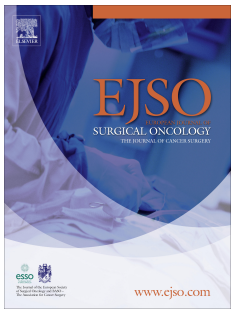
Survival after cystectomy for invasive bladder cancer

R.R. de Vries, J.A. Nieuwenhuijzen, A. Vincent, H. van Tinteren, S. Horenblas

Accepted Manuscript



Title: Survival after cystectomy for invasive bladder cancer

Authors: R.R. de Vries, J.A. Nieuwenhuijzen, A. Vincent, H. van Tinteren, S. Horenblas

PII: S0748-7983(09)00520-4

DOI: 10.1016/j.ejso.2009.11.012

Reference: YEJSO 2923

To appear in: *European Journal of Surgical Oncology*

Received Date: 30 June 2009

Revised Date: 23 November 2009

Accepted Date: 30 November 2009

Please cite this article as: de Vries RR, Nieuwenhuijzen JA, Vincent A, van Tinteren H, Horenblas S. Survival after cystectomy for invasive bladder cancer, European Journal of Surgical Oncology (2009), doi: 10.1016/j.ejso.2009.11.012

Survival after cystectomy for invasive bladder cancer

R.R. de Vries[1], J.A. Nieuwenhuijzen[1], A.Vincent[2], H. van Tinteren[2], S. Horenblas[1]

[1] Department of Urology and [2] Biostatistics, The Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands

R.R. de Vries, M.D., research physician

J.A. Nieuwenhuijzen, M.D., resident in urology

A. Vincent, PhD, statistician

H. van Tinteren, PhD, statistician

S. Horenblas, M.D., PhD, professor of urology

Corresponding author:

S. Horenblas [1]

Phone: +31-20-5122559, Fax: +31-20-5122554, E-mail: s.horenblas@nki.nl

Keywords: Bladder neoplasms, cystectomy, transitional cell carcinoma, survival, high risk non muscle invasive bladder cancer

Words: 2615

Abstract: 247

Abstract

Aim

To determine the difference in survival after cystectomy between patients presenting with primary muscle infiltrating bladder cancer and patients with progression to muscle infiltration after treatment for initial non muscle invasive bladder cancer (NMIBC).

Patients and Methods

We retrospectively analyzed the files of 188 patients who underwent cystectomy for transitional cell carcinoma between 1987 - 2005. Two groups were defined: patients presenting with muscle invasive tumours and those progressing to muscle invasion after initial treatment. This second group was further divided into low-intermediate and high risk according to the EAU grouping for NMIBC.

Results

The 5-year disease specific survival (95% confidence intervals) for all patients was 50%(42%-59%); 49%(40%-60%) in the primary muscle infiltrating group and 52%(37%-74%) in the progressive group (p=ns). The 5-year disease specific survival in the progressive group according to EAU risk groups was 75%(58%-97%) for the initially diagnosed low-intermediate risk tumours and 35%(17%-71%) for the initially diagnosed high risk tumours (p= 0.015). The percentage of patients with non-locally confined tumours (pT3/4-N0 // any pT-N+) was 31% // 45% and 24% // 46% in the primary muscle infiltrating and progressive group, respectively.

Conclusions

Despite close observation of patients treated for non muscle invasive bladder cancer, the survival of patients who progress to muscle invasion is not better than survival of patients presenting with primary muscle infiltrating cancer. Patients with high risk non-invasive tumours (EAU risk categories) who progress to muscle invasive disease have a worse prognosis compared to patients with low or intermediate risk tumours

