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Dysplasia in Normal-looking Urothelium Increases the Risk of Tumour Progression in Primary Superficial Bladder Cancer

L.A.L.M. Kiemeney, J.A. Witjes, R.P. Heijbroek, F.M.J. Debruyne and A.L.M. Verbeek

Random urothelium biopsies were taken at initial endoscopic surgery from 1001 patients with primary superficial bladder cancer. The clinical course of all the patients was assessed prospectively. Actuarial risks of recurrence and disease progression were determined for prognostic characteristics and comparisons were made using log-rank tests. The independent prognostic significance of concomitant intra-aurothelial dysplastic changes was examined with Cox's regression analyses. The 3-year risk of recurrence in patients with dysplasia and carcinoma *in situ* (CIS) in macroscopically normal-looking urothelium was only slightly higher than the risk in patients without dysplastic changes (56, 58 and 51%, respectively; $P = 0.25$). Concomitant dysplasia or CIS significantly increased the 3-year risk of disease progression (17 and 31%, respectively, versus 7%; $P < 0.001$). After adjustment for the effects of age, tumour stage, grade, size and multicentricity, the result of random biopsies had no prognostic significance regarding the risk of recurrence, but the detection of dysplasia or CIS increased the risk of progression by approximately 80%. This result suggests that random urothelium biopsies may be useful as an additional guide in defining therapy in primary superficial bladder cancer.

Key words: bladder cancer, biopsy, dysplasia, prognosis, recurrence, progression
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INTRODUCTION

THE MOST common form of bladder cancer is papillary transitional cell carcinoma (TCC). These carcinomas are usually confined to the bladder mucosa or show superficial invasion into the lamina propria. It has been recognised for some time that at least part of these superficial tumours are manifestations of cystoscopically occult widespread urothelial disease. In these cases, urothelial dysplasia may be detected with random biopsies of normal-looking mucosa. In 1960, Eisenberg and associates were the first to show the clinical relevance of these concomitant dysplastic changes. Patients with cellular atypia in normal-looking mucosa had a poor prognosis, whereas patients with no mucosal atypia had controllable disease [1]. Since then, many authors have confirmed the prognostic significance of intraurothelial dysplasia in patients with superficial bladder cancer.

The presence of dysplastic abnormalities strongly correlates with other, already proven, useful prognostic factors, especially tumour grade [2, 3]. Therefore, to assess the independent prognostic significance of concomitant urothelial dysplasia, adjustment has to be made for this correlation with other factors. However, apart from one small study on 37 patients with a pT1G3 tumour [4], the existing prognostic factors have not been formally adjusted for in the studies on random biopsies published so far.

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PATIENTS AND METHODS

The study cohort

Between January 1983 and December 1989, the Dutch South-East Cooperative Urological Group prospectively documented the patient and tumour characteristics of 1745 cases with histologically verified, primary superficial TCC of the bladder [5]. Superficial was defined as tumour extension limited to the mucosa (TNM stage pTa) or the lamina propria (pT1) of the bladder wall [6]. Muscle tissue from the depth of the transurethral resection of the bladder tumour was required to ascertain the tumour stage. Because of its relatively aggressive behaviour, primary carcinoma *in situ* (CIS); (pTis: $n = 52$) was considered to be different from pTa and pT1 tumours and was, therefore, not included in this series. A proportion of the urologists who participated in the project took preselected cold-cup biopsies (so-called "random" biopsies) of normal-looking urothelium from all their patients during initial endoscopical surgery. The biopsy sites were the left and right lateral wall, the trigone and dome. The results of these biopsies were classified as being positive if dysplasia (either mild, moderate or severe) or

CIS was found in one or more of the specimens. Random biopsies were taken from 1044 patients.

