Urothelial Cell Carcinoma

Leliveld-Kors, Anna

chapter 3

Treatment and outcome in muscle invasive bladder cancer: a population-based survey

World J Urol Vol. 28:439–444, Aug 2010

A.M. Leliveld
B.H.J. Doornweerd
E. Bastiaannet
M. Schaapveld
I.J. de Jong

Abstract

Objective

To assess treatments and survival of patients with muscle invasive bladder cancer (MIBC) in the Comprehensive Cancer Center Northern Netherlands (CCCN) region.

Study Design and Setting

Retrospective cohort analysis. Data of 548 patients with MIBC diagnosed between 1997 and 2002 were collected from the CCCN cancer registry. All had a follow up of at least 5 years. Logistic regression analysis on treatments as well as survival analysis was performed.

Results

The treatments were radical cystectomy in 205/548 (37.5 %) patients. TUR plus radiotherapy in 246 (44.9 %) and palliation in 97 (17.7 %). Multivariate analysis identified TNM stage (P< 0.0001) and age (P< 0.0001) as independent variables for cystectomy. Hospital type and year of diagnosis were not significant different between patients treated by cystectomy versus other type of treatment. TNM stage (P < 0.0001), age (P=0.0043) and comorbidity (p=0.0028) were independent variables for disease specific survival (DSS) after cystectomy.

Conclusion

In the CCCN region only one third of patients with MIBC were treated with radical cystectomy. TNM stage and age were identified as main variables for the choice for cystectomy. TNM stage, age and comorbidity were independent variables for disease specific survival after cystectomy.

Keywords: muscle invasive bladder cancer, cystectomy

3 Treatment and outcome in muscle invasive bladder cancer: a population-based survey

Introduction

Yearly about six hundred patients present with newly diagnosed bladder cancer in the northern part of the Netherlands.[1] About 90% of these tumours is urothelial cell carcinoma (UCC). Approximately one third of the UCC infiltrate the detrusor muscle at the time of diagnosis.[2] Muscle invasion is a major prognostic factor in outcome and requires a more radical treatment compared to tumours confined to the bladder mucosa. At time of treatment of the primary tumour one third of patients with MIBC has undetected metastases.

According to European guidelines on bladder cancer the favoured treatment of MIBC is radical cystectomy with urinary diversion.[3] However it has been shown that only 16- 35 percent of the patients with muscle invasive disease undergo cystectomy.[3–6] Bladder sparing treatments (TUR, interstitial radiotherapy and external radiotherapy with or without systemic chemotherapy) can be considered in patients not suitable for major surgery. To diagnose lymph node metastases a pelvic lymph node dissection (PLND) is required. The extent of pelvic lymphadenectomy has not been sufficiently defined.[3] Patients with metastases can only be treated with palliative intent. Their median survival is only 6 months and can be extended to 14 to 15 months by systemic polychemotherapy.[7]

The aim of this retrospective, population-based survey was to assess the pattern of care in the treatments of newly diagnosed MIBC in the Comprehensive Cancer Centre Northern Netherlands (CCCN) region, to identify factors that affect the choice for cystectomy as treatment and to assess factors associated with survival rates within this group of patients.

Patients and Methods

Patients

We studied a cohort of patients who were diagnosed to have a histological proven UCC with invasion of the detrusor muscle in the period patients from January 1997 till December 2002 within the network of the CCCN. They all had a minimal follow up of 5 years. The CCCN upholds a population based cancer registry covering a region of 2.2 million inhabitants. The CCCN network consists out of sixteen hospitals and three independent radiation oncology departments in the three training hospitals.
The nationwide Dutch network and registry of histo- and cytopathology (PALGA) regularly submits reports of all diagnosed malignancies to the comprehensive cancer centers. The national hospital discharge databank completes case ascertainment. Registry personnel collect data on initial diagnosis, staging, and treatment from the medical records, including the results of histopathologic examinations and surgical reports.

