Prostate biopsy: who, how and when. An update

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Biochemical parameters and pathological features as well as biopsy related morbidity of prostate cancer detected on second, third and fourth repeat prostate biopsy in men with a serum total PSA level between 4 ng/mL and 10 ng/mL were evaluated and compared to those cancers detected on initial prostate biopsy.

In a prospective European Prostate Cancer Detection study, 1051 men with a total PSA level between 4 ng/mL and 10 ng/mL underwent transrectal ultrasound (TRUS)–guided sextant biopsy and two additional transition zone biopsies. All subjects whose biopsy samples were negative for prostate cancer (CaP) underwent a first repeat biopsy after 6 weeks. If also negative a third and even a fourth biopsy was performed at 8 weeks intervals. Those with clinically localized cancers underwent radical prostatectomy. Pathological and clinical features of patients diagnosed with cancer on either initial or repeat biopsy and clinically organ confined disease who agreed to undergo radical prostatectomy were compared.

Cancer detection rates on first, second, third and fourth biopsy were 22% (231/1051), 10% (83/820), 5% (36/737) and 4% (4/94), respectively. Percent free PSA and PSA-TZ were the most powerful parameters to predict cancer on repeat biopsy. Overall, of patients with clinically localized disease (67% of cancers detected), 86% underwent radical prostatectomy and 14% opted for watchful waiting or radiation therapy. Overall, 58.0%, 60.9%, 86.3% and 100% had organ confined disease on first, repeat, third and fourth biopsy, respectively.

Despite statistical significant differences with respect to multifocality (p=0.009) and cancer location (p=0.001) (cancers on second biopsy showing a lower rate of multifocality and a more apico-dorsal location), there were no differences with respect to stage (p=0.2), Gleason score (p=0.3), percentage Gleason grade 4/5 (p=0.2), serum PSA and patient age between first and second biopsy. However, cancers detected on third and fourth biopsy had a significantly lower Gleason score (p=0.001 and 0.001), lower rate of grade 4/5 cancer (p=0.02), lower cancer volume (p= 0.001 and 0.001) and lower stage (p= 0.001). Morbidity of first and repeat biopsy were similar, whereas third and fourth biopsy had a slightly higher complication rate. Interestingly, patients under 60 years of age reported a higher pain apprehension as quantified with the visual analog pain scale (VAS). Further, the use of the Vienna tables allowed an accurate calculation of the number of biopsy cores required based on prostate volume and age. Despite differences in location and multifocality, pathological and biochemical features of cancers detected on initial and second biopsy were similar, suggesting similar biological behavior. Cancers detected on third and fourth biopsy had a lower grade, stage and cancer volume as compared to cancers on first and repeat biopsy. Morbidity of first and repeat biopsy were similar, whereas third and fourth biopsy had a slightly higher complication rate. Hence, a second prostate biopsy in all cases of a negative finding on initial biopsy appears justified. Third and fourth repeat biopsies however, should only be obtained in very selected patients with high suspicion of cancer and/or poor prognostic factors on the first or second biopsy. Power Doppler TRUS will further enhance prostate cancer detection as will artificial neural networks as patient selecting tools

Key Words: prostate cancer, prostate biopsy, repeat biopsy, prostate volume, morbidity, biopsy technique

Introduction

The current concept regarding prostate biopsy is that systematic sextant biopsies, even when laterally directed, do not provide adequate sampling of the prostate. Lowering the PSA is a result of early detection and screening of prostate cancer.[1] Prostate cancer detection rates on repeat biopsy vary in different studies from 10% to 27%.[2,3] Performing repeat prostate biopsy in a systematic fashion[2] leads to an unnecessary invasive procedure in 90% of cases.[2,4] However, if cancer is still present in 1/10 to

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1/5 of patients with a negative initial biopsy, one has to reevaluate the initial biopsy policy.

