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Histological classification and stage of newly diagnosed bladder cancer in a population-based study from the Northeastern United States*

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Abstract

Objective—There are limited data on the distribution of bladder cancers in the general population, classified by World Health Organization (WHO)/International Society of Urological Pathology (ISUP) criteria. This study evaluated the classification and stage of bladder cancers as part of a population-based epidemiological study of bladder cancer in the Northeastern United States.

Material and methods—All New Hampshire residents with bladder cancer newly diagnosed from 1998 to 2000 were identified through the state cancer registry. All slides were reviewed by a single pathologist. Tumors were classified by two sets of standard criteria.

Results—The retrieval rate for cases was over 90%. Of 342 cases reviewed, 15 were excluded for technical reasons or because malignancy was not definitively diagnosed. According to WHO/ISUP criteria, 25.7% of tumors were papillary urothelial neoplasms of low malignant potential (PUNLMP), 34.3% low-grade papillary carcinomas, 22.6% high-grade papillary carcinomas, 10.1% non-papillary urothelial carcinomas and 5.5% carcinoma in situ. By WHO (1973) criteria, 52.5% of tumors were grade 1, 21.4% grade 2 and 26.1% grade 3. Two-thirds of all tumors were stage Ta, 20.8% stage T1 and 7.6% stage ≥T2. 100% of PUNLMPs were non-invasive, 6.3% of low-grade carcinomas were invasive and 64.9% of high-grade carcinomas were invasive.

Conclusions—Compared to clinic or hospital referral-based series, this study documents a higher percentage of non-invasive tumors and a lower percentage of muscle-invasive tumors. There was also a higher percentage of PUNLMP tumors and fewer high-grade papillary carcinomas than in other series. These results may more accurately reflect prevalence data for bladder cancer grade and stage, although geographic variability may exist.

Keywords

Bladder cancer; epidemiology; pathological grade; pathological stage

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Introduction

Cancer of the urinary bladder is the fourth most prevalent non-skin cancer in males in the USA, and ranks ninth in frequency among women [1]. An estimated 61 420 new cases of bladder cancer were diagnosed in the USA in 2006 [1]. Tobacco smoking has been implicated in epidemiological studies as the cause of approximately 50% of bladder cancer cases in men and 30% in women [2]. Various chemical and industrial exposures account for another 25% of these tumors in men and 11 % in women [3–5].

Urothelial (transitional cell) carcinoma is by far the most frequent histological type of bladder cancer [6]. Both tumor grade and stage of urothelial carcinoma are highly correlated with recurrence, progression and patient survival rates [7]. Tumor grade classification is based on cytological characteristics, and tumor stage is determined by the degree of invasiveness and metastasis. Non-invasive papillary urothelial carcinoma is designated as stage Ta, while stages T1, T2, T3 and T4 refer to invasion into the subepithelial connective tissue, muscle, perivesical tissue and adjacent organs, respectively.

Historically, most of the data on the distribution of grade and stage of bladder cancer have been derived from retrospective studies on selected, often hospital- or clinic-based, patient populations [8–13]. Such studies are likely to include a disproportionate number of patients with more aggressive or advanced stage tumors. Only a small number of non-selected, population-based studies of bladder cancer have reported grade and stage data, primarily from Scandinavia [14,15].

The present study was conducted in conjunction with a large, multidisciplinary, epidemiological project in northern New England [16]. This presented a unique opportunity to do concomitantly a population-based study on the histological classification and stage distribution of bladder cancer at the time of clinical presentation. To the authors' knowledge, this is the first such population-based study of these parameters for bladder cancer from the USA that includes the revised World Health Organization (WHO)/International Society of Urological Pathology (ISUP) classification criteria.

Material and methods

All residents of New Hampshire between the ages of 25 and 74 years newly diagnosed with primary bladder cancer from 1 July 1998 to 30 June 2000 were identified through the New Hampshire State Cancer Registry [16]. Inasmuch as the Registry has reciprocal arrangements with all neighboring states, New Hampshire residents in whom the initial bladder cancer diagnosis was made in another state were included in this study. State law requires health practitioners to report all cancer patients to the Registry upon diagnosis. The Registry conducts detailed yearly audits with all hospitals and other reporting sites to ensure compliance with the state law. Study participants completed a detailed questionnaire and underwent an in-depth interview to obtain data on demographic traits and carcinogen exposure.

