5)	ND for overall group
Kim, 2006[23]	Seoul, Korea: 2003–2005	ND	T1c, 21 (66); T2, 11 (34)	ND [6.9/ND]
Lee, 2003[25]	Boston, Mass, 1980–2000	61 [ND/40–76]	T1c, 12 (86); T2a, 2 (14)	5.75 [5.5/0.9–9]
Miyake, 2003[40]	Akashi/Kobe, Japan: 1993–2001	67 [ND/56–76]	T1c, 10 (71); T2a, 4 (29)	4.4 [ND/2.2–48]
Montesino, 2005[43]	Pamplona, Spain: 1992–2004	ND [ND/58–77]	T1c, 19 (95); T2a, 1 (5)	7.4 [8.4/5.2–17.1]
Ochiai, 2005[24]	Houston, Tex: 1997–2003	60 [ND/55–64]	T1c, 58 (79.5); T2a, 15 (20.5)	5 [ND/4–8.1]
Postma, 2005[11]	Rotterdam, the Netherlands: 1994–2003			
RP		62.8 [ND/55–72]	T1c, 65 (63); T2, 36 (35); T3a, 2 (2); Tx, 0 (0)	4.4 [ND/0.9–21]
WW		68.6 [ND/57–77]	T1c, 63 (58); T2, 39 (36); T3, 0 (0); Tx, 6 (6)	3.7 [ND/1.2–24.8]
Ravery, 1996[32]	Paris, France: 1988–1995	ND	Clinically localized	ND
Ravery, 1996[33]	Paris, France: 1988–1995			
RP		ND [64.8/52.3–74.5]	T1a–T1b, 6 (25); T1c, 5 (21); T2, 13 (54)	ND [16.4/1.6–48]
WW		ND [72.5/53–96]	ND	ND [18.4/3.8–44]
Roemeling, 2006[47]	Rotterdam, the Netherlands, 1993–1999	ND [65.7/55–75.3]	T1c, 186 (63.5); T2, 107 (36.5)	ND [4.8/0.3–15]
Taverna, 2006[26]	Milan, Italy: 1998–2004	ND [63.7/50–74]	ND	ND [7.5/ND]
Wang, 1997[37]	Chicago, Ill: 1992–1995	ND	ND	ND
Weldon, 1995[19]	San Francisco/San Rafael, Calif: 1986–1993	67 [ND/42–77]	T1c, 6 (18); T2, 27 (82)	6.5 [ND/1.2–167]
Wills, 1998[38]	Baltimore, Md: ND	ND	Clinically organ confined	ND
Zackrisson, 2004[44]	Goteborg, Sweden: 1995–2000	ND	ND	ND

PSA indicates prostate-specific antigen; ND, no data; DRE, digital rectal examination; T, tumor classification; RP, retroperitoneal prostatectomy; WW watchful waiting.

level of $P = .1$. If heterogeneity was evident, then a random-effects model was used. The results are presented as event rates (risk) in forest plots in which each study is represented by a solid square. Horizontal lines passing through the squares in the plots correspond to the 95% confidence interval, and the overall estimate is represented by a solid diamond at the base of the plot.

RESULTS

All identified studies were retrospective. The origin of the articles and clinical characteristics of the subgroups of patients with microfocal carcinoma are given in Table 1. Four studies reported on men who were diagnosed in the context of the European Randomized Trial for Screening of Prostate Cancer either in the Netherlands[11,21,47] or in Sweden.[44] Details of patient selection are provided in Table 2.

Definition of Small-volume (Microfocal) Cancer on Biopsy

Studies varied in the maximum number of biopsy cores that were allowed to qualify for the definition of microfocal carcinoma and whether or not the maximum length of carcinoma and highest Gleason score were specified. Because the stringency of the definitions may have a bearing on the results, these are presented relative to the number of positive cores allowed and then relative to the increasing values for the maximum length of cancer within the core and the maximum Gleason score, where applicable (Tables 3–6). A single positive core and a cutoff value of 3 mm for the cancer length were the most com-

mon values adopted, but restrictions on Gleason grades varied even among the articles that used these values (Table 4).

