

The prognostic importance of the morphological subdivision of the grade II superficial bladder cancer

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Summary. In this study a morphological subdivision of grade (g)II superficial bladder cancer is proposed and correlated with recurrence and progression rate.

Forty patients, 33 males and 7 females, of 70 years mean age, with initial gII superficial transitional bladder cancer were treated with transurethral resection between January and December 1987 with follow-up for a mean period of 4 years. Recurrences were observed in 24 patients. All histological specimens were reviewed and reclassified to gIIa and gIIb mainly according to the variation in nuclear size, the degree of nuclear atypia and the number of mitoses. 42.1% (8/19) of the gIIa and 76.2% (16/21) of the gIIb tumors recurred. The observed difference in recurrence rate was statistically significant (s.s) - $p < 0.05$. The disease-free interval after the initial presentation was over two years in 50% (4/8) of gIIa and in 6.25% (1/16) of gIIb patients (s.s. difference - $p < 0.05$). None of the patients with gIIa, but 37.5% (6/16) with gIIb urothelial cancer had more than two recurrences (s.s. difference - $p < 0.05$). All gIIa recurred as gIIa superficial cancers, 62.5% (10/16) of gIIb as gIIb (5 superficial and 5 invasive) and the remainder 37.5% (6/16) as invasive gIII tumors. Only one patient with repeated recurrences died two years after the initial presentation. 3 patients died from other causes.

In conclusion: 1. The morphological subdivision of gII urothelial cancer into gIIa and gIIb has a prognostic significance, as it is related to the recurrence rate, the disease-free interval after the initial resection, the number of recurrences and the progression rate. 2. As gIIb urothelial cancer identifies patients at a higher recurrence risk, it is evident that this group requires an adjuvant treatment and a closer follow-up.

Key words: Urinary bladder, Superficial Carcinoma, Grading, Prognosis

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Introduction

It is well established that the outcome of an initial superficial urothelial cancer depends mainly on its histological grade (g). The intermediate gII group, included in all grading systems, comprises the majority of urothelial cancers and demonstrates a wide spectrum of morphological characteristics. Therefore, the diverse natural course of gII tumors may be due to the above factors. In this study a morphological subdivision of gII superficial bladder cancers, based on the variation in nuclear size, the nuclear atypia and the mitotic activity, is proposed and correlated with the biological behaviour.

Materials and methods

A retrospective follow-up study of 40 patients, 33 males and 7 females, with a newly diagnosed superficial papillary gII bladder carcinoma was performed. The mean age of the patients was 70 years and all patients were treated with transurethral resection between January and December 1987 and followed up for four years at least. All histological specimens were reviewed and reclassified into gIIa and gIIb subgroups, using a modified Bergvist system. GII was subdivided into gIIa and gIIb mainly with reference to the impression of cellular disorder, the variation in nuclear size, the nuclear atypia, the nuclear pleomorphism and the mitotic frequency. In gIIa tumors there was a slight to moderate variation in nuclear size, a slight nuclear atypia, rare mitoses but no notable cellular disorder or nuclear pleomorphism (Fig. 1). In gIIb tumors there was a moderate to strong variation in nuclear size, a moderate nuclear atypia, some mitoses and mild cellular disorder and nuclear pleomorphism (Fig. 2).

The morphological grade was then correlated with the clinical course of the disease: the recurrence rate, the number of recurrences, the disease free interval after the initial presentation, the grade and stage of the recurrent tumor and the survival rate.

Statistical analyses of the results were done by means

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of the chi-square test.

Results

According to the criteria of the modifying Berqvist system the 40 superficial papillary gII urothelial bladder carcinomas were reclassified to 19 gIIa and 21gIIb ones. Recurrences were observed in interval biopsies in 24 of the 40 cases (60%). Among the 19 patients with gIIa tumor, recurrence disease was documented for 8 (42.1%) and among the 21 patients with gIIb tumor for 16 patients (76.2%) (Table 1). The observed difference in recurrence rate between the two groups was statistically significant ($p < 0.05$).

Similarly striking was the difference in the disease-

free interval after the initial presentation. 4 of the 8 gIIa recurrent tumors (50%) but only 1 of the 16 gIIb recurrent tumors (6.25%) presented their first recurrence after 2 years (Table 2). The remainder recurred in a shorter time. The difference between the two groups was also statistically significant ($p < 0.05$).

None of the patients with gIIa, but 37.5% (6/16) with gIIb urothelial cancer had more than two recurrences in the 4-year follow-up period (statistically significant difference - $p < 0.05$) (Table 3).

