Urooncology / Üroonkoloji *Review / Derleme*

Transrectal ultrasound-guided prostate biopsy: current approach

Transrektal ultrasonografi eşliğinde prostat biyopsisi: Mevcut yaklaşım

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Abstract

Over the past decade, a significant number of modifications have been made to the technique for prostate biopsy. In this report, we reviewed the literature regarding transrectal ultrasound-guided prostate biopsy (TRUS-BX) in terms of the various techniques of prostate biopsy, number of cores, prophylactic antibiotic selection and use, patient preparation and pain-controlling techniques applied before the procedure. The proposed advantages/disadvantages of transitional zone and seminal vesicle biopsies were also summarized. According to the literature, TRUS-BX rather than transperineal approach should be preferred as the technique of choice in most men undergoing a prostate biopsy. The laterally directed sextant biopsy and extended biopsy approaches decrease the false-negative rate that occurs with the conventional sextant biopsy approach. As a conclusion, considering the baseline biopsy protocol, the current advice is the use of an extended biopsy scheme (12 biopsy cores without transitional zone). Laterally directed biopsies from the anterior horn should be included. Repeat as well as saturation biopsies should include the transitional zone. Local anesthesia using transrectal ultrasound-guided lidocaine injection provides adequate periprostatic nerve blockage and is recommended to reduce the pain associated with prostate biopsy. Broad-spectrum antibiotic therapy should be administered to reduce the risk of infection.

Key words: Biopsy; prostate cancer; transrectal; ultrasonography.

Özet

Geçtiğimiz on yılda, prostat biyopsisi tekniğinde önemli sayıda değişiklik yapılmıştır. Bu yazıda, transrektal ultrasonografi eşliğinde prostat biyopsisine (TRUS-BX) ilişkin literatürü; farklı prostat biyopsi teknikleri, kor sayıları, profilaktik antibiyotik seçimi ve kullanımı, hasta hazırlığı ve işlem öncesi ağrı kontrol yöntemleri yönünden gözden geçirdik. Ayrıca transizyonel zon ve seminal vezikül biyopsilerinin önesürülen avantaj ve dezavantajları da özetlenmiştir. Literatüre göre prostat biyopsisi yapılan erkeklerin çoğunda transperineal yaklaşım yerine TRUS-BX tercih edilen teknik olmalıdır. Lateral yönlendirilmiş sekstant biyopsi ve genişletilmiş biyopsi yaklaşımları, konvansiyonel biyopsi yaklaşımı ile oluşan yanlış-negatif oranı düşürmektedir. Sonuç olarak, ilk biyopsi protokolü dikkate alındığında, mevcut yaklaşım genişletilmiş biyopsi şemasının (transizyonel zon olmaksızın 12 kor biyopsi) kullanılmasıdır. Ön boynuzdan lateral olarak yönlendirilmiş biyopsiler dahil edilmelidir. Doygunluk biyopsileri yanında tekrar biyopsileri de transizyonel zonu içermelidir. Transrektal ultrasonografi eşliğinde lidokain injeksiyonu ile lokal anestezi yeterli periprostatik sinir bloğu sağlar ve prostat biyopsisine eşlik eden ağrıyı azaltmak için önerilir. İnfeksiyon riskini azaltmak için geniş spekturumlu antibiyotik tedavisi verilmelidir.

Anahtar sözcükler: Biyopsi; prostat kanseri; transrektal; ultrasonografi.

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Prostate cancer is a major health problem worldwide and the incidence is rising. After the application of conventional ultrasounds to health care, Watanabe et al.[1] described the first transrectal ultrasound (TRUS) in 1967. During the ’80s, TRUS guided prostate biopsy became the primary technique for the detection of prostate cancer. Because cancers cannot be accurately visualized by conventional ultrasound, sextant biopsy was pioneered by Hodge et al.[2] In their landmark manusript they described obtaining three cores from each lobe in a parasagittal plane at the base, midgland, and apex of the prostate. Subsequent investigators proposed obtaining more cores to improve the diagnostic accuracy of transrectal ultrasound-guided prostate

biopsy (TRUS-BX).[3,4] Over the past decade, a significant number of modifications have been made to the techniques of prostate cancer biopsy.

