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# Are prostate needle biopsies predictive of the laterality of significant cancer and positive surgical margins?

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## OBJECTIVE

To determine whether data obtained from preoperative prostate needle biopsy can predict the laterality of significant cancer and positive surgical margins on final-specimen pathology after laparoscopic radical prostatectomy (LRP).

## PATIENTS AND METHODS

Data from 490 patients undergoing LRP by one surgeon were reviewed retrospectively. The demographic characteristics, intraoperative data and pathological results were analysed. Univariate and multivariate analyses were used to determine which factors before and during LRP influenced the positive surgical margin status.

## RESULTS

There was only minor agreement between the laterality of positive needle biopsies and laterality of any cancer and significant cancer on final-specimen pathology ($\kappa$ = 0.135 and 0.151, respectively). This was irrespective of the number of needle cores obtained or final-specimen Gleason grade. Similarly, the laterality of dominant cancer on needle biopsy had only a minor agreement with the location of positive surgical margins ($\kappa$ = 0.050) and fair agreement with the location of extracapsular extension on final-specimen pathology ($\kappa$ = 0.235).

## CONCLUSIONS

Preoperative needle biopsy data have only a minor correlation with the laterality of significant cancer and positive surgical margins at final pathology of LRP specimens. Recognition of this fact, and the frequent bilaterality of significant cancer, with its potential for contralateral positive surgical margins even when the biopsies are positive only unilaterally, is an important consideration when planning nerve-sparing, and potentially for focal therapy.

## KEYWORDS

prostate, cancer, biopsy, radical prostatectomy, laparoscopy

## INTRODUCTION

Routine screening with serum PSA has increased the number of men diagnosed with prostate cancer, and is responsible for a significant stage migration towards more localized and well-differentiated tumours [1]. As a result, more men with prostate cancer are candidates for nerve-sparing radical prostatectomy (RP). The advent of laparoscopic and robotic technology has led to more patients opting for minimally invasive approaches to RP. Laparoscopic RP (LRP) has been shown to provide equivalent positive surgical margin (PSM) rates to its open counterpart [2].

Nevertheless, specific recommendations about which patients should undergo non-nerve-sparing vs unilateral vs bilateral nerve-sparing have not been clarified. Many open and laparoscopic urological surgeons rely on preoperative needle-biopsy data in terms of the anatomical site of a positive biopsy and dominant lobe to help guide the clinical decision-making for choosing ipsilateral or contralateral nerve-sparing.

The aim of the present study was to conduct a detailed retrospective comparison of preoperative needle biopsy and final specimen pathological data of patients treated with LRP, to determine if the laterality of a positive biopsy should influence the surgeon's decision for ipsilateral nerve-sparing.

## PATIENTS AND METHODS

Between October 2002 and September 2006, 490 hormonally naïve patients with clinically localized adenocarcinoma of the prostate had LRP by one surgeon (I.S.G.). Preoperative biopsy and final-specimen pathological data were available from our prospectively maintained Institutional Review Board-approved LRP registry. Our LRP technique was reported previously [3].

All needle biopsy specimens were taken by referring urologists and were re-reviewed by pathologists at our institution. Following our anatomical pathology protocol, the LRP specimen was sectioned transversely at 3-mm intervals; the sections were then divided into quadrants for analysis. During LRP, frozen sections were obtained in selected patients at the surgeon's discretion for intraoperative assessment of apex and base margins.

Cancer volume was defined as 'low' when it was ≤0.5 mL, 'medium' when >0.5–<2.0 mL, and 'extensive' when ≥2.0 mL. A focal PSM refers to a solitary site of malignant cells at any inked margin, while extensive PSM refers to multiple sites of involvement. Significant cancer in LRP specimens was defined as cancer of medium or extensive (>0.5 mL) volume or any Gleason grade 4 [4–6]. The dominant biopsy side was defined as the only prostate lobe with disease for unilaterally positive biopsy cases, and the lobe with the most positive biopsy cores for bilateral cases. If there was an equivalent number of positive needle cores, the lobe with the greater percentage involvement of cancer in the cores was defined as the dominant side.