All 8 recurrent gIIa tumors reappeared as gIIa superficial cancers, but among the 16 gIIb recurrent tumors, 11 (68.75%) reappeared as invasive and 5 (31.25%) as superficial (statistically significant

Table 1. Correlation of the initial histological grade with recurrence rate.

INITIAL GRADE	RECURRENCE RATE		TOTAL
	+	-	
gIIa	8 (42.1%)	11	19
gIIb	16 (76.2%)	5	21
Total	24 (60%)	16	40

Table 2. Correlation of the initial histological grade with the disease-free interval after the initial presentation.

INITIAL GRADE	DISEASE-FREE INTERVAL				TOTAL
	≤ 1 year	1-2 years	2-3 years	3-4 years	
gIIa	1	3	2	2	8
gIIb	10	5	0	1	16
Total	11	8	2	3	24



Fig. 1. Grade IIa urothelial bladder cancer. H-E. x 200

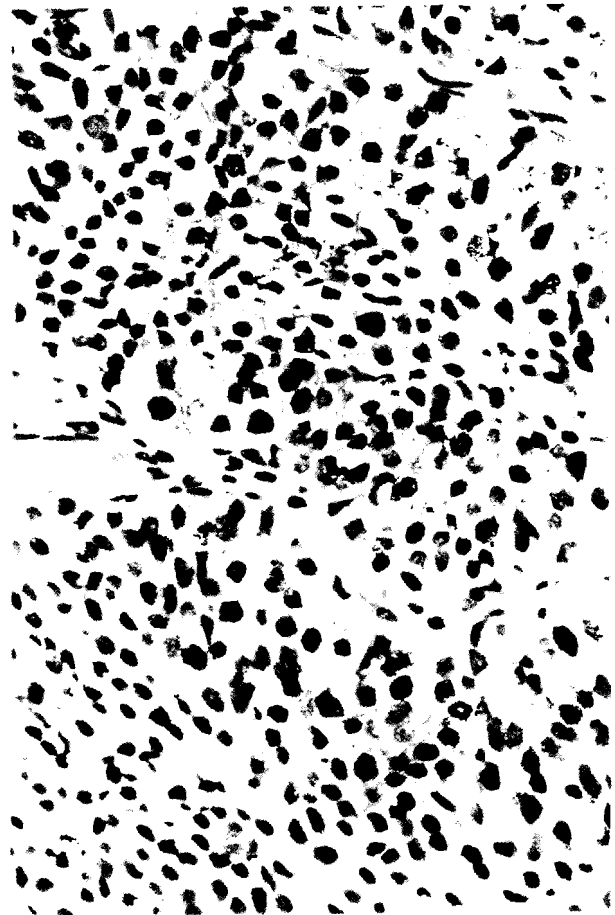


Fig. 2. Grade IIb urothelial bladder cancer. H-E. x 200

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Table 3. Correlation of the initial histological grade with the number of recurrence.

INITIAL GRADE	NUMBER OF RECURRENCES					TOTAL
	1	2	3	4	≥5	
gIIa	5	3	0	0	0	8
gIIb	7	3	1	3	2	16
Total	12	6	1	3	2	24

difference - $p < 0.05$). 62.5% (10/16) of gIIb cancers recurred as gIIb (5 superficial and 5 invasive) and the remainder 37.5% (6/16) as invasive gIII tumors (Table 4). Only one patient with repeated recurrences died two years after the initial presentation. 3 patients died from other causes.

Discussion

The invasive transitional cell tumors of the bladder have as a rule a poor prognosis (Jordan et al., 1987; Eagan, 1989). On the contrary the superficial urothelial bladder cancer is unpredictable; some tumors never seem to grow invasively, whereas others rapidly progress (Jordan et al., 1987; Eagan, 1989). The outcome can be predicted by the identification of factors present at the initial evaluation, such as the size of the tumor and the morphological grade (Jewett et al., 1964; Narayana et al., 1983; Jordan et al., 1987; Eagan, 1989; Kaubisch et al., 1991; Underwood, 1992). Recent approaches such as morphometric, ultrastructural, cytogenetic, flow-cytometry and immunohistochemical studies are also available (Bjelkenkrantz et al., 1982; Helander et al., 1985; Wenzelides et al., 1986; Kirkhus et al., 1988; Pauwels et al., 1988b; Blomjous et al., 1989; Eagan, 1989; Wenzelides, 1989; Lipponen et al., 1990; Sowter et al., 1991; Underwood, 1992). Nevertheless, the histopathological grade of the initial tumor is the most important prognostic factor (Narayana et al., 1983; Jordan et al., 1987; Eagan, 1989; Kaubisch et al., 1991; Webb, 1992).

