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THE INCIDENCE OF HYPERECHOIC PROSTATE CANCER IN TRANSRECTAL ULTRASOUND GUIDED BIOPSY SPECIMENS

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ABSTRACT

Objectives: On transrectal ultrasound (TRUS), prostate cancers are visualized as hypoechoic or isoechoic lesions. The incidence of hyperechoic lesions considered as cancer has been reported to be approximately 1.5%. The aim of the study was to estimate the incidence of TRUS hyperechoic lesions and of hyperechoic prostate cancer in TRUS guided biopsy specimens.

methods: We prospectively studied 200 patients with total PSA <20 ng/mL and/or positive digital rectal examination who had undergone TRUS guided prostate biopsy. Each patient underwent laterally directed systemic six-core biopsy plus cores from abnormal TRUS lesions and rectally palpable lesions. Six to ten biopsy cores were obtained from each patient.

Results: Hyperechoic lesions were found in 19 (9.5%), hypoechoic in 83 (41.5%) and isoechoic in 98 (49.0%) patients. Prostate cancer was diagnosed in 33.0% of study patients. Isoechoic findings on TRUS were recorded in 31.8% of patients diagnosed with prostate cancer, while 60.6% of cancers had hypoechoic and 7.6% hyperechoic lesions. There was no significant difference in the mean Gleason score between isoechoic cancers (mean 5.4) and hypoechoic cancers (mean 5.6). However, hyperechoic cancers had a mean Gleason score of 7.0, which was higher when compared with isoechoic and hypoechoic cancers.

Conclusion: Biopsy of hyperechoic lesions was positive for prostate cancer in a higher percentage of patients than previously reported in the literature, and Gleason score of these cancers was higher when compared with isoechoic and hypoechoic cancers.

Key words: prostate biopsy; transrectal ultrasound; hyperechoic lesions; prostate cancer

INTRODUCTION

Prostate cancer is a very common entity, with the incidence increasing with age. The majority of these patients are free from symptoms and less than 3% of patients with pathologically confirmed diagnosis die from prostate cancer.[1] The introduction of transrectal ultrasound (TRUS) probe by Wantanabe et al.[2] and development of the diagnostic procedure first applied in 1981 by Holm and Gammelgard[3] have significantly contributed to the early diagnosis of prostate cancer. Besides having a major role in positioning the needle trajectory for prostate biopsy, TRUS enables visualization of focal lesions suspected of prostate cancer.[4-8] A definitive protocol regarding the number of biopsy cores for prostate biopsy has not yet been established, and the number of cores taken *per* biopsy varies from 4 to 30.[9-11] Recently, the average number of biopsies has been gradually increasing, however, the detection rate remains unchanged and the need of repeat biopsy is increasing. Despite the high rate of false negative biopsy findings (20-30%), as reported by Rabbani et al.[12] and Fleshner and al.[13], sextant biopsies are still in wide use.[14,15] Hyperechoic lesions are usually considered as benign, whether benign prostate hyperplasia (BPH), prostatitis or prostate infarction.[8] On TRUS, prostate cancer is visualized as a hypoechoic lesion in 60-70%, and as isoechoic lesion in 30-40% of cases. Hyperechoic lesions are rare, with an incidence of approximately 1.5%.[16-19] Some unusual types of prostatic adenocarcinoma have been reported to appear as hyperechoic lesions, e.g., in case of ductal adenocarcinoma with central necrosis, dysmorphic calcifications and deposition of intraluminal crystals.[16] The aim of this study was to estimate the incidence of TRUS hyperechoic lesions and of hyperechoic prostate cancer in TRUS guided biopsy specimens.

PATIENTS AND METHODS

This prospective study included a series of 200 patients with total PSA <20 ng/mL and/or positive digital rectal examination (DRE), age range 54-78 (mean 67.5) years, PSA 2.4-19.3 (mean 9.9) ng/mL, and prostate volume 16-78 (mean 37.4) ccm.

All study patients served as both experimental and control group. Each patient underwent TRUS and biopsy. Suspect lesions found on TRUS were classified as hypo- or hyperechoic. Mixed lesions were considered as hypoechoic TRUS findings.

All patients underwent TRUS guided prostate biopsy and histopathologic findings were compared with TRUS findings.

