

Chapter 2:

Local Recurrence after Cystectomy and Survival of Bladder Cancer Patients; a Population Based Study in Greater Amsterdam

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Abstract

Purpose: To determine retrospectively in a population based study the survival of patients with bladder cancer and the local recurrence rate (LRR) after cystectomy.

Materials and Methods: All bladder cancer cases diagnosed between 1988 and 2001 (vital status updated until September 2003) were selected from the Amsterdam Cancer Registry, which covers a population of 2.84 million people. For all patients who underwent a cystectomy between 1988 and 1997 in 18 participating hospitals, information on local recurrence and the vital status was collected from the medical records.

Results: Five-year relative survival for all bladder cancer cases combined (n=8,321) was 75%. For clinical stage 0-a this was 99%, decreasing to 85% for stage 0-is and 82% for stage I, and to 44%, 28% and 9% for stages II, III and IV, respectively. Five-year relative survival after cystectomy was 81%, 44% and 23% for stages II, III and IV, respectively. The LRR after cystectomy (n=566) was 19% for all cases and institutions combined. The LRR increased with higher pT-stages and reached 11%, 23% and 31% for stage II, III and IV respectively, and was slightly lower in oncological centres (18%) than in community hospitals (20%) (not significant).

Conclusions: Survival is higher than the European average, but below the figure for the United States. Only one in three stage II-III patients was treated with cystectomy. A relative high stage-specific survival is experienced after cystectomy, in spite of a local recurrence in 1 out of 5 patients.

Introduction

Bladder cancer is the sixth cancer in the Netherlands.¹ Compared to other European countries, the incidence of bladder cancer is relatively low.² In the Netherlands, more than two-thirds of all new bladder cancer patients presents with superficial disease³, which can be sufficiently treated with (repeated) local treatments. A cystectomy is usually offered as treatment of first choice to patients presenting with muscle invasive bladder cancer and to patients in whom local treatment of superficial bladder cancer is unsuccessful. Studies on the local recurrence after cystectomy are often hospital-based and local recurrence rates (LRR) have been reported from 7% to 25%.⁴⁻⁷

This study aims to investigate in a population-based setting the survival of bladder cancer patients and the LRR after cystectomy in the region of the Comprehensive Cancer Centre Amsterdam (CCCA).

Methods

Cancer registry data

All primary bladder tumours diagnosed in patients with residence in the CCCA-region (population: 2.84 million) between January 1st 1988 and December 31st 2001 were selected from the Amsterdam Cancer Registry, a population-based cancer registry with complete regional coverage.

Registration clerks extract information for the registry from detailed hospital records. Apart from demographic data, data are collected on morphology, stage and primary treatment. Stage grouping in this study was according to the 5th edition of the TNM-classification (table 1).⁸ cTNM was used for the survival analysis including all patients, pTNM was used in a subset analysis of cystectomy cases. We converted older TNM-data

to the 5th edition, but all T4-tumors were classified as stage IV, because the sub-classification into T4a/b was not available for all cases.

Follow-up

The vital status of all patients was updated by linking files with deceased persons to the cancer registry. These electronic data files, covering 1988-1999, were made available by the majority of the municipal population registers and included all deceased residents (irrespective of cause of death). Active follow-up in the hospitals was performed for patients residing in the remaining municipalities and if electronic data did not fully cover 1988-1999. Subsequently, the vital status of all patients still alive at last follow-up was updated until

Table 1: Stage grouping according to the 5th edition of the TNM-classification

Stage	Tumour	Lymph Nodes	Metastasis
0-a	Ta	N0	M0
0-is	Tis	N0	M0
I	T1	N0	M0
II	T2a, b	N0	M0
III	T3a, b	N0	M0
	T4a	N0	M0
IV	T4b	N0	M0
	Any T	N1, N2, N3	M0
	Any T	Any N	M1

September 1st 2003 by linkage to the electronic death register of the Central Office for Genealogy (COG), which contains all deceased Dutch residents from October 1st 1994. This register is updated on a daily basis with data from all municipal population registers in the Netherlands. Patients whose follow-up ended before October 1st 1994 were checked in the personal record card register of the CBG, containing all deceased Dutch residents before October 1st 1994. Finally, patients not known by COG were assumed to be alive at September 1st 2003. Completeness of follow-up is estimated to be over 99.5%.⁹

Cystectomy

A subset of patients was defined by selecting patients from the cancer registry who underwent cystectomy during 1988-1997. Data from two small hospitals (out of 20) could not be included, because one hospital refused permission to extract data from the medical records, and because many patient-files had been destroyed in another. Patients referred to the oncological centres from outside the CCCA-region were excluded to keep data population based. Patients for whom cystectomy was not the primary treatment were included, but in several hospitals these cases could not be included because of missing data in the medical records department.

