

Handling and reporting of radical prostatectomy specimens: A practice survey among pathologists

Radikal prostatektomi materyalleri değerlendirme anketi: Nasıl örnekleniyor? Nasıl rapor ediliyor?

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ABSTRACT

There are controversies on how to best sample and report radical prostatectomy specimens in order to accurately assess prognostic factors. The propensity for obedience to proposed guidelines are controversial likewise. We conducted a survey among Turkish pathologists and residents to assess the attitudes on this issue. Participants were asked about their pathology practice and how they fix, cut and sample the gland or report histologic-based prognostic factors. The results are discussed in the light of the current literature. Fifty-five percent of the 103 participants were studying in centers reporting over 10000 surgical specimens per year, 20% of which were non-university settings. The results showed that submission of whole gland (55%) and volume assessment (25%) were usually practiced in university hospitals ($p<0.001$ and $p=0.02$, respectively). Whole mount sectioning was not performed in any center. None of the participants use an alternative grading system, 19% comment upon tertiary Gleason pattern but define it as either the third most frequent pattern (10%) or the highest grade constituting less than 5% of tumor (8%). Prognostic factors of proven significance as Gleason score, extraprostatic extension, vesicula seminalis invasion, and margin status are searched and commented by all respondents while the factors that require validation in multivariate studies are generally assessed by university members.

Key words: Radical prostatectomy, prognostic factors, tissue sampling, survey, Gleason grading

ÖZET

Radikal prostatektomi materyallerinin makroskopik inceleme yöntemleri ve üzerinde durulması gereken prognostik faktörler konusunda görüş ayrılıkları mevcuttur. Çalışmamız patoloji pratiğinin farklı kademele- rindeki kişilerin görüşlerini almak amacı ile düzenlenmiş bir anket çalışması niteliğindedir. Katılımcılara kaç yıldır patoloji ile uğraştıkları, çalıştıkları kurumlar, çalıştıkları kurumlarda değerlendirilen yıllık genel biyopsi sayısı ve prostat materyallerinin sayıları yanısıra radikal prostatektomi materyallerini nasıl tespit ettikleri, örnekledikleri ve nasıl rapor ettikleri sorulmuş, yanıtlar güncel literatür bilgileri ışığında tartışılmıştır. Anketi yanıtlayan 103 katılımcının %55'i, yıllık biyopsi sayısı 10000'nin üzerinde olan merkezlerde çalışmaktadır. Bu merkezlerin %20'si üniversite/egitim hastanesi dışı merkezlerdir. Sonuçlara göre radikal prostatektomi materyalinin tamamının örneklenmesi (%55) ve hacim hesaplaması (%25) yalnızca üniversite hastanelerinde uygulanmaktadır (sırasıyla $p<0.001$ ve $p=0.02$). "Tüm lambo kesit" yönteminin kullanılmadığı görülmüştür. Katılımcıların hiçbiri Gleason derecelendirme sistemi dışında bir sistem kullanmamaktadır, %19'u "tersiyer Gleason derecesi" hakkında yorum yapmakta ancak %10'u bunu "üçüncü en sık görülen patern" olarak tanımlarken, %8'i "tümörün %5'inden az en yüksek patern" olarak tanımlamaktadır. Sonuç olarak, Gleason skoru, ekstraprostatik yayılım, veziküla seminalis invazyonu ve cerrahi sınırların durumu gibi prognostik değeri kanıtlanmış özelliklerin tüm katılımcılar tarafından değerlendirildiği ve rapor edildiği; buna karşılık prognostik değeri çok yönlü çalışmalarla kanıtlanması gereken özelliklerin genellikle üniversite merkezlerinde araştırıldığı ve rapor edildiği görülmüştür.