The widely used classifications of urothelial bladder tumors do not seem to be entirely satisfactory because of the heterogeneous gII group (Bjelkenkrantz et al., 1982; Kirkhus et al., 1988; Pauwels et al., 1988a; Eagan, 1989; Carbin et al., 1991a; Webb, 1992). GI tumors can usually be controlled throughout the life by local resection only, whereas gIII and anaplastic tumors have a poor outcome and need more radical intervention (Jordan et al., 1987; Eagan, 1989). It is therefore well established that the gII superficial urothelial bladder cancers have an uncertain natural course and constitute a clinically as well as a histologically heterogeneous group (Kirkhus et al., 1988; Pauwels et al., 1988a; Eagan, 1989; Carbin et al., 1991a). It is evident that a morphological subdivision of the gII tumors into two subgroups could be meaningful in the assessment of prognosis and choice of treatment.

In our study a grading system was applied in a retrospective study of 40 gII superficial urothelial

Table 4. Correlation of the initial histological grade with the grade and stage of the recurrent tumor.

INITIAL GRADE	RECURRENCE GRADE AND STAGE				TOTAL
	gIIa (S)	gIIb (S)	gIIb (In)	gIII (In)	
gIIa	8	0	0	0	8
gIIb	0	5	5	6	16
Total	8	5	5	6	24

S: superficial; In: Invasive.

bladder carcinomas using a modified Bergvist classification. The separation was based mainly on the following histological features: 1) the impression of cellular disorder; 2) the variation in nuclear size; 3) the mitotic frequency; 4) the nuclear atypia; and 5) the nuclear pleomorphism. (Pauwels et al., 1988a; Eagan, 1989; Carbin et al., 1991a). The classification showed high reproducibility.

Our data suggest that the morphological subdivision of gII into gIIa and gIIb might have a prognostic significance, as the two groups showed different biological behaviour in a four-year follow-up. There was a statistically significant difference in the recurrence rate, the number of recurrences, the time interval from presentation to recurrence and the progression to invasive disease. Our findings are in accordance with the conclusions of other studies (Malmstrom et al., 1987; Pauwels et al., 1988a; Carbin et al., 1991b). The separation of gII group by morphometric studies, which comprise a more subjective grading, as they overcome the considerable observer inconsistency in the histological grading, also proved a different clinical course between the two groups (Wenzelides et al., 1986; Kirkhus et al., 1988; Pauwels et al., 1988b; Blomjous et al., 1989; Wenzelides, 1989; Lipponen et al., 1990; Sowter et al., 1991). According to some studies the gIIb group has the same prognosis as gIII (Carbin et al., 1991b).

The stage of the disease also carries important prognostic information that must be considered along with histological grade (Jewett et al., 1964; Eagan, 1989). In some studies there was a statistically significant difference in cancer mortality between gIIa and gIIb groups, since invasive urothelial carcinomas were included in the gIIb subgroup (Pauwels et al., 1988a; Carbin et al., 1991b). In our study only one patient died of the disease within the four-year follow-up. The above finding can be explained by the fact that all the cases included in our series referred to superficial carcinomas. Moreover, all recurrent gIIa cancers reappeared as superficial tumors and 68.75% of the recurrent gIIb cancers reappeared as invasive gIIb or gIII tumors. The latter cancers are regarded as those most likely to kill the patients in the future.

The tumor grade and stage are important guidelines when designing the treatment of a transitional cell carcinoma (Malmstrom et al., 1987; Eagan, 1989). As the morphological subdivision of the gII group identifies

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some tumors with a slow growth and others with a rapid growth, it is evident that it offers practical advantages, since the former can be treated conservatively and followed up closely, and the latter need an urgent radical intervention, including intravesical Bacillus Calmette-Guerin treatment, radiation therapy, total cystectomy and adjuvant chemotherapy (Eagan, 1989; Eure et al., 1992; Mukherjee et al., 1992).

