Re: Pathologic Features of Prostate Cancer Found at Population-Based Screening With a Four-Year Interval

A recent report in the Journal (1) reported on the first two rounds of population-based screening at intervals of 4 years in the European Randomized Study of Screening for Prostate Cancer. A total of 4133 men aged 55–75 years were screened in the first round, and 2385 of these men were screened in the second round, 4 years later. Sextant biopsy specimens were obtained under ultrasound guidance during both rounds of screening, with all cores embedded separately; the total amount of cancer in needle biopsy sets and the percentage of adenocarcinomas of Gleason score 7 or higher were calculated.

The main result of Hoedemaeker et al. (1) was that the second round of screening found less cancer (median of 4.1 versus 7 mm in the biopsies) and fewer cancers of Gleason score 7 or higher (median of 16% versus 36%) than the first round of screening. On the basis of these data, the authors assume that the cancers were smaller in the second round of screening than in the first round.

However, the U.S. literature is replete with evidence that the amount of cancer found in sextant biopsies of the prostate [such as the sextant biopsies of Hoedemaeker et al. (1)] is unrelated to the volume or grade of the largest (index) cancer in the prostate as determined by radical prostatectomy. For example, a recent study from my group (2) shows the absence of any relationship between the index (largest) cancer volume in 222 radical prostatectomy specimens and the number of positive sextant biopsies, the total length of cancer in the biopsies, and the percentage of cancers with Gleason grade 4/5 in sextant biopsies (Fig. 1). In this study, all 222 biopsies were reviewed by the same expert pathologist who later determined the index (largest) cancer volume from 3-mm step-sections, a protocol we have used at Stanford since 1983 in over 2000 consecutive cases.

Fig. 1. A) Correlation between number (No.) of positive cores in biopsies and cancer volume in radical prostatectomy specimens. B) Correlation between total length of cancer in biopsies and cancer volume in radical prostatectomy specimens. C) Correlation between percent of Gleason Grade 4/5 on biopsies and cancer volume in radical prostatectomy specimens. We used 0.5 cc as cutoff for clinically significant cancer volume. Used with permission from American Urological Association Education and Research, Inc.

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prostates. All biopsy results were determined long before the prostate specimen was reconstructed. As Fig. 1 shows, the Pearson correlations are much too low to be of any practical or theoretical use. More important, the vertical spread of index cancer volume is so wide at any given value for the three volume-related measurements in the biopsies that the relationship between the results of sextant biopsies and the size of the largest cancer in the prostate is meaningless. Because these biopsy parameters are essentially the same as those measured by Hoedemaeker et al. (1), the authors should look for reasons other than a reduction in cancer volume as the cause of the differences in positive biopsy rates between the first and second screens.

One reason why sextant biopsies are inadequate for estimation of the index cancer volume is the propensity of multiple biopsies to sample smaller secondary cancers that are independent of the index tumor. These small secondary independent cancers are present in 83% of radical prostatectomies performed at Stanford (3). We found earlier that 14% of secondary cancers less than 0.2 cm$^3$ and 44% between 0.2 and 0.5 cm$^3$ were sampled by the sextant biopsy technique (4).

**RESPONSE**

Dr. Stamey questions whether the use of needle biopsy characteristics justifies the conclusions in our report. Indeed, a large number of studies report a limited predictive value of needle biopsies for tumor features in the prostate, for instance (1,2). We agree that the low correlation coefficients found in these studies constitute major limitations for the prediction of tumor characteristics from needle biopsy findings on an individual patient basis. This is unfortunate because a number of studies have shown that, especially in conjunction with prostate-specific antigen, needle biopsy parameters seem to be the best predictors of tumor characteristics (3,4).

Our study was not performed to predict prostate cancer characteristics on an individual patient basis but compares two large groups of patients (consisting of 210 and 94 men). Furthermore, the main purpose of our report was not to predict tumor characteristics in radical prostatectomy specimens but to reveal biopsy-related prognostic factors at rescreening after 4 years. With the current uncertainties concerning the effects of early detection and treatment of prostate cancer, the urgent clinical need remains to predict the outcome of localized prostate cancer by pretreatment parameters rather than on the characteristics of radical prostatectomy specimens. We are encouraged by the fact that, in a study comparing biopsy and radical prostatectomy characteristics (5) as well as in the most relevant natural history studies (6,7), progression-free survival and disease-specific survival show a statistically significant correlation with biopsy features.

Prostatic biopsy features, therefore, do have predictive value for clinical outcome, especially when large groups of patients are compared. The observed decline in the amount of cancer in the needle biopsies in the men with prostate cancer in the second screening round of our study was considerable. The median amount of tumor in needle biopsies in round 2 was nearly half that in round 1. Furthermore, men with high prostate-specific antigen levels ($\geq$10 ng/mL) showed an even more pronounced decline in the median amount of cancer (from 14.6 mm in round 1 to 4.2 mm in round 2) and in the tumor detection frequency (from 58% in round 1 to 23% in round 2). Especially when these results are viewed in the context of other observations in our study, such as the statistically significant decline in needle biopsy grade and the considerable shift toward more favorable tumor categories, both of which were observed in round 2, it is highly unlikely that the observed decreased amount of tumor in the biopsy cores of round 2 is a chance finding. In our view, the main conclusion of our report, which is not that the tumors in round 2 are smaller than the tumors in round 1 but that there is a lack of evidence for an increase in size and a decrease in degree of differentiation in round 2 tumors, seems justified.

**NOTES**

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