Methods

Detailed information was collected from the medical files in fifteen of sixteen hospitals in the northern part of the Netherlands. Information on diagnostics, stage and primary treatment as well as follow-up was collected from the cancer registry. TNM classification was used to stage tumours.[8] We could not differentiate between patients with T4a and T4b carcinoma, all were classified as stage IV disease group. In addition we collected data from the medical files including comorbidities (diabetes, hypertension, cardiovascular disease, pulmonary disease and any other significant comorbidity). Comorbidities were grouped in none, one or two or more. A complete Charlson Comorbidity Index (CCI) could not be obtained as comorbidity was not registered in the appropriate way. Hospitals were divided in non-teaching (n=12) and teaching (n=3) based on whether there is training for urologic residents.

Statistics

Logistic regression analysis was used to assess differences between patients that underwent radical cystectomy and patients that did not. In survival analysis, an event in disease free survival (DFS) was defined as any kind of recurrence of UCC. Patients with stage IV disease were excluded from DFS analysis. Event with regards the DSS was defined as dying of the disease or treatment for disease. We used both the community registrations of death as well as the individual medical records. Univariate (log rank) and multivariate (Cox' proportional hazard model) analyses were used to assess the factors associated with survival.

Characteristic	Number	Percentage
Sex		
Male	427	77.9
Female	121	22.1
Age		
≤60	101	18.4
61-74	243	44.4
≥75	204	37.2
Stage		
II	254	46.4
III	153	27.9
IV	141	25.7
Comorbidity		
None	171	31.2
One	194	35.4
Two or more	183	33.4
Treatment		
Palliative/ none	97	17.7
No cystectomy	246	44.9
Cystectomy	205	37.4
With PLND	147	71.7*
Without PLND	58	28.3*
* of patients that underwent cystectomy		

Table 1 Patient characteristics (n=548)

Results

Characteristics

Initially, 792 patients with MIBC were found. One hospital refused participation and in another hospital files were not complete which meant 217 patients could not be included. 27 patients were excluded because they had no UCC, so 548 patients could be included. Patient characteristics are shown in Table 1. More than 75% of the patients were male and 37% of all patients were 75 years or older. The treatments were radical cystectomy in

Chapter 3

	% Cystectomy	Univariate analysis		Multivariate analysis	
		OR	p-value	OR	p-value
Sex					
Male	37.2	Ref			
Female	38.0	1.03 (0.68-1.57)			
			0.876		
Age					
≤60	61.4	**Ref**		**Ref**	
61-74	48.6	**0.59 (0.37-0.95)**		**0.51 (0.30-0.86)**	
≥75	12.3	**0.09 (0.05-0.16)**		**0.06 (0.03-0.11)**	
			<0.0001		**<0.0001**
Comorbidity					
None	48.5	**Ref**		Ref	
One	36.6	**0.61 (0.40-0.93)**		0.88 (0.53-1.46)	
Two or more	27.9	**0.41 (0.26-0.64)**		0.58 (0.34-0.98)	
			0.0003		0.0973
Hospital					
Non-teaching	39.6	Ref		Ref	
Teaching	34.0	0.78 (0.55-1.12)		0.77 (0.50-1.19)	
			0.186		0.238
TNM stage					
II	32.0	**Ref**		**Ref**	
III	60.1	**3.22 (2.12-4.89)**		**4.14 (2.50-6.84)**	
IV	22.7	**0.65 (0.41-1.04)**		**0.41 (0.24-0.69)**	
			<0.0001		**<0.0001**

