Review – Prostate Cancer

Does the Extent of Carcinoma in Prostatic Biopsies Predict Prostate-Specific Antigen Recurrence? A Systematic Review

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Abstract

Context: The biologic potential of prostate cancer (pCA) is variable, and the ability to identify tumours that might cause morbidity and mortality is limited.

Objective: This systematic review sought to establish whether measurement of tumour extent in biopsies provides additional prognostic information on the risk of disease progression.

Evidence acquisition: A comprehensive 31-step search strategy was run in MEDLINE, EMBASE, and the Web of Knowledge (January 1990–July 2007) and supplemented by the hand-searching of references in retrieved articles and relevant journals to identify publications related to the measurement of the length of cancer in biopsies and biochemical or clinical recurrence or pCA death. Thirteen papers reporting on at least 100 patients were identified and included patients treated by watchful waiting or hormonal therapy (n = 1), radical prostatectomy (n = 11), or radiotherapy (n = 1). Only two studies reported on clinical progression or mortality. Sources of bias included patient selection and missing data resulting from the retrospective nature of the studies. Confounding factors included differences in biopsy strategies and measurement methods.

Evidence synthesis: The percentage of cancer in biopsies (overall percentage or the greatest percentage in the most involved core) was an independent predictor of prostate-specific antigen (PSA) and clinical outcomes regardless of the form of treatment and was generally superior to simply counting the number of positive cores. The marked variability in study design, conduct, and reporting precluded meta-analysis of the data and precise risk estimation.

Conclusions: Tumour quantitation is a promising prognostic tool in the assessment of risk of pCA progression. However, well-designed, population-based studies, controlling for confounding factors, are required to provide more accurate risk estimation and develop management strategies. This review highlights the need for new approaches in the assessment of pathologic prognostic factors to reach the level of evidence achieved in other areas of medical practice.

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1. Introduction

One of the major problems facing urologic oncologists and urologists today is how and when to treat asymptomatic men with prostate cancer (pCA). Offering radical therapy is associated with potential morbidity resulting from urinary, bowel, and sexual dysfunction [1–4]. Active surveillance, whereby treatment with curative intent is only instituted if there are signs of progression, is seen as a viable option to avoid “over-treatment” [5] and is most appropriate for patients at low risk of progressive disease. Assessing the magnitude of this risk in individual patients remains a challenge, as current nomograms [6–8] and risk tables [9,10], incorporating pretreatment prostate-specific antigen (PSA) levels, Gleason score, and stage of disease provide relatively wide estimates. More detailed biopsy information, particularly the percentage of positive cores, is used in clinical practice to refine risk assessment, particularly for low-risk patients [11–18], and these predictive tools have been validated [19,20]. However, methods of estimating the linear length of cancer have varied among studies, with no consistency in approach even among dedicated uropathologists [21], and these measurements are used with caution by urologists [22].

The aim of this systematic review was to identify and summarize all studies relating linear extent of cancer on biopsy with recurrence, progression, or death from pCA and to determine which, if any, of these pathologic variables should be reported in routine practice to stratify patients into groups at different risk of progression. It also sought to establish whether these more complex measurement methods were superior to the simple measure of counting the number of positive cores.

2. Methods

A comprehensive 31-step search strategy was developed composed of a thesaurus and text-word terms describing pCA, outcomes, and pathology to identify studies reporting the pathology of pCA [23]. There were no language restrictions. The initiation of the search date (1990) coincided with the establishment of transrectal ultrasound (TRUS)-guided biopsy procedures and was updated to July 2007. The resulting bibliographic database (Fig. 1) was then searched using biopsy as a search term. Two authors scanned titles and abstracts for relevant studies. Only fully published studies were retrieved for further assessment. The electronic search was supplemented by hand-searching bibliographies of the retrieved papers and relevant recent cancer journals. A sample size of 100 patients was considered a minimum for meaningful statistical analyses. Papers addressing the specific issue of microfocal carcinoma were reviewed separately [24]. The selection process resulted in 13 papers examining the relationship of the absolute length (in millimetres) [25–27] or the relative length (percent) [28–37] of cancer in biopsy material with pCA mortality, clinical recurrence, or PSA recurrence. Two groups reported initial [29,34] and extended [30,33] follow-up data on overlapping groups of patients. The early reports are included, as they took a different analytic approach and contain comparative data on the significance of the number of positive cores. All were retrospective studies except one in which some of the data were collected prospectively [33].

