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Risk groups in bladder cancer patients treated with radical cystectomy

Eva Mallen[1], Pedro Gil[2], Maria Jesus Gil[2]

[1]Department of Urology, Hospital Royo Villanova, Zaragoza, Spain; [2]Deparment of Urology Hospital Miguel Servet, Zaragoza, Spain

ABSTRACT

Objective: To stratify patients with bladder cancer into homogeneous risk groups according to statistically significant differences found in PFS (progression-free survival). To identify those patients at increased risk of progression and to provide oncological follow-up according to patient risk group.

Materials and Methods: A retrospective study of 563 patients treated with radical cystectomy (RC). In order to determine which factors might predict bladder tumour progression and death, uni- and multivariate analyses were performed. The risk groups were identified according to "inter-category" differences found in PFS and lack of differences, thus revealing intra-category homogeneity.

Results: Median follow up time was 37.8 months. Recurrence occurred in a total of 219 patients (38, 9%). In 63% of cases this was distant recurrence.

Only two variables retained independent prognostic value in the multivariate analysis for PFS: pathological organ confinement and lymph node involvement. By combining these two variables, we created a new "risk group" variable. In this second model it was found that the new variable behaved as an independent predictor associated with PFS. Four risk groups were identified: very low, low, intermediate and high risk:

- Very low risk: pT0 N0
- Low risk: pTa, pTis, pT1, pT2 and pN0
- Intermediate risk: pT3 and pN0
- High risk: pT4 N0 or pN1-3.

Conclusions: We retrospectively identified 4 risk groups with an independent prognostic value for progression-free survival following RC.

Differences in recurrence patterns after RC between risk groups have led us to set different intervals in monitoring for cancer.

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INTRODUCTION

Bladder cancer is major health problem in Spain, with high incidence and elevated mortality (1-3). Radical cystectomy is the standard treatment for patients with muscle-invasive bladder cancer, however this is generally insufficient. In fact, it is very important to identify those at high risk of progression because these patients could benefit from adjuvant treatment and closer monitoring. Other authors (4, 5) have opted to divide patients into homogeneous risk groups according to statistically significant differences found in PFS and CSS (cancer-specific survival). A novel development in this study is the identification of the new risk group "Very low risk", which includes patients with a lower probability of suffering

from disease progression. These patients are therefore less likely to require adjuvant treatment, and follow--up intervals may also be more distanced. We propose a follow-up strategy for RC-treated bladder cancer patients that identifies most cases of recurrence while at the same time avoids monitoring patients too closely. This implies in a reduction of costs related to tests and number of visits.

While it is true that our study is not a multidisciplinary project, we believe that our single-center study includes a sample sufficiently large to draw conclusions similar to those drawn from studies undertaken by multidisciplinary groups (6). The aim of the present study was establish risk groups and tailor follow-up accordingly with a schedule appropriate to the likelihood of progression.

MATERIALS AND METHODS

Patient Population

We retrospectively reviewed all patients who underwent radical cystoprostatectomy and pelvic lymphadenectomy for bladder cancer with curative intent at Miguel Servet University Hospital between 1975 and 2007. The study population consisted of 599 patients who underwent radical cystectomy. Thirty-six patients were eliminated from the study due to missing data. Therefore, analysis was performed on the 563 remaining patients.

Radical cystoprostatectomy and lymphadenectomy were always performed according to standard protocol; indications for cystectomy did not change during the time period studied. Cystectomy is indicated in patients with invasive bladder carcinoma, endoscopically uncontrollable superficial bladder cancer and high risk bladder tumors and for those with BCG-resistance bladder tumors. Radical cystectomy and limited pelvic lymph node dissection were performed in 84% of the patients. In only 10 cases it was performed an extended pelvic lymphadenectomy. It is true that currently, this procedure is routinely performed in most cases.

All cystectomy specimens were subjected to routine pathological examination. In the last two decades the same pathologist examined the specimens microscopically. Primary tumors and lymphadenectomy were restaged based on the 2002 UICC TNM system.

Statistical analysis

"FileMaker Pro 11.0, version 11.0 v2" (FileMaker Inc©) was used as database software and "PASW Statistics 18, version 18.0.0" (IBM©) was used as statistics software.