Table 2 Logistic regression analysis for cystectomy as treatment regimen

	n DFS	5-yrs DFS	HR	p-value
Sex				
Male	133	70.8	Ref*	
Female	40	57.6	1.6 (0.8-3.0)	
				0.2
Age				
≤60	49	84.7	Ref*	
61-74	101	61.0	1.7 (0.8-3.5)	
≥75	23	49.0	1.9 (0.6-6.0)	
				0.4
Comorbidity				
None	74	68.1	**Ref***	
One	57	75.0	**0.6 (0.3-1.2)**	
Two or more	42	55.7	**1.7 (0.9-3.6)**	
				0.013
Hospital				
Non-teaching	107	70.2	Ref	
Teaching	66	64.5	1.2 (0.7-2.1)	
				0.5
Lymph node dissection				
Yes	117	71.5	Ref*	
No	56	59.2	1.2 (0.7-2.5)	
				0.3
TNM stage				
II	81	79.4	**Ref***	
III	92	58.2	**2.7 (1.4-5.1)**	
IV	-	-		
				0.002

Table 3 Disease free survival (DFS) in patients that underwent radical cystectomy (stage IV patients excluded in DFS analysis). * HR in multivariate analysis

	n DSS	5-yrs DSS	HR	p-value
Sex				
Male	159	58.9	Ref*	
Female	46	39.1	1.4 (0.9-2.3)	
				0.2
Age				
≤60	62	67.6	Ref*	
61-74	118	52.5	**1.7 (0.99-2.9)**	
≥75	25	26.2	**3.5 (1.7-7.4)**	
				0.004
Comorbidity				
None	83	59.2	**Ref***	
One	71	59.9	**0.6 (0.4-1.1)**	
Two or more	51	40.2	**1.6 (0.9-2.6)**	
				0.003
Hospital				
Non-teaching	133	53.2	Ref	
Teaching	72	57.3	0.8 (0.5-1.2)	
				0.3
Lymph node dissection				
Yes	147	59.1	Ref*	
No	58	43.9	1.5 (0.9-2.5)	
				0.08
TNM stage				
II	81	76.0	**Ref***	
III	92	44.0	**2.6 (1.5-4.5)**	
IV	32	29.5	**5.5 (2.9-10.6**	
				<0.0001

Table 4 Disease specific survival (DSS) in patients that underwent radical cystectomy (stage IV patients excluded in DFS analysis).
* HR in multivariate analysis

	n OS	5-yrs OS	HR	p-value
Sex				
Male	159	46.5	Ref	
Female	46	35.3	1.3 (0.8-1.9)	
				0.3
Age				
≤60	62	63.8	Ref*	
61-74	118	38.6	**2.0 (1.2-3.2)**	
≥75	25	16.5	**4.6 (2.4-8.7)**	
				<0.001
Comorbidity				
None	83	51.8	**Ref***	
One	71	42.6	**0.9 (0.6-1.4)**	
Two or more	51	33.2	**1.6 (0.9-2.6)**	
				0.02
Hospital				
Non-teaching	133	42.6	Ref	
Teaching	72	46.6	0.8 (0.5-1.2)	
				0.3
Lymph node dissection				
Yes	147	47.0	Ref	
No	58	36.9	1.3 (0.9-2.5)	
				0.1
TNM stage				
II	81	65.0	**Ref***	
III	92	31.4	**2.4 (1.5-3.8)**	
IV	32	25.3	**3.7 (2.2-6.5**	
				<0.0001

Table 5 Overall survival (OS) in patients that underwent radical cystectomy (stage IV patients excluded in DFS analysis).
* HR in multivariate analysis

205 patients (37.4%) and TUR +/- radiotherapy in 246 patients (44.9%). 71,7% of those who had cystectomy (147 patients) also underwent a pelvic lymph node dissection. 97 patients (17.7%) had no curative treatment. None of the patients have been treated with (neo) adjuvant chemotherapy.

Cystectomy

The results of a logistic regression analysis for determinants for cystectomy are shown in table 2. The odds of having a cystectomy did not differ from the three hospitals with a urological training program and the twelve without. Younger patients (60 years or younger) underwent a cystectomy more frequently; 61.4% versus 48.6% for 61-74 years and 12.3% for patients 75 years and older (p<0.0001). In univariate analysis comorbidity was associated with having a cystectomy (p=0.0003), but adjusted for age the presence of comorbidity was no longer associated with receiving a cystectomy (p=0.097). There was no interaction in the model between age and comorbidity (p=0.29). Hospital type and year of diagnosis were not significant different with regards patients treated by cystectomy versus other type of treatment.