All the patients were initially treated with transurethral resection (TUR) of the tumour(s). 43 patients received additional treatment with interstitial radiotherapy, external radiotherapy or cystectomy because of residual tumour after TUR. These 43 patients were excluded from the analyses. Of the remaining 1001 patients, 607 were treated with TUR alone and 394 received prophylactic adjuvant intravesical therapy [doxorubicin, mitomycin or bacille Calmette-Guérin (BCG)]. The patients were followed with cystourethroscopy and urinary cytology every 3 months for a period of 1 year. If there were no recurrences during this period, the patients were subsequently followed at 6-month intervals. Once yearly, follow-up data were registered concerning the disease status and vital status. In 1991, all the data from the project were reviewed using the medical files. The median follow-up period for the study cohort was 3.5 years. At the time of the present analysis, 300 patients have been followed-up for more than 5 years.

Statistical methods

Time to recurrence and time to progression, calculated from the date of initial TUR, were used as endpoints in this study. Progression was defined as a shift to a higher tumour stage category or the development of regional or distant metastases. The follow-up of patients without tumour recurrence and disease progression was censored to the date of the last hospital visit. In case of death not related to the bladder cancer, the follow-up was censored to the date of death.

We used the actuarial method (with the log-rank test) to assess the prognostic effect of the following factors: age, gender, tumour stage (pT1 versus pTa), tumour grade (grade 3 versus 2 versus 1, according to the WHO grading system [7]), tumour multicentricity (multiple versus solitary), tumour extent and the result of random bladder biopsies (CIS versus mild, moderate or severe dysplasia versus normal). Tumour extent was defined as the number of bladder areas involved (three or more versus two versus one) instead of the size of the tumour. We distinguished the following bladder areas: bladder neck, trigone, dome, anterior and posterior wall, and left and right lateral wall. Urinary cytology was performed in all the patients, but its result was not systematically documented. Therefore, cytology was not part of this analysis.

The independent prognostic effect of dysplastic mucosa or CIS in random biopsy specimens on time to recurrence and time to progression was analysed in multivariate analyses using the proportional hazards model [8]. In these multivariate analyses, we first evaluated all the factors for inclusion in the model (with a stepwise procedure on level $P = 0.10$), except for the random biopsy result. In this first phase, we also took the therapy into account (intravesical chemotherapy or BCG versus TUR alone). Only after arriving at the final model did we include the random biopsy result, and test the improvement of the model with the likelihood ratio test. The possibility of a different prognostic effect of random biopsies in subgroups of patients was tested by means of interaction factors (cross-product terms).

RESULTS

During the period of follow-up, 513 of the 1001 patients suffered at least one recurrence, 102 patients had a recurrence in a higher tumour stage category or developed regional or distant metastases. The results of the univariate analyses on prognostic factors for the risk of recurrence and the risk of progression are summarised in Tables 1 and 2, respectively.

Table 1. Univariate analysis of prognostic factors for tumour recurrence

Factor	No.	3-year actuarial risk of recurrence	*P* value (log-rank test)
Age (years)			
0–49	90	0.49	0.96
50–59	178	0.52	
60–69	319	0.52	
70–79	306	0.54	
80 +	108	0.51	
Gender			
Male	817	0.53	0.45
Female	184	0.48	
Tumour stage			
pTa	687	0.47	< 0.001
pT1	314	0.64	
Tumour grade			
1	371	0.46	0.01
2	456	0.56	
3	174	0.56	
Tumour extent			
One area	616	0.46	< 0.001
Two areas	222	0.58	
Three or more	163	0.71	
Multicentricity			
Solitary	725	0.48	< 0.001
Multiple	270	0.63	
Unknown	6		
Random biopsies			
Normal	793	0.51	0.25
Dysplasia	137	0.56	
CIS	71	0.58	

CIS, carcinoma *in situ*.

The 3-year actuarial risk of recurrence in patients with dysplasia or CIS in normal-looking urothelium was 56 and 58%, respectively (Table 1). In patients without dysplastic abnormalities, the 3-year risk of recurrence was only slightly lower, 51% ($P = 0.25$). Tumour stage, tumour extent, multicentricity and tumour grade were significant prognostic indicators for the risk of recurrence.