Paper-based patient records were reviewed and data were analyzed for possible predictive factors. Univariante analysis was performed using the Kaplan-Meier (or Mantel-Haenszel) test. Significant variables ($p<0.05$) and those close to significance ($p<0.1$) from univariate analysis were analyzed using backwards multivariate analysis with the Cox proportional hazards regression model. To search for a clinical application and to check the strength of the model, a new model was set up, with the combination of the statistically most powerful variable taken from multivariate analysis. We created a new variable called "risk groups", to try to identify any differences in PFS and CSS between the different categories of this variable. The risk groups identified were compared using the Kaplan-Meier method and log-rank test.

RESULTS

Cystectomy was indicated for muscle-invasive bladder cancer (MIBC) in 493 patients. In the remaining 70 patients, the indication for cystectomy was superficial bladder cancer. In these 70 cases, 33 underwent cystectomy for multifocal recurrence of NMBC (non muscle-invasive bladder cancer) such as TaG1-2 T1G1-2, 36 patients for recurrent high-grade tumours (TaG3, T1G3, and CIS) and in one case the reason for cystectomy was not specified. These data are summarized in the chart below (Figure-1).

The variables investigated in patients treated with cystectomy in the period of study were grouped into: pre-, peri- and post-cystectomy variables, as shown in Table-1.

At the time of cystectomy, median patient age was 65.3 years (IQR 13.1). In the analysis by decades it can be seen that patients were progressively older, with statistically significant differences.

Median follow-up time was 37.8 months (IQR 83.4, range 1,1-288,2). Of note are those variables that underwent changes over the decades

Figure 1 - Indication of radical cystectomy.