Here, we reviewed the literature for the various techniques of prostate biopsy cores, descriptions of prophylactic antibiotic selection and use, patient preparation and pain-controlling techniques applied before the procedure. In addition, advantages/disadvantages of transitional zone and seminal vesicle biopsies, and complications related with the procedure itself are discussed.

Patient preparation for TRUS and biopsy

In clinical practice, patient preparation for transrectal prostate biopsy has three basic steps: rectal preparation, antibiotic prophylaxis, and analgesia. The 2009 European Association of Urology (EAU) guidelines recommend oral or intravenous antibiotics for prophylaxis, particularly with ciprofloxacin. For pain management, ultrasound-guided peri-prostatic block is recommended and low dose aspirin is no longer an absolute contraindication.[5] But, there is still considerable variability in patient preparation for prostate biopsy among urologists.

Is prebiopsy bowel cleansing necessary?

Although various bowel preparations have been administered for optimal TRUS imaging and to minimize infectious complications, there are several studies which reported no benefit to perform rectal preparation. Carey and Korman[6] advocated that the use of a cleansing enema before biopsy increases cost and patient discomfort without providing a clinically significant improvement in outcome. In a study with 448 patients undergoing transrectal biopsy under antibiotic prophylaxis with ciprofloxacin 500 mg, the authors reported that clinically significant complications developed in 4.4% of patients who had prebiopsy enemas compared with 3.2% of those who did not. They regarded routine use of prebiopsy enemas as the cause for high cost and patient discomfort. Similarly, Vallancien et al.[7] showed an increase of infectious complications in patients receiving cleaning enemas and revealed that rectal irritation secondary to washing would facilitate bacteremia. Jeon et al.[8] demonstrated that the number of biopsy cores and prebiopsy rectal preparation use were statistically significant risk factors for infectious complications after prostate biopsy. The study with the largest number of patients that evaluated the necessity of prebiopsy bowel preparations was published in 1997.[9] Sieber et al. performed a total of 4,439 biopsies without bowel preparation and patients were treated with 500 mg ciprofloxacin twice daily for 8 doses beginning the day before biopsy. They reported very low symptomatic infection rates (approximately 0.1%), thereby placing into question the necessity of enemas before a TRUS prostate biopsy.[10] In contrast, Lindert et al.[11] strongly proposed that bacteremia may be significantly minimized by a prebiopsy phosphate enema independent of antibiotics prescribed. Initially, Brown et al.[12] showed a smaller rate of patients with urinary tract infection and fever in the group of patients receiving povidone-iodine enemas. A recent study published this year proposed similar data. Park et al.[13] evaluated 481 patients and concluded that povidone-iodine melted into the rectum and decreased the bacterial colony count, thereby minimized the risk of infectious complications. In the United States, 79-81% of patients received an enema preparation before biopsy.[14,15] In Japan, this ratio was reported as 49% in 2006.[16] Therefore, there is not a consensus or protocol in current clinical practice and in the literature about this topic. Both the American Urological Association (AUA) and EAU guidelines do not have any recommendation about prebiopsy bowel cleansing. Based on the above information, we feel that a routine enema is not necessary.

Antibiotic prophylaxis

Most recent EAU guideline (2009) recommends routine antibotic prophylaxis with quinolones.[5] This approach significantly decreases major complications such as bacteremia and sepsis.[17,18] However, resistance rate to fluoroquinolones is becoming a major challenge. The main causative microorganisms for bacteremia/urinary tract infection are *Escherichia coli*, *Klebsiella pneumoniae*, and other gram-negative rods.[19] A prospective study by Kapoor et al.[20] showed that biopsy with no antibiotic prophylaxis was associated with a 5% rate of symptomatic urinary tract infection and a 2% rate of hospitalization. Another study by Aron et al.[19] reported a 19% rate of bacteriuria and a 7% rate of pyrexia when an antibiotic prophylaxis was not applied.