Introduction

Non muscle invasive bladder cancer (NMIBC) comprises of a heterogenic group of tumours, with variable biological behavior and malignant potential. The probability to progression to muscle invasion varies from 6%-48% .(1) Identifying the patients in whom NMIBC will progress despite bladder sparing therapy is a major challenge. The 2006 EAU guidelines on bladder cancer defined three risk groups for NMIBC: a low-risk group (single, low grade (G1), non-invasive (Ta) lesion smaller than 3 cm); a high risk group (lamina propria invasion (T1), high grade (G3), multifocal or highly recurrent, or CIS) and an intermediate group with all other non muscle invasive tumours (e.g. Ta-T1, G1-G2, over 3 cm).(2) In low risk NMIBC, a bladder sparing regimen is uniformly advised, consisting of transurethral resection (TUR) followed by a single immediate instillation of intra-vesical chemotherapy. High risk disease is usually treated with TUR followed by intra-vesical BCG. The undisputable indication for cystectomy is histological evidence of muscle invasion during follow-up. We hypothesized, that the intensive monitoring of patients with NMIBC during bladder sparing management would

lead to an early discovery of muscle invasion with consequently better survival than patients presenting initially with muscle invasion. To test this hypothesis, we compared survival in patients presenting with NMIBC that progressed to muscle invasive disease with patients presenting with primary muscle invasive bladder cancer, all treated by cystectomy and regional lymph node dissection.

Patients and methods

Preoperative assessment and patient selection

Between 1987 and 2005, 286 patients underwent cystectomy for transitional cell carcinoma (TCC) at our institute. Being a tertiary referral centre, patients were referred after diagnosis and/or treatment at other hospitals. Reasons for referral were: NMIBC progressing to muscle invasive disease or muscle invasive disease at first diagnosis. Data from referring hospitals were reviewed for date of initial diagnosis of bladder cancer and follow-up until referral. Forty-four patients presented with high risk non muscle invasive urothelial cancer treated with cystectomy before muscle invasion and were excluded from analysis. Four patients were excluded from analysis because of incomplete data. Another 50 patients were excluded from analysis as they underwent salvage cystectomy after brachytherapy or external beam radiotherapy (EBRT). They have been reported earlier.(3)The remaining 188 patients were divided into two groups based on initial presentation. We distinguished a primary muscle invasive group: patients with muscle invasion at first presentation (pT≥ 2) and a progressive group: patients with a history of non muscle invasive disease progressing to muscle invasion after TUR with or without adjuvant intravesical therapy. The progressive patients were stratified according to EAU risk-categories after last TUR for NMIBC. (2) Patients with muscle invasive disease within three months after first TUR for non muscle invasive bladder cancer were included in the primary muscle infiltrating group.

Staging

Clinical stage was determined by physical examination, TUR, chest x-ray, and pelvic/abdominal computerized tomography scan (CT-scan). All stages were converted to the IUCC 2002 TNM classification.(4)

When imaging was highly suspicious for tumour positive lymph nodes, a bilateral regional lymph node dissection or fine needle biopsy was performed before cystectomy. Otherwise patients underwent regional lymph node dissection at cystectomy. The accuracy of clinical staging was assessed by comparing clinical primary stage and pathological tumour stage after cystectomy.

Treatment

Patients with NMIBC were initially treated with TUR at the referring hospitals. Patients with muscle-invasion at follow-up were referred for cystectomy and regional lymph node dissection. Boundaries of pelvic node dissection until 2000 where: distally the circumflex vein and the node of Cloquet, laterally the external iliac artery, medially the bladder and the prostate and proximally the hypogastric artery. From 2000 the boundaries were enlarged proximally to the crossing of the ureter over the common iliac artery and laterally to the genitofemoral nerve. Patients with histologically or cytologically proven positive lymph nodes before cystectomy received neo-adjuvant chemotherapy. Since 2000 patients considered high risk for recurrence after cystectomy (≥ pT3and/or ≥N1) have been randomized between early or late chemotherapy, according to the EORTC-30994 protocol.

Statistical analysis

Disease specific survival was defined as time between cystectomy and death of disease or treatment or last contact. Survival estimates and 95% confidence intervals were calculated using the Kaplan-Meier method. Log-rank tests were used to assess differences in survival between the primary muscle infiltrating and progressive group. To evaluate the impact of EAU risk stratification on survival we compared the initially low-intermediate non muscle invasive with the initially high risk non muscle invasive tumours in the progressive group.

