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Natural History of Early Bladder Cancer

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Abstract Non-invasive transitional cell carcinoma (TCC) occurs as two distinct growth patterns, papillary and non-papillary (flat), which display significant differences in biologic potential. Papillary carcinoma usually presents as a low-grade lesion which frequently recurs multiple times prior to invasion; conversely, non-papillary (flat) carcinoma *in situ* is usually high-grade at presentation (carcinoma *in situ*) and frequently associated with invasion. These lesions may occur together, although papillary cancer is more easily visualized cystoscopically due to its exophytic growth; flat carcinoma *in situ* is often cystoscopically invisible.

This report reviews existing data concerning the prognostic value of pathologic grading and staging of non-invasive and early invasive TCC. Emphasis is placed on those studies reporting surgical treatment rather than other forms of treatment.

Key words: bladder, carcinoma *in situ*, dysplasia, invasion

It is difficult to determine the natural history of non-invasive TCC because of numerous problems with pathologic classification and staging [1]. Until recently, grading of urothelial lesions has been inconsistent, with no consensus of opinion or standardization of criteria; however, efforts by the World Health Organization (WHO) in the past two decades have resolved many of these grading issues [2]. Some pathologists accept the existence of benign papilloma [3], whereas others consider these to be low-grade carcinoma [4,5]. Staging of TCC in superficial biopsies has always been difficult due to sampling error and the frequent inability to determine the presence or extent of invasion; some reports have provided only the clinical evaluation of stage rather than the pathologic stage [6]. Many publications have failed to provide precise information and definitions of grading and staging, making comparison with other reports difficult (see Tables I and II). Also, intravesical immunotherapy with Bacillus Calmette-Guerin (BCG) has been shown to reduce the risk of recurrence in many cases [7–10], and its widespread use precludes the study of the natural history of TCC in a large number of patients in whom only excision is undertaken.

PAPILLOMA VS. GRADE 1 NON-INVASIVE PAPILLARY CARCINOMA

The separation of benign papilloma and low-grade papillary carcinoma remains unresolved. As long ago as the late nineteenth century, two leading pathologists disagreed on the biologic potential of low-grade papillary lesions; Virchow considered them benign (papilloma), whereas Rokitansky classified them as malignant (carcinoma). Today, the papilloma-papillary carcinoma controversy persists, although the majority of pathologists in the United States consider any papillary urothelial lesion to be malignant [4]. Review of the literature reveals that these lesions have a 0–67% likelihood of recurring within about 5 years (Table I, Fig. 1) [11–22]; this wide range reflects the variable diagnostic criteria employed by different authors. Those employing strict criteria (small, solitary lesion fewer than 7 cells in thickness with no atypia) have reported recurrence rates at the low end of this range (closer to 0%). The likelihood of developing invasive carcinoma (0–21%) and can-

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TABLE I.