Findings in the Radical Prostatectomy Specimen

One question that is relevant to patients is how often, after a diagnosis of microfocal carcinoma, the operation may be considered as over treatment because no tumor is found in the surgical specimen.

TABLE 2
Details of Methods of Patient Identification and Exclusions

Method of patient identification
Review of biopsy database for cases of microfocal carcinoma and patients treated by
Radical prostatectomy[11,15,17,20–23,25,26,37,40,41,43,44]
Watchful waiting[11,31]
Any modality[18,28,47]
Review of radical prostatectomy database to determine preoperative predictors of favorable pathologic findings and report on subgroup with microfocal cancer on biopsy[16,24,29,30,32,34–36,38,42,46]
Criteria for excluding patients
Neoadjuvant therapy[29,30,42,47]
Prior transurethral resection[39,46]
Slides unavailable for review[28,39,42]
Incomplete data on
Clinical stage[37,46]
Preoperative PSA value[37,46]
Biopsy cancer volume[15,32,41,46]
No. of biopsies taken[29,35]
Clinical follow-up[11]

Of the 15 articles that provided complete information in this area, 10 articles[16–18,21–24,40,45,48] reported tumor present in all specimens, and 5 articles[11,25,26,43,47] reported no tumor (pathologic T0 tumor classification) in a small percentage of patients. Overall, there was no tumor reported in 0.8% of patients (7 of 879 patients).

Concentrating on articles with the smallest maximum length of cancer in the positive core (Table 3), 6 studies[16,22,25,26,38,41] reported an EPE that ranged between 4% and 45% (median, 13.5%). The overall estimate of the risk (Fig. 1) that patients with microfocal cancer would present with EPE was 17.6% (95% confidence interval, 7.9%–34.8%). When margin positivity was reported,[16,22,25,28,41] it ranged between 5% and 19% (median, 11%). The combined estimate (Fig. 2) suggested that approximately 12% of men with small-volume disease had positive surgical margins at radical prostatectomy (risk, 11.7%; 95% confidence interval, 8.3%–16.3%). Even when the definition was restricted further by a maximum Gleason score of 6, the proportion of patients with EPE ranged between 4% and 45% (median, 14%)[22,25,33] and between 7%[25] and 9%[22] of patients had positive margins.

By using a previously suggested definition of microfocal carcinoma[49] (Table 4), 7 articles[11,17,19,20,21,23,38] reported variations in the frequency of extraprostatic disease ranging between 0% and 51.5%. The overall

TABLE 3
Correlations of Microfocal Disease on Biopsy With Radical Prostatectomy Findings: One Biopsy Core Positive, Most Restrictive Lengths of Cancer

Reference	Maximum cancer, mm*	GS: Maximum/Median [Mean/Range]	No. of biopsies: Median [Mean/Range]	No. of patients/ No. lost to follow-up	Adverse pathologic features in RP specimen: No. of patients (%)
Allan, 2003[22]	0.5	6 [ND]	ND [6.3/3–8]	54/0	EPE, 2 (4); EPE with tumor ≥0.5 cc and/or GS >6, 18 (33); positive margins, 5 (9)
Lee, 2003[25]	5%	6/ND [ND/5–6]	ND [ND/4–10]	14/0	EPE, 2 (14); positive margins, 1 (7); EPE and/or tumor >0.2 cc and/or GS 4/5 and/or positive margins, 13 (93)
D'Amico, 2000[16]	5%	7	ND: Sextant strategy	66/0	EPE, 4 (6); positive margins, 7 (11); cancer involving at least half of 1 lobe, 61 (92)
Guzzo, 2005[41]	5%	Any/ND [5.4/2–8]	ND	102/ND	EPE, 14 (14); tumor ≥5% of the gland, 51 (50); positive margins, 12 (12)
Wills, 1998[38]	1	6	ND	18/10	EPE, 8 (45): Focal, 5 (28); extensive, 3 (17)
Taverna, 2006[26]	1	Too small for grading	ND [13/8–20]	79/0	EPE, 10 (13); tumor >5% of gland volume and/or GS >6, 48 (61)
Ravery, 1996[32]	<10%	Any [ND]	Sextant strategy	<37/ND	EPE and/or positive margins, ND (12.5)
Dietrick, 1995[36]	2	6/ND, no grade 4 or 5	Sextant strategy	14/ND	Tumor ≥0.5 cc,7 (50)
Bruce, 1996[28]	2	Any [ND]	ND	27/ND†	EPE, 7/27 (26); seminal vesicle invasion, 1/26 (4); positive margins, 5/26 (19); positive lymph nodes, 2/27 (7)