Survival

The 5-year DFS for patients with MIBC older than 75 years was 37.3% and the 5 years DSS 29.1%. Five years DFS and DSS were 70.8% and 58.9% in males and 57.65 and 39.1% in females. Compared to older patients DSS, but not DFS, was better in younger patients. Comorbidity was associated with both DSS as DFS; patients with two or more comorbidities had worse survival rates. Besides age and comorbidity also TNM stage was an independent variable for DSS after cystectomy. Results of all survival analysis are shown in Table 3, 4 and 5.

The 5 years DFS, DSS and overall survival (OS) of the cystectomy group were 66.3, 54.6 and 44.1 respectively versus 44.7 (p<0,001), 34.6 (p<0,001) and 15.1 (p<0,0001) in the no cystectomy group.

Discussion

A population based study as this creates a unique opportunity to reveal common practice in urology. We included 548 patients with muscle invasive UCC of the bladder with a follow up of at least 5 years. This group represents nearly seventy percent of all patients with a muscle-invasive bladder cancer diagnosed in a period of seven years in the northern part of the Netherlands. Demographic and pathologic data of this group were not

significantly different from those of the whole group of patients with, so the cohort was representative for the whole group.

Overall 37.4 % had a cystectomy, which is higher than the 33 % in a comparable population-based study in the USA.[5] However this means that the majority of patients with MIBC were not treated by cystectomy. Age was a strong predictor for the treatment choice. In our study 25 out of 204 patients older than 75 years (12.3%) had a cystectomy. So compared to Snyder's data they were treated less aggressively.[9] However another Dutch study on the patterns of care for the treatment of MIBC revealed with regards cystectomy in patients older than 75 years a percentage of only 6.7% .[10] Prout and co-workers specified their data of their older patients with MIBC: in the age group of 75-79 years 24% had radical cystectomy, 16% in the age group of 80-84 and 4% in those older than 85.[5] Figueroa et al have shown that aggressive, curative, radical surgery may be a viable treatment for properly selected elderly patients.[11] Acceptable mortality and morbidity can be achieved in elderly patients.[12,13] Patients with more comorbidity less frequently underwent cystectomy. Adjusted for age in multivariate analysis turned out to be not a significant factor (OR for two or more versus no comorbidity 0.58; 95% CI 0.34-0.98, p= 0.09). This comorbidity was subdivided in three different groups; with none, one and two or more comorbidities. Standardized classification like the Charlson Comorbidity Index (CCI) could not be used as the comorbidity was not registrated according to CCI. From the individual medical files we were not able to extract all data properly to use the CCI. However, Charlson 0 equals 0 comorbidity as well as Charlson equal or greater than two is equal to our two or more co morbidities.[14] 22.7% of those with no co morbidities underwent radical cystectomy and 13.3% and 5.9% of patients with one or two or more co morbidities respectively (p=0.020). Similar results have been reported before.[5] None the less, age is a more important factor in the consideration of treating patients with cystectomy than comorbidity. Only in the oldest patient group, comorbidity was a significant factor.

Results on survival after cystectomy compared to no cystectomy suggests a rather good DSS and DFS for the no cystectomy group. Though we will stress that there will be confounding by indication bias as it is a retrospective study. Unfortunately, no randomized, prospective data proving the benefit on survival of cystectomy compared to other treatment regimen are available. According to European guidelines radical cystectomy remains nevertheless the gold standard in the treatment of MIBC.[15]

Within the CCCN network, where all patients have access to the different

treatment modalities for MIBC, a significant part of the cohort then was not treated with the recommended surgical treatment. Most of the patients were treated with TUR with external beam radiation therapy. A small group underwent a TUR and interstitial irradiation with or without external beam radiation therapy. The Netherlands is one of the few countries in Europe where brachy therapy is a treatment option of solitary MIBC. In two Dutch series brachy therapy showed no inferior survival rates, with preservation of the bladder.[16,17] Possibly the recent data will reflect the gradually changed clinical practice pattern throughout the years.