FIRST AUTHOR	YEAR	PATHOLOGIC CRITERIA	GRADE	#PTS	FOLLOW-UP (MONTHS)	THERAPY (INITIAL)	#RECUR.	%RECUR.	#INVASION	%INVASION	#DEAD	%DEAD
NON-INVASIVE PAPILLARY LESIONS (pTa)												
KRETSCHMER	1949	<7,NO ATYPIA	P	100	60+	ALL MODALITIES	46	46	10	10	5	5
DEMING	1950	ASH/BRODERS	P	52	36MIN	ALL MODALITIES	36	69	8	15		
EWERT	1951	NOT GIVEN	P	79	UP TO 120	EXCISION	30	38				
LUND	1955	NOT GIVEN	P	183	96AVG	PREDOM EXCISION	72	39	15	8	12	7
NICHOLS	1956	NA	P	35	60MIN	EXCISION	16	46	7	20	2	6
ROYCE	1959	ASH	P	100	60+	ALL MODALITIES	67	67			9	9
PYRAH	1964	<=5+MATYPIA	P	207	36MIN	PREDOM EXCISION	112	54	44	21	24	12
BERGKVIST	1965	<7	G0	12	96MIN	PREDOM EXCISION					0	0
MILLER	1969	<=5+MATYPIA	P	26	NA	EXCISION	0	0	0	0	0	0
LERMAN	1970	>7+MILDATYP	P	125	64AVG	PREDOM EXCISION	66	53	12	10	6	5
HENEY	1983	NA	G0	5	39MED	EXCISION			0	0	0	0
Totals								0-67		0-21		0-12
GIBBONS	1969	>7	G1	30	60MIN	EXCISION	20	67	6	20	3	10
MILLER	1969	<5+MATYPIA	G1	622	NA	PREDOM EXCISION					57	9
GREENE	1973	WHO	G1	100	180MIN	EXCISION	73	73	10	10	10	10
GILBERT	1978	>7+ATYPIA	G1	155	60MIN	PREDOM. EXCISION ONLY	92	59			9	6
ENGLAND	1981	WHO	G1	135	12-240	ALL MODALITIES	94	70		0	4	3
POCOCK	1982	WHO	G1	34	44AVG	EXCISION					0	0
HENEY	1983	NA	G1	85	39MED	EXCISION			2	2		
JORDAN	1987	WHO	G1	91	120MIN	EXCISION,XRT,THIO	36	40	4	4	4	4
TORTI	1987	NA	G1	135	62AVG	EXCISION						
TAKASHI	1991	WHO	G0-G1	58	50MED	EXCISION		38 @5YRS				3@10YRS
Totals								40-73		0-20		0-10
GIBBONS	1969	>7 + ATYPIA	G2	30	60MIN	EXCISION	17	57	6	20	4	13
ENGLAND	1981	WHO	G2	5	12-240	ALL MODALITIES	3	60		0	1	20
HENEY	1983	NA	G2	50	39MED	EXCISION			3	6		
TORTI	1987	NA	G2	51	62AVG	EXCISION						
TAKASHI	1991	WHO	G2	106	50MED	EXCISION		45@5YRS				14@10YRS
Totals								45-67		0-20		13-20
GIBBONS	1969	>7+ATYPIA	G3	5	60MIN	EXCISION	4	80	1	20	0	0
GIBBONS	1969	>7+CIS	CIS	13	60MIN	EXCISION	11	85	3	27	4	31
GILBERT	1978	>7+SEV.ATYP	G3	23	60MIN	ALL MODALITIES	15	65	12	52	8	35
HENEY	1983	NA	G3	4	39MED	EXCISION			1	25		
TORTI	1987	NA	G3	4	62AVG	EXCISION						
Totals								65-85		20-52		0-35

cer-specific death (0–12%) after surgical excision is virtually identical to that of grade 1 non-invasive papillary carcinoma (see below). Based on these findings, some authors recommend elimination of papilloma as a diagnostic category [3], whereas others argue in favor of retaining the strictly defined papilloma [4,5].

NON-INVASIVE PAPILLARY CARCINOMA (pTa CARCINOMA)

Three grades of non-invasive papillary carcinoma are recognized by the WHO in the most widely used grading scheme based on the degree of cellular anaplasia [2]: grade 1 has the least degree of anaplasia, grade 2 is intermediate, and grade 3 has the most (Fig. 1). The utility of the grading scheme has been confirmed in most studies addressing this issue. In a multivariate analysis, Torti *et al.* [23] showed that tumor grade was the most significant prognostic factor. The likelihood of recurrence, invasion, and cause-specific death appears to correlate positively with increasing tumor grade (Table I, Fig. 2) [19,21,23–29]. The overlap in ranges of outcomes for different grades may be due to problems in determining the presence or depth of invasion in many biopsies, contributing to significant understaging. This problem persists, and appears at present to be unavoidable [30]. BCG therapy appears to reduce the risk of recurrence for pTa carcinoma [7,9,10].

TABLE II.