Anahtar sözcükler: Radikal prostatektomi, prognostik faktörler, makroskopik inceleme, anket, Gleason derecelendirmesi

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INTRODUCTION

Over the last decades there has been an increase in the incidence of prostate cancer. Thus, surgical pathologists have to cope with more radical prostatectomy specimens, handling of which are difficult, time consuming and have significant resource implications, especially if total specimens are submitted. There are challenging questions regarding how to best sample and report these specimens in order to accurately assess prognostic factors. Besides it is also controversial which of the prognostic factors are of importance in patient care and should be mentioned in pathology report. Some of the controversial topics are partial or total submission of the entire gland, assessment of tumor volume, reporting tertiary Gleason grade, etc. We surveyed Turkish pathologists and residents to assess the current knowledge and attitudes of handling and reporting of these specimens.

MATERIAL and METHODS

To investigate a variety of practice settings, 250 questionnaires were distributed during XVI. National Pathology Symposium. First group of questions were descriptive, as personal pathology experience of respondents, location of their practices and workload of laboratories they worked. To reduce the hesitation of respondents and to facilitate participation to the survey, it was not obligatory for the participants to express their identity or their institutions' name. However, we encouraged the ones who were willing, also to give their contact addresses. Second group of questions were about specimen handling, fixation, and sampling. Third group of questions were on reporting histologic-based prognostic factors (1,2), such as grading, tumor volume, intraglandular extent of tumor, laterality, margin status, extraprostatic extension (EPE), vesicula seminalis invasion (VSI) and other prognostic factors such as perineural invasion (PNI), vascular invasion, nuclear anaplasia, etc.

Residents were asked to express their institutions' protocol and their personal opinion about above-mentioned contradictory issues. The results were evaluated by frequency analysis and expressed as the "valid percentage" of respondents who answered affirmative for each respective question. For comparative analysis on controversial issues, the participants were also grouped according to their experience in pathology as uropathologists, residents, junior pathologist and senior pathologists whose pathology experience in the field was more than 10 years. The attitudes of participants from university and non-university settings were also evaluated. Survey results were also compared with the survey conducted by American Society of Clinical Pathologists (3). Chi square test and Fisher's exact test were used for comparative analysis. A p value of <0,05 was accepted as significant.

RESULTS

Practice characteristics

One hundred and three participants including residents (47%) completed surveys. Twenty-nine percent of the respondents were experienced pathologists working over 10 years (senior pathologists). The main topic of interest was urinary pathology in 7% of them who were working in the field for a mean of 7.55 ± 7.74 years (Range: 2-24 years). The majority of the participants (80%) were from university hospitals, 18% worked in state hospitals and 2% worked in private laboratories. Most of them (55%) were studying in centers reporting over 10.000 surgical specimens per year (Table 1).

Table 1. Workload of centers.

Number of biopsies per year (n)	1-1.000	1.000-5.000	5.000-10.000	10.000-20.000	>20.000
Percent of respondents (%)	1	13	31	42	14

Handling of radical prostatectomies

Survey results on handling of surgical specimen and comparison of results with the survey of ASCP are summarized in Table 2. The results showed that 90% percent of the participants fix the specimen before cutting, record dimensions and weight (96% and 64% respectively). Sixteen percent measure only the largest diameter. Fixation overnight with 10% neutral formalin was the preferred fixation method, but gluteraldehyde was used by 3% as well. Fifty seven percent submit the gland in entirety whereas 41% submit partially. When they were asked for their personal opinion and reasons of choice about

embedding the entire gland, 22% favored submission in entirety to achieve accurate surgical margin status, tumor volume or sampling main tumor mass, since most of them are grossly indistinguishable. Half of the 22 respondents who answered affirmative to this question were residents who declared that the main reason for favoring total submission that they cannot identify tumor grossly. Sixteen percent preferred partial sampling since the total sampling is time consuming and expensive. Later on at the end of the questionnaire participants were asked about their opinion on total or partial sampling of specimens once more, this time without asking the reasons, 54% selected total submission whereas 46% of them preferred partial sampling. As a partial sampling method, 19% of the respondents admit that they submit only the grossly pathologic areas. Other techniques declared include submitting all posterior lobes or submitting two mid anterior sections including posterior and anterior lobes plus apical and basal surgical margins along with the base of vesicula seminalis. There were also participants who choose partial or total submission depending on the PSA values or lymph node status of the patients. Sampling of the specimen generally required more than 12 blocks. None of the respondents use whole mount sections. Majority of the respondents declared that they submit apical (distal), basal (bladder neck) and vas margins separately (97%, 91% and 74% respectively) and sample prostate-vesicula seminalis junction (64%).