A supplementary data set including date of surgery, intent of the surgery (curative or palliative), presence of residual disease after surgery, and the occurrence and date of local recurrence (i.e. recurrence in the soft tissue within the true pelvis) was extracted from medical records. In case the cystectomy was not the primary treatment, TNM and morphology at date of cystectomy were also registered. Patients were followed at least 5 years after cystectomy.

Statistical methods

Because the cause of death is not available in the population registers, we were unable to calculate disease specific survival. Instead, we calculated relative survival using STATA according to Dickman *et al.*¹⁰ This method corrects crude survival for expected mortality according to annual life tables of the general population.

For the comparison of LRR between hospitals a standardized LRR was calculated. Based on the stage-specific LRR for all hospitals combined and the stage distribution in a specific hospital, an expected number of local recurrences was calculated for each hospital. The expected numbers were compared with the observed numbers and a stage-standardized local recurrence rate (SLRR) was calculated as the ratio between the observed and expected numbers. Exact 95% confidence intervals (CI) based on the Poisson distribution of O, and Kaplan-Meier survival curves were calculated using STATA.

Results

Primary treatment of patients with primary bladder cancer

A total of 8,321 patients with primary bladder cancer was diagnosed between 1988-2001. About three quarters of all patients received local treatment only as primary treatment (table 2).

Table 2: Primary treatment of primary bladder cancer in Greater Amsterdam, 1988-2001

cTNM-stage*/ age group	Number of Patients	Primary treatment (%)			
		Local treatment only	Cystectomy (with or without radiotherapy)	Radio- therapy	Other
0-a	3,698	98%	<1%	<1%	2%
0-is	191	88%	2%	1%	9%
I	1,914	90%	3%	5%	2%
II	1,170	33%	30%	36%	1%
< 75 years	711	22%	44%	33%	<1%
75 or older	459	51%	6%	41%	1%
III	457	24%	30%	40%	7%
< 75 years	253	15%	44%	35%	5%
75 or older	204	36%	9%	46%	9%
IV	572	42%	11%	29%	18%
Unknown	240	31%	24%	13%	33%
Not applicable	79	28%	4%	3%	66%
TOTAL	8,321	76%	8%	11%	5%

* Stage grouping according to the 5th edition of the TNM Classification⁸, but T4 classified as stage IV

Of the patients presenting with clinical stage II and III, 33% and 24% received local treatment only. In stage II and III, more patients underwent radiotherapy (36% and 40%, respectively) than cystectomy (30% and 30%). Patients of 75 years and older underwent cystectomy less often than younger patients (chi²-test: $p < 0.001$).