Data were extracted and verified by at least two authors and consisted of study design and location, patient characteristics, details of biopsy pathology and method, types of interventions, statistical analysis, and clinical and/or PSA outcomes. Additional information concerning the measurement method was requested from the authors when required and was received in all but one case [35].

3. Results

3.1. Measurements expressed in millimetres

The study characteristics and findings of the three relevant papers [25–27] are summarized in Tables 1
and 2. All patients were treated by radical prostatectomy.

3.2. Cumulative cancer length (sum of cancer in all cores)

In the report by King et al [26], values were spread across a wide range (1–44 mm), with cumulative lengths of cancer >9 mm in 43% of patients, and only this measure was significantly associated with biochemical recurrence (Table 2). Noguchi et al reported negative results [27]; 36% of patients had a cumulative cancer length of <3 mm, 30% had values of 3.1–6 mm, 13% had values of 6.1–9 mm, and only 21% had >9 mm of cancer. In the first study, cumulative length was analyzed as a continuous variable, but in the negative study, the mean value (6 mm) was used as the cut-off point. The skewed distribution and the choice of cut-off points may explain the negative findings.

3.3. Maximum length of cancer in any one core

Maximum length of cancer in any one core was predictive of biochemical failure in the study by Egawa et al [25] but not that of King et al [26]. In this case, the use of a cut-off point resulted in a significant result [25], which was not reproduced when data were analyzed as continuous variables [26]. When patients were then stratified into three risk groups depending on clinical stage, presenting serum PSA levels, and biopsy Gleason score [25]—which were further subdivided (one positive biopsy and <3 mm of cancer, one positive biopsy or <3 mm, two or more positive biopsies, and >3 mm of cancer)—there was no improvement in risk stratification for PSA recurrence. However, the maximum number of patients in any of these subgroups was 39, and the statistical power may have been insufficient to detect a significant difference.

3.4. Relative value of the number of positive cores versus cancer length (in millimetres)

One study found that only the number of positive cores was significantly associated with biochemical recurrence [27] and another that it was also predictive [25]. Both of these studies dichotomized this variable, whereas the third, reporting negative results, did not [26]. The values were widely spread in this study (range: 1–11), and there were relatively few cases with three (19%) or four or more (15%) positive cores [26].

3.5. Cancer lengths expressed as a percentage

The key characteristics of these 10 studies [28–37] are summarised in Table 3. The different methodologies are detailed in Table 4, and the findings are presented in Table 5.

3.6. Total percentage of cancer

Cuzick et al reported on pCA mortality in patients treated conservatively after a diagnosis made either in transurethral resections or biopsy cores [28]. There were no data specific to measurement in biopsy material, but overall, the total percentage of cancer was more predictive for pCA death at 10 yr than clinical stage in multivariate models, although the major factor predictive of cancer mortality was Gleason grade followed by PSA levels. In the remaining papers, all patients underwent radical prostatectomy.

Using the Shared Equal Access Regional Centre Hospital (SEARCH) database, Freedland and co-workers [29] reported that the total percentage of cancer was the strongest predictor of PSA recurrence when analyzed as a continuous value but was similar to other predictors as a categorical variable
When added to baseline PSA levels and Gleason score data to predict PSA recurrence, the area under the receiver operating characteristic curve (AUC) increased significantly from 0.653 to 0.722 ($p = 0.020$). The optimized cut-off points (Table 4) also significantly improved risk stratification for PSA recurrence within risk groups defined by serum PSA and biopsy Gleason score (low risk: PSA $<10$ ng/ml and biopsy Gleason score $<7$; intermediate risk: PSA $10–20$ ng/ml and biopsy Gleason score $<7$; high risk: PSA $>20$ ng/ml or biopsy Gleason score $>7$).