Pathology reports and slides were requested from the pathology laboratories at which the initial diagnoses were made. All slides were reviewed by a single pathologist without knowledge of the submit diagnosis. Tumors were classified according to both 1973 WHO [17] and WHO/ISUP [18] criteria. The latter classification has been adopted without significant revision in the most recent edition of the WHO classification [19]. Tumors were staged according to TNM criteria of the American Joint Commission on Cancer [20]. Tumors without any papillary component were categorized as non-papillary (i.e. solid); all other tumors, either purely papillary or mixed papillary/solid, were categorized as papillary. Intraobserver variability in the pathology classification was tested by conducting a masked re-review of 35 randomly selected bladder tumor cases.

Results

The retrieval rate of slides from pathology laboratories was over 90%. A total of 342 cases from the study period were initially reviewed. Of these, 15 were excluded from analysis because either pathological review failed to confirm an unequivocal diagnosis of urothelial neoplasia or a benign diagnosis was favored. Thus, the final study population numbered 327 cases.

Differences in the distribution of gender and age were tested between tumors classified by tumor type and stage in each classification system. For tumors classified by WHO/ISUP criteria, the percentage of women was larger for papillary urothelial neoplasms of low malignant potential (LMP tumors) than for the other categories of urothelial tumors (i.e. low-grade and high-grade papillary carcinomas) (*p*-value 0.028); no statistically significant difference was found by age (data not shown). No differences in either gender or age were evident for tumor stage or for tumors classified by WHO criteria.

Tumor classification data according to both WHO/ISUP and WHO criteria are presented in Table I. In brief, low-grade papillary lesions, comprising neoplasms of LMP and low-grade papillary carcinomas, accounted for 60.0% of tumors. High-grade papillary carcinomas accounted for 22.6%, while high-grade carcinomas without a papillary component accounted for another 10.1%; 5.5% of cases presented as carcinoma in situ, and 1.5% of tumors were non-urothelial in type. Table I also presents stage distribution data for this set of tumors.

Distribution of tumors by WHO (1973) grading criteria and stage showed the following results: grade 1 tumors comprised 52.5% of the total, grade 2 tumors 21.4% and grade 3 tumors 26.1%. Overall, 21.7% of all tumors in this population were invasive (stage T1 or greater). Only 5% of grade 1 tumors were invasive, 13.3% of grade 2 tumors were invasive and more than 80% of grade 3 tumors were invasive. The interrelationships between the grades of papillary tumors in the WHO/ISUP and WHO classification systems are presented in Table II.

In the test of intraobserver variability, there was 100% agreement on the determination of urothelial versus non-urothelial tumors, 100% agreement on tumor stage, 94% on morphological tumor type, 86% on WHO (1973) grade and 83% on WHO/ISUP grade.

Discussion

This study was population based within a large, defined geographic region. The case collection methodology, utilizing a state cancer registry to which cancer reporting is mandated by state law, ensured that the biopsies reviewed were from the time of the initial diagnostic work-up. Cooperation from pathology laboratories was excellent, with a greater than 90% slide retrieval rate. Virtually all cases were reviewed by a single urological pathologist to maximize standardization and uniformity of diagnostic criteria.

All these parameters suggest that the distribution of tumors in the present population-based study more accurately reflects prevalence for bladder cancer grade and stage than do studies based on clinic- or hospital referral-based patient series. Referral populations are potentially skewed by patients with higher stage, difficult-to-treat or otherwise problematic tumors that may constitute a significant proportion of the patient population in academic or specialized medical centers. The present findings suggest that the distribution of tumor types may vary by gender and age, and thus the demographics of the selected referral population could affect the distribution of tumor types.

Table III compares pathological stage distribution between the present population-based study and representative previously reported studies [8–14,21,22], all but one of which [14] were based on selected, hospital- or clinic-based patient populations. The hospital- or clinic-based

series show a range of non-invasive (stage pTa) tumors between 30 and 49%, compared with 66% in this population-based sample. Conversely, muscle invasive tumors (stage T2 or greater) in hospital- or clinic-based series range from 12–54%, compared with only 8% in the present study. One of these studies [21], although stated as unselected, comprised a consecutive group of "randomly" referred patients to a university hospital, and the data from that study are entirely in keeping with all of the other hospital- or clinic-based series. By contrast, the one previous study with a population-based design comparable to the current study shows a very similar stage distribution. These data highlight the higher proportion of non-invasive (stage Ta) tumors and lower proportion of high-stage (≥T2) tumors in general population series than depicted in selected series.