FIRST AUTHOR	YEAR	PATHOLOGIC CRITERIA	GRADE	#PTS	FOLLOW-UP (MONTHS)	THERAPY (INITIAL)	#RECUR.	%RECUR.	#INVASION	%INVASION	#DEAD	%DEAD
CIS (pTIS)												
MELAMED	1964		CIS	25	UP TO 67	5CYS;3XRT+CYS;17EXCIS			8	32	3	12
UTZ	1970		CIS	62	60-144	3CYS;2XRT;57 EXCISION	51	82	37	60	24	39
YATES-BELL	1971		CIS	5	UP TO 36	2CYS;2RADTX;1EXCISION			3	60	2	40
ALTHAUSEN	1976		CIS	12	60MIN	EXCISION	11	92	10	83	7	58
LIEBER	1984		CIS	92	48-108	38THIO;NO OTHER	58	63	31	34	2	2
Totals								63-92		32-83		2-58
pT1 CANCER												
ENGLAND	1981	WHO	G1	105	12-240	ALL MODALITIES	75	71	13	12	7	7
POCOCK	1982	WHO	G1	18	28AVG	EXCISION					0	0
HENEY	1983	NA	G1	7	39MED	EXCISION			0	0	7	39
TORTI	1987	WHO	G1	10	62AVG	EXCISION						
Totals								71		0-12		0-39
ENGLAND	1981	WHO	G2	59	12-240	ALL MODALITIES	47	80	29	49	20	34
POCOCK	1982	WHO	G2	39	23-30AVG	EXCISION	26	67	15	38	9	23
HENEY	1983	NA	G2	29	39MED	EXCISION			6	21	20	51
TORTI	1987	WHO	G2	25	62AVG	EXCISION					9	31
TAKASHI	1991	WHO	G2	30	50MED	EXCISION		67@5YRS				17@10YRS
Totals								67-80		21-49		17-51
GILBERT	1978	>7+SEV.ATYP	G3	25	60MIN	ALL MODALITIES	13	52	6	24	8	32
ENGLAND	1981	WHO	G3	28	12-240	ALL MODALITIES	13	46	11	39	8	29
POCOCK	1982	WHO	G3	7	21AVG	EXCISION+CYS	5	71			5	71
HENEY	1983	NOT GIVEN	G3	27	39MED	EXCISION			13	48	7	25
TORTI	1987	WHO	G3-4	16	62AVG	EXCISION						
YOUNES	1990	NOT GIVEN	G3-4	25	36MIN	EXCISION						
TAKASHI	1991	WHO	G3	23	50MED	EXCISION		37@5YRS				41@10YRS
Totals								46-71		24-48		25-71

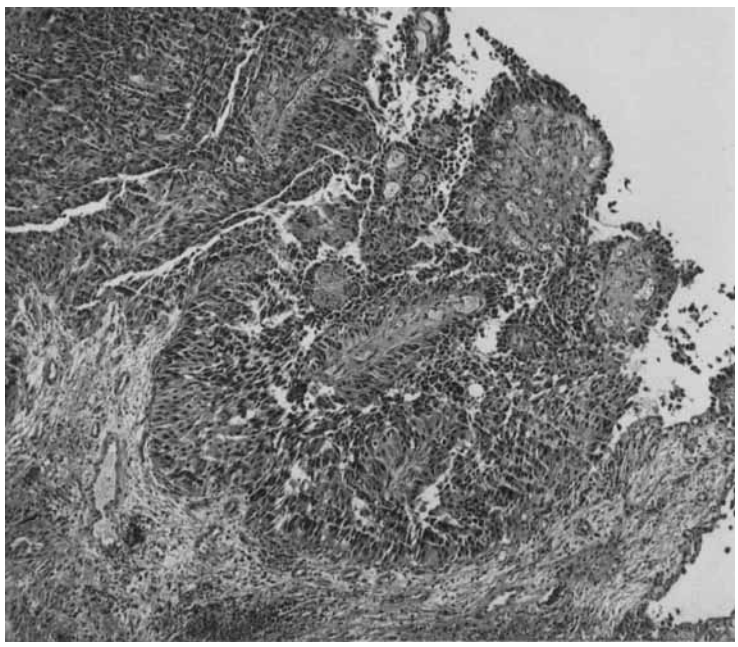

Fig. 1. Grade 2 non-invasive papillary carcinoma.