These researchers then developed a preoperative model for the 2-yr risk of PSA recurrence following radical prostatectomy\[30\], using cut-off values for the percent of cancer on biopsy ($<20\%$, $20–40\%$, and $>40\%$), serum PSA ($<10$, $10–20$, $>20$ ng/ml), and biopsy Gleason score ($<7$, $3 + 4$, $4 + 3$). For a patient with a Gleason sum score of $3 + 4$ and a preoperative serum PSA level of $<10$ ng/ml, the risk of biochemical failure increased from $13\%$ (95% CI, 10–16) if $<20\%$ of cancer was present on biopsy to $30\%$ (95% CI, 13–47) if $>40\%$ of the tissue was involved. Sebo et al\[37\] and Ravery et al\[36\] demonstrated that the total percentage of cancer was predictive of PSA recurrence in univariate analysis\[37\] or by log-rank test\[36\]. Except for PSA density, all other preoperative parameters (age, clinical stage, PSA, Gleason score, the percentage of positive cores, and whether cancer was unilateral or bilateral) were not significantly associated with biologic progression.

### Table 2 – Summary of findings of papers investigating the length (in millimetres) of cancer on biopsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Measures reported</th>
<th>Definition of PSA Recurrence/number (%) of recurrences</th>
<th>Statistical analyses</th>
<th>Correlation with PSA recurrence</th>
<th>Hazard ratio (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egawa et al, 2001 [25]</td>
<td>1. Maximum length of cancer (&lt;3 or $\geq$ 3 mm)</td>
<td>2 consecutive rises $\geq$0.1 ng/ml, 1 mo apart/58 (33%)</td>
<td>Likelihood ratio test</td>
<td>Both measures in conjunction with PSA, stage, and Gleason score significantly improved prediction of biochemical failure ($p = 0.009$)</td>
<td>No details</td>
</tr>
<tr>
<td></td>
<td>2. Number of positive cores (1 or $&gt;1$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>King et al, 2005 [26]</td>
<td>1. Total cancer length on biopsy (mm)</td>
<td>Detectable postoperative PSA $&gt;0.05$ ng/ml/28 (24%)</td>
<td>Multivariate logistic regression analysis</td>
<td>Only total cancer length significant ($p = 0.05$)</td>
<td>No details</td>
</tr>
<tr>
<td></td>
<td>2. Maximum tumour length (mm)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Number of positive cores</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>4. Percent of positive cores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noguchi et al, 2003 [27]</td>
<td>1. Total cancer length on biopsy (&lt;5, $\geq$ 6 mm)</td>
<td>$\geq$0.07 ng/ml, increasing in subsequent samples/39 (18%)</td>
<td>Multivariate Cox proportional hazards model</td>
<td>Neither factor significant in univariate analysis, number positive significant on multivariate analysis</td>
<td>Number positive: 2.54 (1.04–6.20), $p = 0.041$</td>
</tr>
<tr>
<td></td>
<td>2. Number of positive cores (&lt;2, $\geq$2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen; CI, confidence interval; mm, millimetres.
<table>
<thead>
<tr>
<th>Study</th>
<th>Institution (dates)</th>
<th>n</th>
<th>Stage</th>
<th>Age (years)</th>
<th>PSA ng/ml</th>
<th>Biopsy number</th>
<th>Gleason score</th>
<th>Primary treatment</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson et al, 2002 [34]</td>
<td>University of Michigan Hospitals, Ann Arbor, MI, USA, 1994–1998</td>
<td>588</td>
<td>T1 = 413, T2 = 175</td>
<td>≤55 = 28%</td>
<td>≤10 = 82%</td>
<td>≤6–9</td>
<td>RP</td>
<td>Mean: 16 (4–48)</td>
<td></td>
</tr>
<tr>
<td>Potters et al, 2002 [35]</td>
<td>Memorial Sloan Kettering, New York, NY, USA, 1992–1999</td>
<td>1073</td>
<td>T1c = 641, T2a = 377, T2b = 55</td>
<td>Median: 69.8</td>
<td>Median: 7.6 (0.17–112)</td>
<td>6</td>
<td>2–10</td>
<td>Brachytherapy</td>
<td>Median: 34.7 (6–91)</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen; ND, no data; RP, radical prostatectomy; WW, watchful waiting.
rence-free survival after radical prostatectomy were serum PSA ($p < 0.01$) as a continuous variable, biopsy Gleason score ($< 7, 7, > 7, p = 0.04$), and the greatest percentage of cancer ($< 0.01$). Using these three parameters, a multivariate model was highly predictive of recurrence-free survival ($p = 0.0001$).