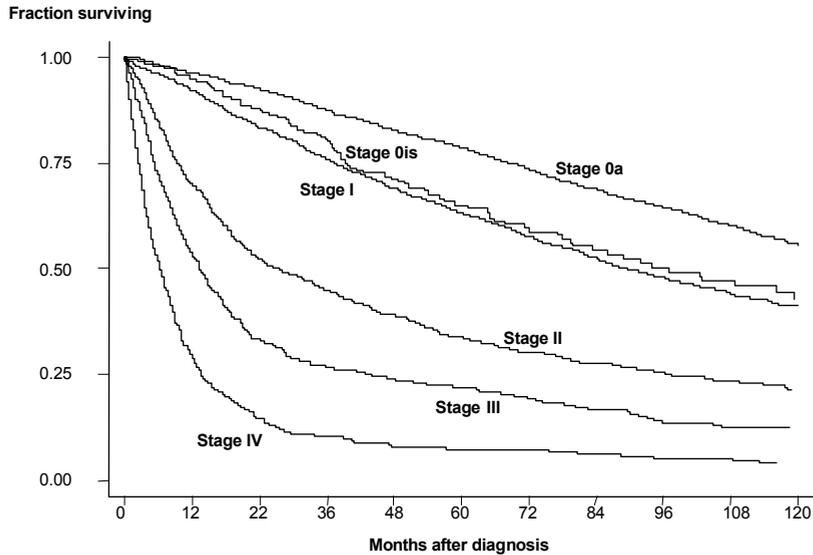
Survival for all patients

One- and five-year crude survival of all patients combined was 83% and 58%. Crude survival according to stage is shown in figure 1. The one- and five-year relative survival rate (RSR) was 87% and 75% (table 3). The ten-year RSR was 67% (95% CI: 65-70%). The RSRs decrease with increasing age.

For females, the RSR after five and ten years was 6% lower than for males. This was caused by a less favourable stage distribution in females (14% of all females were diagnosed as clinical stage II, 7% stage III, and 10% stage IV, compared to 14% stage II, 5% stage III, and 6% stage IV in males). Stage-specific RSRs in females (five-year RSRs of 79%, 42% and 16% for stage I, II and III, respectively) were also lower than in males (five-year RSRs of 83%, 44% and 33% for stage I, II and III). Survival for patients diagnosed between 1999-2001 was almost equal to survival of patients diagnosed about 10 years earlier (1988-1991).

Up to five years after diagnosis, patients with stage 0-a bladder cancer experienced a survival almost equal to the general population (RSR: 99%, CI: 97-101%), but the ten-year RSR was 92% (CI: 88-95%). For patients with stage 0-is and stage I five-year RSRs (85% and 82%, respectively) and ten-year RSRs (78% and 73%) were almost equal.

Figure 1: Crude survival according to clinical stage after diagnosis of bladder cancer in Greater Amsterdam, 1988-2001



Patients with muscle-invasive bladder cancer experienced five-year survival decreasing from 44% for stage II, to 28% for stage III, and 9% for stage IV. The ten-year RSR was 36%, 21% and 6% for stage II, III and IV. Adenocarcinoma, squamous cell carcinoma and undifferentiated carcinoma of the bladder resulted in lower survival figures than transitional cell carcinoma (table 3). The five-year RSR for grade I tumours was 101%, decreasing to 88% for grade II, 52% for grade III and 26% for grade IV.

Local recurrence after cystectomy

577 patients underwent a cystectomy between 1988-1997 (number of cystectomies per hospital/year: 0-12), of whom eleven had macroscopic residual disease (three stage III, eight stage IV tumours). In 110 (19%) of the remaining 566 patients a local recurrence occurred (table 4). Of thirteen patients medical records were not accessible and it could not be established whether a local recurrence had occurred. Most of them died within a year after cystectomy.

Table 3: Relative survival (%) of bladder cancer patients in Greater Amsterdam, 1988-2001

Parameter	Number of Cases	Years after diagnosis (95% confidence interval)		
		1	5	10
<i>Period of diagnosis</i>				
1988-1991	2,182	88 (86-90)	75 (72-77)	67 (63-70)
1992-1995	2,453	86 (85-88)	76 (74-79)	69 (65-72)
1996-1998	1,809	86 (84-88)	73 (71-76)	
1999-2001	1,877	88 (86-90)		
<i>Sex</i>				
Males	6,560	89 (88-90)	76 (75-78)	69 (66-71)
Females	1,761	80 (78-82)	70 (67-73)	63 (58-67)
<i>Age group*</i>				
15-44	251	95 (92-97)	90 (85-93)	86 (80-90)
45-54	738	94 (92-96)	86 (83-88)	80 (75-83)
55-64	1,690	92 (90-93)	79 (77-81)	73 (70-76)
65-74	2,905	88 (87-89)	76 (73-78)	67 (63-70)
75+	2,733	80 (78-82)	66 (63-70)	56 (49-63)
<i>cTNM- stage**</i>				
0-a	3,698	101 (100-101)	99 (97-101)	92 (88-95)
0-is	191	99 (95-102)	85 (75-94)	78 (61-93)
I	1,914	97 (95-98)	82 (79-85)	73 (68-78)
II	1,170	74 (71-77)	44 (40-48)	36 (31-41)
III	457	56 (51-61)	28 (23-34)	21 (16-28)
IV	572	30 (26-34)	9 (6-12)	6 (3-9)
Unknown	240	68 (61-75)	49 (40-57)	37 (26-49)
TNM not applicable	79	37 (26-48)	22 (12-34)	14 (6-28)
<i>Morphological type</i>				
Transitional cell ca.	7,973	89 (88-90)	77 (76-79)	70 (67-72)
Squamous cell ca.	113	38 (29-47)	23 (14-32)	18 (8-31)
Adenocarcinoma	76	70 (58-80)	38 (26-51)	21 (10-36)
Undifferentiated ca.	82	37 (27-48)	14 (6-25)	11 (3-25)
Sarcoma	19	65 (39-83)	29 (10-53)	22 (6-47)
Unknown***	58	27 (16-40)	18 (8-32)	15 (5-31)
<i>Morphological grade</i>				
Grade 1	1,626	101 (99-101)	101 (98-103)	94 (89-99)
Grade 2	2,594	96 (95-97)	88 (86-90)	80 (76-84)
Grade 3	2,858	75 (73-77)	52 (50-55)	43 (39-47)
Grade 4	191	44 (37-52)	26 (19-34)	19 (11-29)
Grade unknown	1,052	84 (82-87)	73 (69-77)	66 (61-72)
TOTAL	8,321	87 (86-88)	75 (74-76)	67 (65-70)