The κ statistic and 95% CI were used to compare the laterality of positive biopsy with the laterality of carcinoma on final pathology; κ values of 0.01–0.20 were considered to represent minor agreement, 0.21–0.40 a fair agreement, 0.41–0.60 a moderate agreement, 0.61–0.80 high agreement and 0.81–1.00 very high agreement. The chi-square test was used to compare all the categorical values.

## RESULTS

The demographic data of the patients are outlined in Table 1. The median (range) number of biopsies taken for each patient was 10.3 (6–24) and the median cores positive for cancer was 2.84 (1–12). Unilateral and bilateral nerve-sparing was performed in 70 (14%) and 287 (59%) patients, respectively.

The final specimen pathological data are also shown in Table 1. Extracapsular extension (ECE) was present in 111 patients (23%), with bilateral ECE in 51 (10%). In patients with needle biopsies positive exclusively in the right lobe, the final specimen pathology showed that the contralateral (left) lobe had a PSM, ECE or significant cancer in 10%, 11% and 5%, respectively. Similarly, in 156 patients with needle biopsies positive exclusively in the left lobe, the contralateral (right) lobe had a PSM, ECE or significant cancer on final specimen pathology in 12%, 8% and 7%, respectively (Table 2). Compared to the preoperative needle biopsy Gleason score, the final Gleason score remained unchanged in 59% of patients, was upgraded in 35%, and downgraded in 6% ($P < 0.001$).

A PSM occurred in 104 patients (21%; Table 3); PSM rates with and without intraoperative real-time TRUS guidance were 11% vs 27% ($P = 0.006$). Stratified by pathological stage with or without intraoperative TRUS, PSM rates for pT2a/b disease were 10% with TRUS vs 9% without TRUS ($P = 0.89$), for pT2c were 9% vs 24% ($P = 0.001$), and for pT3 disease were 15% vs 41% ($P < 0.001$). Most PSMs were apical (60%). Stratified by year of surgery, there was a trend towards a progressive decline in PSM rates between 2003, 2004 and 2005 (33%, 25% and 12%, respectively) with a slight increase in 2006 (17%). These findings tended to correlate with increasing surgeon experience and use of intraoperative TRUS, which was used in 20% of patients in 2003 (25/126), 34% in 2004 (41/121), 68% in 2005 (68/100) and 24% in 2006 (34/143).

A comparison of the laterality of positive needle biopsy with laterality of *any* carcinoma on final-specimen pathology is

| Variable | Mean (SD, range) or *n* (%) |
|---|---|
| Age, years | 59.4 (6.8, 40–76) |
| PSA level, ng/mL | 6.5 (8.9, 0.3–28.6) |
| Body mass index, kg/m$^2$ | 27.4 ± 4.1 (14.9–37.8) |
| Biopsy location of cancer | |
| Right | 154 (31.4) |
| Left | 156 (31.8) |
| Bilateral | 180 (36.8) |
| Biopsy Gleason grade | 6.4 (0.6, 5–9) |
| 5–6 | 320 (65.3) |
| 7 | 156 (31.8) |
| 8–10 | 14 (2.9) |
| Clinical stage | |
| T1c | 436 (89.5) |
| T2 | 51 (10.4) |
| T3 | 3 (0.6) |
| Median (range): | |
| Biopsies/patient | 10.3 (6–24) |
| Cores positive for cancer | 2.84 (1–12) |
| **Final pathology** | |
| Pathological Gleason grade | 6.7 (0.6, 5–9) |
| 5–6 | 182 (37.1) |
| 7 | 283 (57.8) |
| 8–10 | 25 (5.1) |
| Pathological stage | |
| pT2a/b | 51 (10.4) |
| pT2c | 315 (64.3) |
| pT3 | 124 (25.3) |
| Cancer volume | |
| Low | 104 (21.4) |
| Medium | 268 (54.7) |
| Extensive | 118 (24.1) |
| Specimen weight, g | 53.6 (21.6, 20–210) |
| ECE | 111 (22.6) |
| Unilateral | 60 (12.2) |
| Bilateral | 51 (10.4) |
| Seminal vesicle involvement | 16 (3.2) |
| Urethral shave | |
| Positive* | 5 (1.1)† |
| Negative | 193 (39.4) |
| Not done | 292 (59.5) |
| Bladder neck shave | |
| Positive* | 10 (2.1)† |
| Negative | 480 (97.9) |