A multivariate Cox proportional hazards model was constructed to determine the association of gender, focality (single or multiple), age, and patient grouping (primary and progressive muscle infiltrating) with disease specific survival. A backward stepwise elimination procedure was performed to identify factors associated with survival at the 0.05 significance level. The association between number of TUR (≤2 TUR and >2 TUR before cystectomy) disease specific survival, tumour upstaging after cystectomy was assessed in the progressive invasive patient group using a log-rank test and Chi square test.

Differences in characteristics of patients in progressive and primary muscle infiltrating groups were tested using chi-square, Fisher-exact and Mann-Whitney-Wilcoxon tests where appropriate. No imputation of missing data was performed. The significance level was set at 0.05 for all tests.

Results

Patient Characteristics

134 patients presented with primary muscle infiltrating bladder cancer and 54 patients with progressive bladder cancer. The distribution of patient and tumour characteristics between these two groups are presented in Table 1a. Mean age at cystectomy was 61 years and the male to female ratio was roughly 3:1. The definitive pathological stage of the primary tumour (pT-stage) was higher than the pathological stage of the TUR specimen in 19% of primary muscle infiltrating patients, while 2% had pathological stage lower than clinical stage. This was 26% and 0% for the progressive group. Pathological lymph node stage (pN) was higher than clinical lymph node stage (cN) in 16% of primary patients and 26% in the progressive group. There was no significant difference in stage distribution after cystectomy between both groups. The proportion of patients with multifocal tumours was significantly higher in the progressive group than in the primary muscle infiltrating group ($p<0.001$) (see Table 1a).

Patients' characteristics and both clinical (NMIBC and muscle invasive stage) and pathological stage for the progressive subgroups are shown in table 1b. There was no significant difference in stage distribution after cystectomy between both subgroups. Both the definitive pathological stage of the primary tumour (pT-stage) and the pathological lymph node stage (pN) were higher than in the TUR specimen in 28% (N=7) of the low risk patients, and 24% (N=7) in the high risk patients. No patients had lower pathological T or N stage than clinical stage.

Treatment History

A total of 61 patients received neoadjuvant chemotherapy, 46 in the primary muscle infiltrating group and 15 in the progressive invasive group. In the primary muscle invasive group 44 achieved a complete or partial response to neoadjuvant chemotherapy, in the progressive invasive group this was 15. Ten patients received adjuvant chemotherapy, 7 in the primary muscle infiltrating group and 3 in the progressive invasive group. There was no significant difference in the number of patients receiving either neoadjuvant or adjuvant chemotherapy.

In the high- and low-risk progressive subgroups, neoadjuvant chemotherapy was given to 4 and 11 patients respectively, and adjuvant chemotherapy was given to two and one patients respectively. Again there was no significant difference in clinical response to neoadjuvant treatment.

Survival

At the time of analysis 89 patients had died, all but twelve of either bladder cancer or treatment. The median follow-up after cystectomy was 3.4 years, which was not different between groups.

The 5-year disease specific survival estimate (95% confidence intervals) for all patients was 50% (42%-59%); 49% (40%-60%) in the primary muscle infiltrating group and 52% (37%-74%) in the progressive group (Fig 1a, log-rank, p=ns); stratified by risk group: 75% (58%-97%) in the low and 35% (17%-71%) in the high risk tumours (Fig 1b p=

0.015). The difference in disease specific survival between muscle invasive and low-intermediate risk tumours was not significant (Fig 1c).

Patients with organ confined lymph node negative tumours (pT2N0) had a 5-year disease specific survival of 80% (65%-97%) and 93% (82%-100%) for the primary muscle infiltrating group and the progressive group respectively (p=ns, Table 2a). Stratified by risk group these figures were: 100% and 88% (67%-100%), for the low and high risk groups respectively. (Table 2a, p=ns).

