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Invited Review

When prostate cancer remains undetectable: The dilemma

Prostat kanseri ne zaman saptanamaz olarak kalır; bir ikilem

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ABSTRACT

Since the first report on the efficacy of sextant biopsy under transrectal ultrasound guidance, there have been many modifications related to the total number of cores and the localization of biopsies to improve the prostate cancer (PCa) detection rate. The 2010 National Comprehensive Cancer Network Early PCa Detection Guidelines noted the 12-core biopsy scheme as the standard. However, this extended biopsy scheme still fails to detect 20% of high-grade PCa that can be detected by detailed pathological evaluation of radical prostatectomy; therefore, there is need for saturation biopsies. The existence of suspicions of PCa after previous negative biopsy or biopsies represents a valid indication for saturation biopsy. There has been no significant increment in morbidity or in insignificant PCa detection rates when a saturation biopsy scheme was used with an extended biopsy scheme. Along with the improvement in the PCa detection rate, accurate oncological mapping of PCa is another important consideration of saturation biopsies. The ideal number of cores and the diagnostic value of saturation biopsy after the failure of initial therapy are some of the issues that need to be addressed. Preliminary reports have shown that magnetic resonance imaging can improve the PCa detection rate, save patients from unnecessary biopsies, and decrease the need for a high number of cores; however, multiple limitations continue to exist.

Key words: Prostate; prostate biopsy; prostate cancer

ÖZET

Transrektal ultrason rehberliğinde sekstant biyopsinin etkinliği üzerine ilk rapordan bu yana, toplam kor sayısı ve biyopsilerin lokalizasyonu hakkındaki pek çok değişiklik prostat kanseri (PCa) saptama hızını geliştirmeye adapte edildi. 2010 ulusal kapsamlı kanser ağı erken PCa saptama kılavuzu standart olarak 12 kor biyopsi şemasını teklif etti. Ancak bu genişletilmiş biyopsi şeması hâlâ radikal prostatektominin ayrıntılı patolojik değerlendirmesi ile saptanan yüksek grade PCa'ların %20'sini saptamada başarısızdır, bu yüzden satürasyon biyopsisi gereksinimi doğmaktadır. Önceki olumsuz biyopsi veya biyopsiler sonrasında PCa şüphesinin varlığı satürasyon biyopsisi için geçerli bir endikasyonu gösterir. Satürasyon biyopsi şeması genişletilmiş bir biyopsi şeması ile birlikte yapıldığı zaman ne morbiditede anlamlı artış görülür ne de önemsiz PCa saptamasında artış olur. PCa saptama hızında iyileşmenin yanı sıra, PCa'nın doğru onkolojik haritalaması satürasyon biyopsisinin önemli hususları arasında yer almaktadır. Başlangıç tedavisinin başarısızlığından sonra ideal kor sayısı ve satürasyon biyopsisinin tanı değeri tanımlanmayı bekleyen birçok konu arasındadır. Ön raporlar Manyetik rezonans görüntülemenin PCa saptama hızını artırdığını, hastayı gereksiz biyopsilerden koruduğunu ve fazla sayıda kor ihtiyacını azalttığını gösterdi, ancak hâlâ birçok sınırlamalar mevcuttur.

Anahtar kelimeler: Prostat; prostat biyopsisi; prostat kanseri.

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History of prostate biopsy (PBx)

Watanabe et al.[1] first introduced the use of transrectal ultrasound-guided (TRUSG) biopsy into the armamentarium of prostate cancer (PCa). Hodge et al.[2] reported on the efficacy of sextant biopsy under TRUS guidance for PCa detection. Initially, only ultrasonically detected hypoechoic areas were sampled.[3,4] In 1995, Stamey et al.[5] suggested that biopsy should be obtained from a more lateral location to better sample the anterior horn of the peripheral zone. Similarly, Norberg et al.[6] noticed that the second set of sextant biopsies performed immediately after the first set increased the PCa detection rate by as much as 30%. These findings prompted investigators to seek alternative biopsy schemes with an increased number of biopsy cores and/or sampling of the lateral peripheral zones for improved PCa detection.[7-15] Mc Neal et al.[16]

provided the ground for better sampling of peripheral zones with special attention to the anterior horn. These modifications related to the total number of cores and the localization of biopsies improved the PCa detection rate.

