Tumor Amount in Prostatic Tissues in Relation to Patient Outcome and Management

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The clinical significance of prostate cancer extent in prostatic tissue is dependent on the prostatic tissue sample type. For prostate needle core tissue and prostatic chips from transurethral resection of the prostate (TURP), the amount of cancer is of established clinical significance, whereas the intraglandular extent of cancer in radical prostatectomy tissues, although prognostic, is not routinely used for patient management.

In the December 2008 and January 2009 issues of the Journal, Vollmer1,2 contributes important knowledge on the relationship of the amount of prostate cancer in needle core tissue1 and radical prostatectomy tissue2 with patient outcome. Prominent strengths of these investigations include the rigorous statistical analyses, the size of the characterized patient populations (>400 patients in each), and the facts that these were prospective studies and the clinical end point was overall survival.

Prospective research studies reduce the capacity for selection bias that is a striking feature of retrospective studies. The pathology literature would benefit by inclusion of more studies that were designed as prospective. Commonly used end points in prostate cancer research studies are pathologic stage and Gleason grade and elevation of the serum prostate-specific antigen (PSA) level after treatment (so-called PSA or biochemical failure). However, PSA failure is a surrogate for survival, and not all men who experience a rising PSA level after treatment will have diminished life expectancy. Survival is often considered the “gold standard” end point for cancer treatment trials and should be the gold standard in characterization of the clinical significance of pathologic features in prostatic tissues, including tumor extent. Overall survival and cancer-specific survival have been used. Cancer-specific survival can be instructive in older patient groups that generally have a high incidence of comorbidities and intercurrent deaths. Few studies have linked tumor extent in prostatic tissue to overall survival like the studies by Vollmer1,2 have.

Amount of Cancer in Prostate Needle Core Biopsy Tissue

The amount of cancer in prostate needle core tissue is an important prognostic indicator that is linked to pathologic and clinical end points and can be used clinically in patient management. Tumor extent in needle core tissue has been correlated with the pathologic end points of tumor volume, pathologic stage, and margin status,3-5 although the correlations are modest. In combination with clinical factors and Gleason grade, tumor extent in needle core tissue can be used to define criteria that predict pathologically (and thereby potentially clinically) insignificant prostate cancer.6 These Epstein criteria can be used to enroll patients into active surveillance (watchful waiting) management programs and trials.7 Furthermore, clinical nomograms that incorporate tumor extent in needle core tissue (millimeters of cancer) have been developed to predict the probability of insignificant cancer in the whole gland.8,9 Tumor extent in needle core tissue is predictive of response to surgery10 and radiation therapy,11 and nomograms have been devised to predict response to therapy based on pretreatment clinical and needle biopsy findings, including needle biopsy tumor extent quantified as the number of positive cores and number of negative cores.12

There are several different measures of tumor extent in needle core tissue Table 1, and these are highly interrelated,
as previously shown and as shown for percentage of tumor and tumor length by Vollmer. Based on the main finding of this study, that men who die prematurely after the diagnosis of prostate cancer have a greater quantity of tumor in needle biopsy tissue, Vollmer recommends reporting one of the measures of tumor extent (percentage of tumor or length of tumor in millimeters) in needle core tissue. Reporting of needle biopsy tumor extent is also recommended by the College of American Pathologists (CAP) and the World Health Organization. Most urologic pathologists (80%) report the number of involved cores and percentage of tissue involved, with 41% reporting millimeters of cancer length. I report for each prostate needle biopsy carcinoma case 3 measures of tumor extent: number of positive cores of the total number of cores, percentage of tumor (by simple visual inspection), and total tumor length in millimeters. I report all of these measures because different clinical nomograms use different measures of tumor extent in needle biopsy tissue. I report by container (and there should be no more than 2 cores and, preferably, 1 core submitted in each container).

In cases where there is fragmentation of cores, one can report the number of positive core fragments of the total number of fragments, and here, percentage of tumor and linear millimeters are particularly important to report. In determination of percentage of carcinoma and linear millimeters of carcinoma, there is no accepted approach on how to address discontinuous foci of carcinoma.

An important consideration is the time and effort needed to report these different measures, and Vollmer addresses this in the “Discussion” section of the article. Of these measures, assessment of linear millimeters may take the longest but may be quickly performed by using a plastic ruler placed directly on the glass slide or by using the ruler to measure dots or lines placed by pen next to the foci of cancer. Of course, if one wants to use a micrometer, this is an option too.