For a patient with Gleason sum score of 7 and a preoperative serum PSA level of 10 ng/ml, the 2-yr risk of biochemical failure increased from 5% (95% CI, 1–10), if the greatest percentage was $< 10\%$, to 16% (95% CI, 10–21), if it was $\geq 60\%$. The extended study [33] also demonstrated that the greatest percentage

<table>
<thead>
<tr>
<th>Study</th>
<th>Terminology</th>
<th>Measurement method</th>
<th>Intervening benign tissue excluded</th>
<th>Cut-off points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuzick et al, 2006 [28]</td>
<td>Percent of cancer in biopsy</td>
<td>Sum of cancer lengths in each core/sum of each core length</td>
<td>Yes</td>
<td>$\leq 6%, &gt; 6$–$20%$, $&gt;20$–$40%$, $&gt;40$–$75%$, $&gt;75$–$100%$</td>
</tr>
<tr>
<td>Freedland et al, 2003 and 2004 [29,30]</td>
<td>Percent cancer in biopsy</td>
<td>Sum of cancer lengths in each core/sum of each core length</td>
<td>Yes</td>
<td>Continuous variable and $&lt; 20%$</td>
</tr>
<tr>
<td>Gretzer et al, 2002 [31]</td>
<td>Maximal percentage of biopsy core with cancer</td>
<td>Estimate of the linear amount of cancer in the single most involved core</td>
<td>No</td>
<td>Continuous variable and $&lt; 50%$ vs $&gt; 50%$</td>
</tr>
<tr>
<td>Linson et al, 2002 [32]</td>
<td>Percentage of core length with cancer</td>
<td>Sum of lengths of cancer in each core/number of cores (assumed that all are of the same length)</td>
<td>Yes</td>
<td>$&lt; 25%$ vs $&gt; 25%$</td>
</tr>
<tr>
<td>Nelson et al, 2002 and 2003 [33,34]</td>
<td>Greatest percentage of cancer</td>
<td>Estimate to the nearest 5% of the linear percent of cancer in the single-most involved core</td>
<td>Yes</td>
<td>2002: Stratification by 10% intervals and $&lt; 10%$, 10–59%, $\geq 60%$ 2003: 60–100% vs 0–59% Continuous variables</td>
</tr>
<tr>
<td>Ravery et al, 2000 [36]</td>
<td>Length of core invaded by cancer</td>
<td>Sum of cancer lengths in each core/sum of each core length</td>
<td>Yes, yes also periprostatic tissues</td>
<td>$&lt; 15%$, 15–29%, 30–49%, 50–100%</td>
</tr>
<tr>
<td>Sebo et al, 2002 [37]</td>
<td>Percent surface area involved with cancer</td>
<td>Visual estimate in 5% increments of the amount of tumour relative to the total length of cores</td>
<td>Yes, yes</td>
<td>Continuous variables</td>
</tr>
</tbody>
</table>

ND, no data.