The 3-year risk of tumour progression in patients with concomitant dysplasia or CIS was much higher than the risk in patients with microscopically normal mucosa: 17 and 31%, respectively, compared to 7% ($P < 0.001$) (Table 2). In contrast to its effect on the risk of recurrence, the result of random biopsies was one of the most discriminating factors regarding the risk of progression. The same was true for tumour grade, which was strongly correlated with the result of random biopsies: the frequency of dysplastic abnormalities was 11, 20 and 47% in patients with tumour grades 1, 2 and 3, respectively.

In the multivariate regression model of time to first recurrence, tumour stage, tumour extent and multicentricity had statistically significant prognostic effects at the $P = 0.10$ level (Table 3). In this study, age, gender and tumour grade had no (statistically significant) independent prognostic value. The same was true for concomitant dysplasia or CIS. Adding the result of random biopsies to the model did not improve the model (-2 log likelihood = 0.94; df = 2, $P > 0.50$). The estimated hazard ratios for dysplasia and CIS were only 1.12 and 1.10, respectively. In addition, none of the interaction terms of the random biopsy result with other factors was statistically significant,

Table 2. Univariate analysis of prognostic factors for disease progression

Factor	No.	3-year actuarial risk of progression	*P* value (log-rank test)
Age (years)			
0–49	90	0.02	0.002
50–59	178	0.08	
60–69	319	0.09	
70–79	306	0.13	
80 +	108	0.16	
Gender			
Male	817	0.09	0.35
Female	184	0.12	
Tumour stage			
pTa	687	0.07	< 0.001
pT1	314	0.17	
Tumour grade			
1	371	0.04	< 0.001
2	456	0.09	
3	174	0.26	
Tumour extent			
One area	616	0.07	< 0.001
Two areas	222	0.11	
Three or more	163	0.18	
Multicentricity			
Solitary	725	0.07	< 0.001
Multiple	270	0.17	
Unknown	6		
Random biopsies			
Normal	793	0.07	< 0.001
Dysplasia	137	0.17	
CIS	71	0.31	

CIS, carcinoma *in situ*.

indicating the absence of prognostic relevance of random biopsies in subgroups of patients. The results of the model of time to progression are summarised in Table 4. Tumour grade appeared to be the strongest prognostic factor. The risk of tumour progression in the patients with a grade 3 tumour was more than four times higher than the risk in the patients with a grade 1 tumour. Other factors with predictive value for disease progression were age and multicentricity. In contrast to the effect on time to recurrence, random urothelium biopsies had additional prognostic relevance regarding time to progression (-2 log likelihood = 7.3; df = 2, $P < 0.01$). However, as opposed to the results from the univariate analyses, the increase in risk appeared to be fairly similar with the presence of dysplasia and CIS (hazard ratio 1.7 and 1.9, respectively). This suggests that the presence or absence of dysplasia (of any grade) is more important than the severity of dysplasia. Inclusion of interaction factors led to no improvement in the model, indicating that the prognostic effect of mucosal abnormalities was approximately the same for different patient subgroups.

Table 3. Results of multivariate proportional hazards regression model of time to first recurrence

Factor	Hazard ratio	90% confidence interval
Tumour stage		
pT1 versus pTa	1.51	1.30–1.76
Tumour extent		
Two areas versus one	1.18	0.98–1.44
Three or more areas versus one	1.68	1.36–2.17
Multicentricity		
Multiple versus solitary therapy	1.20	1.00–1.45
Instillations versus TUR alone	0.70	0.60–0.82
Random biopsies		
Dysplasia versus normal	1.12	0.91–1.38
CIS versus normal	1.10	0.82–1.47

TUR, transurethral resection; CIS, carcinoma *in situ*.