GS indicates Gleason score; RP, radical prostatectomy; ND, no data; EPE, extraprostatic extension.

* Percentages in this column indicate the percentage of the core was positive.

† Surgery was abandoned in 1 patient because of lymph node metastasis on frozen section at operation.

TABLE 4
Correlations of Microfocal Disease on Biopsy With Radical Prostatectomy Findings: One Biopsy Core Positive, Cancer Length Cutoff, 3 mm

Reference	GS: Maximum/Median [Mean/Range]	No. of biopsies: Median [Mean/Range]	No. of patients/ No. lost to follow-up	Adverse pathologic features in RP specimen: No. of patients (%)
Weldon, 1995[19]	6/ND, no grade 4 or 5	ND	33/0	EPE, 17 (51.5); EPE or tumor ≥0.5 cc, 31 (94)
Wills, 1998[38]	6/ND	ND	28/ND	EPE, 9 (32): Focal, 5 (18); extensive, 4 (14)
Hoedemaeker, 2003[21]	6/ND, no grade 4 or 5	6 ± 1		EPE, 3 (9); EPE and/or tumor ≥0.5 cc and/or GS 4 or 5, 12 (40); positive margins, 5 (15)
Postma, 2005[11]	6/6 [ND/4–6], no grade 4 or 5	Sextant strategy	105/13	EPE, 5 (5); positive margins, 15 (14); EPE and/or tumor >0.5 cc and/or GS 4 or 5 and/or margins positive, 38 (35)
Boccon-Gibod, 2005[20]	6 [ND]	ND: Strategy 6 then 10 from 1996	56/0	EPE, ND (8); tumor ≥0.5 cc, 32 (57) tumor ≥0.5; GS ≥ 7, 40 (71); positive margins, 0 (0)
Cupp, 1995[35]	6 [ND]	ND [ND/4–10]	15/ND	Tumor ≥1.0 cc, 13 (87); tumor ≥0.5 cc, 14 (93)
Egevad, 1998[29]	6 [ND]	ND (ND) 8–10	6/ND	ND (all tumors <1 cc)
Gardner, 1998[17]	6/5 [ND/3–6]	ND [ND/6-ND]	83/0	EPE, 22 (26); tumor ≥5% of gland volume, 75 (90); positive margins, 8 (10)
Kim, 2006[23]	6/ND [2–6]	ND	32/0	EPE, 0 (0), tumor ≥0.5 cc and/or GS >6, 27 (84)
Barthelemy,1996[15]	Any/ND [5.44/3–9]	9 [9/9]	16/ND	EPE, 1 (6); tumor >0.5 cc, 13 (81)
Wang, 1997[37]	Any [ND]	ND	42/17	Tumor ≥0.5 cc, 24 (57)

GS indicates Gleason score; RP radical prostatectomy, ND, no data; EPE, extraprostatic extension.

TABLE 5
Correlations of Microfocal Disease on Biopsy With Radical Prostatectomy Findings: One Biopsy Core Positive With No Restriction on Cancer Length

Reference	GS: Maximum/Median [(Mean/Range]	No. of biopsies: Median [Mean/Range]	No. of patients/ No. lost to follow-up	Adverse pathologic features: No. of patients (%)
Miyake, 2003[40]	4/3 [2.9/2–4]	ND	14/0	EPE, 4 (29)
Ravery, 1996[33]	Any/7 [6.5/3–9]	Sextant strategy	24/ND	EPE, ≥7 (29); positive margins, 4 (17)
Ochiai, 2005[24]	Any/ND [ND]	ND [ND/10–11]	73/0	EPE, 5 (7); EPE and/or dominant tumor >0.5 cc and/or margins positive and/or GS 4/5, 42 (57.5)
Huber, 2006[45]	Any/ND [ND]	ND	42/ND	EPE, 5 (12)

