Early detection of prostate cancer with ultrasound-guided systematic needle biopsy

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Introduction: *Prostate biopsy strategies have greatly evolved over the past 2 decades.*

Methods: *We performed a literature review which addressed the initial and repeat biopsy schemes, pathologic risk factors for a positive repeat biopsy, and the ideal timing as well as the number of repeat biopsy sessions.*

Results: *Extended biopsy schemes (11-13 cores) should be used at initial and repeat biopsy. In the era of extended biopsy schemes, high-grade prostatic intraepithelial neoplasia no longer represents an independent predictor of prostate cancer on repeat biopsy. Conversely, the risk is appreciably increased with atypical small acinar proliferation, and its presence warrants a repeat biopsy, which may be performed as soon as the pathologic findings of the previous biopsy become available. Second and subsequent repeat biopsies carry a low detection yield. In most instances, the decision regarding the indications and the timing of a third or subsequent biopsy may be made after a 6 to 12 months interval following the repeat biopsy.*

Conclusion: *Biopsy strategies and pathologic predictors of an increased risk of prostate cancer have appreciably changed over the past 2 decades.*

Key Words: biopsy, prostate cancer, high-grade prostatic intraepithelial neoplasia, atypical small acinar proliferation

Introduction

In 1989 and 1990, reports from Hodge and Cooner transitioned the urologic community from the era of tactilely guided biopsies to ultrasound-guided biopsies. Cooner demonstrated that the detection rate may be increased from 1.7% to 14.6% when ultrasound-guided biopsies are performed instead of tactilely guided biopsies.[1] Hodge determined that in men with palpably suspicious prostates, 66% of biopsies may be expected to be positive for cancer.[2] Moreover, Hodge showed that additional systematic biopsies add valuable information on cancer volume, Gleason grade and the potential location of surgically positive margins.[3] In 1995, two investigators suggested that sextant biopsies may miss a substantial proportion of cancers located in prostates larger than average.[4,5] These observations were further explored with computer simulations.[6,7] Results from a three-dimensional computer model of the prostate, suggested that one peripheral zone biopsy should be obtained for each 5 cc of total prostate volume. Therefore, sextant biopsy appeared adequate in men with 30 cc glands. Conversely, 12 cores were recommended in men with 60 cc glands.[7] These findings prompted a reassessment of biopsy strategies with the intent of maximizing the yield of detection. Laterally directed sextant biopsies were suggested by Stamey.[8] Others suggested increasing the density of sampling.[6,7]

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Initial biopsy schemes

Eskew et al reported a prospective trial of sextant versus 13 core biopsy strategy, which demonstrated that the sextant approach was associated with a 35% false negative rate.[9] The grade of missed cancers was predominantly (83%) Gleason 6 or higher. Levine et al performed two consecutive sets of sextant biopsies

and found a 30% false negative rate, when sextant was compared to a double sextant approach.[10]

Investigators at the MD Anderson Cancer Center used digitized whole mount radical prostatectomy specimens to simulate several biopsy schemes, which ranged from 2 to 18 cores.[11] The highest detection rate was noted with an 11 core regimen (9 PZ + 2 TZ), which detected 94% of all cancers. The 13-core biopsy scheme, suggested by Eskew, detected 86% of all cancers, and the sextant approach detected 73%. Thus, a 29% increase in detection was noted for the 11-core approach and a 13% increase in yield was noted for the 13 core approach. These were respectively associated with a 50% and 24% increase in the detection of clinically insignificant prostate cancer (cancer volume 0.5 cc or less). Investigators from Baylor College of Medicine also examined the trade-off between significant and insignificant cancer detection in men subjected to 12 PZ biopsies.[13] Their data demonstrated that when 12 core biopsies are performed, the rate of clinically insignificant prostate cancer detection increases by 10.8% (from 22.7% to 33.5%). This was offset by improved detection of clinically significant cancer, which increased by 15.3%.