Survival at 5 years of patients with non-organ confined disease and tumour negative nodes was: 56% (42%-75%) for the primary muscle infiltrating group and 37% (14%-97%) for the progressive group (p=ns, table 2a). Stratified by risk group: 71% (45%-100%) and 0%, for the low and high risk groups respectively (Table 2a; p=ns).

Eighty-five patients had tumour positive lymph nodes after cystectomy: 60 (45%) in the primary muscle-invasive group and 25 (46%) in the progressive group. Stratified by risk group: there were 10 (40%) in the low risk and 15 (51%) in the high risk subgroup.

The 5 year disease specific survival rates for lymph node positive patients were 28% (17%-46%) for the primary muscle infiltrating group and 40% (24%-69%) for the progressive group. Stratified by risk group: 63% (37%-100%) and 25% (9%-67%), for the low and high risk groups respectively. (Table 2a; p=0.04)

In the multivariate analysis gender was significantly associated with disease specific survival. Females had a higher risk of dying from disease than males (HR=2.16 (1.7-2.8); p=0.0009). Focality, age, and patient grouping (primary vs. progressive) showed no significant association with survival. (Table 2b)

Finally, there was no significant association between the number of TUR disease specific survival, and upstaging in the progressive group.

Discussion

The undisputable indication for cystectomy in patients with NMIBC is progression to muscle invasion. Follow up schedules are aimed at the earliest possible detection of progression, leading to the best possible survival. In our study all patients were followed up according to the EAU-guidelines which in theory should lead to low stage disease at cystectomy.(2) Nevertheless, patients with NMIBC progressing to muscle invasion had no better survival after cystectomy than patients with primary muscle invasive bladder cancer. This is in accordance to others, while some showed an even worse survival.(5-7) These studies suggest that cystectomy should ideally be done before any bladder muscle invasion occurs or at a stage when the bladder tumour is still locally confined. This notion is not new and has been echoed by those who advocate an early cystectomy.

Understaging, swift progression and poor survival of the progressive group

What could be the reasons and explanations for these findings?

First, standard follow up was unable to detect occult progression, exemplified by 26% under staging in non locally confined disease and 26% under staging in tumour positive lymph nodes. It is a sobering fact that despite close monitoring these figures are not different at all from clinical under staging in patients presenting primarily with invasive disease.(8) Because our hospital is a tertiary center patients with higher stages are

referred to our hospital, exemplified by a relatively high incidence (45%) of positive lymph nodes after cystectomy in both groups as compared to contemporary cystectomy series.(8-10) Secondly the swift occurrence of progression, indicated by 24% non locally confined disease and 46% lymph node invasion after cystectomy in the progressive group. Most of these patients have a history of non muscle invasive disease and are under surveillance for NMIBC so one would expect these percentages to be lower than in the primary invasive group.

Thirdly the poor survival rates of high-risk non invasive bladder cancer progressing to muscle invasion. This was significantly worse compared to patients with a low-intermediate-risk tumour (76% versus 20%). As there was no difference in TNM distribution after cystectomy for both groups this difference in prognosis must be explained by other factors, like tendency for early dissemination of these high grade tumours. This underlines the poor prognosis of the high-risk group providing further weight to arguments for early cystectomy. Five year survival rates of approximately 90% have been published when cystectomy is performed before evidence of muscle invasion.(10;11) Our study also demonstrates a rather good prognosis for patients with muscle invasive disease after cystectomy for locally confined disease.

Fourthly the urological community is alert on the high risk of progression in patients presenting with T1G3 tumours and the subsequent poor survival.(1) However our study suggests equal (poor) survival rate in high grade Ta-disease.(12) In addition we find patients with low grade (low or intermediate risk) tumours that have progressed rapidly to a locally advanced tumour with lymph node metastases.

The number of prior TUR and survival

Analysis of TUR prior to cystectomy did not show survival differences and upstaging in those who had less than 2 TUR in comparison to those with more than 2 TUR. This is in contrast to a recent study by Wiesner et al. who reviewed the files of 219 patients with non-muscle-invasive TCC that progressed to muscle invasion. They found tumour positive lymph nodes in 33 patients (15%). The number of TURs correlated with the prevalence of lymph node metastases.(13)

Survival in women stage for stage is less than in males. Findings that are supported by others (14)

Optimal timing of cystectomy

How can we solve the dilemma of too early cystectomy (increase of survival but at the cost of too many bladders removed) and too late cystectomy (jeopardizing survival of the patient)?