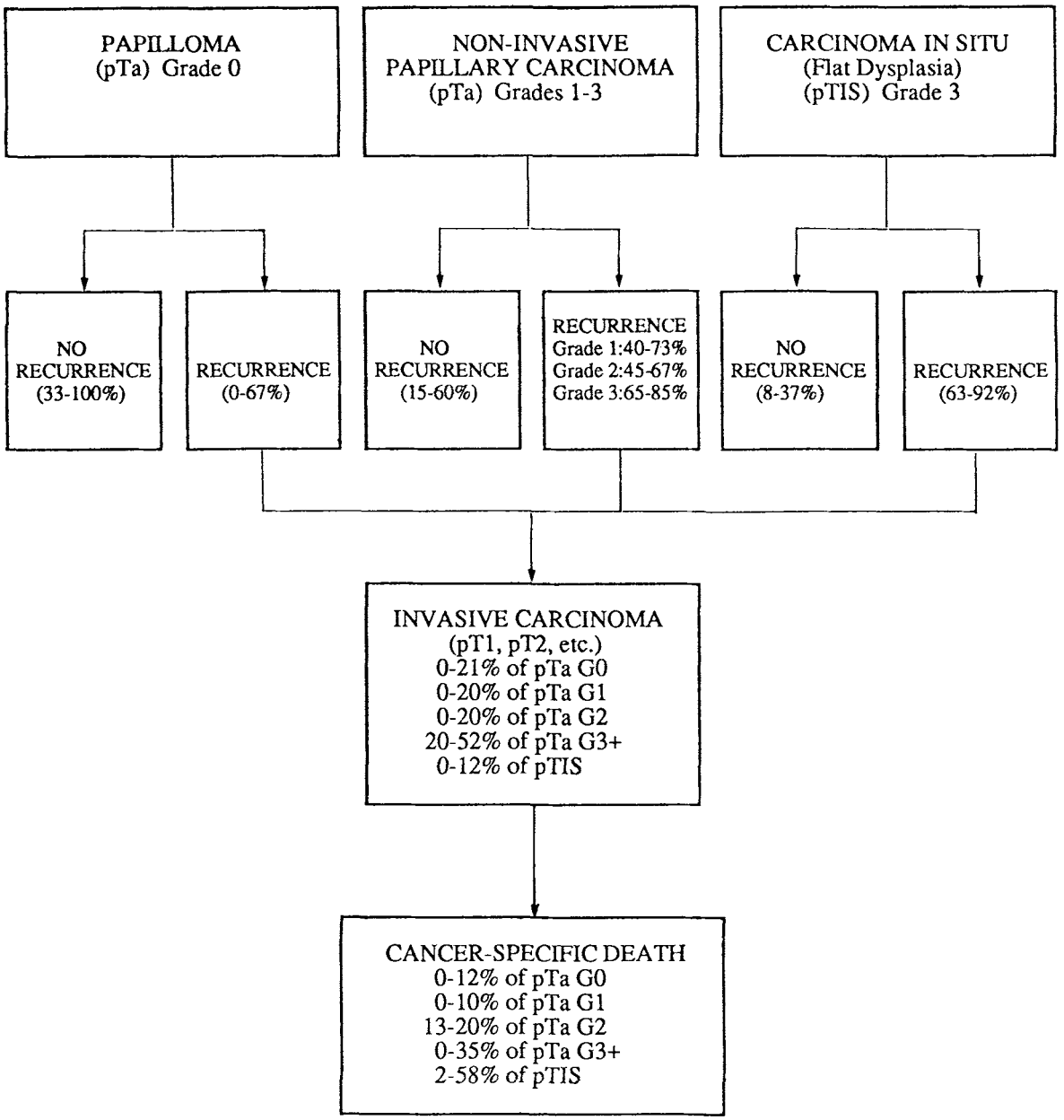

Fig. 2. Recurrence and progression in predominantly surgically treated non-invasive TCC (data from Table I).

NON-INVASIVE FLAT CARCINOMA (pTIS CARCINOMA; CARCINOMA *IN SITU*)

In 1964, Melamed [31] demonstrated the prognostic importance of transitional cell carcinoma *in situ* and the need to distinguish it from non-invasive papillary carcinoma (Fig. 3). Cumulative data from the literature show that this lesion has a high recurrence rate (63–92%), high likelihood of invasion (32–83%), and a significant rate of cause-specific death (up to 58%) after surgical excision (Table II, Fig. 4)