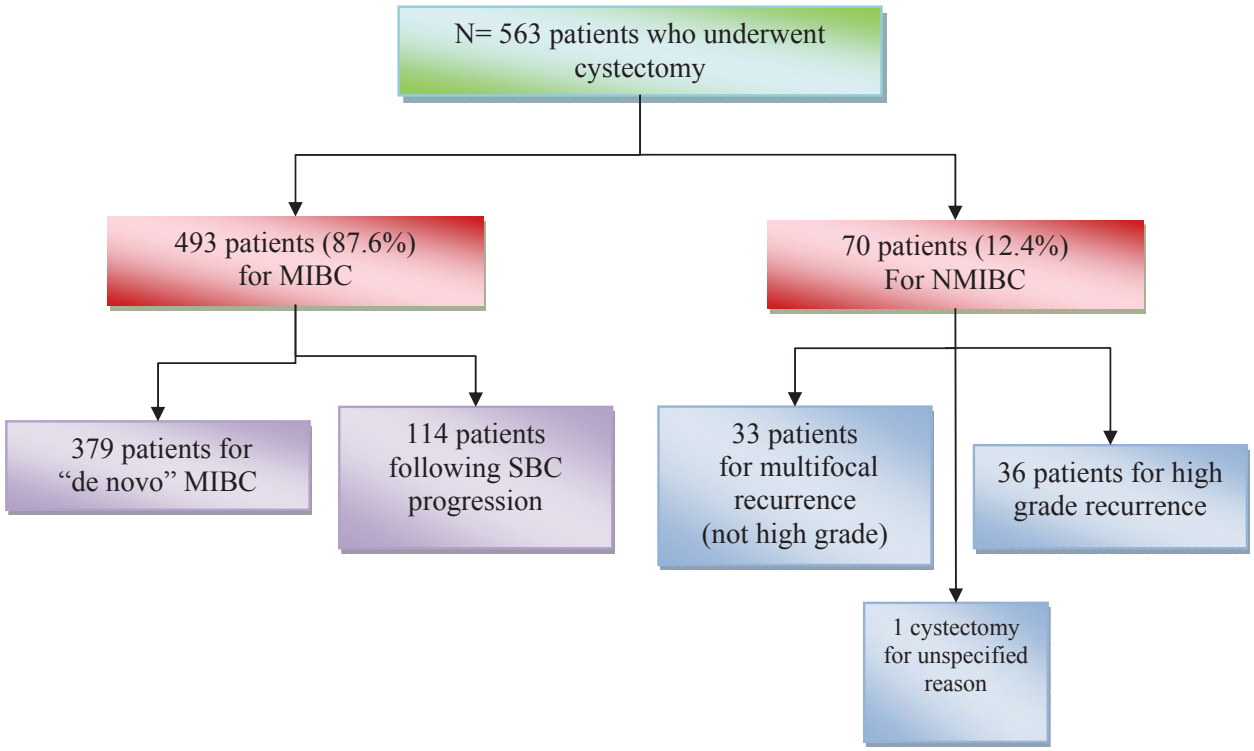


Table 1 - Variables studied.

Variables Pre-Cystectomy	Variables Peri-Cystectomy	Variables Post-Cystectomy
Gender	Transfusion	Hospital stay
Age	Type of catheterisation	Follow-up
Smoker	Ureteral reimplantation	Adjuvant CT
Alcohol	Pathological stage (pT)	Major perioperative complications
Risk occupation	Tumour grade	Minor perioperative complications
Living environment	Lymph node involvement (pN)	Late-onset complications
Comorbidity	Presence of CIS	Tumour recurrence in UUT
Clinical presentation	p53	
Clinical stage of TURBT	Anatomical pathology Terminal ureter	
History of UC in UUT	Ureterectomy	
Neoadjuvant CT	Anatomical pathology type	
	Organ confinement	
	Tumour in UUT concomitantly with BC	

TURBT = Transurethral resection of bladder tumour; **SBC =** superficial bladder cancer; **UC =** urothelial carcinoma; **UUT =** upper urinary tract; CT: chemotherapy; **BC =** Bladder cancer

studied, such as for example the number of units transfused (p<0,00), length of hospital stays and the number of complications (p<0.03). All these variables decreased in number/duration. Conversely, continent urinary derivations (p<0.00) increased during the study period. In terms of studied tumor characteristics no clear differences were observed over the four decades of the study. In the percentage of patients with organ-confined tumors there were no statistically significant differences (p=0.714). In the case of lymph node involvement prevalence increased over the decades, but not significantly (p=0.250).

Progressive disease occurred in 219 patients of the total series (38.9%). We classified recurrence as: local, regional lymph node and distant. Local recurrence: we considered this to be the appearance of local recurrence in the pelvis urothelial tumor, surgical site and/or urinary tract without distant involvement. Locoregional nodal recurrence: this included pathological lymph node involvement and distant metastasis.

In patients who progressed, the predominant type of progression was distant metastasis in 63% of cases. Mean PFS (progression-free survival) in the 563 patients was 157 (144.2-169.9) months (the median could not be calculated).

It can be observed that almost all events (recurrence from bladder cancer) occurred in the first two years of follow up. In fact, by the end of the second year of follow-up, 77% of the events had already occurred. There was a 73% probability of survival in the first year, falling to 55% at the end of the fifth year, with little further change to the end of the tenth year (51%) (Figure-2 and Table-2).

In patients who progressed, n=219 (38.9%), median progression-free survival was 9.7 months (CI 95% 8.3-11.1); there were no differences in PFS by type of progression. Progression appeared to occur shortly before lymph node recurrence (median PFS=8.6 months [6.3-11]), but significant differences were found in the univariate analysis.

Univariante analysis demonstrated that pathological organ confinement, lymph node involvement, tumour grade, terminal ureter involvement and the administration of adjuvant chemotherapy were variables that were significantly

Figure 2 - PFS in 563 patients.

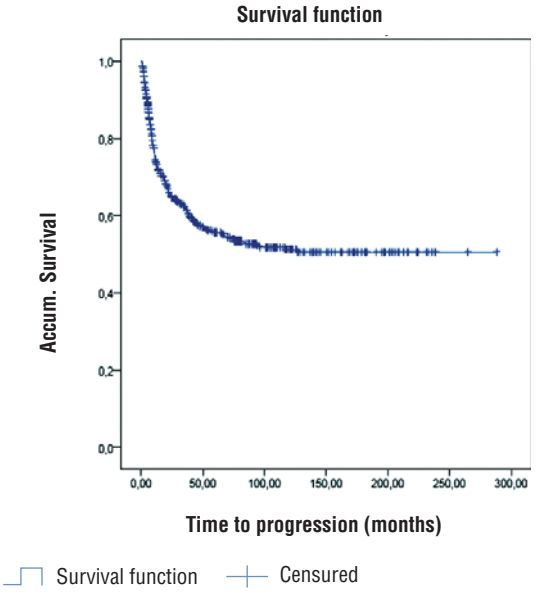


Table 2 - Mean PFS in the whole series.