<table>
<thead>
<tr>
<th>Study</th>
<th>Reported outcomes; number (%)</th>
<th>Statistical analyses</th>
<th>Correlation with reported outcomes</th>
<th>Hazard ratio (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuzick et al, 2006 [28]</td>
<td>Death from pCA; ND (24%)</td>
<td>Multivariate \ PHM</td>
<td>Percent cancer significant in univariate and multivariate analysis</td>
<td>No details for biopsy subgroup 8.25 (3.06–22.22), $p &lt; 0.001$ compared to: Gleason score 1.34 (1.11–1.62) $p = 0.003$ PSA 1.03 (1.01–1.05), $p = 0.003$</td>
</tr>
<tr>
<td>Freedland et al, 2003 [29]</td>
<td>Biochemical failure: PSA $&gt; 2$ ng/ml or two values of 2 ng/ml; 89 (25%)</td>
<td>Multivariate \ CPHM</td>
<td>Percent cancer as a continuous variable stronger independent predictor of PSA recurrence than biopsy Gleason score and serum PSA. Percent of positive cores not independent predictor.</td>
<td></td>
</tr>
</tbody>
</table>
was significantly associated with clinical recurrence or metastases independently of Gleason score.

As reported by Gretzer and associates [31], the greatest percentage of cancer was also predictive of recurrence in a subgroup of patients with T1c pCA after radical prostatectomy. Using a PSA cut-off of 10 ng/ml and a biopsy Gleason sum of 7, two groups were defined with biochemical recurrence-free probabilities at 10 yr of 96% (95% CI, 94–98%, group T1cI) and 73% (95% CI, 62–81%, group T1cII; p = 0.0001). The first group was not investigated further because biopsy data were unlikely to improve prognostication; in the second group, the 5- and 10-yr PSA recurrence-free probability was

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<th>Correlation with reported outcomes</th>
<th>Hazard ratio (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedland et al, 2004 [30]</td>
<td>Biochemical failure: PSA &gt;2 ng/ml or 2 values of 2 ng/ml; 118 (26%)</td>
<td>Logistic regression and CPHM</td>
<td>Using cut-offs, percent of cancer significant independent predictor of PSA failure similar to biopsy Gleason score and serum PSA</td>
<td>1.64 (1.25–2.15) compared with: Gleason score 1.62 (1.28–2.05) PSA 1.51 (1.17–1.97) (all p &lt; 0.001) 1.02 (1.01–1.03), p = 0.008</td>
</tr>
<tr>
<td>Gretzer et al, 2002 [31]</td>
<td>Biochemical failure: ≥0.2 ng/ml PSA; ND</td>
<td>Recursive partitioning, Kaplan-Meier, and multivariate Cox regression</td>
<td>Maximum percentage of cancer (&lt;50% or ≥50%) independent predictor of PSA failure; PSA, Gleason score, and number of positive cores not significant Both cancer volume measures significant predictors of PSA recurrence in univariate analysis; only percent of positive cores significant in multivariate analysis (p = 0.03)</td>
<td>1.449 (1.025–2.049), p = 0.0357</td>
</tr>
<tr>
<td>Linson et al, 2002 [32]</td>
<td>Biochemical failure: 2 consecutive levels &gt;1.0 ng/ml; ND</td>
<td>Univariate and multivariate Cox regression</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Nelson et al, 2002 [34]</td>
<td>Biochemical failure: PSA &gt;0.2 ng/ml; 71 (12%)</td>
<td>Cox regression</td>
<td>PSA, Gleason, and greatest percent cancer highly predictive of PSA recurrence (p = 0.0001), number of positive cores not significant</td>
<td>ND</td>
</tr>
<tr>
<td>Nelson et al, 2003 [33]</td>
<td>Biochemical failure: PSA &gt;0.2 ng/ml; 183 (13%)</td>
<td>Multivariate CPHM</td>
<td>GPC significant predictor of PSA recurrence-free survival with natural log PSA and biopsy Gleason score; number of positive cores not significant GPC significant predictor of clinical recurrence or metastasis independent of Gleason score (p = 0.0065) compared to: Gleason score 7–2.29 (1.60–3.27), score 8–3.17 (1.79–5.61) PSA 2.67 (2.15–3.32), all p &lt; 0.0001</td>
<td>ND</td>
</tr>
<tr>
<td>Potters et al, 2002 [35]</td>
<td>Biochemical failure: 3 rises, not necessarily consecutive; 88 (8%)</td>
<td>Principal components analysis and Somers D rank correlation</td>
<td>Significant in univariate analysis: mean percent cancer in an involved core, percent cancer at apex and midgland, maximum percent at base; percent positive cores not significant</td>
<td>ND</td>
</tr>
<tr>
<td>Ravery et al, 2000 [36]</td>
<td>Biochemical failure: PSA &gt;0.5 ng/ml before September 1991; then PSA &gt;0.1 ng/ml; ND</td>
<td>Kaplan Meier CPHM</td>
<td>Percent core length invaded by cancer and PSA density significantly predict biological progression, percent positive cores not significant Log-rank test 30.1 Compared with PSA density 35.5, both p = 0.0001 Not included in multivariate analysis</td>
<td></td>
</tr>
<tr>
<td>Sebo et al, 2002 [37]</td>
<td>Biochemical failure: PSA ≥0.4 ng/ml or local recurrence or systemic progression; 73 (16%)</td>
<td>Kaplan-Meier</td>
<td>Both percent positive cores (RR 1.02, 95% CI, 1.01–1.03) and surface area (RR 1.03, 95% CI, 1.02–1.04) significant predictors of cancer progression on univariate analysis (p &lt; 0.001)</td>
<td></td>
</tr>
</tbody>
</table>
significantly higher (90% and 85%, respectively) if there was <50% involvement of the length of any one core compared to >50% (75% and 56%, \( p = 0.03 \)).