We used a Siemens SI-400 ultrasound device with biplane transrectal probe Siemens 5,0/7,5 MHz type 5727 LE 888. Biopsy was performed by an automatic Magnum gun with selective penetration of 15 or 22 mm, Magnum biopsy needle of 250 mm in length with 18 gauge and sampling needle of 19 mm in length. The procedures were performed on an outpatient basis. Patients took laxatives for one day and fluoroquinolone therapy for five days prior to biopsy, as recommended by Webb and Woo[20] and Sieber et al.[21] Transrectal ultrasound and biopsy were performed in standard position without anesthesia. DRE was performed first, followed by the measurement of prostate volume. Ultrasound was performed in detailed fashion, starting from the apex to the base. Biopsy was performed in sagittal view. The number of biopsies was determined according to DRE and ultrasound findings. If both were negative, six biopsy cores were obtained from the apex laterally, mid-laterally and base-laterally from both lobes. If hypo- or hyperechoic lesions were found, additional **ultrasound guided** biopsies were done from those lesions. **Cores from these areas were inked on distal margin, and submitted on pathology in accordingly marked, separate container thus provided correct correlation between TRUS**

and pathological findings. Only patients with positive cores obtained from hypo- or hyperechoic TRUS lesions were included in hypo- or hyperechoic group. Biopsies were also obtained from areas appearing abnormal on DRE.

An improved pre-embedding method for all biopsy specimens was applied, as described by Rogatsch et al.[22] Specimens were fixed in 10% buffered formaldehyde, embedded in paraffin, cut at 5 μm thickness, and routinely stained with haematoxylin and eosin. In some cases, the material was stained with p63, HMW-CK and alcian-PAS. Alcian-PAS positive staining was not used as the only criterion since it is well known that such positivity might be seen in mimickers of cancer such as atrophy and adenosis.

Statistical analysis was performed using χ^2-test and Student's *t*-test. The level of significance was set at $p<0.05$.

RESULTS

Results of PSA and TRUS findings in 200 patients were given in Table 1. One hundred and twenty (51.0%) patients had abnormal TRUS findings; 83 (41.5%) had hypoechoic lesions and 19 (9.5%) had hyperechoic lesions. The remaining 98 (49.0%) patients had isoechoic findings. **Forty six (23.0%) patients had abnormal DRE, out of them 26 (56.5%) had normal PSA. TRUS in patients with positive DRE revealed 14 (30.4%) hypoechoic and 3 (6.5%) hyperechoic lesions.** A total of 1539 biopsies were done with 6-10 cores (mean 7.6) *per* patient and prostate cancer was diagnosed in 66 (33.0%) patients. Nine (0.58%) biopsy specimens were excluded from the study due to inadequate tissue for appropriate microscopic analysis. Isoechoic lesions were recorded in 21 (31.8%), hypoechoic lesions in 40 (60.6%), and hyperechoic lesions in five (7.6%) patients with prostate cancer (Table 2, Figure 1).

In patients with hyperechoic carcinoma, a total of 43 (mean 8.6) biopsy cores were obtained, including 30 (69.8%) cores from peripheral zone and 13 (30.2%) from transitional zone. There were 14 (32.6%) (ranged from 2 to 4 per patients, mean 2.8) cancer positive cores, including 9 (64.0%) in peripheral zone and 5 (36.0%) in transitional zone.

Overall, prostate cancer was detected in 26.3% of patients with TRUS hyperechoic lesions. In other hyperechoic lesions, the diagnosis of prostatic hyperplasia suggested (26.3%) and prostatitis was found in 47.4% of cases. Biopsies of TRUS visible focal lesions detected a significantly higher number of prostate cancers (68.2 %) when compared to TRUS negative prostate biopsies (31.8%) (p=0.001).

The mean value of PSA was 10.1 ng/mL (ranged from 3.4 to 17.4) in patients with focal lesions and 9.8 ng/mL (ranged from 2.4 to 19.3) in patients with normal TRUS finding. In

patients with hyperechoic carcinoma the mean value of PSA was 10.2 ng/mL (ranged from 5.4 to 16.5), in patients with hypoechoic carcinoma was 10.5 ng/mL (ranged from 3.8 to 16.3) and in patients with isoechoic carcinoma was 10.3 ng/mL (ranged from 3.6 to 19.3). The mean prostate volume was 38.2 ccm (ranged from 18 to 77) in patients with abnormal TRUS and 36.4 ccm (ranged from 16 to 78) in patients with normal TRUS. In patients with hyperechoic carcinoma the mean prostate volume was 36.6 ccm (ranged from 22 to 68), in patients with hypoechoic carcinoma was 37.2 ccm (ranged from 18 to 73), and in patients with isoechoic carcinoma 37.5 ccm (ranged from 19 to 69). Statistical analysis showed no significant difference in PSA value and prostate volume between the analyzed groups ($p>0.05$).