When compared the attitudes of the respondents from university hospitals and non-university settings on macroscopic examination of the specimens, we saw that weighing the specimen and embedding the entire prostate was usually practiced in university hospitals (55 participants vs. 6 participants, 59 participants vs 5 participants in non-university hospitals, $p<0,01$ and $p<0,01$ respectively). Accordingly, number of blocks submitted was higher in the former ($p<0.01$). Also participants from university hos-

Table 2. Handling of radical prostatectomies and comparison with survey of ASCP (3)

	Affirmative (%) Doğanavşargil et al	Affirmative (%) True LD 3
Macroscopic description		
Record specimen weight	64	95
Record three dimensions	96	97
Record largest diameter	16	*
Fixation and handling		
Sample the specimen before fixation	5	40
Fix before sampling	90	53
Use another fixation	3	
Sampling		
Embed entire gland	57	12
Sample grossly identifiable pathologic areas	18	
Use other sampling methods	15	
Embed 1-4 blocks	1	5
Embed 5-8 blocks	8	19
Embed 9-12 blocks	13	29
Embed >12 blocks	78	34
Sampling surgical margins		
Embed entire apical (distal) margin	97	64
Embed entire basal (bladder neck) margin	91	62
Embed ductus deferens margin	74	
Sampling vesicula seminalis		
Sample vesicula seminalis	86	*
Embed vesicula seminalis-prostate junction	64	94
Sample distal part of vesicula seminalis	58	*
Embed whole vesicula seminalis	7	

*Not surveyed

pitals were more prone to total submission. But a group of participants (5%) from university hospitals submit the entire gland although they favor partial sampling rather than total embedding. These participants felt that they should follow a previously decided macroscopy protocol within their laboratories. Cutting the specimen before fixation was more common in non-university hospitals ($p<0.01$). One of the interesting issues was 17.5% of the participants claim that they do not or could not sample vesicula seminalis properly since the entirety of this appendix is generally ruined, if it is not removed.

Reporting histologic findings

Survey results on reporting histologic findings and comparison of them with survey of ASCP were summarized in Table 3. All participants use Gleason grading system (4) but participants from university hospitals assign primary and secondary Gleason grades separately more often (17 participants from university hospitals vs 8 participants from non-university hospitals, $p<0.05$). Interestingly, 24% of participants evaluated the most undifferentiated area for primary Gleason pattern, while the rest used the original criteria of Gleason, assigning the dominant pattern as the primary. Half of these “false” respondents were residents, the ratio of juniors and seniors were 25% each. More surprisingly, 2/3 of them were from university hospitals. Nineteen percent comment upon tertiary Gleason pattern but defines it as either the third most frequent pattern (10%) or the highest grade constituting less than 5% of tumor (8%). University members also assigned tertiary patterns more often although statistically insignificant. Uro-pathologists report tertiary patterns more often ($p<0.01$). Volume assessment stated by 25% of the participants was usually practiced in university hospitals ($p<0.05$). A discrepancy was observed when evaluating the answers about intraglandular extension of tumor, assessment of surgical margins and status of capsule, and vesicula seminalis invasion. Although the partici-

pants answered affirmative when they were asked if they search for these main topics, there was a lot of missing in the questions on details of their final report (Table 3). Uro-pathologists report percent involvement of each lobe, status of apical margins more often ($p<0.05$, $p=0.05$,