Extended biopsy scheme

Uzzo et al.[17] and Karakiewcz et al.[18] were the first to demonstrate an increase in the PCa detection rate in proportion to the number of biopsy cores obtained. Their findings provided the foundation for extended PBx where at least 10 cores are taken. Chen et al.[19] examined various biopsy schemes to define the approach associated with the highest PCa detection rate. They suggested that an 11-core biopsy strategy may present the ideal detection scheme as it resulted in the highest detection rate relative to the standard sextant biopsy scheme (29%).[20] A number of studies have supported the same findings; Noberg et al.,[6] Elabbady et al.,[7] Babian et al.,[8] Eskicorapci et al.,[9] Ravery et al.,[21] Durkan et al.,[22] and Singh et al.[23] all showed an increment in the detection rate from 15% to 31% with the number of cores ranging from 10 to 12 (Table 1).

Some authors started moving beyond 12 cores. Eskew et al.[24] first examined 13 cores; they found that this particular scheme resulted in a 35% increase in the PCa detection rate. Similarly, Scattoni et al.[25] assessed the diagnostic yield of a scheme using 18 cores in 1776 patients and compared it with the 12-core biopsy strategy. No statistically significant difference in the PCa detection rate was observed between the 2 strategies except in patients with a prostate volume of less than 55 cc (+6.7% gain was recorded).[25] It is clear that the yield of sextant biopsy can be significantly improved when extended biopsy is performed. However, as the number of cores exceeds 10, the gain becomes more marginal. The cancer detection benefit associated with the 10-core scheme has been reported to range from 15.5% to 29.4% compared with 11.6% to 31% for the 12-core biopsy scheme. To date, no study has demonstrated a meaningful benefit when 12 cores are taken instead of 10-core biopsy. Nonetheless, the 2010 National Comprehensive Cancer Network Early PCa Detection Guidelines reported the 12-core biopsy scheme as the standard.[26]

Table 1. Extended versus sextant core biopsy scheme.

	Patients (n)	Biopsy cores (n)	Increase in PCa detection rate (%)
Norberg et al.[6]	512	6 vs. 8-10	15
Ravery et al.[21]	303	6 vs. 10-12	17
Babian et al.[8]	362	6 vs. 11	33
Durkan et al.[22]	493	6 vs. 12	19
Eskicorapci et al.[9]	303	6 vs. 12	25
Elabbady et al.[7]	289	6 vs. 12	12
Singh et al.[23]	179	6 vs. 12	31

PCa: prostate cancer; n: number

Saturation biopsy

The need for saturation biopsies came from the fact that extended biopsy approaches still fail to detect 20% of high-grade PCa that can be detected by detailed pathological evaluation of radical prostatectomy.[27] Prostate saturation biopsy was initially introduced by Borboroglu et al.[28] and consisted of at least 20 biopsy cores. Saturation biopsy may provide increased accuracy for the predictability of PCa volume and grade. Most studies have shown that TRUSG biopsy can be a useful diagnostic tool in men with prior negative biopsies with a cancer detection rate of 14%–34%.[29-32] As for the initial saturation biopsy scheme, several investigators have tested saturation biopsy schemes where more than 20 cores were obtained. De la Taille et al.[33] showed that a 21-core initial biopsy procedure increases the PCa detection rate by as much as 37.9% relative to sextant biopsy and by as much as 10.6% relative to a 12-core biopsy scheme in patients with prostate gland volumes of ≥40 cc. However, Ravery et al.[34] showed a 20% increase in the detection rate when an initial 20-core biopsy scheme was used compared with a 10-core biopsy scheme. This benefit was observed only in patients with prostate-specific antigen (PSA) levels of <6 ng/mL.[34] Delonchamps et al.[35] found no benefit of saturation biopsy over the 18-core biopsy scheme. Pepe et al.[36] showed a virtually equivalent PCa detection rate when using an initial 12-core (39%), an 18-core (49%), or saturation biopsy (range of 24-37 cores; 46.9%). Guichard et al.[37] also found no significant increase in the PCa detection rate when a 21-core biopsy scheme (42.5%) was chosen over an 18- or 12-core biopsy scheme (41.5% and 38.7%, respectively). It is very clear that most of the studies did not support the use of an initial saturation biopsy scheme with more than 12 cores.

Repeat PBx and saturation biopsy

One of the most valid indications for saturation biopsy is previous negative biopsy or biopsies with a continued suspicion of PCa. As a rule, standard repeat biopsy should consist of at least 10-12 biopsy cores. Several studies have reported an improvement in the PCa detection rate when saturation biopsy was used.[13,30,33] The detection rate with repeat saturation biopsy has been reported to range from 13%-41%.[13,28-30,32,38] The differences in PCa detection with repeat saturation biopsies are related to the number of previous negative biopsies and number of cores. Therefore, high detection rates (30%-40%) with repeat saturation biopsies have been reported when a negative sextant scheme was previously used and a detection rate of 22% was reported when saturation biopsy was used after previous negative extended biopsy.[36] Walz et al.[13] reported a detection rate of 41% when saturation biopsy of 18 cores was used after at least

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2 previously negative 8-core biopsy sessions. Among those who had at least ≥2 negative biopsies, 14% were found to harbor PCa of Gleason score 8-10 at subsequent saturation biopsy.[39] Taken together, repeat saturation biopsies result in PCa detection rates comparable to those of standard extended biopsy. There have been no convincing data supporting a benefit from the use of saturation biopsy after previous negative extended initial biopsy. Use of repeat saturation biopsy may be reserved for individuals who had ≥2 extended biopsies with benign findings but the clinical context still dictated the need for additional biopsies.