T (months)	Cumulative survival probability
12m	83.1%
36m	65.5%
60m	61.5%
120m	55.2%

associated with lower progression-free survival (Table-3).

In the multivariate analysis (Table-4) we entered the significant variables detected in the univariate analysis and found that pathological organ confinement and lymph node involvement were independent variables that were significantly associated with PFS.

In order to identify patients at increased risk of urothelial disease progression or recurrence following cystectomy, we developed a classification system based on the multivariate predictive variables for PFS: pathological organ confinement and lymph node involvement. We created a new variable called “risk groups”, using a combination of the two previous variables (pT and pN), in order

Table 3 - Univariante analysis of predictive factors for PFS.

Long rank (Mantel-Cox)	Chi²	Df	Sig.	Variable	% patients
Organ confinement	66.035	1	0.000	≤ pT2	54%
				> pT2	46%
Pathological lymph node status	105.106	1	0.000	pN0	74%
				pN+	26%
Tumour grade	8.651	2	0.013	G_1-G_2	27%
				G3	73%
Terminal ureter	5.621	1	0.018	Normal	90%
				pathological	10%
Adjuvant CT	7.511	1	0.006	-	6%

PFS = progression-free survival; **CT =** chemotherapy

Table 4 - Multivariate analysis. Predictive model for PFS.

Variable	B	SE	Wald	Gl	p	O.R.	95% CI for EXP(B)	
							Lower	Upper
Pathological organ confinement	1.077	0.283	14.445	1	0.000	2.936	1.685	5.117
Lymph node involvement	0.861	0.214	16.219	1	0.000	2.365	1.556	3.595

PFS = progression-free survival

to identify any differences in PFS between the different categories of this variable.

We analysed the survival for each pT variables (pT0 vs. pTa-Tis-T1 vs. pT2 vs. pT3-4) and pN variables (pN0 vs pN1-3). We observed clear differences between the patients with pT0 and the group stages PTa, pTis, pT1, pT2, and of course among the rest of groups, which led us to differentiate between a group of very low risk, separating it from the rest. According to this analysis, four independent groups were identified (Table-5).