The mean Gleason score in isoechoic, hyperechoic and hypoechoic cancers was 5.4 (ranged from 4 to 9), 5.6 (ranged from 5 to 9) and 7.0 (ranged from 6 to 9), respectively. There was no statistically significant difference in Gleason score between isoechoic and hypoechoic cancers ($p>0.05$). In hyperechoic tumors, Gleason score was higher as compared with the other two groups**; however, the number of patients in the hyperechoic group was too small for statistical analysis** (Table 2).

COMMENT

It is believed that TRUS guided biopsy is the only accurate preoperative method for early diagnosis of prostate cancer. The average number of biopsies has been gradually increasing, however, sextant biopsies are still widely used.[14,15]

In our study, hypoechoic lesions were found in 41.5% and hyperechoic lesions in 9.5% of patients. Forty nine percent of the patients had normal findings on transrectal ultrasound.

We diagnosed cancer in 66 (33.0%) patients; 68.2% of them had focal lesions on TRUS, while 31.8% had normal ultrasound findings. In our study, the number of diagnosed cancers with abnormal TRUS was moderately higher as compared with the study conducted by Vo et al.[23] that diagnosed 62.9% of prostate cancers in patients with abnormal TRUS findings and PSA >4. Finne et al.[24] studied 200 patients with median PSA value of 13.2 ng/mL and found carcinoma in 26% of patients. We diagnosed a higher number of carcinomas than Finne at al.[24], where median PSA value was higher than that recorded in our study (13.2 vs. 9.9 ng/mL). Loch et al.[7] report on a 29% rate of prostate cancer in patients with PSA >4. The patients included in their study had no limited PSA value. In our study, all patients had PSA <20, and we diagnosed a higher percentage of prostate cancers compared to Loch et al.[7] The higher percentage of cancer detected in our study could probably be ascribed to additional biopsies that were obtained in hyperechoic lesions, where another five carcinomas were identified.

There was no statistically significant correlation between serum PSA values and ultrasound findings. The mean PSA value in patients with abnormal TRUS findings was almost the same as the mean value recorded in patients with normal ultrasound findings (10.1 ng/mL vs.

9.8 ng/mL). Also, we found no significant difference between PSA value in hyperechoic, hypoechoic and isoechoic carcinoma.

Review of the literature shows very rare findings of prostate cancer originating in hyperechoic lesions. The reported incidence is 1-1.5%.[16-19] Egawa et al.[16] performed transrectal ultrasonography prior to radical prostatectomy in 157 patients with prostate cancer and hyperechoic cancers were diagnosed in only two (1.3%) patients. Shinohara et al.[17] diagnosed 70 carcinomas, of which only one was hyperechoic (1.4%). Malika et al.[18] performed biopsy in 100 patients suspected of carcinoma and diagnosed 23 carcinomas, none of which was hyperechoic. They also found and submitted to biopsy 11 hyperechoic lesions but none of them was diagnosed as carcinoma. Stilmant and Kuligowska[19] report on only one prostate cancer originating from a hyperechoic lesion. Our findings in 19 patients with hyperechoic lesions, five of them with diagnosed carcinoma (7.6% of all diagnosed carcinomas in our study) indicated a higher rate of hyperechoic cancers than that reported in the literature.[16-19] **Of the 5 patients with hyperechoic cancer, 3 underwent radical prostatectomy, which confirmed diagnosis, 1 was treated with radiation therapy and 1 recived androgen ablation therapy.**

Ellis and Brawer[25] confirmed that Gleason score was independent of ultrasound findings, but biopsies were done on hypoechoic lesions. In our study, the mean Gleason score of carcinoma in patients with hypoechoic lesions and normal ultrasound findings was not significantly different, but carcinomas in patients with hyperechoic lesions had a higher mean Gleason score. **Distribution of Gleason score in patients with hyperechoic carcinoma was equal to or greater than the median for all patients together (n = 66). In patients with**

isoechoic and hypoechoic carcinoma, an approximately equivalent number of patients was distributed below and above the median.