References

- Bjelkenkrantz K., Herder A., Groentoft O. and Stal O. (1982). Cytophotometric characterization of the WHO grades of transitional cell neoplasms. *Pathol. Res. Pract.* 174, 68-77.
- Blomjous C.E., Smeulders A.W., Baak J.P., Vos W., van Galen C.M. and Meijer C.J. (1989). A comparative study in morphometric grading of transitional cell carcinoma of the urinary bladder. *Anal. Quant. Cytol. Histol.* 11, 426-432.
- Carbin B.E., Ekman P., Gustafson H., Christensen N.J., Sandstedt B. and Silfversward C. (1991a). Grading of human urothelial carcinoma based on nuclear atypia and mitotic frequency. I. Histological description. *J. Urol.* 145, 968-971.
- Carbin B.E., Ekman P., Gustafson H., Christensen N.J., Silfversward C. and Sandstedt B. (1991b). Grading of human urothelial carcinoma based on nuclear atypia and mitotic frequency. II. Prognostic importance. *J. Urol.* 145, 972-976.
- Eagan J.W. (1989). Urothelial neoplasms: Pathologic anatomy-urinary bladder. In: *Uropathology*. Hill G.S. (ed). Churchill Livingstone, Edinburgh. pp 719-841.
- Eure G.R., Cundiff M.R. and Schellhammer P.F. (1992). Bacillus Calmette - Guerin therapy for high risk stage T₁ superficial bladder cancer. *J. Urol.* 147, 376-379.
- Helander K., Kirkhus B., Iversen O.H., Johansson S.L., Nilsson S., Vaage S. and Fjordvang H. (1985). Studies on urinary bladder carcinoma by morphometry, flow cytometry, and light microscopic malignancy grading with special reference to grade II tumors. *Virchows Arch. (A)* 408, 117-126.
- Jewett H.J., King L.R. and Shelley W.M. (1964). A study of 365 cases of infiltrating bladder cancer: relation of certain pathological characteristics to prognosis after extirpation. *J. Urol.* 92, 668-678.
- Jordan A.M., Weingarden J. and Murphy W.M. (1987). Transitional cell neoplasms of the urinary bladder. Can biologic potential be predicted from histologic grading? *Cancer* 60, 2766-2774.
- Kaubisch S., Lum B.L., Reese J., Freiha F. and Tosti F.M. (1991). Stage T₁ bladder cancer: Grade is the primary determinant for risk of muscle invasion. *J. Urol.* 146, 28-31.
- Kirkhus B., Claucen O.P., Fjordvang H., Helander K., Iversen O.H., Reitan J.B. and Vaage S. (1988). Characterization of bladder tumours by multiparameter flow cytometry with special reference to grade II tumours. *ARMIS* 96, 783-792.
- Lipponen P.K., Collan Y., Eskelinen M.J., Pesonen E. and Sotarauta M. (1990). Morphometry in human transitional cell bladder cancer. Nuclear area and standard deviation of nuclear area - relation to tumor grade (WHO) and prognosis. *Eur. Urol.* 17, 155-160.
- Malmstrom P.U., Busch C. and Norlen B.J. (1987). Recurrence, progression and survival in bladder cancer. A retrospective analysis of 232 patients with greater than or equal to 5-year follow-up. *Scand. J. Urol. Nephrol.* 21, 185.
- Mukherjee A., Persad R. and Smith P.J.B. (1992). Intravesical BCG treatment for superficial bladder cancer: long term results using two different strains of BCG. *Br. J. Urol.* 69, 147-150.
- Narayana A.S., Loening S.A., Slymen D.J. and Culp D.A. (1983). Bladder cancer: factors affecting survival. *J. Urol.* 130, 56-60.
- Pauwels R.P.E., Schapers R.F.M., Smeets A.W.G.B., Debruyne F.M.J. and Geraedts J.P.M. (1988a). Grading in superficial bladder cancer (1). Morphological criteria. *Br. J. Urol.* 61, 129-134.
- Pauwels R.P.E., Smeets A.W., Schapers R.F., Geraedts J.P. and Debruyne F.M. (1988b). Grading in superficial bladder cancer (2). Cytogenetic classification. *Br. J. Urol.* 61, 135-139.
- Sowter C., Slavin G., Sowter G., Rosen D. and Hendry W. (1991). Morphometry of bladder carcinoma: morphometry and grading complement each other. *Anal. Cell Pathol.* 3, 1-9.
- Underwood J.C.E. (1992). Prognostic indices in epithelial neoplasms. In: *Recent advances in histopathology*. Antony P.P. and Mac Sween R.N.M. (eds). Churchill Livingstone. Edinburgh, London, Madrid, Melbourne, New York, Tokyo. pp 17-36.
- Webb J.N. (1992). Aspects of tumors of the urinary bladder and prostate gland. In: *Recent advances in histopathology*. Antony P.P. and Mac Sween R.N.M. (eds). Churchill Livingstone. Edinburgh, London, Madrid, Melbourne, New York, Tokyo. pp 157-176.
- Wenzelides K., Hufnagl P., Voss K., Guski H. and Simon H. (1986). Grading von Harnblasentumoren mittels automatischer Mikroskopbildanalyse. *Zentralbl Allg Pathol.* 132, 301-306.
- Wenzelides K. (1989). Grading von Harnblasentumoren mit der automatisierten Mikroskopbildanalyse. *Gegenbaurs Morphol. Jahrb.* 135, 63-66.

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