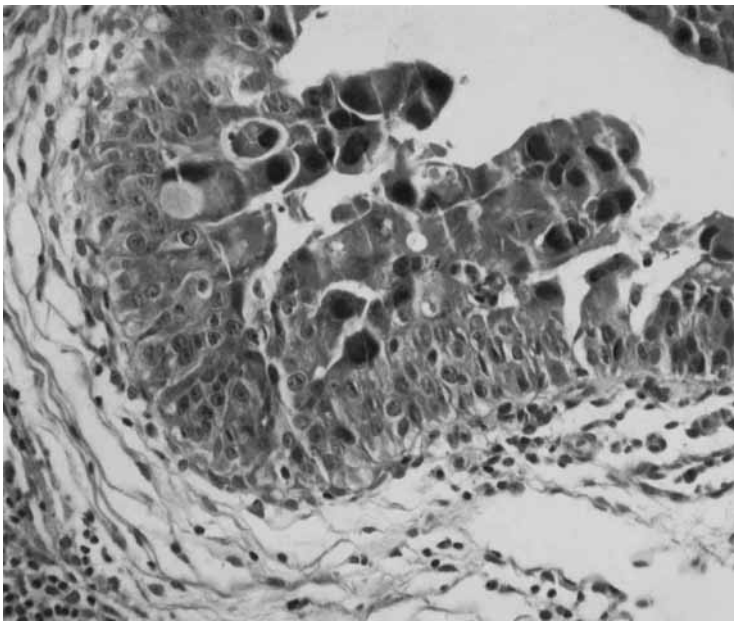

Fig. 3. Carcinoma *in situ*.

[31–35]. Recurrences may arise in urothelial locations outside of the bladder (renal pelvis, ureters, urethra, or prostate), and are frequently multifocal.

Flat urothelial lesions with cytologic abnormalities have also been referred to as "dysplasia," transitional intraepithelial neoplasia (TIN), and intraurothelial neoplasia (UIN) [36]. Such proposals describe the morphologic continuum of cytologic changes and provide grading schemes (mild, moderate, and severe, or 1, 2, 3); carcinoma *in situ* (CIS) represents the most severe end of the continuum. However, there is a high degree of inter-observer variability in the grading of urothelial dysplasia (flat non-invasive lesions which fall short of CIS), particularly with low-grade lesions [37,38].

CIS is frequently invisible cystoscopically, and may coexist with papillary neoplasms. To overcome the potential diagnostic difficulty of CIS, urine cytology is recommended. Cytology is of considerable diagnostic value with all urothelial lesions, but is particularly useful with CIS in which the exfoliated cells exhibit severe cytologic atypia [39,40]. Some have suggested that unrecognized CIS may be responsible for the poor outcome sometimes seen in patients with low-grade papillary carcinoma, particularly those who rapidly develop high-grade invasive tumors.

CARCINOMA WITH INVASION OF THE LAMINA PROPRIA (pT1 CARCINOMA)

Until recently, invasive TCC was defined as tumor involving the muscularis propria; those without such involvement were classified as "superficial." However, reports in the past decade have demonstrated the prognostic utility of identifying tumors with subepithelial invasion (invasion limited to the lamina propria), and these are included in the current Tumor-Nodes-Metastasis (TNM) staging system as pT1 tumors. As expected, these tumors have a likelihood of progression (muscle invasion or cancer-specific death) which is intermediate between non-invasive lesions pTa and pTIS, and muscle-invasive tumors, pT2+ (Table II, Fig. 2) [21,23, 27,29–41]. With widespread recognition of this important subset of tumor staging, we recommend that use of the term "superficial" be discouraged and the more precise terminology of TNM staging be employed.

The majority of patients with pT1 carcinoma treated with BCG will still progress with muscle invasion within 5 years [7,9,10].