Over the past decade, a considerable number of modifications have been made to the technique for prostate cancer biopsy. Several extended biopsy techniques have recently been introduced that improve the prostate cancer detection rate compared with systematic sextant biopsy.[5-9]

These techniques vary in the number of cores used and the location from which samples are taken. Most recently Djavan and Remzi proposed and validated the use of the Vienna nomogram[4,5] to decide the number of biopsy cores in the first biopsy depending on patient age and prostate volume in the PSA range of 2 ng/ml – 10 ng/ml.

Extended biopsy protocols

Several researchers have compared the lateral sextant biopsy with the extended biopsy technique. O'Connell et al[10] compared one set of lateral sextant biopsies with two sets of lateral sextant biopsies. The second biopsy set increased the cancer detection yield by 7.7%. There was a significant negative association between a cancer diagnosis on the first biopsy and prostate volumes greater than 50 cc.

Presti et al[7] investigated a 12-core biopsy strategy, including sextant biopsies and laterally directed sextant biopsies, in a multi-practice community study involving 2299 men. The laterally directed sextant biopsies detected 83% of the cancers and were superior to the sextant biopsies, which detected 78%. The 10-core biopsy scheme that included apex, base, and laterally directed sextant biopsies detected 97% of the cancers and was superior to the 10-core biopsy that included the sextant, lateral mid and lateral base (93%).

Taille et al[11] investigated a 21-core biopsy strategy (sextant, lateral sextant, transition zone 6x, and midline 6x) in 303 men. The cancer detection incidences for sextant (six cores), sextant plus lateral sextant (12 cores), sextant plus lateral sextant plus transition zone (18 cores), and sextant plus lateral sextant plus transition zone plus midline (21 cores) were 22.7%, 28.3%, 30.7%, and 31.3%, respectively. The 21-core biopsy detected 36.7% of the cancers (58/158) with prostate volumes less than 40 cc compared with 25.5% of the cancers (37/145) with prostate volumes greater than 40 cc. The 21-core and 12-core biopsies improved the diagnostic yield (48.3% and 23.8%, respectively), compared with sextant biopsy in patients with prostate volumes greater than 40 cc, whereas in patients with prostate volumes less than 40 cc, these techniques improved the detection rate by 32.0% and 25.2%, respectively.

Vienna nomogram

The Vienna nomogram is a validated mathematical model to showing the optimal number of cores in prostate biopsies, depending on total prostate volume and age of the patient in the PSA range of 2 ng/ml-10 ng/ml. The number of cores varies from 6-18 cores, being more extended in younger patients and larger prostates.[4,5] Overall prostate cancer detection rate in the validation study was 36.7%.[5] This is comparable to other described extensive biopsy protocols.[6-11] In comparison with the European prostate cancer detection study (EPCDS)[4] with a study population of significantly higher PSA and patient age, the Vienna momogram biopsy protocol detected 66.4% more cancers in a single procedure. Even with the addition of the number of cases detected with systematic repeat biopsy after 6 to 8 weeks, the prostate cancer detection rate with the Vienna nomogram remained higher, even though the difference was not significant. Djavan et al showed that cancers detected on first and repeat biopsy are significant cancers.[12]

The key to the higher prostate cancer detection rate with the use of the Vienna nomogram is the variation of the number of cores according to prostate volume and age.[4] Prostate volume is a known risk factor for missing prostate cancer on prostate biopsy, because of sampling error from larger prostates. Remzi et al,[13] Djavan et al[14] and Ung et al[15] stressed the importance of prostate volume in prostate cancer detection, showing a prostate cancer detection rate that is dependent on prostate volume, especially in the low PSA range of 2 ng/ml-10 ng/ml. In the Vienna nomogram validation study[5] the majority of the patients had 8 to 12 biopsy cores with a prostate cancer detection of 32%. Patients who received more than 12 biopsy cores had significantly larger prostate volumes, but the prostate cancer detection rate was comparable (36%, n=30/83) (ChiSquare test p = 0.75). This is another evidence to show that the use of Vienna nomogram was able to detect similar number of prostate cancer cases in men with larger prostates. So using the Vienna nomogram will eliminate the prostate volume bias for prostate cancer detection in patients with PSA from 2 ng/ml-10 ng/ml.