Saturation biopsy: Questions remain to be answered

There are a number of issues and questions regarding saturation biopsies that need to be addressed; there has been no consensus on the ideal number of cores, no study has reported on the diagnostic value of saturation biopsy after the failure of initial therapy, insignificant cancer versus number of cores, and the difference between the transrectal and transperineal approaches remains unclear. Regarding the number of cores, some authors have gone beyond saturation to supersaturation or extensive PBx. Stewart et al.[30] in 2001 coined saturation biopsy or extensive prostate sampling to be repeat on prostate biopsy, including up to 22 cores with a PCa detection rate of 30%. Merick et al.[40] reported a detection rate of 42.2% when 50 cores were taken; Simon et al.[41] also reported a detection rate of 45% when 64 cores were taken. At the MD Anderson Cancer Center (MDACC), we conducted a study regarding saturation biopsies (under consideration for publication); the PCa detection rate was 47.9% when 59 cores were taken. Currently, the studies of Merick et al.[40] and Simon et al.[41] and our study represent the studies where the highest number of cores was taken. It remains to be seen if the number of cores will extend beyond these numbers in future and when saturation biopsy will be saturated.

Transrectal versus transperineal biopsy

The majority of PBxs are performed transrectally; however, a few saturation biopsies are performed using the transperineal approach. The transperineal method has the advantages of fewer complications and higher PCa detection rate.[42,43] Transperineal biopsy can detect cancer in the anterior horn of the prostate; this is due to the fact that transperineal biopsy can provide good access to the apex and upper part of the base of the prostate. Many studies have demonstrated that the apical region in general and the apex in particular have a significantly higher incidence of cancer than the rest of the prostate gland.[40,44] In our study at MDACC, we used transperineal saturation biopsy in patients who had failed primary therapy (radiation and/or brachytherapy); the detection rate in treated and untreated patients was 58.82% and 41.17%, respectively. Abdollah et al.[45] conducted a comparison between the 2 approaches using 472 patients where 70% had undergone transrectal biopsies and 30% had undergone trasperienal biopsies; the researchers found no difference in the detection rate between the approaches (31.4% versus 25.7%; p=0.3). Accordingly, the transperineal technique can be a valid approach for patients who need supersaturation biopsies, particularly for those who have received prior treatment with radiation and/or cryotherapy because the anterior part and the apex are the most common regions for recurrence.

Safety of saturation biopsy

Many studies have reported on the safety of extended and saturation biopsy and there has been no significant difference between these approaches. Djavan et al.[46] reported on the morbidity and safety of repeat transrectal PBx; the authors concluded that it was generally well-tolerated with minor morbidities that rarely require treatment. Merrick et al.[47] reported on the morbidity of transperineal template-guided prostate mapping biopsy and concluded that it was a promising procedure with comparable results in terms of urinary, bowel, and erectile function and difference in the incidence of temporary urinary retention. Simon et al.[41] reported that hematuria occurred in 40% of patients who underwent extensive saturation biopsies. Walz et al.[13] reported that urinary retention occurred in 1.24% patients and the morbidity rate was 2.48%. Moran et al.[44] stated that 10% had urinary retention after repeat transperineal PBx. Akbal et al.[48] described that saturation biopsy with a median of 22 cores had a minimal risk of temporary erectile dysfunction. It is clear that morbidity associated with saturation biopsies is not significantly greater than that associated with an extended PBx scheme.

