The Number of Cores Taken in Patients Diagnosed with a Single Microfocus at Initial Biopsy is a Major Predictor of Insignificant Prostate Cancer

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Abbreviations and Acronyms

AS = active surveillance

ECE = extracapsular extension

GS = Gleason score

LNI = lymph node invasion

MiFC = microfocus of prostate cancer

PCa = prostate cancer

pIPCa = pathologically confirmed insignificant prostate cancer

PSA = prostate specific antigen

RP = radical prostatectomy

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Purpose: Patients with a single microfocus of prostate cancer at initial biopsy represent the ideal candidates for active surveillance. We investigate whether the number of cores taken affects the concordance rate between microfocus of prostate cancer and the confirmation of a pathologically insignificant prostate cancer at radical prostatectomy.

Materials and Methods: Data were analyzed from 233 patients with a single microfocus of prostate cancer at initial transrectal prostate biopsy (a single focus of Gleason 6 involving 5% or less of the core) subsequently treated with radical prostatectomy. The chi-square test, cubic spline analyses and logistic regression analyses were used to depict the relationship between the number of cores taken and the probability of confirming the presence of an indolent disease (pathologically confirmed insignificant prostate cancer defined as radical prostatectomy Gleason score 6 or less, tumor volume 0.5 ml or less and organ confined disease).

Results: Overall 65 patients (27.9%) showed pathologically confirmed insignificant prostate cancer at radical prostatectomy. The rate of pathologically confirmed insignificant prostate cancer was 3.8%, 29.6% and 39.4% in patients who underwent biopsy of 12 or fewer cores, 13 to 18 cores and 19 or more cores, respectively ($p < 0.001$). After adjusting for the available confounders, age ($p = 0.04$), number of cores taken ($p < 0.001$) and prostate specific antigen density ($p < 0.02$) were independent predictors of pathologically confirmed insignificant prostate cancer.

Conclusions: Of patients diagnosed with a single microfocus of prostate cancer the number of biopsy cores taken was a major independent predictor of having pathologically confirmed insignificant prostate cancer at radical prostatectomy. Therefore, when active surveillance is considered as a possible alternative in patients with microfocus of prostate cancer, the number of cores taken should be taken into account in decision making.

Key Words: prostatic neoplasms, watchful waiting, prostate, biopsy

PATHOLOGICALLY confirmed insignificant prostate cancer at radical prostatectomy is defined as a low grade, small volume and organ confined prostate cancer that may be indolent and is unlikely to progress to clinical significance without treatment.[1–3] In this context Epstein et al have previously described the widely accepted criteria to define pIPCa at RP (patho-

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logical GS 6 or less, tumor volume 0.5 ml or less and organ confined disease).[2]

During the last 2 decades the rate of patients diagnosed with pIPCa has been increasing due to the widespread use of PSA and the introduction of extended core biopsy schemes. To date, the incidence of pIPCa ranges between 2% in the overall population and 31% when considering only series including low risk patients.[1,2,4–9]

Patients harboring pIPCa represent the ideal candidates for active surveillance.[10] Moreover, accurate pIPCa prediction may help clinicians avoid overtreatment and potential treatment induced complications.[11] Therefore, several efforts have been made to predict pIPCa by relying on clinical characteristics at initial biopsy. In this regard Epstein et al developed a preoperative model to identify these patients.[1] Specifically they found that the combination of PSA density 0.15 ng/ml/cm^3 or less, GS 6 or less, fewer than 3 positive cores at prostate biopsy and less than 50% of cancer involvement per core provided 73% accuracy in predicting pIPCa. However, this finding implies that approximately 30% of patients with favorable clinical characteristics had disease under staged, resulting in a nonnegligible underestimation of the extent of PCa.[7,12,13] Nomograms based on clinical and pathological variables have also been developed with a concordance index ranging from 65% to 90%.[8,14–17] Finally, more stringent clinical criteria have been tested to identify pIPCa, and the concept of MiFC, defined by a single neoplastic lesion 5% or less in 1 biopsy core, or 0.5 mm or less in length, was recently proposed.[18] However, after having systematically reviewed the literature available on this issue, Harnden et al suggested that between 33% and 84% of patients with a single, minute focus of cancer at initial biopsy had at least 1 unfavorable pathological feature in the RP specimen.[19]