Table 4. Results of multivariate proportional hazards regression model of time to progression

Factor	Hazard ratio	90% confidence interval
Age		
Each year in relation to the mean age of 66 years	1.02	1.01–1.04
Tumour grade		
Grade 2 versus 1	1.98	1.20–3.26
Grade 3 versus 1	4.34	2.54–7.41
Multicentricity		
Multiple versus solitary	1.69	1.20–2.37
Random biopsies		
Dysplasia versus normal	1.75	1.16–2.63
CIS versus normal	1.90	1.18–3.04

CIS, carcinoma *in situ*.

DISCUSSION

The coexistence of dysplastic abnormalities in normal-looking epithelium adjacent to urinary bladder tumours was first reported in the 1950s [9]. In 10 total cystectomy specimens, cellular abnormalities were seen ranging from hyperplasia and dysplasia to CIS. Five control tumour-free bladders, obtained from autopsy cases, showed only occasional cellular hyperplasia. Other histological examinations of cystectomy specimens and of random mucosal biopsies *in vivo* have confirmed the high prevalence of atypia and CIS in areas not cystoscopically suspected of harbouring malignancy [10–12]. In all the studies which examined the correlation with tumour grade, the frequency of dysplastic abnormalities was found to be higher in patients with less differentiated exophytic tumours. A correlation was also found with multicentricity and tumour stage [3, 11].

Eisenberg and associates were the first to report on the prognostic relevance of concomitant cytological changes in bladder biopsies [1]. More recent studies confirmed this prognostic significance, both for tumour recurrence and tumour progression [2–4, 13–22]. However, the results of some of these studies are difficult to interpret because biopsies were not only taken at initial diagnosis, but also during follow-up [16], or because biopsies were also taken from macroscopically suspicious mucosa [14, 21]. The results of these biopsy procedures are hardly comparable with those from biopsies from normal urothelium taken at initial diagnosis [10]. In addition, some of the studies were very small, with patient numbers of less than 50. The small study size is probably one of the reasons why none of the studies analysed the independent prognostic effect of

random biopsies in an unselected series of patients. In newly diagnosed, superficial bladder cancer, conventional histopathology (tumour stage and tumour grade) and the clinical factors, multicentricity and tumour size, are routinely used as prognostic factors. It is not very likely that random urothelium biopsies will replace one or more of these factors, but they may be useful as an additional prognostic test [23]. To our knowledge, the present study is the first to focus on the independent effect of dysplastic abnormalities in normal-looking urothelium, and suggests that random biopsies add very little prognostic information to the risk of recurrence, but do add prognostic information to the risk of progression.

The major hypothesis for the prognostic relevance of dysplastic changes in mucosal biopsies is that these changes reflect a premalignant state of the entire urinary bladder surface. New tumour occurrences originate from these intraurothelial lesions [24]. If this hypothesis is true, why then (at least in our study) did the random biopsies have very little predictive value regarding the risk of recurrence? One possible reason is the very high frequency of recurrences in superficial bladder cancer which may obscure a relatively small extra risk because of intraurothelial abnormalities. A second reason may be the diluting effect that adjuvant intravesical chemotherapy may have had on the 'natural history' of patients with concomitant dysplastic abnormalities (miltivariate analyses do not adjust optimally for such an effect). Another possible explanation for the absence of a prognostic effect on the risk of recurrence relates to the interpretation of random urothelium biopsies. Considerable variability exists in the assessment of the presence and classification of flat, dysplastic lesions and the separation of these, presumably premalignant, changes from reactive changes [25]. In a recent study by the British Medical Research Council (MRC), six expert pathologists examined 92 representative random biopsy slides. The reproducibility of interpretation appeared to be so poor that the authors questioned random biopsies as a useful guide for defining therapy. For example, one expert pathologist found mild or moderate dysplasia in 60% and severe dysplasia or CIS in 27% of the slides compared to another pathologist who found dysplasia in 6% and CIS in a further 7%. Pathologists replicated their first assessment on only 62% of occasions, although most of the disagreement was by only one grade [26]. In our study, data on reproducibility of interpretation of random biopsy slides were not available. Only the tumour and biopsy specimens from patients who entered in one of the controlled, randomised trials in which our group is involved were reviewed. This may have had some effect on our results, although, in a prognostic factor analysis using data from these randomised trials, we found that review pathology had no effect on the results of that analysis [27].