In clinical practice, the heart of the matter lies in defining progression and the early notion of therapy resistance. In high risk disease the above notion has led to a "change of paradigm", advising early cystectomy before histological proof of muscle invasion.(15) Failures of BCG therapy in high risk disease are now defined as progression to higher grade or T-category, the appearance of carcinoma in situ during therapy and a recurrence at both 3 and/or 6 months. In low-intermediate risk disease, the indication for cystectomy

has traditionally been histological proof of muscle invasion. In this risk category the challenge is to better define failure, preferably before muscle invasion.

The EORTC risk tables, based on six tumour characteristics (number of tumours, tumour size, prior recurrence rate, T category, carcinoma in situ, and grade) are currently the most accurate tool to predict the risk of recurrence and progression in non muscle invasive bladder cancer patients.(1;16)

The major limitations of our study are the retrospective character, the potential selection bias, and the limited number of patients. Our patients with progressive non muscle invasive bladder cancer come from a large undefined pool of patients. Therefore our results can only be used as an illustration of the fate of patients progressing to muscle invasion.

It is our belief that follow-up should be aimed at the detection of failures at the earliest possible moment, preferably before muscle invasion has occurred. In this respect, identifying patients in whom initial therapy is not successful is the major challenge.

Conclusions

Despite close observation of patients treated for NMIBC, survival in patients who progress to muscle invasion is not better than patients presenting with primary muscle infiltrating cancer. Patients with high-risk NMIBC who progress to muscle invasive disease before cystectomy have a worse prognosis compared to patients with low-intermediate risk NMIBC who progress to muscle invasion. The number of patients with locally advanced and lymph node positive disease was unexpectedly high in the

progressive group, underlining the need for improved identification of the patient in need of early cystectomy. For now, we advocate active restaging (re-TUR) during conservative management of non muscle invasive bladder cancer. The indication for cystectomy should be at a stage preferably before histological proof of muscle invasion, EORTC tables can be helpful. T-stage and grade progression are probably just as important signs for early cystectomy as the traditional criterion of muscle invasion.

Reference List

1. Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DW, Kurth K. Predicting Recurrence and Progression in Individual Patients With Stage Ta T1 Bladder Cancer Using EORTC Risk Tables: a Combined Analysis of 2596 Patients From Seven EORTC Trials. *Eur Urol* 2006; **49**(3): 466-5.

2. Oosterlinck W, van der Meijden AP, Sylvester R, Bohle A, Rintala E, Solsona E, Lobel B. Guidelines on TaT1(non-muscle invasive) Bladder cancer. 1-3-2006.
Ref Type: Generic

3. Nieuwenhuijzen JA, Pos F, Moonen LM, Hart AA, Horenblas S. Survival After Bladder-Preservation With Brachytherapy Versus Radical Cystectomy; a Single Institution Experience. *Eur Urol* 2005; **48**(2): 239-45.

4. Ch.Wittekind, F.L.Greene, D.E.Henson, R.V.P.Hutter, L.H.Sobin. *TNM Classification of Malignant Tumours*.Wiley-Liss, 2002.

5. Schrier BP, Hollander MP, van Rhijn BW, Kiemeney LA, Witjes JA. Prognosis of Muscle-Invasive Bladder Cancer: Difference Between Primary and Progressive Tumours and Implications for Therapy. *Eur Urol* 2004; **45**(3): 292-6.

6. Yiou R, Patard JJ, Benhard H, Abbou CC, Chopin DK. Outcome of Radical Cystectomy for Bladder Cancer According to the Disease Type at Presentation. *BJU Int* 2002; **89**(4): 374-8.