Number of cores versus insignificant PCa

The increased detection rate of insignificant PCa (defined as a tumor volume of <0.5 cc, no Gleason 4–5 pattern, and organ-confined disease) represents one of the potential drawbacks of extended initial and repeat PBxs. The rate of clinically-insignificant PCa increased by 12% when extended PBx was used instead of the sextant biopsy scheme.[23] Similarly, Hass et al.[49] showed that an extended PBx increased the detection rate of insignificant cancer by 22%. Other studies found no difference in the proportion of clinically insignificant PCa between a 12-core biopsy scheme and the sextant strategy.[50] Eskew et al.[51] also found no difference in the rate of clinically insignificant PCa between 13 cores and the sextant biopsy scheme. In recent study by Plousard et al.,[52] it was shown that a considerable number of patients that were considered for the active surveillance program according to preoperative parameters, e.g., Gleason scores of ≤6, had significant cancer according to the histopathological report. In the present study from MDACC, 82% of the patients had Gleason scores of ≥7 and all patients except one had ≥3 positive cores; the length of cancer was >5 mL for all patients except 2. Thus, individuals with clinically insignificant PCa at the time of extended biopsy should be considered for saturation biopsy before the cancer can be definitely

classified as clinically insignificant and before active surveillance or focal therapy are considered. Currently, at MDACC, second extended biopsy is used to select patients for active surveillance. Confirmation of insignificant PCa may present the most valid and beneficial indication for saturation biopsy. Accordingly, saturation biopsy can be used in patients who are candidates for active surveillance in order to have an accurate oncological mapping for PCa**.** These arguments were corroborated by Delongchamps et al.[53] and Berglund et al.[54] when they examined a cohort of 107 patients who were active surveillance candidates who underwent 14-core repeat biopsy; the researchers found a rate of upgrading/upstaging of 27%. It is expected that approximately 30% of individuals with small volume and/or low-grade disease at initial biopsy will harbor a higher-grade disease. Therefore, there has been no convincing evidence that the extended PBx scheme increased the rate of insignificant PCa detection beyond that of the sextant biopsy scheme.

Saturation biopsy to predict the pathologic specimen at radical prostatectomy

The rate of incorrect grade assignment relative to RP ranged from 25%-57% with the sextant-biopsy scheme.[55-57] Extended biopsy with more than 10 cores improved the concordance by 13% relative to sextant biopsy.[58] Further studies reported improvements that ranged from 15% to 35.2%.[7,59] Therefore, increasing the number of scores clearly improves the ability of surgeons to predict the oncological features of PCa with RP specimens. The rate of Gleason score upgrading decreased from 47.9% to 23.5% when the 12-core biopsy scheme was replaced with an 18-core biopsy scheme.[60] This also can be considered as an important consideration for an extensive initial PBx along with an improvement in the cancer detection rate.

Presence of extraprostatic disease has been one of the prognostic factors for patients with PCa. The follow-up policy and necessity for further treatment, such as radiotherapy or hormonal therapy, can be determined according to the extraprostatic involvement. Unfortunately, the negative predictive value of uninvolved cores in the extended PBx scheme has been reported to be low (24%-31%).[61] Consequently, the negative extended Bx findings cannot safely justify the use of focal therapies or define the need for further treatments.[61] As for new tests that may help in solving the dilemma of undetectable PCa, genetic testing, such as that related to prostate cancer antigen 3 (PCA3), may play a significant role in detecting PCa and decrease the number of unnecessary PBxs; however, the availability and technical issues may limit the use of these tests.[62]

Role of 3 Tesla multiparametric magnetic resonance imaging (3TMPMRI) in the detection of PCa

Reducing the number of cores and saving patients from unnecessary PBxs is an ideal target in the detection of PCa. Magnetic resonance imaging-guided PBx has demonstrated a high PCa detection rate; the tumor detection rate was 82.6%, and the targeted cores versus systematic core detection rate was 30% and 8.2%.[63] The specificity and sensitivity of 3TMPMRI were 85% and 97%, respectively, with a positive predictive value of 74.6%.[64] In a large study where 844 patients underwent 3TMPMRI, there were 438 patients with PSA levels of ≥4 ng/mL and ≥1 negative TRUSG biopsy sessions.[65] The authors concluded that the PCa detection rate was 41% and the majority of cancers were significant (87%).[65] Kuru et al.[63] compared the standard systematic TRUSG biopsy with 3TMPMRI; the authors concluded that although 3TMPMRI improved the PCa detection rate, it still had some limitations and systematic biopsies should not be omitted at present. In general, 3TMPMRI-guided PBx does improve the PCa detection rate. It is preferable for patients with negative systematic PBx(s). Cost-effectiveness, availability, systematic restrictions, and vagueness of its diagnostic value in treated patients, particularly in patients after radiation, are the most important limitations of 3TMPMRI.

In conclusion, the urologic literature suggests that an extended biopsy scheme should consist of 12 cores. Use of a saturation biopsy scheme for repeat biopsy results in an increase in the PCa detection rate from 30%–40% without a significant increase in morbidity compared with sextant biopsy. Introduction of 3TMPMRI in PBx can be promising; it improves the PCa detection rate and saves patients from high number of cores and unnecessary biopsies. However, a number of limitations are still present. Patients who are expected to undergo active surveillance can consider saturation biopsy for accurate oncological mapping of PCa.

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