*TABLE 1*
*Baseline demographics and pathology data*

**second shave negative; †10 patients (2%) had malignant cells on frozen section analysis at the bladder neck and five (1%) had similar findings on urethral shave. Of the five patients with a positive frozen section on urethral shave, two had an apical PSM on final pathology. Conversely, of the 193 patients with a negative frozen section on urethral shave, only nine (4.7%) had an apical PSM on final pathology ($P = 0.005$).*

*TABLE 2 Findings in the contralateral lobe on final specimen pathology compared to the needle biopsy data*

| | | Contralateral lobe | | |
|---|---|---|---|---|
| Positive biopsies | *N* | PSM | ECE | Significant cancer |
| Right lobe only | 154 | 16 (10.3) | 17 (11) | 8 (5.2) |
| Left lobe only | 156 | 18 (11.5) | 13 (8.3) | 10 (6.4) |
| R-side dominant* | 254 | 19 (7.5) | 6 (2.4) | 7 (2.7) |
| L-side dominant* | 236 | 25 (10.6) | 5 (2.1) | 13 (5.5) |

**The dominant biopsy side was defined as the only prostate lobe with disease for unilaterally positive biopsy cases, and the lobe with the most positive biopsy cores for bilateral cases. If there was an equivalent number of positive needle cores, the lobe with the greater percentage involvement of cancer in the cores was defined as the dominant side.*

*TABLE 3 Positive surgical margin rates associated with pathological and technical variables*

| PSM | *n* (%) |
|---|---|
| Total | 104/490 (21.2) |
| Focal | 74/104 (71.2) |
| Extensive | 30/104 (28.8) |
| According to pathological findings | |
| pT2a/b | 6/51 (11.7) |
| pT2c | 60/315 (19.0) |
| pT3 | 38/124 (30.6) |
| Without use of TRUS | 86/322 (26.7) |
| With use of TRUS | 18/168 (10.7) |
| According to location (%) | |
| Apex | 63/104 (60.6) |
| Lateral | 19/104 (18.3) |
| Posterior | 19/104 (18.3) |
| Anterior | 3/104 (2.8) |

*FIG. 1. Correlation of laterality of positive biopsies with laterality of cancer on final pathology.*