7. Lee CT, Dunn RL, Ingold C, Montie JE, Wood DP, Jr. Early-Stage Bladder Cancer Surveillance Does Not Improve Survival If High-Risk Patients Are Permitted to Progress to Muscle Invasion. *Urology* 2007; **69**(6): 1068-72.

8. Ficarra V, Dalpiaz O, Alrabi N, Novara G, Galfano A, Artibani W. Correlation Between Clinical and Pathological Staging in a Series of Radical Cystectomies for Bladder Carcinoma. *BJU Int* 2005; **95**(6): 786-90.

9. Ghoneim MA, bdel-Latif M, el-Mekresh M, bol-Enein H, Mosbah A, Ashamallah A, el-Baz MA. Radical Cystectomy for Carcinoma of the Bladder: 2,720 Consecutive Cases 5 Years Later. *J Urol* 2008; **180**(1): 121-7.

10. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, Skinner E, Bochner B, Thangathurai D, Mikhail M, Raghavan D, Skinner DG. Radical

Cystectomy in the Treatment of Invasive Bladder Cancer: Long-Term Results in 1,054 Patients. *J Clin Oncol* 2001; **19**(3): 666-75.

11. Herr HW, Sogani PC. Does Early Cystectomy Improve the Survival of Patients With High Risk Superficial Bladder Tumours? *J Urol* 2001; **166**(4): 1296-9.

12. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J, Algaba F, Vicente-Rodriguez J. Primary Superficial Bladder Cancer Risk Groups According to Progression, Mortality and Recurrence. *J Urol* 2000; **164**(3 Pt 1): 680-4.

13. Wiesner C, Pfitzenmaier J, Faldum A, Gillitzer R, Melchior SW, Thuroff JW. Lymph Node Metastases in Non-Muscle Invasive Bladder Cancer Are Correlated With the Number of Transurethral Resections and Tumour Upstaging at Radical Cystectomy. *BJU Int* 2005; **95**(3): 301-5.

14. Mungan NA, Kiemeney LA, van Dijck JA, van der Poel HG, Witjes JA. Gender Differences in Stage Distribution of Bladder Cancer. *Urology* 2000; **55**(3): 368-71.

15. Herr HW, Donat SM, Dalbagni G. Can Restaging Transurethral Resection of T1 Bladder Cancer Select Patients for Immediate Cystectomy? *J Urol* 2007; **177**(1): 75-9.

16. Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Bohle A, Palou-Redorta J. EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder. *Eur Urol* 2008; **54**(2): 303-14.

List of Abbreviations

NMIBC: Non Muscle Invasive Bladder Cancer

HR: Hazard Ratio

CIS: Carcinoma in situ

TUR: Transurethral resection

BCG: Bacillus Calmette Guérin

TCC: Transitional Cell Carcinoma

EBRT: External Beam Radiotherapy

IUCC: International Union Against Cancer

MMC: Mitomycin C

EORTC: European Organisation for Research and Treatment of Cancer

EAU: European Association of Urology

Table1a Patients' characteristics.

		Progressive Inv. N=54	Primary Inv. N=134	Total N=188	Significance
Gender	male	41 (76%)	103 (77%)	144 (77%)	ns
	female	13 (24%)	31 (23%)	44 (23%)	
Age (years)	Mean	63	61	61	ns
Clinical T stage					
cTis/a/1	N0	-	-	-	
cT2	N0	30 (56%)	53 (40%)	83 (44%)	ns
cT3/4	N0	11 (20%)	39 (29%)	50 (27%)	
cT any	N+	13 (24%)	42 (31%)	55 (29%)	
Path. T stage					
pTis/a/1	N0		1 (1%)	1 (1%)	
pT2	N0	16 (30%)	31 (23%)	47 (25%)	ns
pT3/4	N0	13 (24%)	42 (31%)	55 (29%)	
pT any	N+	25 (46%)	60 (45%)	85 (45%)	
Focality					
Single		13 (24%)	81 (60%)	94 (50%)	
Multifocal		40 (74%)	50 (37%)	90 (48%)	p<0.001
Unknown		1 (2%)	3 (2%)	4 (2%)	

Progressive Inv.: progressive group
Primary Inv. : primary muscle infiltrating group

Table 1b Patients' characteristics progressive subgroups.