In the survey analysis by Davies et al.[21] 81% of the participant doctors only administered an oral fluoroquinolone before the procedure, whereas fluoroquinolone plus aminoglycoside was preferred for 17% of the participants. In a multicenter study of Urooncological Association in Turkey, it was observed that all of the centers participated in this survey analysis administered antibiotic prophylaxis before the procedure.[22] Most of the participants (75%) used single type (oral or parenteral) antibiotic, whereas 21% used combined regimen. These data were quite similar with the results of Davies et al.[21] However, in recent years, the emergence of antibiotic

resistant microorganisms is becoming worrisome, and in some settings it is becoming a cause of antibiotic prophylaxis failure.[23-25]

Recently, Horcajada et al.[25] from Spain, evaluated 411 biopsy procedures in order to determine whether the incidence of bacteremia after TRUS-BX diminished with the application of a new preventive protocol which is 2 g cefoxitin 1 h before the procedure and ciprofloxacin 750 mg p.o. bid the day before the procedure and 3 days after the procedure. They compared outcomes with old preventive protocol (which previously caused an increased incidence of bacteremia with a high prevalence of antibiotic resistant microorganisms): amoxicillin-clavulanate 500 mg tid the day before the procedure and 1 day after the procedure. Extended spectrum beta lactamase isolates and amoxicillin-clavulanate resistance were not observed in new preventive protocol group, although ciprofloxacin resistance rates were comparable between groups. It can be concluded that addition of a single dose cefoxitin may significantly decrease the incidence of bacteremia. Lange et al.[26] from Canada, retrospectively reviewed a group of 24 men who presented with urosepsis after undergoing TRUS-BX, and observed that, 22 out of 24 men had been previously given prophylactic ciprofloxacin. In Turkey, ciprofloxacin resistance among *E. Coli* strains were ranged between 8.3% and 38%.[27,28]

The length of oral treatment is also under controversy, and there are studies supporting that three or four days of oral treatment significantly diminishes the rate of infectious complications.[29,30] AUA Update Series (2007) suggests that a 1-day treatment with a fluoroquinolone is likely to be sufficient for healthy patients, with extended coverage for 3-4 days in patients with comorbid conditions.[31] However, Young et al.[32] have presented evidence that this scheme of treatment might no longer be adequate in today's clinical urologic practice. The use of antibiotics is common among some of the urologists who aimed to reduce prostate specific antigen (PSA) elevation mainly caused by an inflammatory process. Major disadvantage for this approach is the risk for development of resistant bacterial species that might expose the patient to more resistant and aggressive sepsis after an eventual transrectal biopsy procedure.[33]

If the patient has taken a fluoroquinolone antibiotic within the previous 8 months, the use of a second- and/or third-generation cephalosporin or an aminoglycoside with metronidazole or clindamycin is recommended.[32] In current clinical practice, this option should be kept in mind to prevent infectious complications.

Anesthesia and analgesia

Men undergoing prostatic biopsy are quite anxious about the pain. It is also believed that an anxious and tense patient is more likely to perceive pain. Several techniques such as periprostatic nerve blockage, rectal administration of lidocaine gel, intravenous propofol, inhalation of nitrous oxide, and the use of tramadol have been described in the literature for adequate pain control during biopsy. The discomfort during the prostatic biopsy is proportional to the number of cores.[34] The periprostatic nerve block has become the standard for pain control during the biopsy. However, this is a relatively complicated technique and needs to be applied correctly to provide an adequate pain control. Recently, Akpınar et al.[35] reported a new method to block pelvic plexus with the aid of color doppler ultrasonography and compared its efficacy with widely used periprostatic nerve block for TRUS-BX. They achieved better results with Doppler ultrasound-guided biopsy. After the identification of injection sites by color Doppler ultrasound, they injected 2 mL of 2% lidocaine into the region of the pelvic plexus lateral to the tip of vesicula seminalis on each side. They have not reported any major complications related with the technique.

It is widely accepted that the most effective pain relief is probably achieved by combining the anorectal application of a topical anesthetic and periprostatic nerve block.