These findings indicate that the increase in detection rate will be invariably associated with an increase in the detection of clinically insignificant prostate cancer. This is in agreement with earlier observations made by Terris who determined that systematic sextant biopsies yield a 30% rate of clinically insignificant prostate cancer (cancer volume less than 0.5 cc).[13] Despite this worrisome finding, additional benefits of extended biopsy schemes have been reported. Data from Baylor College of Medicine suggested that despite increased detection of clinically insignificant prostate cancer, the 12 core biopsy regimen provides valuable staging information.[14] Improved staging of prostate cancer was also reported by investigators at MD Anderson Cancer Center, when the 11-core regimen was examined.[15] Concurrently, investigators from Stanford University, relinquished their reluctance towards the 12 core biopsy regimen and reported that 12-core biopsy outperformed all other regimens, especially in men aged 60 years or less or those with PSA values 7 ng/ml or less.[16]

In summary, these findings indicate that a sextant biopsy scheme is associated with a 35% false negative biopsy rate when it is compared to more extensive sampling schemes, such as 11 or more cores. Increasing the number of biopsies will also increase the detection of clinically insignificant prostate cancer up to 30%. However, this disadvantage is offset by the concomitant increase in the detection rate of significant cancer and in improved staging information. Clinical and computer simulation data indicate that between 11 and 13 cores are indicated when the initial biopsy of the prostate is contemplated.[9-12,16] Although, investigators from MD Anderson Cancer Center suggest two TZ biopsies, others suggest exclusive PZ biopsies,[11] at the time of initial biopsy.[9,10,12,16] Based on these data, 12-core PZ biopsy appears to be the ideal biopsy strategy and is recognized as a standard of care at our institution. This biopsy scheme includes traditional sextant cores plus six laterally directed PZ biopsies, taken from the base, mid and apex. In men with prostate volumes in excess of 60 cc, one additional biopsy is taken for each 5 cc of PZ tissue in excess of the 60 cc, as suggested by computer simulation data.[7] Finally, at initial biopsy we refrain from TZ sampling, as substantiated by previous observations.[17,18]

Repeat prostate biopsy

Repeat biopsy has received a similar extent of attention to initial biopsy, with respect to efforts aimed at elucidating the optimal biopsy scheme. Based on findings from men undergoing initial prostate biopsy, it may be extrapolated that a sextant biopsy is no longer adequate in those presenting for a repeat biopsy. Basillote and colleagues demonstrated that the false negative rate on initial biopsy was higher in men with large prostates (50 cc or greater) than in small prostates.[19] This contention was formally tested by Babaian and colleagues, who demonstrated that after an initial negative 11 core biopsy, a repeat 11 core biopsy will on average yield a 22% positive biopsy rate.[20] McCullough and colleagues performed 13-core repeat biopsies and found cancer in 31% of men with one previous negative sextant biopsy, in 33% of men with two previous negative sextant biopsies, and in 38% of men with one negative 13-core biopsy.[21] More extensive sampling schemes have been examined by Amling and colleagues, who have found a 30% rebiopsy rate, when 22 cores were taken under intravenous sedation.[22] Lieber and colleagues have assessed the yield of a 23 core scheme, performed under general anesthesia, spinal anesthesia, or intravenous sedation and reported a 34% positive rebiopsy rate.[23] These findings indicate that an extended biopsy scheme is indicated at repeat biopsy. When more extensive, repeat sampling schemes are used, one in three men may be expected to be diagnosed with prostate cancer. Although, more detailed sampling than with sextant approach is justified, saturation biopsy schemes (22 cores or

higher) have not yielded better results than the 13-core biopsy scheme. Based on these findings, at our institution a 12-core PZ biopsy is recognized as a standard of care for men requiring a repeat biopsy. Based on considerations suggested by Basillote and based on computer simulation data, in men with large prostates (in excess of 60 cc), one additional biopsy is taken for each 5 cc of PZ tissue in excess of 60cc.[7,19] Peripheral zone biopsies are performed at the discretion of the attending urologist. However, this is not done routinely, as only 4.1% of cancers, represented cancers that were exclusively diagnosed with TZ biopsies in a large cohort of 847 consecutive patients evaluated with PZ and TZ biopsies.[17]