		Low-intermediate risk N=25	High risk N=29	Significance
Gender	male	21 (84%)	20 (69%)	ns
	female	4 (16%)	9 (31%)	
Age (years)	Mean	62	63	ns
NMIBC Stage				
TaG1-2		11	-	
T1G1-2		14	-	
Tis		-	11	
T1G3		-	14	
TaG3		-	4	
Clinical T stage				
cTis/a/1	N0	-	-	
cT2	N0	16 (64%)	14 (48%)	ns
cT3/4	N0	6 (24%)	5 (17%)	
cT any	N+	3 (12%)	10 (34%)	
Path. T stage				
pTis/a/1	N0	-	-	
pT2	N0	8 (32%)	8 (28%)	ns
pT3/4	N0	7 (28%)	6 (21%)	
pT any	N+	10 (40%)	15 (52%)	
Focality				
Single		5 (20%)	8 (28%)	
Multifocal		19 (76%)	21 (72%)	ns
Unknown		1 (4%)	0 (0%)	

Table 2a Disease specific survival according to tumour group stratified according to tumour extension.

Tumour Group	N	5-year DSS % (95% C. I.)
Primary muscle infiltrating	134	49 (40 60)
Organ confined, N-	32	80 (65-97)
Extravesical, N-	42	56 (42-75)
Node positive, N+	60	28 (17-46)
Progressive	54	52 (37-74)
Organ confined, N-	16	93 (82-100)
Extravesical, N-	13	37 (14-97)
Node positive, N+	25	40 (24-69)
Low risk	25	75 (58-97)
Organ confined, N-	8	100(-, -)
Extravesical, N-	7	71 (45-100)
Node positive, N+	10	62 (37-100
High risk	29	35 (17-71)
Organ confined, N-	8	88 (67-100)
Extravesical, N-	6	0 (-, -)
Node positive, N+	15	25 (9-67)

Table 2b Cox-regression multivariate analysis

		HR	95% CI	P
Group	progressive primary	0.97	0.55-1.71	0.9
Gender	male female	2.16	1.70-2.80	<0.001
Age		0.99	97-1.02	0.5
Focality	single multi	1.23	0.74-2.04	0.4

Legends

Table 1a. Patient characteristics

Table 1b. Patients characteristics progressive subgroups.

Table 2a Disease specific 5-year survival according to subgroup.

Table 2b Cox-regression multivariate analysis

Fig 1a. Disease specific survival curves comparing primary muscle infiltrating and progressive groups (p=ns).