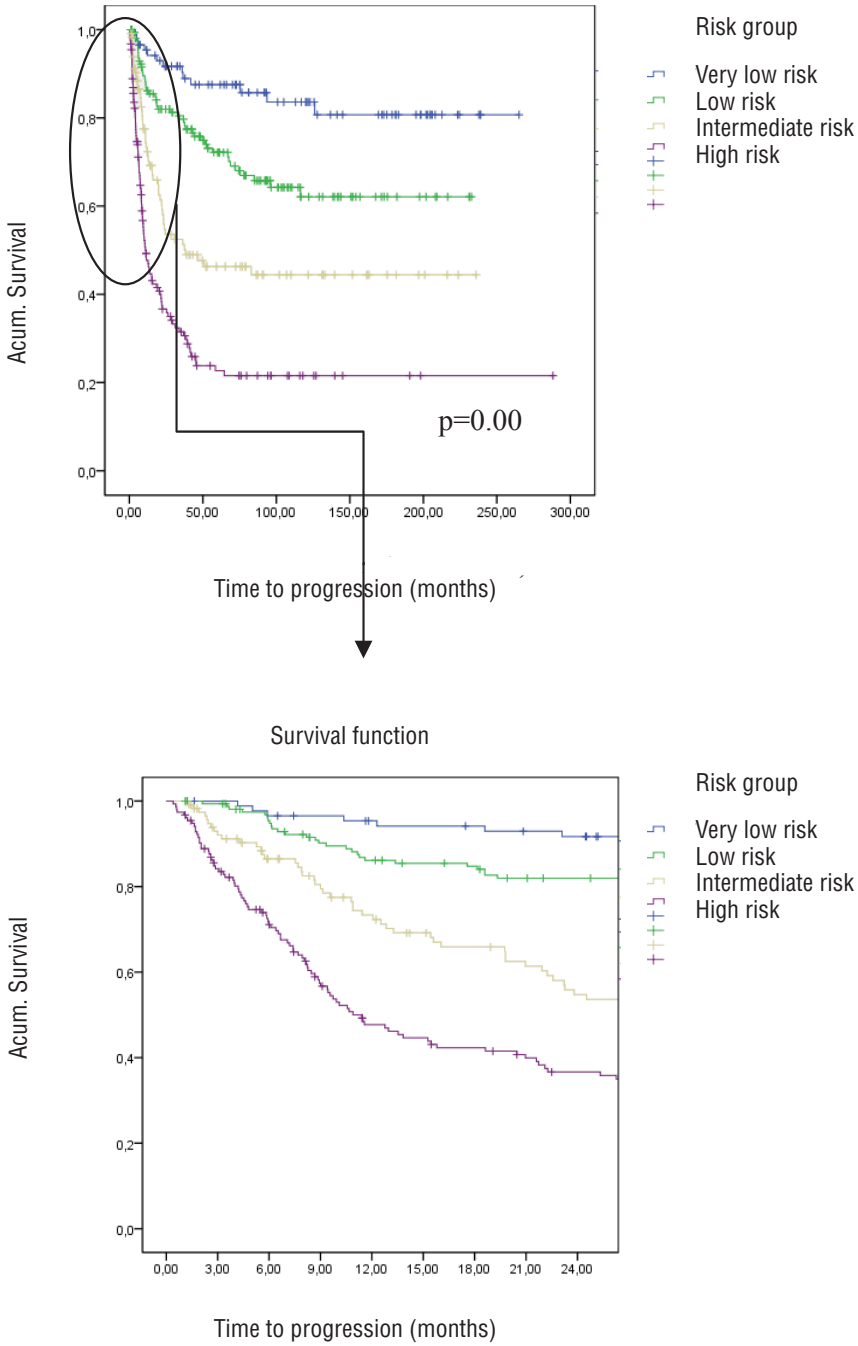
With respect to the survival graph (Figure-3), firstly it can be seen that there are statistically significant inter-category differences (p<0.001), which appear to confirm the homogenous nature of the composition of the four categories. Of note are the findings in PFS in the

Table 5 - Risk groups.

"Risk group" variable	
Categories	Description
Very low risk	pT0 and pN0
Low risk	pTa, pT1, pTis or pT2, and pN0
Intermediate risk	pT3 and pN0
High risk	pT4N0 or pN1-3

"Intermediate risk" and "High risk" groups. It is particularly striking that events occur so early in these groups. After two years of follow-up, 84% (45 out of 53) events relating to progression have appeared in the "Intermediate risk" group, and 84% (89 out of 105) in the "High risk" group.

Figure 3 - PFS by risk group.



Risk groups	p-value	OR
Very low vs. high	0.00	9.7
Low vs. high	0.00	4.25
Intermediate vs. high	0.00	2.04

The survival graphs show that the risk of progression stabilizes. This is similarly reflected in the survival table (Table-6). This shows the probability of reaching a certain time point, in the post-cystectomy follow-up, without progression.

In this second model it was found that the new "risk group" variable behaved as an independent predictor associated with PFS.

From the data of Table-7 it can be deduced that a patient in the high risk group has an OR of progression that is 9.7 times (1/0.103) higher than patients with a very low risk. The same high risk patient has an OR that is 4.25 times (1/0.235) higher for progression than low-risk patients.

DISCUSSION

This study was undertaken primarily due to the high rates of incidence and mortality of bladder cancer in Spain and in our region, Aragon. Rates are above the mean for Europe (7, 8), and this, together with the marked ageing of population, suggests that the upward trend will continue.