### Amount of Cancer in TURP Chips and Enucleation Tissues

Although not the subject of these 2 articles, it should be noted that the amount of tumor in TURP chips and enucleation (open or simple prostatectomy) specimens should always be reported because for incidentally detected tumors, this amount impacts prognosis and stage. Tumor involving 5% or less of TURP tissue by visual inspection of tissue sections by light microscopy is clinical stage T1a, whereas more than 5% is stage T1b. An option is to also report the number of positive chips of the total number of chips, which predicts prostate cancer–specific mortality. I report both measures: percentage of tissue involved by carcinoma and percentage (number positive/total number) of chips involved by carcinoma.

### Amount of Cancer in Radical Prostatectomy Tissues

In contrast with needle biopsy and TURP chip or enucleation tissues, the extent of carcinoma in whole prostate glands is not of established clinical usefulness and is not embedded in postoperative clinical tools such as nomograms that are used in patient management, such as consideration for adjuvant therapy after surgery. Yet, tumor size in the prostate has been significantly associated with patient outcome in a large number of studies. Also, all definitions of what constitutes pathologically insignificant tumor in the
prostate include tumor size. One key question is whether tumor size imparts additional information, as judged by multivariate analyses, beyond the established prognostic indicators of PSA, pathologic stage, and Gleason grade.

Another question is this: How is tumor size in the prostate best measured? Because it is not feasible to obtain a gross measurement of tumor size in the prostate, this is a histologic task. A number of methods are available for determining tumor size in radical prostatectomy tissues, including visual inspection yielding percentage of tumor, grid morphometric measurement yielding percentage of tumor or tumor volume, measurement of the diameter of the largest tumor focus, counting of the number of blocks involved by tumor, and computer-assisted image analysis yielding tumor volume in cubic centimeters (reviewed by Humphrey and Vollmer20). These different measures, while related, may not provide the same prognostic information. Indeed, in the second article, Vollmer2 makes the important point that of 22 studies that have examined the relationship of tumor size and outcome, just 29% demonstrated that tumor volume in cubic centimeters is related to outcome, whereas 67% showed that percentage of tumor in the prostate gland is related to outcome. Percentage of tumor in the prostate has been shown in several studies to be significant in multivariate analysis in predicting PSA failure after surgery,21-23 even for pathologically organ-confined carcinoma,21,22 and now Vollmer2 shows that it is significant in association with survival in multivariate analysis.

Even though tumor size is not currently used in clinical decision making, it is recommended that an estimate of tumor size be reported for all radical prostatectomy cases.13-15 The CAP13 recommends that “the percentage of tissue involved by tumor can be eyeballed.” In addition, “it may be possible to measure a dominant nodule in at least two dimensions and/or to indicate the number of blocks involved by tumor over the total number of prostatic blocks submitted.” I personally report percentage of carcinoma, as determined by the grid method, but percentage of carcinoma determined by visual inspection is just as highly predictive of image analysis—quantified tumor volume,20 and in a European survey,24 visual estimation of percentage of carcinoma was the most widely reported measure of prostatic tumor size.

Although tumor volume measurements in cubic centimeters are the gold standard for tumor size in a research setting, providing this measurement in routine practice is impractical because of the time-intensive and labor-intensive nature of mapping, the use of image analysis, and the need for complete embedding of the whole prostate gland. In comparison, Vollmer2 estimates that visual inspection estimates to determine percentage of carcinoma take no more than 5 minutes per radical prostatectomy case. Also, percentage of carcinoma estimates are prognostic even for partially sampled glands.25 Currently, percentage of carcinoma in radical prostatectomy tissues provides patients and clinicians with an idea of tumor burden that is related to early death for prostate cancer. In the future, percentage of carcinoma and additional measures of tumor size in the prostate may enable pathologists and clinicians to identify high-risk patients who may benefit from adjuvant therapy.

Overview

A theme from both Vollmer1,2 articles and from the preceding discussion is that the percentage of prostate tissue involved by carcinoma, including needle biopsy tissue, TURP chips, enucleation tissue, and radical prostatectomy tissue, is significantly associated with the outcome for men with prostate cancer. Reporting of percentage of prostatic tissue involved by tumor is recommended for all prostatic tissue specimens.13 Additional measures of tumor amount should definitely be reported for needle biopsy specimens (Table 2), and consideration should be given to reporting additional measures of tumor extent for TURP chips and radical prostatectomy specimens.

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References

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