The greatest percentage of cancer was amongst the 23 biopsy variables investigated in a paper by Potter et al [35] reporting on patients treated by brachytherapy alone (78% of patients) or with additional external beam radiation therapy (22% of patients). When taken as the maximum percentage in any core, it was not significant in univariate analysis; but if restricted to biopsies taken from the base, it was significant.

3.9. Relative value of the number of positive cores versus the greatest percentage of cancer

One group found no association between the number of positive biopsies and PSA recurrence using cut-off points of one (57% of patients), two (29% of patients), or three or more positive cores (14% of patients) [34] or using cut-off points of one versus two or more positive cores (patient distribution not given) [33]. The number of positive cores was not significant in another study, although it was recognized that the fragmented nature of some of the cores and the lack of record of the total number of cores taken limited interpretation [31]. Finally, no significance for the percentage of positive cores was found in patients treated by radiotherapy [35]. Using a model including PSA, Gleason score, and clinical stage, the Somers D rank coefficient was 0.32 (0 represents no discriminating ability, 1 is perfect discrimination). Adding the percentage of positive cores to this model increased the coefficient to 0.34. However, the best predictive model using principal component analysis was where all 23 pathologic variables, ranked by significance into component groups, were included and gave a coefficient of 0.39.

3.10. Mean percentage of cancer and its significance relative to the percentage of positive cores

Linson and colleagues [32] specifically examined whether the mean percentage of core length with cancer provided significantly more information than the percentage of positive cores in predicting postoperative PSA outcome and found that only the percentage of positive cores was independently predictive. This study was restricted to men with intermediate-risk pCA defined as clinical stage 2b (1992 American Joint Consensus Committee criteria), biopsy Gleason score 7, or PSA 10–20 ng/ml, and 80% of patients had ≤50% positive cores.

The radiotherapy study [35] did not clearly define “mean percentage of cancer in an involved core,” and no clarification could be obtained. This measure could be interpreted as representing the total amount of cancer divided by the number of positive cores rather than by the total number of cores, as in the other study [32]. It was a significant predictor of PSA outcome (\( p = 0.008 \)), whereas the percentage of positive cores was not.