In the literature there are several studies on the prognostic value of different variables such as stage, lymph node and lymphovascular involvement, type of urinary diversion, margin status, etc. on invasive bladder cancer progression and survival. However, organ confinement and lymph node involvement are repeatedly found to be independent risk factors for PFS and cancer-specific mortality in most series (4, 9, 10).

In a study at Gregorio Marañón Hospital (4), both pathological stage and lymph node involvement were found to be independent predictors for cancer-specific survival. In that study the authors, like us, also constructed a second model by grouping local stage (pT) and lymph node involvement (pN) into risk groups in order to study CSS. Thus, the association by risk group allowed them to predict the risk of death from bladder cancer more reliably, and to identify patients in whom cystectomy is insufficient and who could benefit from adjuvant treatment.

Solsona (5) also stratified patients by risk. In this study, the records of 298 patients who un-

Table 6 - Survival table (PFS) by "Risk group".

PFS by "Risk group". Survival table							
Categories		End 1st year	End 2nd year	End 3rd year	End 4th year	End 5th year	End 10th year
Very low	pT0 and pN0	0.954	0.917	0.903	0.875	0.875	0.836
Low	pTis, pTa-1, pT2 and pN0	0.861	0.82	0.797	0.758	0.722	0.621
Intermediate	pT3 and pN0	0.734	0.547	0.525	0.476	0.463	0.444
High	pT4 or pN1-3	0.485	0.367	0.315	0.238	0.227	0.215

Table 7 - Subvariables that retain independent statistical significance for PFS.

Variable		B	ET	Wald	gl	P	Exp(B)	95% CI forEXP(B)	
								Lower	Upper
Risk Group	High vs very low	2.27	0.296	59.088	1	0.00	0.103	0.58	0.184
	High vs low	1.44	0.177	66.600	1	0.00	0.235	0.166	0.333
	High vs intermediate	0.715	0.169	17.853	1	0.00	0.489	0.351	0.682

derwent cystectomy were retrospectively analysed and risk groups were established based on lymph node involvement, pathological stage and prostatic stromal involvement as predictors of mortality in the multivariate analysis. Their figures for 5-year CSS, by risk group, were 86.4% for the low risk group (P1-2N0St-), 64.4% for the intermediate risk group (60.9%-65.3%) (P1-2N1St-, P3N0St-, HR=2.7) and 28.1% (0%-47.7%) for the high risk group (N2-3, P4, St+, N1P3, HR=8.7). These figures were not far off our 5-year CSS of 89% for the very low risk group, 75% for low risk, 54% for intermediate and 30% for low grade (data not shown).

Sonpavde (11) investigated bladder cancer risk following cystectomy using pathological factors to facilitate an indication for adjuvant treatment. This series was more similar to ours in terms of sample size and study time (although the follow-up period was longer in their study), and it was also found that pathological stage was a predictor. Like us, these authors constructed a model with prognostic groups and found that stage, lymphovascular involvement and poorly-differentiated cells were predictors of PFS. They distinguished three groups according to the presence of the three variables in the multivariate analysis, assigning a score of 0-4, according to the presence of these variables, and depending on the cumulative score, they divided patients into low, intermediate and high risk groups.

In the case of the Abol-Enein and Ghoneim group (12), which involved a large series because of the high incidence of bladder cancer in Egypt, these authors concluded that PFS predictors are lymph node involvement, stage, lymphovascular invasion and type of urinary diversion. Using these four variables, patients were stratified into four risk groups ranging from low risk (T1,N0, LV-, orthotopic diversion) to maximum risk (T4,N+, LV+, rectal diversion), comparing survival curves and likelihood of progression among these groups. They found a 5-year PFS of 64.5%, which does not differ greatly from our figure of 55.6%. Like these authors, we divided patients into categories or risk groups, with two objectives. Firstly, in reference to follow-up we aimed to identify risk of progression and detect this as early as possible. The second objective was to identify candidates for adjuvant treatment, with the final objective of increasing CSS.

In our study, differences in progression patterns after radical cystectomy suggest the need for varied follow-up protocols for each group. We proposed a stage-based protocol for monitoring of patients with bladder cancer treated with radical surgery that captures most recurrences while limiting over-investigation. Multicenter studies are consistent with our study, showing that in most patients the tumor recurs in the first two years after radical cystectomy and over half of these recurrences are distant (6).