In theory, the effect of patient selection could be diminished by limiting comparisons to low-stage tumors. Table IV presents the WHO/ISUP classification of non-invasive papillary tumors across several studies [23–26]. The data on tumor distribution of this study's patients is close only to the one study [23] that was limited to patients with primary non-invasive (stage Ta) carcinomas that was derived from the general population. In the other two studies, patients of all stages were examined, and the distributions differed. Thus, this comparison would tend to support the premise that patient selection affects the grade as well as the stage distribution.

Table V presents a comparison of the WHO (1973) grading system between hospital- and clinic-based [21,27] and population-based [28] studies. The two studies with population-based design (the current study and that of Holmäng et al. [28]) show very similar grade distribution results. The two hospital- or clinic-based studies [21,27], in contrast, show considerable variation. Such differences could potentially be explained by a non-standard application of grading criteria. For instance, the tendency to lump tumors into the middle grade of a three-tiered grading scheme is one of the flaws of the WHO (1973) system that was cited to help bolster the adoption of the newer WHO/ISUP system [18]. The grade distributions, however, are probably at least as likely to reflect differences in referral patterns and patient case-mix in the patient populations at tertiary care institutions.

The data presented in this report are derived from a geographic location in the continental USA with high incidence and mortality rates from bladder cancer [29], and this could potentially limit the generalizability of the findings. New Hampshire is less industrialized and more uniformly Caucasian in population than many other states. Further, this study was undertaken in the context of a larger study exploring possible environmental influences, including arsenic, on the high incidence of bladder cancer. This could possibly explain the high percentage of cases of urothelial carcinoma in situ in this study in comparison to other studies (Tables I and III); this effect could be related to an excessive environmental exposure, e.g. to arsenic, but this requires further investigation. It is conceivable, although unlikely, that the similarity of the results to those of Holmäng et al. [14,28] from Scandinavia could in part be related to similar ethnic mix, levels of industrialization, lifestyle or other demographic characteristics, rather than to the population-based character of the study population. Future analyses to evaluate potential histological patterns associated with exposure history may provide helpful etiological clues.

The exclusion from the present study of patients older than 74 years means that the population cannot be described as completely non-selected. The age range was determined by the criteria used for an epidemiological case-control study [16]. The rationale for exclusion was based on the facts that not only do response rates tend to be lower among older patients, but also the diagnoses of cancer may be obscured and hence underreported among older patients in whom multiple diagnoses coexist. In the present data, no marked differences in histological characteristics by age were detected. In another study, the mean age at diagnosis of a stage T2 cancer was 75 years [14], while the mean ages for Ta and T1 tumors were 70 and 73 years,

respectively. Thus, the possibility cannot be excluded that omission of cases in patients older than 74 years in the current study could have led to an underestimation of advanced (stage 2 or greater) disease.

Another limitation is that in this study about 10% of bladder cases diagnosed during the study period could not be retrieved. Although there is no reason to suspect a hidden selection bias, this possibility cannot be completely excluded. In addition, the pathological review of cases by a single pathologist maximizes uniformity of diagnostic criteria and standardization, but may result in subjectivity and an idiosyncratic detection bias. The published diagnostic criteria of the WHO/ISUP classification system, however, have been profusely illustrated and described in unusual detail; this was done expressly to reduce diagnostic variability and subjectivity [18,19]. Also, the similarity of the data to those of other studies with a population-based design [14,23,28] suggests similar application of diagnostic criteria. In addition, internal checks for intraobserver variability supported the intrastudy stability of diagnoses.

In conclusion, this study provides grading and staging data from the time of initial bladder cancer diagnosis that cannot be derived from selected, hospital-based population studies. Thus, a considerably higher proportion of non-invasive and low-grade urothelial tumors, and a much lower percentage of muscle-invasive tumors likely exist in the general population than what is inferred from clinical or hospital referral-based patient series.

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Table I

Tumor stage and classification by WHO/ISUP criteria.