GS indicates Gleason score; ND, no data; EPE, extraprostatic extension

TABLE 6
Correlations of Microfocal Disease on Biopsy With Radical Prostatectomy Findings: Up to w Positive Biopsy Cores

Reference	Maximum cancer	GS: Maximum/ Median [Mean]	No. of biopsies: Median [Mean/Range]	No. of patients/ No. lost to follow-up	Adverse pathologic features: No. of patients (%)
Montesino, 2005[43]	5 Malignant glands	Any/ND	ND	20/ND	EPE, 1 (5); tumor ≥5% of prostate or multifocal, 17 (85)
Zackrisson, 2005[44]	Total, 3 mm	Any/ND	ND	60/ND	Tumor ≥0.5 mL, 40 (67)
Furuya, 2002[30]	50% Of any core	6/ND [4.4]	ND	19/0	EPE, 2 (11); tumor ≥0.5 cc, 8 (53)
Kakehi, 2000[18]	50% Of any core	6/5 [ND]	ND [ND/6–8]	48/0 or 42/4	EPE, 12/48 (25); tumor ≥0.5 cc, 22/42 (52)
Roemeling, 2006[47]	Any	6/ND, no grade 4/5	Sextant at least	131/0 or 118/13	EPE, 8/131 (7); tumor ≥0.5 mL, 34/118 (29)

GS indicates Gleason score; ND, no data; EPE, extraprostatic extension.

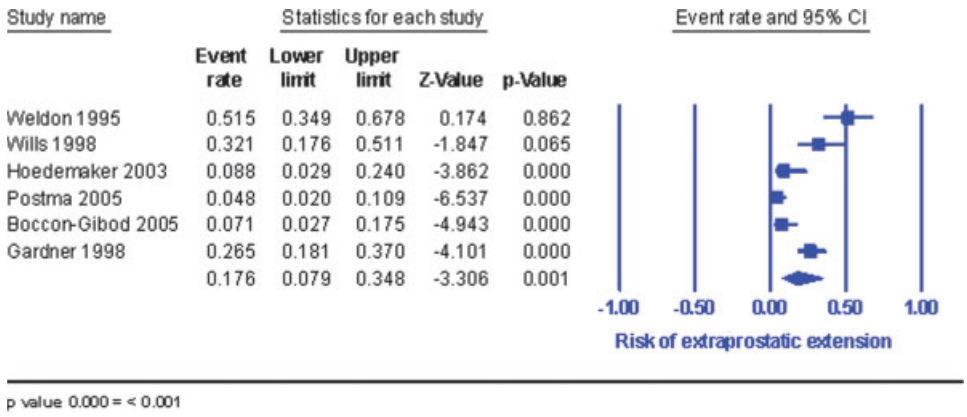

FIGURE 1. This plot illustrates the risk of extraprostatic extension using the most restrictive definition of microfocal carcinoma. 95% CI indicates 95% confidence interval.

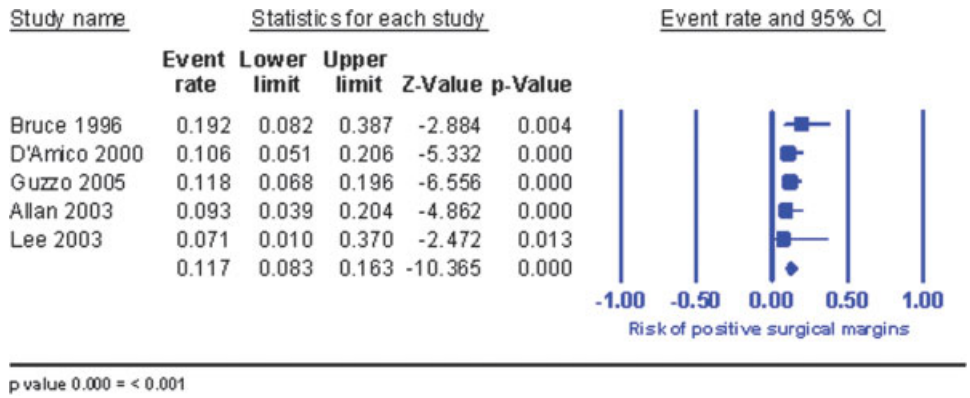

FIGURE 2. This plot illustrates the risk of positive surgical margins using the most restrictive definition of microfocal carcinoma. 95% CI indicates 95% confidence interval.