CONCLUSIONS

Based on our study, we concluded that hyperechoic lesions were positive for prostate cancer in a higher percentage of patients than previously reported in the literature and suggest that additional biopsy of hyperechoic lesions be included in the protocol for prostate biopsy. This procedure, which includes a greater number of cores is well tolerated, has a minimal rate of complications, and should be part of the standard protocol in urological practice.[26,27]

Additional studies are needed to determine the exact rate of hyperechoic cancer and the respective Gleason score.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 55: 74-108, 2005.
2. Watanabe H, Kato H, Kato T, et al. Diagnostic application of ultrasonography to the prostate. J Urol 59: 273-279, 1968.
3. Holm HH, Gammelgard J. Ultrasonically guided precise needle placement in the prostate and the seminal vesicles. J Urol 125: 385-387, 1981.
4. Heijmink SW, Moerkerk H, Kiemenev LA, et al. A comparison of the diagnostic performance of systematic versus ultrasound-guided biopsies of prostate cancer. Eur Radiol 16: 927-938, 2006.
5. McNeal JE, Redwine EA, Freiha FS, et al. Zonal distribution of prostatic adenocarcinoma: correlation with histologic pattern and direction of spread. Am J Surg Pathol 12: 987-996, 1998.
6. Scattoni V, Roscigno M, Raber M et al. Role of ultrasonography-guided prostatic biopsy of hypoechoic areas associated with systematic biopsies in patients with normal and high PSA levels. Acta Ital Urol Androl 74: 273-275, 2002.
7. Loch T, Eppelmann U, Lehmann J, et al. Transrectal ultrasound guided biopsy of the prostate: random sextant versus biopsies of sono-morphologicaly suspicious lesions. World J Urol 22: 357-360, 2004.
8. Sperandeo G, Sperandeo M, Morcaldi M et al. Transrectal ultrasonography for the early diagnosis of adenocarcinoma of the prostate: a new maneuver designed to improve the differentiation of malignant and benign lesions. J Urol 169: 607-610, 2003.

9. Terris MK. Extended field prostate biopsy: too much of a good thing? Urology 55: 457-460, 2000.
10. Littrup PJ, Bailey SE. Prostate cancer: the role of transrectal ultrasound and its impact on cancer detection and management. Radiol Clin North Am 38: 87-113, 2000.
11. Haggarth I, Busch C, Norberg M, et al. Prediction of the volume of large prostate cancers by multiple cores biopsies. Scand J Urol Nephrol 39: 380-386, 2005.
12. Rabbani F, Stroumbakis N, Kava BR, et al. Incidence and clinical significance of false-negative sextant prostate biopsies. J Urol 159: 1247-1250, 1998.
13. Fleshner NE, O'Sullivan M, Faur WR. Prevalence and predictors of a positive repeat transrectal ultrasound guided needle biopsy of the prostate. J Urol 158: 505-508, 1997.
14. Stamey TA. Making the most of six systematic sextant biopsies. Urology 45: 2-12, 1995.
15. Stroumbakis N, Cookson MS, Reuter VE, et al. Clinical significance of repeat sextant biopsies in prostate cancer patients. Urology 49: 113-118, 1997.
16. Egawa S, Wheeler TM, Greene DR, et al. Unusual hyperechoic appearance of prostate cancer on transrectal ultrasonography. Br J Urol 69: 169-174, 1992.
17. Shinohara K, Wheeler TM, Scardino PT. The appearance of prostate cancer on transrectal ultrasonography: correlation of imaging and pathological examinations. J Urol 142: 76-78, 1989.
18. Malik R, Pandya VK, Naik D. Transrectal ultrasonography for evaluation of various benign and malignant prostatic lesions and their histopathological correlation. Ind J Radiol Imag 14: 155-157, 2004.
19. Stilmant MD, Kuligowska E. Transrectal ultrasound screening for prostatic adenocarcinoma with histopathologic correlation. Cancer 71: 2041-2047, 1993.

20. Webb NR, Woo HH. Antibiotic prophylaxis for prostate biopsy. BJU Int 89: 824-828, 2002.

21. Sieber PR, Rommel FM, Agusta VE et al. Antibiotic prophylaxis in ultrasound guided transrectal biopsy. J Urol 157: 2199-2200, 1997.

22 Rogatsch H, Mairinger T, Horninger W, et al. Optimized preembedding method improves the histologic yield of prostatic core needle biopsies. Prostate 42: 124-129, 2000.

23. Vo T, Rifkin MD, Peters TL. Should ultrasound criteria of the prostate be redefined to better evaluate when and where to biopsy. Ultrasound 17: 171-176, 2001.

24. Finne P, Auviena A, Aro J et al. Estimation of prostate cancer risk on the basis of total and free prostate specific antigen, prostate volume and digital rectal examination. Eur Urol 41: 619-627, 2002.

25. Ellis WJ, Brawer MK. The significance of isoechoic prostatic carcinoma. J Urol 152: 2304-2307, 1994.

26. Spajic B, Brigic I, Stimac G, et al. Complications of transrectal ultrasound guided prostate needle biopsy: our experience and review of the literature. Acta Clin Croat 45: 87-90, 2006.