Radical surgery may be a viable treatment for properly selected elderly patients and acceptable mortality and morbidity can be achieved in elderly patients.[12,13] In the individual, older patient, there should be good reasons not to perform surgery. The use of an assessment scale may help in decision making.[18]

It became clear that not all urologists in the CCCN region perform a routine lymph node dissection in patients treated with cystectomy for MIBC. Only 71.7 % of the cystectomized patients that underwent surgery underwent pelvic lymph node dissection. A logistic regression analysis of patients that underwent cystectomy showed no factor that was significantly different in people that underwent a PLND and the group that did not undergo PLND (results not shown). Several reports have been published, showing the benefit of extensive lymphadenectomy in patients with MIBC, especially concerning the outcome in those with limited nodal disease.[19–21] In our view, comorbidity and age may never be the reason not to perform a pelvic lymph node dissection.

Contrary to other reports we did not find a significant difference in survival between males and females. A common explanation for male/female differences is that the latter often are diagnosed at a worse stage of disease. Adjusted to stage, females remain to have a worse prognosis for unknown reasons.[22]

DFS and DSS were better in younger patients than in older patients. We have not stratified these groups while it is not a suitable technique in a retrospective analysis. The common explanation is the less aggressive treatment of elderly patients. In a prospective study of evaluation of a bladder preservation strategy in MIBC authors showed that preserving the bladder is feasible in a non highly selected patients cohort. The reason for this choice was to avoid the surgical risk in elderly patients and patients with comorbidity. However the consequences of a primarily non-surgical approach were need to undergo major complication-related interventions in an emergency setting.

They neither had an explanation for different outcomes in formerly published cystectomy series in elderly patients. Finally, they stressed the absence of a proper instrument to select patients on base of risk versus benefit.[23]

Disease specific survival has been shown to decrease with increasing age and an increasing number of comorbidities in patients treated with radical cystectomy. Nomograms predicting recurrence after cystectomy use age as one of the values in predicting recurrence, but in our study age was not a significant factor in DFS.[24,25] As in the series of Dalbagni, our data show that cystectomy in elderly patients will result in a DFS comparable to that of younger patients, but will result in decreased DSS.[26] Peri-operative mortality is probably being responsible for the worse DSS in older patients.[18] Very recently a validation study showed the usefulness of prediction tools in a low- to intermediate-volume center. Two published nomograms provided accurate predictions of recurrence and survival which were better than TNM stage-based prediction. Apparently it seems useful for the CCCN region to practice these nomograms. It would be of interest to study the effects of this nomogram on changes in current practice and on effects on survival rates in a prospective cohort.[27]

Conclusions

Only onethird of patients with MIBC in the CCCN region were treated by radical cystectomy. TNM stage and age were identified as the main variables with regards the choice for cystectomy. Hospital size and type and year of treatment had no significant effect on treatment. TNM stage, age and comorbidity were independent variables for disease specific survival after cystectomy.