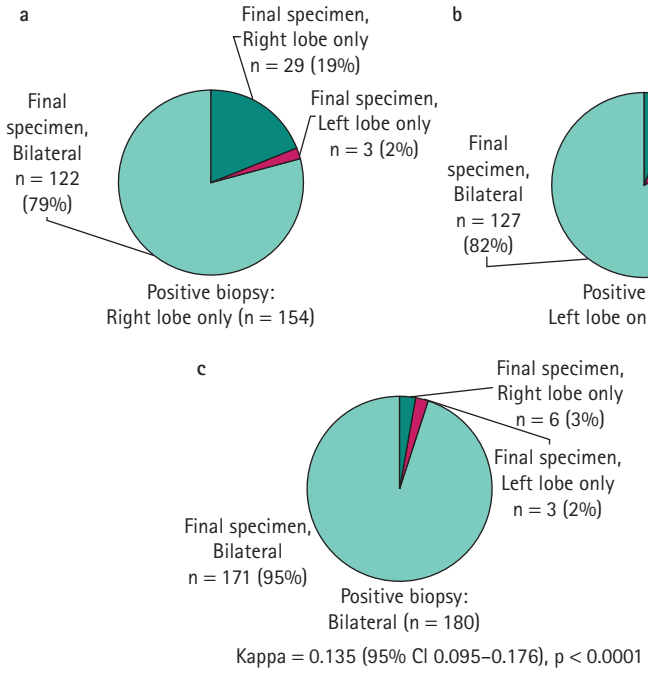
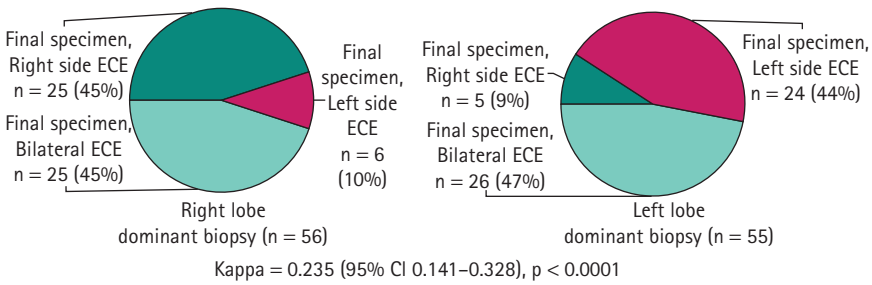



*FIG. 2. Correlation of laterality of positive biopsies with laterality of extracapsular extension on final pathology.*




shown in Fig. 1. For unilaterally positive biopsies, agreement with laterality of any cancer on final pathology was 19% on the right and 12% on the left side. For the 180 bilaterally positive biopsies there was a 95% agreement with final pathology. Taken together, there was only minor agreement between biopsy laterality and laterality of any cancer on final pathology ($\kappa = 0.135$). Furthermore, for unilaterally positive biopsies there was also only minor agreement between biopsy laterality and laterality of *significant* cancer on final pathology ($\kappa = 0.151$) and fair agreement with location of ECE on final specimen pathology ($\kappa = 0.235$, Fig. 2).

The laterality of a positive biopsy with the laterality of carcinoma on final pathology was correlated with the number of cores obtained on biopsy. Needle cores taken were ≤6 in 117 patients (24%), 7–12 in 309 (63%), and >12 in 64 (13%). The number of cores taken had no effect on the comparisons of laterality with final-specimen pathology.

There was only a minor agreement between the laterality of a positive biopsy and laterality of PSMs ($\kappa = 0.050$). Among patients with a PSM, if the right lobe had dominant cancer on needle biopsy, only 58% of PSMs occurred on the same side, while 42% of PSMs occurred on the opposite side. Interestingly, if the left lobe had the dominant cancer on needle biopsy, PSMs were still more common on the right side (49% right vs 39% left).

## DISCUSSION

While many contemporary prostate surgeons take into account the laterality and location of positive biopsies when planning the extent of side-specific nerve-sparing, there has not been sufficient evidence reported to validate or refute this practice. To the best of our knowledge, the present study is the first to correlate preoperative needle biopsy and final specimen pathology for cancer location, ECE and PSMs after LRP. Our data indicate that needle biopsies to diagnose prostate cancer do not accurately reflect the extent of prostate cancer, and as such surgeons should exercise caution when deciding to perform nerve-sparing based exclusively on this information.

Prostate cancer, being multifocal and often bilateral, is not completely sampled with biopsy techniques. For the laterality of tumour, only 37% (180) of the present patients had bilaterally positive biopsies, while on final pathology 86% (420) of patients had bilateral disease, with 58% (285) having significant bilateral cancer. The accuracy of sampling was not significantly improved when the analysis was stratified based on the number of cores or Gleason score.