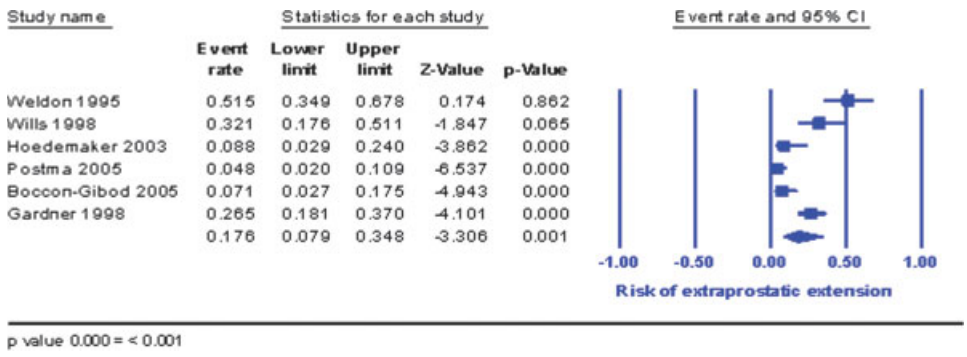

FIGURE 3. This plot illustrates the risk of extraprostatic extension using the most common definition of microfocal carcinoma (a single positive core, length of cancer cutoff of 3 mm, and Gleason score <7). 95% CI indicates 95% confidence interval; PSA, prostate-specific antigen.

risk was estimated at 17.6% (Fig. 3). Too few articles reported on margin positivity to allow a meaningful analysis, but the frequency of positive margins ranged between 0% and 14% of patients (median, 10% of patients).[11,20,35]

Clinical Outcomes

Patients treated by radical prostatectomy

The number of PSA recurrences for patients with microfocal carcinoma ranged from 0% to 26% (median, 8.5%) (Table 7). Small-volume cancer on biopsy

TABLE 7
Recurrence After Radical Prostatectomy With Articles Presented in the Order of Decreasing Stringency of the Definition of Microfocal Carcinoma

	Definition of microfocal cancer			Definition of PSA recurrence			
Reference	Maximum No. of cores	Cancer length, mm*	GS	PSA, ng/mL	No. of measurements	No. of PSA recurrences (%)	Follow-up: Median [Mean/Range], mo
Gardner, 1998[17]	1	3	6	>0.1	1	6/83 (7)	ND [ND/ND]
Postma, 2005[11]	1	3	6	≥0.2	1	4/87 (5)	45 [ND/3–96]
Lee, 2003[25]	1	5%	6	ND		0/14	17.3 [ND]
D'Amico, 2000[16]	1	5%	7	≥0.1	2	ND ("approximately 10%")	ND
Ravery, 1996[32]	1	10%	Any	Rise after undetectable or persistent postsurgery	3	5/23 (22)	ND [ND/6-ND]
Kakehi, 2000[18]	1–2	50%	6	ND		1/48 (2)	21.9 [ND/6.7–74.3]
Roemeling, 2006[47]	1–2	Any	6	>0.1 & Rising		13/136 (10)	ND for subgroup
Ravery, 1996[33]	1	Any	Any	≥0.1	3	ND (26)	ND

PSA indicates prostate-specific antigen; GS, Gleason score; ND, no data.
* Percentages in this column indicate the percentage of the core that was positive.