In the study by Davis et al.[21] 33% of North American urologists did not administer any analgesia to biopsy patients. This rate was reported as 37.5% in a multicenter study performed by "Urooncological Association".[22] Giannarini et al.[36] recently randomized 280 patients to receive combined perianal-intrarectal lidocaine-prilocaine cream and periprostatic nerve block (Group 1), perianal-intrarectal lidocaine-prilocaine cream alone, periprostatic nerve block alone or no anesthesia before transrectal ultrasound-guided prostate biopsy. Lowest pain scores were achieved in Group 1. Disadvantages of periprostatic nerve blocks are needle insertion pain, infection, and the need for technical expertise. But, the complication rates were comparable with other techniques. Raber et al.[37] presented data on the use of lidocaine-prilocaine cream and found that it was useful in younger but not older men. Soloway and Obek[38] proposed the use of periprostatic nerve block for pain control at prostate base and seminal vesicle junction. Rodriguez et al.[39] found that infiltrating lidocaine at each side of the apex is sufficient to control pain. Some investigators found that apical block was more effective than basolateral prostatic block.[40,41] Recently, Shrimali et al.[42] report-

ed excellent results with 1 mL intravenous midazolam alone. Glycerol trinitrate was found to be effective in pain associated with TRUS probe insertion.[43] Left lateral decubitus position was also associated with less pain compared to the lithotomy position.[44]

It has been shown that younger patients and patients with larger prostates require greater pain relief.[36] So, patients who would benefit most from anesthesia should probably be young, anxious patients undergoing an extended or repeat biopsy from a large gland.[45]

Our recommended technique based on this literature review is to infiltrate the area of the junction of the seminal vesicle with the prostate and then inject slowly on the lateral prostate border as the needle is withdrawn towards the apex. Once the needle reaches the apex, more local anesthesia is injected. The procedure is then repeated on the contralateral side. An appropriate amount of time should be waited before the biopsy, usually 5-10 min (Fig. 1 and Fig. 2).

Should antiplatelet/anticoagulant drugs be discontinued?

Men taking low dose aspirin are no longer felt to be at significant risk of bleeding following a TRUS-BX.[5,46] Halliwell et al.[47] evaluated 99 patients taking warfarin who underwent prostate biopsy in terms of hematuria, hematospermia, or rectal bleeding. None have required hospital admission for bleeding complications and all of their bleeding complications were classified as minor, despite the increased incidence of bleeding. They concluded that the use of warfarin during prostate biopsy was safe and that stopping warfarin, with its associated thrombotic complications might indeed be more dangerous. Taking more cores may increase the rectal bleeding and hematuria rate.[48,49] Switching patients to low molecular weight heparin might not be ideal, as animal studies have shown that bleeding is less when anticoagulated with warfarin than with heparin.[50] Nevertheless, we think that both low dose aspirin and warfarin-like drugs should be stopped prior to biopsy, unless there is a significant contraindication.

Sampling sites and number of cores

In 1989, Hodge et al.[2] reported the use of ultrasound-guided systematic sextant biopsy in 136 men with abnormal digital rectal examination findings. Cancer was detected by systematic sextant biopsy in 9% of cases and by directed biopsy in 5% of cases. It has been the gold standard of biopsy techniques for a long time. Several years later, to decrease the number of false-negative results, the sextant technique was modified and sextant biopsies were taken lateral to the mid-parasagittal plain in the peripheral zone where most prostate cancers are typically located.[3,4]

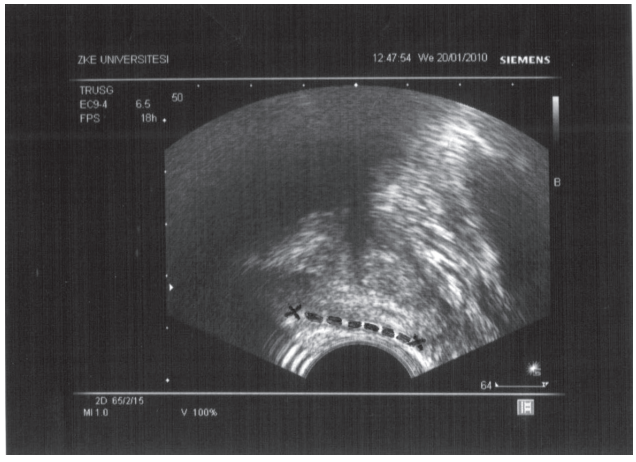

Figure 1 Ultrasonographic appearance of local anesthetic injection pathway.