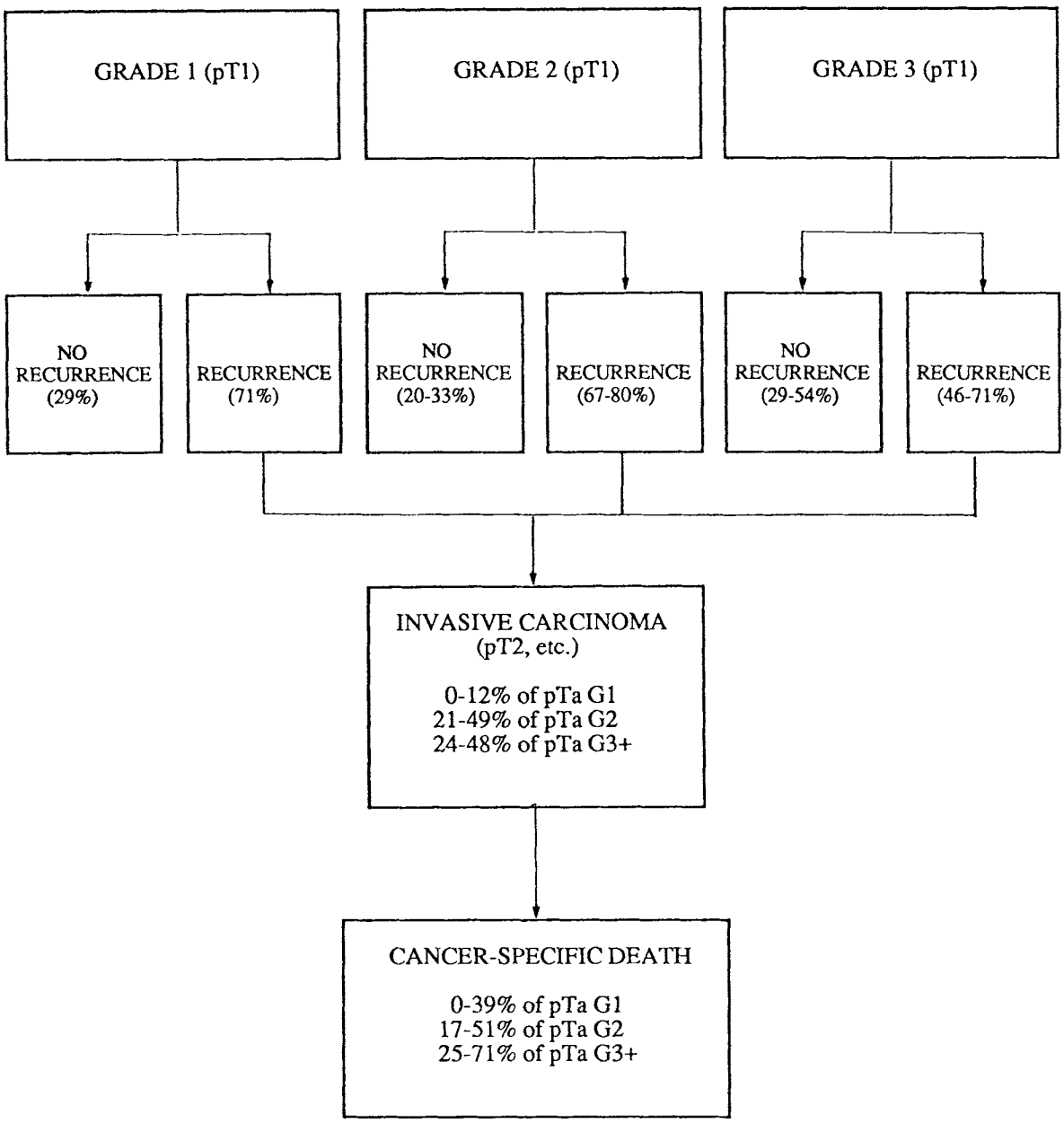

Fig. 4. Recurrence and progression in predominantly surgically treated TCC with lamina propria invasion (data from Table II).

OTHER PROGNOSTIC FACTORS

In addition to tumor grade, growth pattern, and pathologic stage, numerous factors have been described which have significant predictive value for TCC. There is increased risk of recurrence and progression with large tumors, multiple tumors ("field effect"), those with vascular/lymphatic invasion and basement membrane discontinuity, and those with neuroendocrine differentiation (small cell carcinoma) [40,42–44]. Increased risk of cause-specific death is seen

with tumors which lose expression of blood group isoantigen A or oncogene-related protein ORP-p21 [43], or display tumor DNA aneuploidy [43,45]. Acquisition of the invasive phenotype in bladder cancer is correlated with inactivation of tumor suppressor gene p53 [46] and loss of expression of two tumor-associated antigens detected by antibodies M344 and M9A211 [47]. The identification of other prognostic factors which supplement standard clinical and pathologic findings will provide greater precision in stratifying patients for therapy and predicting individual patient outcome.

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