Table 3. Reporting histologic findings and comparison with survey of ASCP⁽³⁾

	Affirmative (%) Doğanavşargil et al	Affirmative (%) True LD3
Grading		
Using Gleason system	100	65
Report combined Gleason score	100	73
Assign Gleason patterns (grades) separately	71	81
Comment upon tertiary pattern	19	*
Assign tertiary pattern as the third most frequent pattern	10	*
Assign tertiary pattern as the highest grade constituting less than 5% of tumor	8	*
Intraglandular extent of the tumor		
Report either one or two lobes are involved	34	*
Comment upon percent involvement of each lobe	43	54
Comment upon multifocality	53	90
Assesment of volume	25	*
Surgical margins		
Report distance of tumor from surgical margins	44	61
Report apical (distal) margin status separately	48	83
Report basal (bladder neck) margin status separately	49	*
Extraprostatic extension		
Report whether tumor extends beyond capsule	72	100
Report whether tumor invades or approaches to capsule	67	*
Vesicula seminalis invasion		
Report vesicula seminalis invasion	96	99
Other prognostic factors		
Comment upon perineural invasion	96	90
Comment upon vascular invasion	82	89
Comment upon nuclear anaplasia and grade	23	50
Mitosis	25	21
Neovascularisation	2	*
DNA ploidy, Androgen receptor status*, biomarkers*	0	

*Not surveyed

respectively). Perineural invasion was searched by all respondents and reported as though. Vascular invasion, nuclear anaplasia, mitosis and neovascularization were reported mainly by participants from university hospitals. But apart from neovascularization reporting these items were more common in among members of non-university hospitals when the ratio corrected according to their total population. Participants were also asked for additional features they report. A few of them answered in favor of high grade PIN but none of them answered affirmative for oncoproteins, DNA ploidy or androgen receptor status.

DISCUSSION

Radical prostatectomy specimens often present challenges in terms of handling the specimens and reporting the findings. According to our personal observations there is a variety of institutional differences in handling of these specimens. Reporting of histopathologic findings, presents even more diversity. Thus, we surveyed Turkish pathologists on the attitudes of handling and reporting these specimens.

The questions of the survey were based on the classification of prognostic factors developed at consensus meetings sponsored by the College of American Pathologists (CAP) in 1994 and 1999 (3,5). Category 1 prognostic factors are those of proven prognostic significance and are useful in patient management such as Gleason score, pathologic stage, and margin status. Category 2 prognostic factors are those that show promise as predictive or prognostic factors based on evidence from published studies but require validation in larger multivariate studies; tumor volume (intraglandular extent), histologic subtype and DNA ploidy fall into this category. Category 3 prognostic factors are potential prognostic markers but the data are too preliminary. Vascular space invasion, perineural invasion, markers of proliferation, oncogenes and their products are the morphologic-based prog-

nostic factors that fit into this category.

Among the survey audience 47% percent of the participants were residents, followed by senior and junior pathologists (29% and 24%, respectively). We also included the residents since we thought that they would reflect their institutions' protocols as well as opinions of a future pathologist. We hope knowing residents' approach will also help in planning educational meetings. Most of the participants were from university hospitals.

Attitudes on specimen handling was surveyed since a systematic approach to handling is mandatory to provide accurate information that will help patient's management. Survey results showed that for dimensional description, although recording weight is more reproducible, because of the irregular appearance of the resected prostate (3), weighing the specimen was less frequently done than measuring the three dimensions especially in non-university settings. Prostate weight also correlates with PSA values (6). Fixation before sectioning is encouraged in the current literature unless fresh tissue is preserved for research purposes (7). Cutting in fresh state may cause thicker sections and false positive surgical margins. Majority of participants (90%) fix the specimen before handling.