3.11. Limitations on interpretation

All studies were biased because of the retrospective nature of data collection and the availability of quantitative biopsy data, in particular. There were variations in the spread of clinical stages (Tables 1 and 3), the definition of PSA recurrence, the number of recorded recurrences (Table 4), and length of follow-up, which was sometimes short (Tables 1 and 3). Furthermore, biopsy strategies and the number of cores obtained varied between and within studies (Tables 1 and 3), potentially affecting the amount of carcinoma sampled in a given patient. There was little information on laboratory handling of the biopsies, but separate embedding of cores was not mentioned, and fragmentation of multiple cores embedded together would make the assessment of the number of cores involved or the maximum amount of cancer in any core less reliable. Only three groups explicitly set quality criteria. Patients were excluded if <4 [29,30] or 6 [27] biopsies were taken, or a core was not measured if it measured <10 mm [36].

Methods of measurement also varied among studies (Tables 2 and 4), further limiting comparability among studies and the possibility of performing a meta-analysis. Two groups estimated the greatest percentage of cancer in the most involved core, but one excluded intervening benign tissue [33,34], whereas the other group included it [31]. Measurement methods were not tested for reproducibility, yet data from the External Quality Assurance Scheme (EQA) in Prostatic Pathology Reporting found that individual pathologists’ measurements were spread along a range of at least 10 mm in as much as 63% of cases [38]. Statistical methods varied, including the determination of cut-off points, which can distort the significance of results.

4. Discussion

This systematic review set out to determine whether measures of tumour extent could significantly improve the estimation of risk in individual patients with pCA. There is a concern about using PSA recurrence as a surrogate for progression because it
may not equate with clinical progression or cancer-specific death. However, the two studies that reported clinical outcomes found that tumour extent was an independent predictor of clinical recurrence or metastases [33] or cancer-specific survival [28], thereby establishing proof of principle of the potential of measures of tumour extent to refine prognostication.

The results of the few studies [25–27] measuring tumour extent in millimetres were inconsistent, possibly because of variations in study design and statistical analyses. The cumulative length of cancer was a significant predictor when analyzed as a continuous [26] but not as a dichotomous variable [27], whereas the converse was true for the maximum length of cancer [25]. The distribution of measurements was also variably skewed, with 43% of patients with ≥9 mm cancer in one study [26] falling to 21% in the other [27]. Given the other limitations on interpretation already described, no firm conclusions can be reached regarding the value of providing measurements as absolute figures.

By contrast, the studies that expressed tumour extent as a percentage were much more consistent, whether using the overall percentage of cancer in the biopsy tissue [28–30,36,37], the greatest percentage in any one core [31,33,34], or other measures [32,35]. Univariate analyses may be of limited relevance given the established value of clinical factors such as presenting PSA, but all except one [32] of the multivariate models [29–33,36], found that the percentage of cancer was independently predictive of PSA recurrence. The dissenting paper reported the average percentage of cancer, which may therefore not be as predictive as the greatest or the total percentage of cancer.

The percentage of positive cores is an established predictor of PSA recurrence following radical prostatectomy [11–20], although a large study by Briganti et al [39] found that the number rather than the percentage of positive biopsies may be more informative. However, these measures may not be the best indicators of tumour burden [13]. Eleven of the 13 studies reviewed here included comparative data on the number or percentage of positive cores and the linear extent of cancer. In two, number [27] or percentage [32] was the independent predictor of PSA outcome, whereas the linear or surface area of cancer was not; in a further two, both parameters were significant—at least in univariate analysis [25,37]. However, number or percentage was not a significant factor in the other reports [26,29,31,33–36]. Possibly, the spread of values was too skewed detect differences. In the few papers with precise information in this regard [26,27,34], at least two-thirds of patients had only one or two positive cores. Furthermore, the issue of fragmentation was not specifically addressed, so that one fragmented core with three separate foci of cancer may have been recorded as one or three cores depending on the interpretation of different pathologists. Nevertheless, the weight of current evidence suggests that the linear percentage of cancer on biopsy may be more valuable in predicting PSA recurrence compared to the number or percentage of positive cores alone. The issue, therefore, is which method should be adopted in clinical practice, although demonstration of the limits of reproducibility—a requirement for any clinical test—could be a problem [38].