The effect of extended biopsy schemes on pathologic biopsy findings

The advent of extended biopsy schemes has changed the status of established pathologic risk factors, that predict a positive repeat biopsy.[24] High grade prostatic intraepithelial neoplasia (HGPIN) includes prostatic intraepithelial neoplasia-2 and prostatic intraepithelial neoplasia-3.[24] The prevalence of HGPIN on needle biopsy varies from 1.5% to 24%, with a median prevalence of 5%-6%. In the era of sextant biopsies, HGPIN on initial biopsy was associated with 27% to 79% rate of prostate cancer on repeat biopsy.[24] However, recent reports indicate that HGPIN on initial 11-core biopsy is associated with at most 22% cancer detection rate at subsequent biopsy.[20] Lieber and colleagues, who used a saturation biopsy approach (23 cores) reported, that men with previous HGPIN were found to harbor prostate cancer on repeat biopsy in 31% of cases.[23] In their study, the risk associated with previous HGPIN was not different from that associated with persistently elevated or rising PSA: 32% with abnormal PSA were found to have cancer on repeat biopsy. A multivariate analysis performed by Fowler, indicated that presence of HGPIN on initial biopsy was not associated with an increased risk for presence of cancer on repeat biopsy.[25] Babaian and colleagues, confirmed these findings, and reported that neither the presence of HGPIN on initial biopsy, nor the number of cores containing HGPIN on initial biopsy represented statistically significant multivariate predictors of cancer on repeat biopsy.[15] Taken together, these data indicate that in men assessed with an extended initial prostate biopsy regimen (11 to 13 cores), the mere presence of HGPIN at initial biopsy no longer represents an indicator for a repeat biopsy. Repeat biopsies may still be indicated due to other pathologic, clinical or biochemical findings.

Atypical small acinar proliferation (ASAP) represents a persistent risk factor for presence of invasive caner at repeat biopsy, even in men subjected to extended biopsy schemes.[24] In most instances the diagnosis of ASAP is established when focal carcinoma is seen, but insufficient architectural or cytological atypia is present to warrant a definitive diagnosis of cancer.[24] Other entities may also be given the diagnosis of ASAP, such as HGPIN, benign mimickers of cancer and reactive atypia.[24] Therefore, definitive treatment is not recommended and a repeat biopsy should be performed. ASAP at initial biopsy was associated with cancer on repeat saturation biopsy (23 cores) in 43% of men studied by Lieber and colleagues.[23] More dated studies, where sextant biopsies were used demonstrate a 42% to 57% rate of prostate cancer on repeat biopsy performed for ASAP on initial biopsy.[24] Brausi and colleagues examined radical prostatectomy specimens of men with ASAP and found invasive cancer in all 25 radical prostatectomy specimens.[26] Despite this controversial report, a repeat biopsy is invariably recommended if the diagnosis of ASAP is made.

The timing and the yield of repeat biopsies

Djavan and colleagues have demonstrated that the rate of prostate cancer diagnosis is respectively 5% and 4%, when a third and fourth consecutive biopsy are performed.[27] Although, these data are based on sextant sampling they demonstrate a sharp decrease in detection, relative to first (22% detection rate) and second biopsies (10% detection rate). In Djavan's cohort of 1051 men, repeat biopsies were performed at 2 to 6 weeks intervals. Equally favorable morbidity profiles were recorded in men subjected to a single biopsy session, as in men exposed to repeat biopsies.[28] These findings suggest that the first repeat biopsy may be associated with the highest cancer detection yield. Moreover, the repeat biopsy session may be scheduled as soon as the pathologic findings of the initial biopsy are available. At our center, in most men a repeat biopsy is scheduled a few weeks after the initial biopsy. We rarely perform more than one repeat biopsy within a 6-12 months interval. In most men with two negative biopsies, the indication and the timing of a subsequent biopsy is determined after a 6 to 12 month interval.

Conclusion

Extended biopsy schemes have replaced sextant biopsy in the 21st century. Between 11 and 13 cores should be obtained at initial biopsy. Extended biopsy schemes

are associated with a 30% detection rate, and perform 15% to 30% better than the sextant scheme. However, up to 30% of men assessed with extended biopsy schemes will harbor insignificant prostate cancer. To compensate for this, extended biopsy schemes provide more informative staging information which may be used to determine the need, the nature and the timing of treatment, if an intervention appears justified.

Extended biopsy schemes are also recommended for men presenting for a repeat biopsy. Similarly, 30% will be diagnosed with prostate cancer when an extended repeat biopsy is performed. Higher prevalence of prostate cancer on repeat needle biopsy should be expected in men with ASAP on initial biopsy, where at least 40% will harbor cancer at second biopsy. Unlike ASAP, HGPIN does not represent an independent risk factor for cancer on a repeat biopsy, if an extended initial biopsy was performed.

A repeat biopsy may be performed weeks after the initial negative biopsy. The same favorable morbidity profile should be expected, when a repeat biopsy is performed. The indications and timing of a third or subsequent biopsies are ideally established after a 6 to 12 months interval. □

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