Despite the current lack of reproducibility in the interpretation of random biopsies, the presence of dysplasia and/or CIS in apparently normal urothelium appears to have prognostic value regarding future tumour progression. Adjusted for the effect of other prognostic indicators, concomitant dysplasia or CIS increased the risk of progression with approximately 80%. The fact that interaction factors were not statistically significant in the multivariate model suggests that this extra risk is fairly similar in different subgroups of patients. Nevertheless, because the result of random biopsies may have special relevance in patients who are not routinely treated with adjuvant intravesical chemotherapy, we examined our data in more details for patients with a solitary pTaG1 tumour. Of 30 patients with a solitary pTaG1 tumor and with microscopical abnormalities in random biopsies (29 dysplasia; 1 CIS), 5 (17%) developed disease progression. This percentage is similar to that in the total case series (Table 2). Of the patients with a solitary pTaG1 tumour who suffered disease progression (n = 9), only 3 (33%) had concomitant mucosal abnormalities, whereas this percentage was 43% in the total case series. Thus, the predictive value of random biopsies does not appear to be higher in "low risk" patients.

The prognostic value of concomitant dysplastic changes for tumour progression does not necessarily mean that is is worthwhile to use random biopsies as an additional guide in the choice of treatment for primary superficial bladder cancer. This also depends, for instance, on the efficacy of adjuvant intravesical chemotherapy or BCG for preventing tumour progression. This efficacy is believed to be rather poor [28, 29], which is in accordance with the absence of any effect of adjuvant therapy in our study (although this finding is difficult to interpret in a non-randomised study). Furthermore, the usefulness of random biopsies depends on the number of patients who will be treated adjuvantly because of concomitant dysplastic abnormalities. Due to the correlation with other prognostic factors, such abnormalities are relatively rare findings in patients who are routinely treated with TUR alone. Therefore, a medical decision analysis is needed to study the clinical relevance of taking random urothelium biopsies on a routine basis.

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Management of Bowel Obstruction in Patients with Advanced Ovarian Cancer

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In a retrospective study, 58 patients with bowel obstruction due to advanced ovarian cancer were analysed. In a forward stepwise proportional hazard regression analysis, we looked for factors influencing bowel obstruction-free survival. Patients who presented with bowel obstruction as the first sign of ovarian cancer and those with a longer interval between last cancer treatment and bowel obstruction did better. Patients with ascites did worse. No other independent factors were found. Based on these data, we classified patients into a favourable prognosis group (no previous treatment or interval since last treatment exceeding 6 months; no ascites) and a poor prognosis group (interval since last treatment shorter than 6 months; ascites). Patients from the favourable prognosis group had a median bowel obstruction-free survival of 8 months, compared to 1 month for the poor prognosis group ($P < 0.001$). Surgery had a marginally significant positive effect on bowel obstruction-free survival when compared to medical treatment in the favourable prognosis group ($P = 0.052$). Surgery had no effect at all in the poor prognosis patients.

Key words: bowel obstruction, ovarian cancer, surgery
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INTRODUCTION

OVARIAN CANCER is still a devastating disease and is responsible for approximately 6% of all cancer deaths in the western world [1–3]. The disease remains the leading cause of gynaecological cancer mortality. Approximately 75–80% of patients present with advanced stage III and stage IV disease, where prognosis is poor despite intensive treatment. Transperitoneal dissemination is the most commonly observed mode of spread of ovarian cancer. The main treatment modality for advanced disease is cytoreductive surgery, followed by combination chemotherapy, using platinum-based regimens.

Cancer-related bowel obstruction is a common problem in patients with advanced disease [1, 4–6]. Usually, patients with obstruction are initially treated by medical means: nasogastric