There is no evidence to support the independent value of the mean percentage of cancer [32,35], but there are consistent data to support the use of either the total percentage of cancer [28–30,36,37] or the greatest percentage of cancer in any one core [31,33,34]. A limited number of studies provided hazard ratios in a multivariate setting [29–31,33]. The method producing the highest reported hazard ratio (8.25) was the measurement of the total percentage of cancer analyzed as a continuous variable [29], which also appeared to have a superior predictive power compared with preoperative serum PSA levels or biopsy Gleason score. However, models using cut-off points for risk stratification rather than continuous variable are easier to adapt to clinical practice, and this was the approach subsequently taken [30]. Hazard ratios were then broadly similar [30] to those reported in papers using the greatest percentage of cancer [31,33] (Table 5). The hazard ratio was higher in the study in which intervening benign tissue was excluded from the measurement of cancer [33] compared to the method including intervening benign stroma [31], but the use of different cut-off points could account for some of this difference.

The greatest percentage may underestimate tumour burden if several cores are involved. There are also theoretical advantages to using the total percentage of cancer, as the issue of fragmentation is not critical. Identification of individual cores is required for the assessment of the greatest percentage of cancer, but processing and sectioning individual cores separately has resource implications. However, fragmentation can be reduced by careful handling; individual cores can be separated between foam pads or other devices, and flat embedding can ensure that each core is fully represented. The disadvantage of measuring the overall amount of cancer is that the result will be
more strongly influenced by the amount of tissue sampled. In addition to the number of cores, which can vary quite widely (Tables 1 and 3), the needle direction is important, as shown by a recent systematic review of the effect of taking additional biopsies: Laterally directed cores increased the yield of pCA significantly ($p = 0.003$), whereas centrally directed cores did not [40]. Additional negative cores will reduce the total percentage of cancer measurement, which may then underestimate large tumours—particularly if unilateral. This limitation might be overcome by measuring the total cancer percentage on the most involved side rather than overall, in the same way that the percentage of positive cores on the dominant side had stronger independent predictive value than the total percentage [41].

5. Conclusions

Until there is better evidence, reporting both the total and greatest percentage of cancer may identify patients who are definitely at low risk of progression if they satisfy the criteria established by both predictive models [30,33]. Reporting the number of positive cores may provide additional information [39] and is recommended in the European Association of Urology (EAU) guidelines on pCA [17]. These different measurement methods are currently being tested within the prostatic biopsy EQA scheme developed in the United Kingdom.

Cumulatively, the studies reviewed have included >7000 patients, but conclusions are limited by the retrospective nature of the studies, the variations in patient characteristics, and the lack of standardized methodology. All have used the traditional method of investigating pathological prognostic factors, which is to identify all patients within an institution or database, select those who have been treated in a specific way, and then perform the analysis on the data available. These observational studies are valuable for generating hypotheses but not for producing definitive answers [42], as has been documented in previous systematic reviews of pathological prognostic factors [23,24,43]. Quality criteria have been established for the investigation of molecular markers [44], but equal rigor should be applied to the more traditional pathological factors. A well-designed prospective trial using current best-practice biopsy protocols [45], well-defined measurement methods, and standardized outcome reporting is the only way to determine the true significance of biopsy quantitative data and how these data should be used to advise patients on the most appropriate management option.

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**Study concept and design:** Coles, Harnden, Mason, Naylor, Shelley.

**Acquisition of data:** Coles, Harnden, Naylor, Shelley.

**Analysis and interpretation of data:** Harnden, Naylor, Shelley.

**Drafting of the manuscript:** Harnden, Naylor, Shelley.

**Critical revision of the manuscript for important intellectual content:** Coles, Harnden, Mason, Naylor, Shelley.

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