The overall early and delayed morbidity rates in the Vienna nomogram group were comparable to the EPCDS[16] which employed sextant biopsy plus two transition zone biopsies. However, hematuria was significantly less in this study and this probably

because no transitional zone cores were taken. The vast majority of complications were minor and self-limitating. Moreover this study illustrated high satisfaction levels among patients even in extended biopsies up to 18 cores.

Power Doppler ultrasound with and without contrast enhancement

Angiogenesis plays a major role in carcinogenesis, especially in bigger tumors.[17] Because of the increased neovascularity found in radical prostatectomy specimens, the use of Power Doppler transrectal ultrasound (PD-TRUS) imaging and guided biopsy has been suggested to improve the prostate cancer detection rate.[18] PD-TRUS is a newly developed method of Color Doppler (CD-TRUS). In contrast to traditional CD imaging which estimates the mean frequency shift of the Doppler signal to determine the velocity and direction of flow, PD displays the total energy of the signal by integrating the Doppler signal. This integration provides the PD signal with a homogeneous background, even when the gain is increased significantly over the level at which the signal begins to obscure the conventional CD imaging. This leads to more precise detection of smaller and lower-flow vessels.

Remzi et al investigated the use of PD-TRUS in 136 men with a PSA of 2 ng/ml-10 ng/ml on first and repeat biopsy.[19] The overall prostate cancer detection rate was 34.7% (35/101) and 25.7% (9/35) on first and repeat biopsy (p 0.54), respectively. Forty-three (42.6%) and 17 (48.6%) were classified as abnormal on PD-TRUS examination on the first and repeat biopsy (p = 0.87), respectively. Prostate cancer detection rate in the abnormal PD-TRUS signal group was 67.4% (29/43) and 47.0% (8/17) on first and repeat biopsy, respectively. On the other hand, prostate cancer detection rate in the normal PD-TRUS signal group was significantly lower at 10.3% (6/58) and 5.6%, (1/18) on initial and repeat biopsy, respectively. Prostate cancer was detected in 33 (94.3%) and 8 patients (88.9%) using the standard gray scale TRUS at first and repeat biopsy strategy. Only 2 (5.7%) and 1 (11.1%) additional patients were found using PD-TRUS guided biopsy on the first and repeat biopsy, respectively. On the contrary, a normal PD-TRUS signal excluded prostate cancer in 89.7% (52/58) and 94.4% (17/18) of the patients on first and repeat biopsies. This would lead to a reduction of unnecessary biopsies in 51.5% (52/101) and 48.6% on first and repeat biopsy, respectively. ROC curve analyses showed a significant greater AUC for the Power Doppler signal on first biopsy to distinguish patients with positive and negative histology on first biopsy, whereas no significant differences were seen on repeat biopsy.

Further studies including newer experimental techniques using contrast agents[20,21] or three-dimensional ultrasound[22] might solve this problem. In addition, further studies are needed to assess, if a normal PD-TRUS signal could accurately predict benign results and spare unnecessary biopsies, as shown in this study.

When to stop the prostate biopsy cascade?