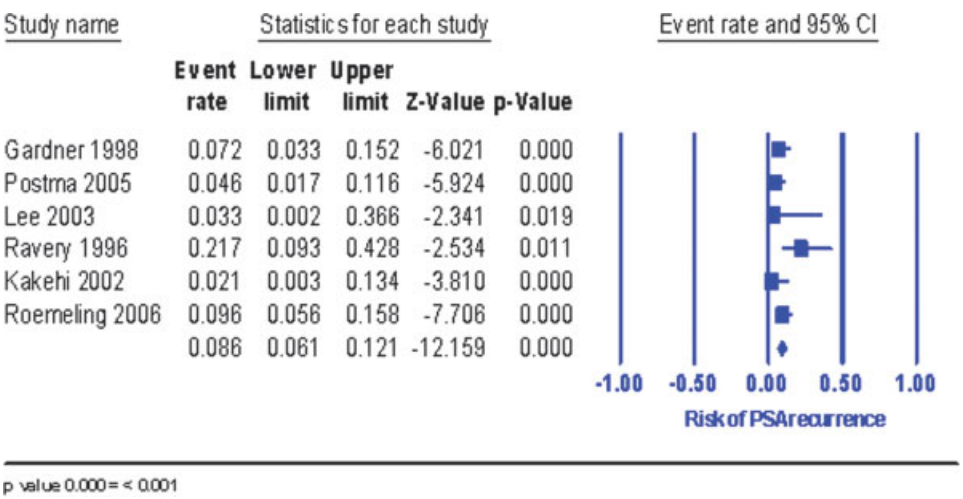

FIGURE 4. This plot illustrates the risk of prostate-specific antigen recurrence after radical prostatectomy. 95% CI indicates 95% confidence interval.

was associated with an estimated risk of developing PSA recurrence of 8.6% (range, 6.1%–12.1%) (Fig. 4). Only 3 articles reported on symptomatic recurrences or death, with no patients,[11,47] 1 of 48 patients (2%),[31] and 2 of 136 patients (1.5%)[47] experiencing recurrence and with 1 reported death.[47].

Patients treated by radical radiotherapy

None of the 3 studies that reported symptomatic recurrences or death provided a specific definition of PSA recurrence for the subgroup that received radical radiotherapy, and 1 study did not provide data on the length of follow-up.[47] PSA recurrences were observed in 0 of 12 patients[18] (0%; median follow-up, 33.1 months; range, 14.6–98.7 months), in 16 of 91 patients (18%),[47] and in 2 of 10 patients (20%; mean follow-up, 29.5 months; range, 6–54 months).[28] Two patients with microfocal carcinoma developed metastases (2%), and 2 patients died of cancer (2%).[47]

Patients treated by androgen-deprivation therapy

One article reported the outcomes a group of 21 patients who had 1 or 2 positive biopsy cores that showed ≤50% cancer involvement.[18] None of those patients had evidence of clinical progression after a median follow-up of 26.8 months (range, 7.1–111 months).

Patients undergoing watchful waiting

The number of patients in each study was small, but a rising PSA levels were reported in 9 of 15 patients who had 1 positive core (60%; mean follow-up, 22

months; range, 6–48 months)[34]; and clinical progression was observed in 1 of 25 patients (4%; median follow-up, 27.3 months; range, 7.7–67.6 months) who had 1 or 2 positive biopsy cores and ≤50% involvement with carcinoma[18] and in 1 of 82 patients (1%; median follow-up, 30 months; range, 5–86 months) who had ≤3 mm of carcinoma in a single core.[11] The latter study also reported that 4 patients (5%), 12 patients (15%), and 18 patients (22%) had PSA doubling times of <2 years, <3 years, and <4 years, respectively. By using PSA doubling times as the only outcome measure, favorable biopsy features (1 or 2 positive biopsy cores with ≤50% involvement by cancer; 38 patients) were only prognostic when combined with World Health Organization grade (grade 1 vs grade 2 or 3) and initial PSA level ($P = .0034$).[31] Conversion to definitive therapy affected 19 of 64 patients (30%; follow-up length and reasons for conversion not given) with 1 or 2 positive cores.[47]