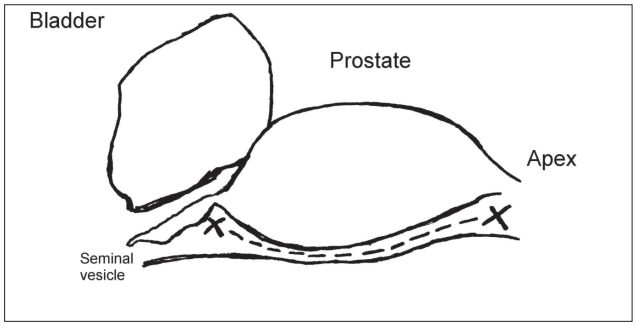

Figure 2 Schematic appearance of local anesthetic injection pathway.

On baseline biopsies, EAU recommends the sample sites to be as far posterior and lateral in the peripheral gland as possible.[5] Eichler et al.[51] analyzed 87 studies with a total of 20,698 patients, and compared the cancer detection rates and complications of different extended prostate biopsy schemes. Sextant biopsy was considered inadequate. They concluded that at a glandular volume of 30-40 mL, at least eight cores might be sampled and more than 12 cores did not add any significant benefit. Currently, some authors consider the routine 12-core (extended) biopsy as an office-based, diagnostic standard for evaluating patients with increasing PSA levels.[52]

Eskew et al.[53] were the first who introduced the systematic extended biopsy technique, which combined the sextant biopsy method with additional biopsy cores. This technique involves a systematic five-region biopsy, including the conventional sextant biopsies 2 cores from the far lateral lobe from each side and 3 cores from the middle of the gland. When the prostate volume is over 50 cc, one additional core is obtained per region. By this way, they showed a 35% reduc-

tion of false-negatives; 88% of the tumors diagnosed, excluded the ones from the sextant, where localized in the most lateral areas (lateral prostatic horns).

Presti et al.[54] biopsied 483 patients taking 10 cores from each side (sextant plus 2 cores from the most lateral zone at each side). The authors reported that they could detect 96% of the tumors; furthermore, if they excluded the cores from the cranial peripheral zone of both lobes they only lost the diagnosis of 1% of the tumors. Ten biopsy scheme detected 96% of cancers, whereas sextant and 8-biopsy schemes detected 78% and 92%, respectively.[4] This means that the classical sextant did not diagnose 20% of the tumors.

Although many variations in extended pattern biopsy have been described; currently, for baseline biopsies, at least 10 to 12 including the apex, mid lobar, mid gland, lateral mid gland, and lateral base, must routinely be performed. When the approach towards patients undergoing repeat biopsies has been a very aggressive scheme, the entity is named as "saturation biopsy." Stewart et al.[55] introduced this concept by the documentation of the largest series. In 224 patients with previous negative biopsies, they took a mean of 23 cores (14-45) under sedation, local or general anesthesia, with a radial mapping from the lateral horns to the most medial zone. They obtained a cancer rate of 34%. Complications occurred in 27 patients (12%) including sepsis in 1, hematuria requiring hospitalization in 12, and urinary retention in 10. In a recent review, Presti[56] summarized the indications for repeat and saturation biopsies. Repeat biopsy should include a minimum of 14 cores, the 12 cores recommended for an initial biopsy and 2 additional cores obtained form the right and left anterior apex. It was reported that the overall cancer detection rate of apical anterior horn biopsies ranged between 29% and 56%.[57] In their study, the apical anterior biopsy was the only site of positive biopsy in 2% of patients. Higher unique cancer detection of the apical anterior site was observed in patients with normal digital rectal examination (6%) and PSA less than 10 ng/mL (4%). Consequtively, a saturation biopsy should be considered in patients for whom those repeat biopsies fail to identify cancer yet the clinical suspicion remains high.