References

1. Cancer Registry IKC.; 2009.
2. Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: Epidemiology, staging and grading, and diagnosis. In: Urology.Vol 66.; 2005:4–34.
3. Stenzl A, Cowan N, De Santis M, Jakse G, Kuczyk M, Merseburger A. The updated EAU guidelines on muscle-invasive and metastatic bladder cancer 2009. Eur Urol. 2009;55(4):815–825.
4. Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou-Redorta J. EAU guidelines on non- muscle-invasive carcinoma of the bladder. Eur Urol. 2008;54(2):303–314.
5. Prout GR, Wesley MN, Yancik R, Ries LA, Havlik RJ, Edwards BK. Age and comorbidity impact surgical therapy in older bladder carcinoma patients: a population-based study. Cancer. 2005;104:1638–1647.
6. Van Rhijn BWG, Burger M, Lotan Y, Solsona E, Stief CG, Sylvester RJ, et al. Recurrence and progression of disease in non-muscle-invasive bladder cancer: from epidemiology to treatment strategy. Eur Urol. 2009;56(3):430–442.
7. Sternberg CN, Vogelzang NJ. Gemcitabine, paclitaxel, pemetrexed and other newer agents in urothelial and kidney cancers. Crit Rev Oncol Hematol. 2003; 46 Suppl:S105-15.
8. Sobin LH, Fleming ID. TNM classification of malignant tumors, fifth edition (1997). Cancer. 1997;80(9):1803–1804.
9. Snyder C, Harlan L, Knopf K, Potosky A, Kaplan R. Patterns of care for the treatment of bladder cancer. J Urol. 2003;169(5):1697–1701.
10. Visser O, Nieuwenhuijzen JA, Horenblas S. Local recurrence after cystectomy and survival of patients with bladder cancer: a population based study in greater amsterdam. J Urol. 2005;174(1):97–102.
11. Figueroa AJ, Stein JP, Dickinson M, Skinner EC, Thangathurai D, Mikhail S, et al. Radical cystectomy for elderly patients with bladder carcinoma: an updated experience with 404 patients. Cancer. 1998;83(1):141–147.
12. Clark PE, Stein JP, Groshen SG, Cai J, Miranda G, Lieskovsky G, et al. Radical cystectomy in the elderly: Comparison of survival between younger and older patients. Cancer. 2005;103:546–552.
13. Stroumbakis N, Herr HW, Cookson MS, Fair WR. Radical cystectomy in the octogenarian. J Urol. 1997;158(6):2113–2117.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–383.
15. Stenzl A, Cowan N, De Santis M, Jakse G, Kuczyk M, Merseburger A. Guidelines on bladder cancer, muscle-invasive and metastatic. Eur Assoc Urol Guidel. 2009.
16. 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):239–245.
17. Van der Steen-Banasik E, Ploeg M, Witjes JA, et al. Brachytherapy versus cystectomy in solitary bladder cancer: A case control, multicentre, East-Netherlands study. Radiother Oncol. 2009;93(2):352–357.
18. Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. J Am Geriatr Soc. 2005;53(3):424–429.
19. Ghoneim M, Abol-Enein H. Lymphadenectomy with cystectomy: is it necessary and what is its extent? Eur Urol. 2004;46(4):457–461.
20. Mills RD, Turner WH, Fleischmann A, Markwalder R, Thalmann GN, Studer UE. Pelvic lymph node metastases from bladder cancer: outcome in 83 patients after radical cystectomy and pelvic lymphadenectomy. J Urol. 2001;166(1):19–23.
21. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001;19:666–675.
22. Mungan NA, Aben KK, Schoenberg MP, Visser O, Coebergh JW, Witjes JA, et al. Gender differences in stage-adjusted bladder cancer survival. Urology. 2000;55(6):876–880.
23. Lodde M, Palermo S, Comploj E, Signorello D, Mian C, Lusuardi L, et al. Four years experience in bladder preserving management for muscle invasive bladder cancer. Eur Urol. 2005;47(6):773–778.
24. Bochner BH, Kattan MW, Vora KC. Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. J Clin Oncol. 2006;24(24):3967–3972.
25. Karakiewicz PI, Shariat SF, Palapattu GS, Gilad AE, Lotan Y, Rogers CG, et al. Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. J Urol. 2006;176(4 Pt 1):1352–1354.
26. Dalbagni G, Genega E, Hashibe M, Zhang ZF, Russo P, Herr H, et al. Cystectomy for bladder cancer: a contemporary series. J Urol. 2001;165(4):1111–1116.
27. Zaak D, Burger M, Otto W, Bastian PJ, Denzinger S, Stief CG, et al. Predicting individual outcomes after radical cystectomy: an external validation of current nomograms. BJU Int. 2010;106(3):342–348.