Fifty seven percent submit the gland in entirety and 78% embed more than 12 blocks. It was surprising to find an almost 5-fold difference in frequency of respondents of the ASCP survey in which only 12% of the participants indicated that they processed the entire prostate specimen (3). The main reason for this discrepancy is the difference in practice location of respondents and presence of residents in our survey. Majority of the respondents (72%) were from non-university hospitals in the survey of ASCP and submission of entire prostate was generally practiced in academic centers for research or educational purposes. Besides residents may affect the results in favor of supporting total submission in several ways, either feel incapable for evaluating gross macroscopy or strictly fol-

low predefined macroscopy protocols or underestimate financial issues. But, contradictory to these comments, total samplers were more than partial samplers among the nonresident respondents. However respondents who believe in necessity of total sampling were less than the latter, which can be summarized as “most of the audience is not against partial sampling but feel them obliged to submit totally since they don’t want to miss anything that may have prognostic implication now or in the future”. Some of the participants especially from nonuniversity settings described different partial sampling methods. But among them especially the ones disregarding anterior sections have the potential risk to miss nonpalpable T1c tumors. A variety of partial submission methods have been described in the literature, and the preferred method should depend on whether the specimen represents palpable (stage T2) or impalpable (stage T1c) disease (8,9).

Assessment of margins and seminal vesicles are also very important for pathologic staging. No question was addressed about inking for surgical margin identification but to our personal observation it is performed in most of the laboratories although generally with a single color. Over 90% of the respondents declared that they sample apical, basal and ductus deferens surgical margins separately. At the apex, prostatic adenocarcinoma is typically very close to the true specimen margin, and margins positive at the bladder neck indicate a higher risk of failure (7). Although the tips of the ductus deferens can be removed, these margins are uncommonly involved (7).

Vesicula seminalis-prostate junction was sampled by 64% of the respondents. Since cancer first involve the base of the seminal vesicle either directly via the ejaculatory duct or by extension out the prostate, it is very important to sample and record this part. But interestingly 18% percent of the participants suggested that the integrity of the seminal vesicles are ruined or destroyed. This is a very important point,

which should be evaluated with the surgeons as well.

In the last part of the survey upon reporting the final histopathologic diagnosis, among the morphologic based Category 1 prognostic factors, Gleason system seems to be used by all of the participants, on the contrary to survey of ASCP in which 35% of the participants used grading systems other than Gleason’s. But although it is widely used, when the participants were asked how they report Gleason patterns, interestingly, 24% of them declared that they assign the highest grade as the primary pattern. Half of these “false” respondents were residents and to our surprise one fourth of them were senior pathologists. Totally 70% of them were university members. But, it is well known that most of the senior pathologists in university hospitals have different topics of interest and loose their familiarity with prostate pathology. These senior pathologists generally do not sign any urologic pathology report that may have a word on patients’ care and prognosis. So the main interest should be focused on residents, who are supposed to know the basics of Gleason system even in their first year of pathology. In context of Gleason system, 71% assign primary and secondary grades separately whereas 19% record tertiary pattern. The respondents who comment upon tertiary Gleason pattern majority of which are from university hospitals define it as either the third most frequent pattern (10%) or the highest grade constituting less than 5% of tumor (8%). There was no comment in survey of ASCP about tertiary Gleason patterns since the “popularity” of tertiary patterns was lesser when the survey was published in 1994. Current proposal for radical prostatectomy specimens is, one should assign the Gleason score based on the primary and secondary patterns with a comment as to the tertiary most frequently seen pattern (10).

When the survey audience was asked about their approach on reporting intraglandular extent of tumor they declare that they search for

extension of tumor but when questioned in detail about how and which of the features they report, contradictory answers were given. According to this, 25-55% of the participants report whether the tumor involved one or two lobes or comment upon the multifocality of tumor or the percentage of involvement in each lobe. These features were reported in detail mostly by university members and uropathologists. The response rates for the same topics in the survey of ASCP were 54-90% (Table 3). Involvement of one or two lobes alters tumors' stage. Thus involvement of each lobe should be reported in the pathology report. Among the Category 2 prognostic factors volume was assigned by 25%. Assessment of these prognostic features mainly requires total submission of gland if not whole mount sections. Survey results also show that there is a lack of clarity in reporting the status of surgical margins and capsule as well. Patients with positive margins have a significantly increased risk of progression as compared to those with negative margins so it should be clearly indicated in the pathology report (7). Reporting apical surgical margin involvement separately which was emphasized in the survey of ACSP has lost its potential importance because it has been demonstrated that it does not correlate independently with progression (11).