Regarding transperineal approach, Crawford et al.[58] displayed on cadavers and radical prostatectomy specimens a model of transperineal prostatic biopsy. They divided the gland in quadrants of 5 mm and 10 mm, respecting the urethra, and took cores from each quadrant with a depth of 23 mm. They observed high proportion of tumors been clinically insignificant, mainly in the anterior (transitional) zone. They found a high proportion of tumors clinically irrelevant in the peripheral posterior zone. The results of this computer simulation revealed that 5- and 10-mm grid biopsies detected three-quarters and a third, respectively, at autopsy, of patients with the disease localized to one side of the prostate. Taira et al.[59] evaluated an alternative approach, transperineal template-guided mapping biopsy, in the initial and repeat biopsy setting in 373 men and observed 76% cancer detection rate for the initial biopsy. For men with 1, 2, and ≥3 prior negative biopsies detection rates were 55.5%, 41.7%, and 34.4%, respectively. Those ratios suggest that transperineal approach with the help of new modalities should rather be preferred in a group of patients with previous three negative biopsies for cancer and in men without rectum.

Transition zone and seminal vesicle biopsies

Indications for seminal vesicle biopsies are not well defined. At PSA levels >15-20 ng/mL, a biopsy is only useful if the outcome will have a decisive impact on treatment.[5] Transition zone (TZ) sampling during baseline biopsies provides a very low detection rate and TZ sampling should therefore be confined to repeat biopsies.[5] Terris et al.[60] evaluated 161 consecutive patients who underwent TZ and the seminal vesicle (SV) biopsies, and observed that 0.6% of cases had cancer in only the anterior biopsies, whereas 3.7% had cancer involving SV. Another study from Austria revealed that TZ confined tumor was only 0.6%.[61] Prostate cancer detection did not improve even in patients with rebiopsy. Considering more invasive nature of TZ and SV biopsies, a limited group of patients should undergo TZ and/or SV biopsies.

Complications

Both transrectal and transperineal prostate biopsies have a risk of complications, however there appears to be no significant differences in terms of complications between transrectal and transperineal procedures.[62] Transient side effects, such as local pain, hematuria, vasovagal reactions, hemospermia, dysuria, and rectal bleeding have been reported in a large number of patients.[63,64] Bacteriuria occurs in 20-53% and bacteremia in as many as 73% of patients,[65,66], and rectal bleeding has been reported in 75%.[67-69] Fever associated with genitourinary symptoms is described in 3-0% and septicemia in <5% of patients following a biopsy of the prostate.[65,66,70] Despite use of prophylactic antibiotics and withdrawal of anticoagulants prior to the application of biopsy, there are numerous case-reports of significant adverse events reported in the literature. Erdoğan et al.[71] reported a case of *E. Coli* meningitis after TRUS-BX. Arroja et al.[72] had recently reported two

cases with major rectal bleeding which were resolved with endoscopic coagulation and elastic band ligation. A massive retroperitoneal hematoma secondary to injury of the right prostatic artery, which required arterial embolization for treatment has previously been published.[73] Excluding those anectodal cases, TRUS-BX should still be considered as a procedure that can be performed in the office setting. Out of 367 men, Matin et al.[74] reported one (acute bacterial prostatitis) case as the most significant adverse event.

Naughton et al.[34] correlated bleeding rates with the number of cores and the performance of more medial biopsies. In a large survey analysis from Japan, including 212,065 procedures, hematuria, rectal bleeding, and hematospermia were reported in 12%, 5.9%, and 1.2% of cases, respectively.[75] Voiding symptoms were reported in 1.9% and urinary retention in 1.1% of cases. Fever was observed in 1.1% and sepsis occurred in 0.07%. Hospitalization was required in 0.69% of cases for the treatment of biopsy-related complications. However, infectious complication rates were significantly higher in transrectal when compared with transperineal approaches.

Conclusion

TRUS-BX rather than transperineal approach is preferred as the technique of choice. The laterally directed sextant biopsy and extended biopsy approaches decrease the false-negative rate that occurs with the conventional sextant biopsy approach. Considering the baseline biopsy protocol, the current advice is the use of an extended biopsy scheme (12 biopsy cores without TZ). Laterally directed biopsies from the anterior horn should be included. Repeat as well as saturation biopsies should include the TZ. Local anesthesia using TRUS-guided lidocaine injection is recommended to reduce the pain associated with prostate biopsy. Wide spectrum antibiotic therapy and certain previous rectal preparation should also be performed.

Conflict of interest

No conflict of interest was declared by the authors.

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