Prevailing wisdom indicates that small foci of well-differentiated prostate cancer might not compromise the cancer-specific survival of patients, which is more probably driven by the dominant or significant cancer nodule [4]. The discrepancy in unilateral disease found on biopsy vs bilateral disease on final-specimen pathology could be related to insignificant contralateral tumours. With this in mind we compared the laterality of a positive biopsy with the laterality of significant cancer on final pathology, yet still found only a minor correlation in cases with a unilaterally positive biopsy. Thus, despite exclusively unilaterally positive biopsies, significant cancer could still be present bilaterally or contralaterally.

Several groups have correlated preoperative clinical and biopsy characteristics with the incidence of ECE and biochemical recurrence [7–11]. Taneja *et al.* [7] reported that the positive predictive value of individual cores for locating ECE was not adequate to guide decisions for nerve-sparing for open RP. Conversely, Elliott *et al.* [8] reported that side-specific biopsy results can predict ECE ipsilaterally, but they used multiple biopsies (≥15) to improve the predictive capacity of their biopsy results. Others have developed validated tools which take into account preoperative characteristics for predicting side-specific ECE [12,13]. In the present series, the laterality of the dominant side on biopsy correlated with the side of ECE in only 44% of cases, probably due to the presence of bilateral ECE in almost half of patients with ECE. Our data indicate that despite negative needle biopsies from one side of the prostate (310 patients), that side can still have a PSM in 11%, ECE in 10% and significant cancer in 6% of patients. Therefore we recommend against using dominant-laterality biopsy data as the sole criterion for deciding whether or not to use unilateral nerve-sparing.

The information from this study is also pertinent in the light of increasing interest in focal therapy for prostate cancer. The lack of correlation of the laterality of cancer between the biopsy and final specimen analysis should alert clinicians to the potential for incomplete treatment with focal therapy. Such measures as saturation biopsy and correlation with various imaging methods might improve the ability to predict the location of tumours and increase the accuracy of focal treatments.

The overall PSM rate was 21%, which decreased to 11% with the use of intraoperative real-time TRUS. There was a progressive yearly decline in PSM with a slight increase in 2006, which correlated with the decreased use of intraoperative TRUS during that year, for logistical reasons. These results concur with the findings of Ukimura *et al.* [14]. The availability of intraoperative TRUS is limited for most urologists. Nevertheless, preoperative TRUS can provide information on tumour location and possible ECE [15].

An interesting finding of the present study was the higher right-sided PSM rate regardless of the dominant side of disease on biopsy. This might be due to a natural tendency of a right-handed surgeon, as is the senior author, to unwittingly attempt a more aggressive nerve-sparing dissection on the right side of the prostate. As such, right-handed surgeons should keep this in mind when approaching right-sided neurovascular bundle dissection. Further studies are needed to confirm these findings.

The limitations of this study are inherent in its retrospective nature. In addition, the biopsy technique and number of cores obtained could not be standardized, as all patients were diagnosed locally and then referred for RP to our centre. The median (range) number of biopsy cores, at 10.3 (6–24), was fewer than is commonly obtained in many practices at present, and results should be considered with this in mind. Nevertheless, our study represents an extensive analysis of the correlation of preoperative needle biopsy and final specimen pathology after LRP.

In conclusion, there is only a minor correlation between the laterality of cancer on prostate biopsy with the laterality of significant prostate cancer on final pathology. Therefore, the laterality of a positive biopsy should not be the only criterion for sacrificing or preserving the ipsilateral neurovascular bundle. Recognition of the frequent bilaterality of significant cancer, with its potential for contralateral PSM, is important even if preoperative needle biopsies are positive only unilaterally.

## CONFLICT OF INTEREST

None declared.

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Abbreviations: **(L)RP**, (laparoscopic) radical prostatectomy; **PSM**, positive surgical margin; **ECE**, extracapsular extension.