Status of capsule should be carefully evaluated histologically since the prostatic capsule is not well defined. Although most of the participants evaluate extraprostatic extension, when reporting the findings there is a confusion about the terminology of "capsular incision", "capsular invasion" and "capsular penetration" especially for the ones who are less familiar with the prostate pathology. This confusion probably caused decreased response rates in detailed questions upon reporting extraprostatic extension. Vesicula seminalis invasion was searched and reported by majority of the participants and it is in conjunction with ASCP survey.

One of the interesting findings of this survey was; perineural invasion which was consi-

dered to be a category 3 prognostic factor was reported by all of the participants. Vascular invasion and nuclear features were also reported by quite number of respondents. This attitude may result from population characteristics of respondents who were experienced in general pathology in which perineural and vascular invasion are one of the major topics of prognostic interest rather than uropathology.

Our survey showed that prognostic factors of proven significance as Gleason score, extraprostatic extension, vesicula seminalis invasion, and margin status were searched and commented by all respondents. But it seems there is a lack of standardization and terminological unity in reporting these items of which seems to be one of the major differences from the survey results of ASCP. Prognostic factors that require validation in larger multivariate studies such as volume assessment or tertiary Gleason grading are reported by respondents particularly from university hospitals. We hope the results of this survey will help us to develop routine protocols and educational strategies to assist training pathologists in reporting relevant information.

Acknowledgement

The authors thank to all respondents participated in above declared field research. It has been regarded that the answers of the participants reflect their personal opinions and do not represent their affiliated institutions' official approach to prostate pathology.

REFERENCES

1. Bostwick DG, Grignon DJ, Hammond EH. Prognostic Factors in Prostate Cancer. Collage of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000;124:995-1000.
2. Srigley JR. Key issues in handling and reporting radical prostatectomy specimens. Arch Pathol Lab Med 2006;130:303-317.
3. True LD. Surgical pathology examination of the prostate gland. Practice survey by American society of clinical pathologists. Am J Clin Pathol 1994;102:572-579.
4. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological

- grading and clinical staging. *J Urol* 1974;111:58-64.
5. Henson DE, Fielding LP, Grignon DJ, Page DL, Hammond ME, Nash G, et al. College of American Pathologists Conference XXVI on Clinical Relevance of Prognostic Markers in Solid Tumors: summary. *Arch Pathol Lab Med* 1995;119:1109-1112.
 6. Sakamoto W, Iwata H, Kamikawa S, Tsurusaki K, Sugimoto T, et al. Role of the transition zone for elevating serum prostate-specific antigen in benign prostatic hyperplasia. *Int J Urol* 1998;55:163-166.
 7. Epstein JI, Amin M, Boccon-Gibod L, Egevad L, Humphrey PA, et al. Prognostic factors and reporting of prostate carcinoma in radical prostatectomy and pelvic lymphadenectomy specimens. *Scand J Urol Nephrol Suppl* 2005;216:34-63.
 8. Hall GS, Kramer CE, Epstein JI. Evaluation of radical prostatectomy specimens. A comparative analysis of sampling methods. *Am J Surg Pathol* 1992;16:315-324.
 9. Sehdev AE, Pan CC, Epstein JI. Comparative analysis of sampling methods for grossing radical prostatectomy specimens performed for nonpalpable (stage T1c) prostatic adenocarcinoma. *Hum Pathol* 2001;32:494-499.
 10. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL. Update on the Gleason grading system for prostate cancer: results of an international consensus conference of urologic pathologists. *Adv Anat Pathol* 2006;13:57-59.
 11. Fesseha T, Sakr W, Grignon D, Banerjee M, Wood DP Jr, Pontes JE. Prognostic implications of a positive apical margin in radical prostatectomy specimens. *Urol* 1997;158:2176-2179.