Limitations on Interpretation

Data on the clinical characteristics of the patient population were not always given, but there were marked variations in the proportion of men who were diagnosed because of a raised PSA alone, from 18.5%[22] to 95%[43] (Table 1), indicating differences in patient selection. Other biases inherent to retrospective studies also were apparent, particularly in terms of incomplete data (Table 2); so that the proportion of patients excluded from the final analysis was up to 29%,[37] although, in most studies, this proportion was not clear (Tables 3–6). Final sample sizes were not always given, were limited by the number of patients treated in individual institutions, and usually were small, ranging from 6 patients[29] to 131 patients[42] (median, 34 patients) (Tables 3–6). Not all articles provided complete information on biopsy technique; however, when they did, biopsy strategies and the actual numbers of cores obtained varied (Tables 3–6), and it is possible that a small focus of carcinoma in 1 of 10 biopsies may be less significant than in 1 of 2 biopsies. Only 1 article compared the outcomes of patients who had undergone ≤6 biopsies versus ≥7 biopsies and reported no significant differences in the frequency of EPE or positive margins.[31]

Finally, there were large variations in the reported outcomes of patients undergoing radical treatment, but how much of this was attributable to treatment rather than to biologic tumor characteristics was unclear, because no details were provided about surgical expertise or the specifics of the radiotherapy treatment, although radiation dose was altered according to clinical stage in 1 study.[28]

DISCUSSION

To our knowledge, this is the first systematic review of the evidence for a relation between small tumor volume in diagnostic prostatic biopsies and patient outcomes. This review focused on the specific question of the significance of small-volume cancer, because this is an increasingly common clinical situation, and greater proportions of men are diagnosed with clinically localized prostate cancer that is detected through PSA testing. The number of patients reported within these retrospective studies was relatively small, and comparisons were limited because of differences in the definition of microfocal carcinoma and in the outcome measures reported between studies. Nevertheless, the overall findings indicate that a small volume of cancer in prostatic biopsies is not necessarily indicative of a good prognosis.

In the majority of articles, the treatment was surgical, and correlations were made between small-volume cancer in the diagnostic biopsies and findings at radical prostatectomy. Tumor was present in the surgical specimen in >99% of patients. Because of concerns about over detection and over treatment of indolent prostate cancer,[2] there have been attempts to differentiate "significant" disease (potentially life-threatening) from "insignificant" disease on the basis of radical prostatectomy findings and to identify preoperative parameters that would differentiate between the 2 disease types. Small tumor volume in the prostatectomy specimen is considered to be an indication of indolence because of the relatively slow doubling time of prostate cancer.[50] It has been suggested that tumors ≤0.5 cc are unlikely to reach a significant size within the lifespan of the individual.[51] In this review, few articles provided data on volume alone; however, all[20,35,36] but 1 study[47] indicated that at least 50% of patients had tumors ≥0.5 cc (Tables 3–5). Because extraprostatic spread, margin positivity, and high Gleason scores also are adverse prognostic factors, organ confinement, margin negativity, and a maximum Gleason score of 6 subsequently were added to the definition of "insignificant" cancer.[52] We observed that the pooled estimate of the risk of extraprostatic spread was significant for patients with microfocal carcinoma on biopsy regardless of how this was defined (18.2% [see Fig. 1] and 17.6% [see Fig. 3]). The pooled estimate for margin positivity also indicated a significant risk (11.7% [see Fig. 2]). Overall, between 33%[22] and 84%[23] of patients in this review had at least 1 adverse pathologic feature in the radical prostatectomy specimen and, thus, were considered to have "significant," potentially progressive carcinoma. The authors concluded that microfocal carcinoma on biopsy could not be used as an

absolute criterion in the selection of patients for conservative management.

Adverse pathologic findings are not necessarily associated with subsequent relapse, but the pooled estimate of the risk of PSA relapse after radical prostatectomy also was significant in patients with microfocal disease (8.6%) (see Fig. 4). Clinical recurrences or deaths from cancer rarely were observed in this group of patients. However, prostate cancer typically progresses slowly, and 2 years may be considered as a minimum postoperative follow-up, after which patients who have not suffered a biochemical relapse have a 90% recurrence-free survival rate.[53] The average length of follow-up was >2 years in only 1[11] of the 3[11,18,25] studies that provided this information (Table 7). Therefore, the risk of relapse in the surgical series may have been underestimated in the remaining reports. Follow-up generally was longer in the 3 small studies that investigated recurrences after radiotherapy, and PSA recurrences were reported in up to 20% of patients.[28] Deaths because of prostate cancer also were recorded.[47] Thus, microfocal cancer on biopsy, particularly if the definition is not restricted by Gleason score[28] or length of cancer present,[47] also is not necessarily indicative of a good prognosis in patients who receive are treated by radiotherapy.