Tumor designation	No. of cases	% of cases	Stage[c]				
			Tis *n* (%)	Ta *n* (%)	T1 *n* (%)	>T2 *n* (%)	Total T1+T2 *n* (%)
Carcinoma in situ[a]	18	5.5%	18 (100%)				
Papilloma	1	0.3%		1 (100%)			
PUNLMP	84	25.7%		84 (100%)			
PUC-LG	112	34.3%		105 (93.7%)	6 (5.4%)	1 (0.9%)	7 (6.3%)
PUC-HG	74	22.6%		26 (35.1%)	41 (55.4%)	7 (9.5%)	48 (64.9%)
Non-PUC	33	10.1%			19 (57.6%)	14 (42.4%)	33 (100%)
Other[b]	5	1.5%			2 (40.0%)	3 (60.0%)	5 (100%)
Total tumors	327	100.0%	18 (5.5%)	216 (66.1%)	68 (20.8%)	25 (7.6%)	93 (28.4%)

WHO =World Health Organization; ISUP =International Society of Urological Pathology; PUNLMP =papillary urothelial neoplasm of low malignant potential; PUC-LG =papillary urothelial carcinoma, low grade; PUC-HG =papillary urothelial carcinoma, high grade; Non-PUC =non-papillary urothelial carcinoma.

[a]Includes one case with microinvasion.

[b]Two small cell carcinoma, two squamous cell carcinoma, one adenocarcinoma.

[c]One tumor (urothelial carcinoma in situ with questionable stromal invasion) with indeterminate stage is excluded.

Table II

Interrelationships of papillary bladder tumors by WHO (1973) and WHO/ISUP classification systems.

	WHO (1973)						
WHO/ISUP classification	**Carcinoma in situ**	**Papilloma**	**Grade 1**	**Grade 2**	**Grade 3**	**Other**	**Total**
Carcinoma in situ[a]	18	0	0	0	0	0	18
Papilloma	0	1	0	0	0	0	1
Papillary urothelial neoplasm of low malignant potential	0	0	84	0	0	0	84
Papillary urothelial carcinoma - low grade	0	0	60	52	0	0	112
Papillary urothelial carcinoma - high grade	0	0	0	5	69	0	74
Non-papillary urothelial carcinoma	0	0	0	2	31	0	33
Other[b]	0	0	0	0	0	5	5
Total	18	1	144	59	100	5	327

WHO = World Health Organization; ISUP = International Society of Urological Pathology.

[a] Includes one case with microinvasion.

[b] Includes two small cell carcinomas, two squamous cell carcinomas and one adenocarcinoma.

Table III

Comparison of pathological stage at presentation with eight selected, hospital- or clinic-based studies.

Stage (no. of pts)	Population-based		Hospital- or clinic-based							
	Present series (322)	Holmäng [14] (595)	Pauwels [13] (168)	Takashi [10] (264)	Holmäng [12] (230)	Lutzeyer [8] (900)	Kiemeney [11] (2705)	Heney [9] (538)	Wolf [21] (498)	Fosså [22] (331)
Tis	5%		2%				2%		1%	3%
Ta	66%	63%	48%	49%	38%	30%	44%	32%	42%	47%
T1	21%	20%	24%	20%	48%	28%	18%	14%	19%	23%
≥T2	8%	17%	26%	31%	12%	35%	36%	54%	38%	27%

Table IV

WHO/ISUP tumor distribution of stage pTA (non-invasive) papillary tumors: comparison between population-based and hospital- and clinic-based studies.

	Population-based		Hospital- or clinic-based		
Tumor classification (no.)	**Present study (235)**	**Oosterhuis [23] (320)**	**Samaratunga [24] (134)**	**Yin [25] (84)**	**Cheng [26] (164)**
Papilloma	<0.5%	5%	2%	—	—
PUNLMP	39%	36%	22%	14%	15%
Papillary-LG	49%	44%	54%	63%	67%
Papillary-HG	12%	14%	22%	23%	18%

WHO =World Health Organization; ISUP = International Society of Urological Pathology; PUNLMP =papillary urothelial neoplasm of low malignant potential; Papillary-LG = papillary urothelial carcinoma, low grade; Papillary-HG = papillary urothelial carcinoma, high grade.

Table V

Comparison of population-based vs hospital- or clinic-based studies by WHO (1973) grade (all stages).

	Population-based		Hospital- or clinic-based	
Grade (no. of pts)	**Present study (304)**	**Holmäng [14] (616)**	**Lipponen [27] (537)**	**Wolf [21] (475)**
1	53%	43%	41%	7%
2	21%	25%	41%	47%
3	26%	32%	18%	46%

WHO =World Health Organization.