In another recent study Djavan et al presented the results of a prospective study of the pathological features found in first, second, third and fourth prostate biopsy.[12] Of those with a negative result on the first, second and third biopsy 820/ 829, 737/756 and 94/101 agreed to undergo repeat biopsy. Cancer detection rates on first, second, third, and fourth biopsy were 22% (231/1051), 10% (83/820), 5% (36/737) and 4% (4/94), respectively. Regarding all of patients with clinically localized disease (67% of cancers detected), 86% underwent radical prostatectomy and 14% opted for watchful waiting or radiation therapy. Of cancers detected on initial (n = 231), repeat (n = 83), third (n = 36) and fourth biopsy (n = 4), 148/231 (64%), 56/83 (67.5%), 33/36 (91.6%) and 4/4 (100%) had a clinically localized disease, and were offered radical prostatectomy or radiation therapy. Watchful waiting was not offered as a primary option. Ten of one hundred forty-eight (6.7%), 3/56 (5.3%), 1/33 (3%) and 0/4 (0%) respectively, opted for radiation therapy and thus, 138/148 (93.3%), 53/56 (94.7%), 32/33 (97%) and 4/4 (100%), underwent radical retropubic prostatectomy. All specimens underwent histopathological evaluation by a single pathologist at each institution. Overall, 58.0%, 60.9%, 86.3% and 100% had organ confined disease on first, second, third and fourth biopsy, respectively. No differences were noted with respect to organ confinement (OC) (p = 0.15), extracapsular extension (ECE) (p = 0.22) and seminal vesical invasion (SV) (p = 0.28) between first and repeat biopsy, whereas the same parameters were significantly different (higher values for organ confinement and lower for all other parameters) for cancers on third versus first biopsy (p = 0.001, p = 0.02, p = 0.01, respectively) as well as cancers on fourth versus first biopsy (p = 0.001, p = 0.01, p = 0.001, respectively). Positive margins (R+) were noted in 23%, 18% (p = 0.23), 8% (p = 0.03) and 0% respectively. No differences were noted between

cancers detected on initial versus repeat biopsy in the biopsy Gleason score (6.0 versus 5.7; p = 0.252) as well as in Gleason score of the surgical specimen (5.3 versus 4.9; p = 0.358). The same accounted for the % Gleason grade 4/5 (31.1% versus 29.8%; p = 0.10). Cancers detected on initial biopsy expressed a higher rate of multifocality (p = 0.009), whereas overall cancer volume was identical (p = 0.271) on first and second biopsy. In contrast, cancers detected on third and fourth biopsy had a significantly lower biopsy Gleason score (4.6, p=0.02 and 4.4, p = 0.01), Gleason score of the specimen (4.2, p=0.001 and 4.0, p = 0.001), grade 4/5 cancer (8.2%, p=0.02 and 0%), rate of multifocality (p= 0.009 and p= 0.008), cancer volume (0.83 cc, p= 0.001 and 0.79 cc, p = 0.001) and stage (p= 0.001 and p = 0.001), respectively when compared to cancers detected on first biopsy.

Their current data suggest that cancers detected on repeat biopsy have similar stage and grade distribution, total and free PSA levels as cancers found on initial biopsy. Moreover, specific biological determinants such as % Gleason grade 4/5, Gleason score and cancer volume were identical in both groups, suggesting similar biological properties and at least identical characteristics.

Conclusion

How many cores have to be taken (according to the Vienna nomogram or to increased sampling techniques) is not yet clear. It seems that traditional sextant biopsies become obsolete in future designed trials since a body of evidence supports that this technique is far from optimal especially in patients with large prostates. Whether the future lies in performing biopsies more laterally, increasing the number of biopsies to 10, 12, 15 or even 18, using a tailored model like the Vienna nomogram or simply repeating the biopsy still needs to be verified.

The Vienna nomogram offers an easy tool to select the optimal number of prostate biopsy cores based on patient age and total prostate volume in the PSA range of 2 ng/ml-10 ng/ml. Overall PCa detection rate was 36.7%. The use of Vienna nomogram in the PSA range of 2 ng/ml-10 ng/ml thus eliminates the prostate volume factor in prostate cancer detection.

PD-TRUS signals have an adequate sensitivity and specificity, especially on the first biopsy, and provide additional information during "conventional" gray-scale prostate biopsy. A normal PD-TRUS signal might help to exclude prostate cancer patients. PD-TRUS resulted in a reduction of unnecessary prostate biopsies in 51.5% (52/101) and 48.6% on first and repeat biopsy, respectively. Further studies are needed to meliorate the use of PD-TRUS guided biopsies, for example the use of contrast agent enhanced PD and/or 3D ultrasound.

Current data suggest that cancers detected on repeat biopsy have similar stage and grade distribution as cancers found on initial biopsy. Moreover, specific biological determinants such as percentage of Gleason grade 4/5, Gleason score and cancer volume seem identical, suggesting similar biological properties and at least identical characteristics. □

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