In the current study we investigated the role of clinical and pathological features at initial biopsy in low risk patients with PCa in confirming the presence of pIPCa, taking into account only patients affected with a single MiFC at initial transrectal biopsy. Moreover, we tested the hypothesis that the number of cores taken affects our ability to confirm pIPCa after diagnosis of a single MiFC.

MATERIALS AND METHODS

Of 8,375 consecutive patients who underwent an initial transrectal prostate needle biopsy from November 2000 to February 2011 at our institution, 6.4% (536) were diagnosed with a single MiFC, defined as a single neoplastic lesion with a GS of 6 in a single biopsy core involving 5% or less of the core, or 0.5 mm or less in length. Of those patients 233 (43%) were subsequently treated with RP and represent the study cohort.

The number of cores taken at prostate biopsy was decided according to the clinical characteristics of the patients and the urologist preference. Although the role of saturation biopsy as an initial strategy is controversial,[20,21] from September 2005 to June 2008 we prospectively performed a 24-core biopsy scheme in 617 consecutive patients suspected of harboring PCa to identify the optimal combination of sampling sites that permits the detection of 95% of the cancer with the minimum number of cores.[22] Therefore, the number of cores taken at prostate biopsy in our cohort was up to 24 and 42.5% of patients were submitted to a saturation biopsy scheme at initial evaluation (19 or more cores, table 1). On the other hand, the minimum number of cores taken in our patient cohort was 6 and only 9 patients had fewer than 10 cores taken.

All patients had complete clinical and pathological evaluations including age, PSA at diagnosis, clinical stage, prostate volume, biopsy Gleason score and number of cores taken. At RP all prostates were inked, whole mounted and step sectioned at 3 mm intervals. All sections were examined by the same genitourinary pathologist (MF). At final pathology, pIPCa was defined according to Epstein's criteria (RP Gleason score 6 or less, tumor volume 0.5 ml or less, and organ confined disease).[2] Tumor volume was calculated by visual inspection. The percentage involvement of each slide was visually estimated, and the assessment of tumor volume for the entire prostate was accomplished by summing and averaging the area on each slide, and then multiplying by the specimen weight. Visual measurement allowed the overall tumor volume to be calculated by considering multifocality and irregular shapes.

The variable depicting the number of cores taken was considered as a continuously coded variable in all univariable and multivariable regression analyses, for avoiding subjective and arbitrary selection. In addition, we relied on cubic spline analyses to depict a potential nonlinear effect between the number of cores taken and the end point of interest. Finally, patients were arbitrarily divided according to the number of cores taken at prostate biopsy into the 3 groups of sextant biopsy scheme (12 or fewer cores), extended biopsy scheme (13 to 18 cores) and saturation biopsy scheme (19 or more cores).

The chi-square test and cubic spline analysis were used to evaluate the incidence of pIPCa according to the number of cores taken at biopsy and the correlation between the number of cores taken and the probability of having pIPCa at radical prostatectomy, respectively. Finally, we relied on univariable and multivariable logistic regression analyses to identify potential predictive factors of pIPCa at RP. Two models were derived to avoid overfit in multivariable analyses. In the first model we tested patient age, PSA at biopsy, prostate volume and number of cores. In the second model we tested patient age, number of cores and PSA density without including PSA and prostate volume. Except for clinical stage and PSA density, for which we tested the cutoff value identified by Epstein et al of 0.15 ng/ml/cm^3,[1] all variables tested in regression models were considered continuously coded variables. All analyses were per-