Table-6 shows the probabilities of progression-free survival at a certain time point according to risk group. Looking at how to apply these data in clinical practice, we can draw up guidelines and recommendations for monitoring these patients. To date, there has been no consensus on how to follow up these patients after surgical intervention. Available guidelines include the National Comprehensive Cancer Network and the European Association of Urology recommendations, which acknowledge the need for risk-stratified surveillance but do not clearly delineate any protocols (13, 14) .The ESMO (European Society for Medical Oncology) guidelines, by contrast, do not address any stage-specific surveillance regimen (15).

In the very low risk group, patients could be followed up less frequently from the second year onwards. This would not be recommendable in the low risk group until the third year, when the probability of progression becomes stable. In contrast, patients in the intermediate and high risk groups should continue six monthly follow-ups until the fourth or fifth year. However, there is a high probability of progression and early-onset of events in the intermediate and high risk groups during the first months of follow-up, especially in the high risk group. 15% of patients in this group experience progression by the end of the third month and 48% by the end of the first year. The risk of progression is almost 10 times higher than in the very low risk group and two times higher in comparison with the intermediate risk group. For this reason we suggest three-monthly follow-up for the first year in the high risk group, as shown in Table-8. Later, the probability of progression drops,

Table 8 - Follow-up recommendations.

Risk group	1st year	2nd year	3rd year	4th year	5th year	6th-10th year
Very low	Six monthly	Six monthly	Yearly	Yearly	Yearly	Yearly
Low	Six monthly	Six monthly	Six monthly	Yearly	Yearly	Yearly
Intermediate	Four monthly	Six monthly	Six monthly	Six monthly	Yearly	Yearly
High	Three monthly	Six monthly	Six monthly	Six monthly	Yearly	Yearly

so follow-up can be performed at six-monthly intervals until the probability of progression stabilises (in the 4th year). In the low risk group, patients could be followed up less frequently from the third year onwards, when the probability of progression stabilises. Faysal et al. (6) proposed stage-based protocols for surveillance of patients with bladder cancer based on recurrence patterns that coincide with our group in terms of the frequency of visits especially in the first year of follow-up in patients with very high risk of recurrence.

Since there is such a high probability of progression in the intermediate and high risk groups, intensive follow-up of these patients is clearly essential. However, the aim must be to prevent progression from occurring or to delay it as much as possible. Therefore, an assessment should be made of whether to administer adjuvant chemotherapy in these two groups of patients.

It is true that there are no randomised trials that demonstrate the superiority of adjuvant chemotherapy in MIBC treatment, but until such studies are available, we would recommend that chemotherapy - preferably within the framework of a clinical trial - as it is one of the few tools at our disposal that lengthens CSS.

Our study has several potential limitations, including those inherent to any retrospective study. For example, the variable margin status; this was not studied in the early years of the study period and therefore could not be included in the study. Extent of surgery, such as the upper limit of lymph node dissection, changed slightly and was not consistent during the study period. Our median follow-up time may seem short (37.8 months) however these are patients with an ominous prognosis. Furthermore, this is a single institution study. Findings must be evaluated externally in a larger patient cohort and validated prospectively for practical use.

CONCLUSIONS

Non-organ confinement and lymph node involvement in radical cystectomy specimens are factors that retain independent prognostic value in progression-free survival in the multivariate analysis. We retrospectively identified four risk groups (very low, low, intermediate and high) with an independent prognostic value for progression-free survival following radical cystectomy. This would be useful in order to provide information to patients and physicians and to improve stratification for future clinical trials. This would serve to optimize indications for treatment, avoiding excessive monitoring and reducing costs.

ABBREVIATIONS

PFS = progression-free survival
RC = radical cystectomy
CSS = cancer-specific survival
MIBC = muscle-invasive bladder cancer
NMBC = non muscle-invasive bladder cancer

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Eva Mallen, MD
Department of urology
Hospital Royo Villanova
Avenida San Gregorio, 30,
Zaragoza, 50015, Spain
E-mail: evamallen@hotmail.com