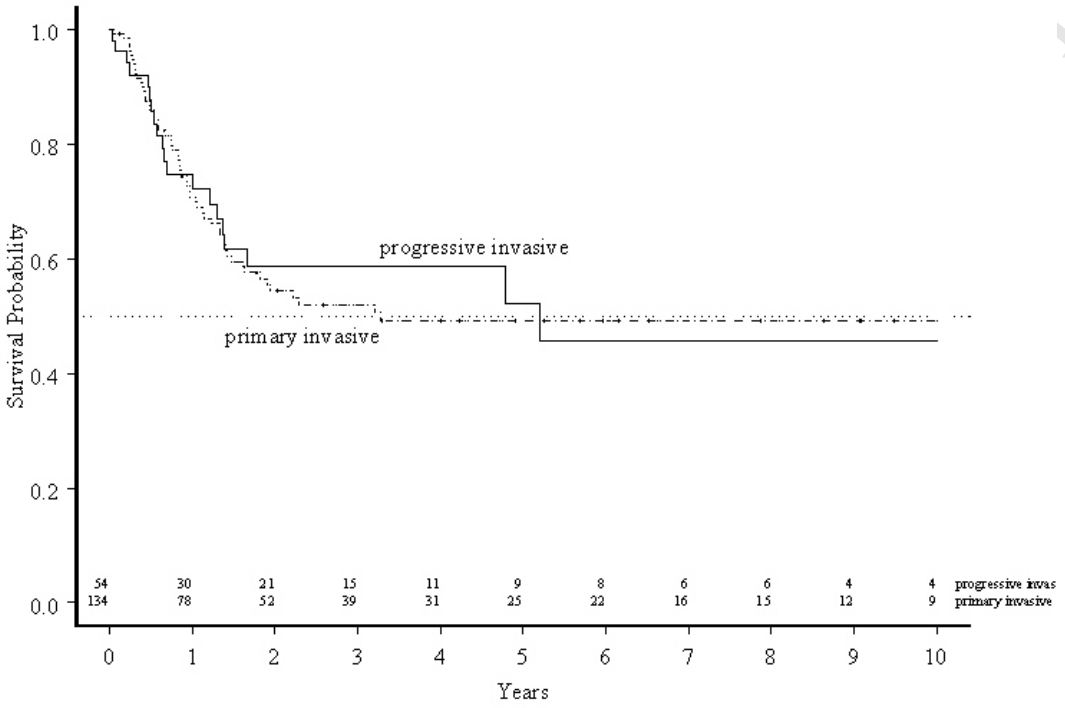


Fig. 1b Disease specific survival after cystectomy for muscle invasive bladder cancer comparing low-intermediate and high risk tumours in the progressive group (p= 0.015).

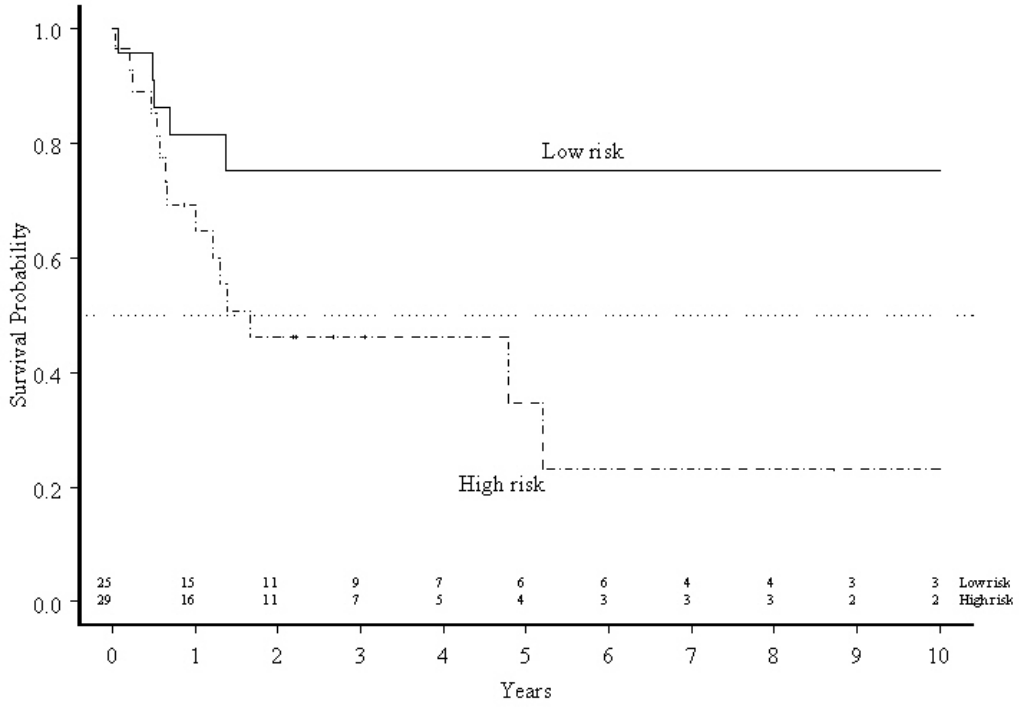


Fig.1c. Disease specific survival after cystectomy for muscle invasive bladder cancer comparing low-intermediate risk tumours in the progressive group and the primary muscle infiltrating group (p= ns).