Only 5 studies investigated the outcomes of patients who opted for watchful waiting; and comparisons were difficult, because different outcome measures were used (PSA doubling times or rising PSA) in addition to differences in the definition of microfocal carcinoma. Nevertheless, even by limiting the amount of cancer to 3 mm in a single core and excluding patients with high-grade disease (Gleason 4 or 5) in their biopsies, 22% of patients had a PSA doubling time <4 years in 1 report.[11]

One of the reasons for the lack of correlation between microfocal carcinoma on biopsy and good outcomes may be that biopsy findings are not representative of the overall tumor burden unless large numbers of cores are taken. Limited data were given regarding biopsy numbers, precluding a detailed analysis. Nevertheless, the study with the highest mean number and range of biopsy numbers still demonstrated that >60% of patients with microfocal carcinoma on biopsy had significant disease in the radical prostatectomy specimen.[26] Furthermore, 1 article looked at this specific issue and observed no differences in the rates of extraprostatic extent or margin positivity relative to the number of biopsies taken.[41] Nevertheless, given the limitations of the biopsy instruments, each needle core, at most, will sample only sample 0.01 cc of the prostate, representing far less than 1% of an average gland. In addition, needle placement and reach may be important factors, because it has been demonstrated that, regardless of the number of biopsies taken, anterior tumors are particularly difficult to diagnose by using the transrectal approach.[54,55] Sampling error, therefore, is an inevitable problem in prostatic cancer.

Another issue to consider is the variation in the frequency of adverse findings between studies, particularly in the surgical series, leading to relatively wide ranges for the estimated risks. Some of these variations may have been caused by differences in the definition of microfocal carcinoma, because, for instance, the frequency of PSA recurrence was highest (range, 22%–26%) when there were no restrictions on the Gleason score[32,34] and lowest (range, 2%–7%) when the cancer length was restricted and the Gleason score was $\leq$6.[11,17,25,31] Some of the variations in the frequency of EPE also may have been attributable to patient selection, because EPE was reported less commonly in studies of screened populations[11,21] and in studies that included a high proportion[20,25] (rather than a low proportion[19]) of patients with PSA-detected (T1c) prostate cancer (Figs. 1, 3). Finally, although patient selection also may have been a factor in the reported differences for other adverse pathologic and clinical outcomes, variations in both margin positivity[56] and PSA recurrence[57] also may be influenced by surgical expertise, because it has it has been estimated that approximately 63% of the variation in the frequency of PSA relapses could be explained by genuine differences in surgical skill and approach.[57] These potential confounding factors obviously affect studies of all patients with prostatic carcinoma and not only those with microfocal carcinoma.

The final consideration regarding our estimations of the risk associated with microfocal carcinoma is whether the patient samples investigated in the original studies were representative of the population of patients with prostatic carcinoma. In fact, patients were referred to individual institutions and were identified for treatment using individual selection protocols. In addition, all of the studies were retrospective, and not all of the data pertaining to each patient were collected routinely. Most studies dealt with these missing data by omitting the patients who were affected from the final analysis. However, unless the data were missing completely at random, the results of the studies could be biased[58]; however, because it was not always clear how many patients were lost, the magnitude of the potential problem could not be assessed.

In conclusion, despite the differences in study design and reporting, a significant proportion of

patients with microfocal cancer, regardless of how it is defined, have adverse pathologic findings and a significant risk of PSA recurrence after radical prostatectomy. Biochemical and clinical recurrences also were observed after radiotherapy or watchful waiting. Therefore, patients with microfocal carcinoma on biopsy should be advised that their disease is not necessarily "insignificant" and should be counseled accordingly.

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