27. Berger AP, Gozzi C, Steiner H et al. Complication rate of transrectal ultrasound guided prostate biopsy: a comparison among 3 protocols with 6, 10 and 15 cores. J Urol 171: 1478-1481, 2004.

Figure 1. Hyperechoic lesion in peripheral and transitional zone (volume of the prostate 1.2 ccm). Biopsy revealed a high grade prostatic adenocarcinoma (Gleason score 8 (4+4).

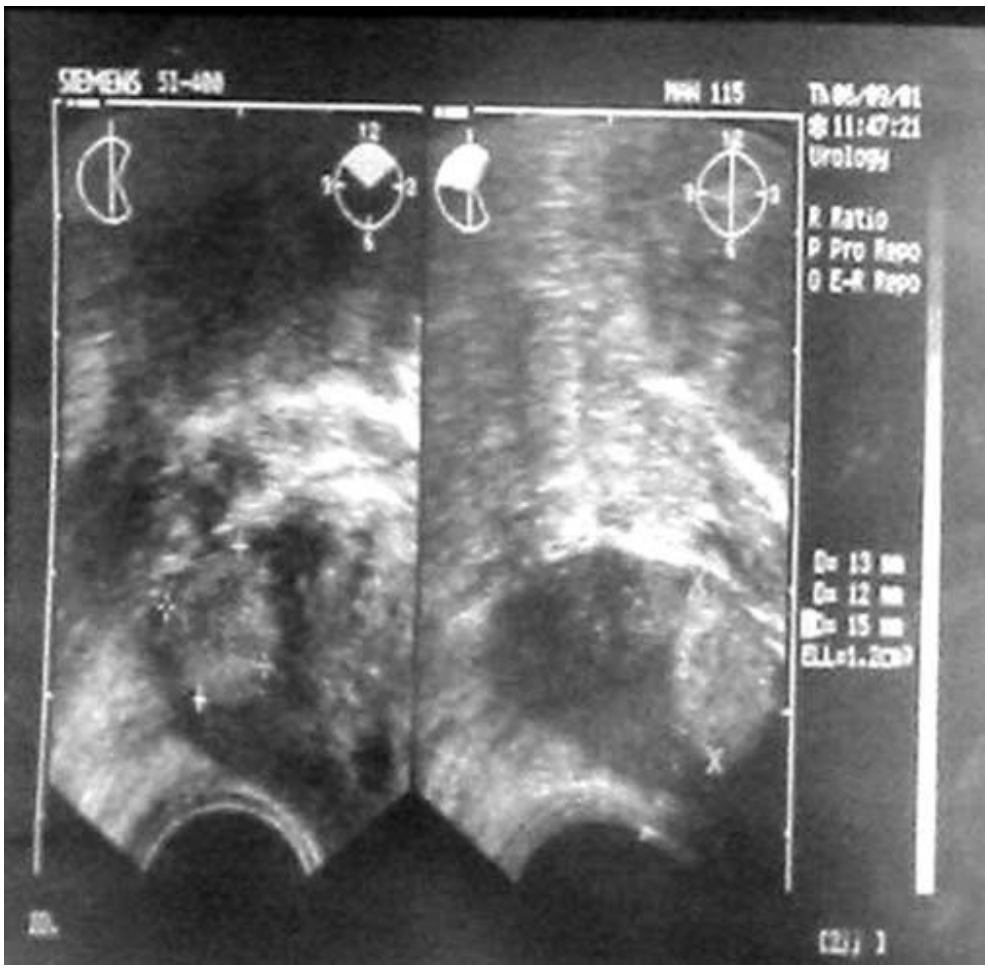

Table 1. Results of PSA and TRUS findings in 200 patients

PSA	TRUS			Total
	isoechoic	hyperechoic	hypoechoic	
< 4.0	10 (5.0%)	2 (1.0%)	14 (7.0%)	26 (13.0%)
4.01 - 10.0	43 (21.5%)	8 (4.0%)	29 (14.5%)	80 (40.0%)
10.01 – 20.0	45 (22.5%)	9 (4.5%)	40 (20.0%)	94 (47.0%)
Total	98 (49.0%)	19 (9.5%)	83 (41.5%)	200 (100%)

Table 2. Transrectal ultrasound (TRUS) findings in diagnosed carcinomas (n=66) and mean Gleason score

	Number of cases	Gleason score
Isoechoic carcinoma (n=21)	21 (31.8%)	5.4
Hypoechoic carcinoma (n=40)	40 (60.6%)	5.6
Hyperechoic carcinoma (n=5)	5 (7.6%)	7.0