* 4 cases 0-14 year

** stage grouping according to the 5th edition of the TNM Classification, but T4 classified as stage IV

*** no pathological confirmation

Table 4: Local recurrence rate after cystectomy for bladder cancer in Greater Amsterdam, 1988-1997 (cystectomies with palliative intent and/or macroscopic residual disease excluded)

Parameter	Cystec- tomies	Local Recurrence			
		Yes (%)	Odds Ratio	No (%)	Unknown (%)
Sex					
Males	448	85 (19)	1 (Ref.)	355 (79)	8 (2)
Females	118	25 (21)	1.0 (0.6-1.8)	88 (75)	5 (4)
Morphological group*					
Transitional cell ca.	214	97 (19)	1 (Ref.)	406 (79)	11 (2)
Squamous cell ca.	27	3 (11)	0.4 (0.1-1.4)	22 (81)	2 (7)
Adenocarcinoma	18	7 (39)	2.4 (0.8-6.7)	11 (61)	-
Undifferentiated ca.	7	3 (43)	2.4 (0.5-11)	4 (57)	-
cTNM-stage**					
0 (Ta/Tis)	22	1 (5)	1 (Ref.)	21 (95)	-
I	74	11 (15)		63 (85)	-
II	123	13 (11)	0.8 (0.4-2.0)	110 (89)	-
III	258	59 (23)	2.2 (1.1-4.4)	189 (73)	10 (4)
IV	83	26 (31)	3.0 (1.4-6.7)	54 (65)	3 (4)
Unknown	6	-		6 (100)	-
Residual disease					
R0	490	90 (18)	1 (Ref.)	395 (81)	5 (1)
R1	42	13 (31)	1.4 (0.7-2.9)	27 (64)	2 (5)
RX	34	7 (21)	1.0 (0.4-2.3)	21 (62)	6 (18)
Hospital					
Community hospital	458	91 (20)	1 (Ref.)	354 (77)	13 (3)
Oncological centre	108	19 (18)	0.8 (0.5-1.5)	89 (82)	-
TOTAL	566	110 (19)		443 (78)	13 (2)

* stage grouping according to the 5th edition of the TNM Classification⁸, but T4 classified as stage IV

** R0 = no residual disease; R1 = microscopic residual disease; RX = unknown

There was little difference in the LRR between males and females (19% and 21%, respectively). The LRR was decreased for squamous cell carcinoma compared to transitional cell carcinomas. For adenocarcinomas and undifferentiated carcinomas the LRR was increased (not significant). For the lower stages, the LRR was 5% in stage 0-a/0-is, 15% in stage I, and 11% in stage II. For stage III (LRR 23%, odds ratio 2.2, CI 1.1-4.4) and stage IV bladder cancer (LRR 31%, odds ratio 3.0, CI 1.4-6.7) the LRRs were significantly increased. The presence of microscopic residual disease after cystectomy was an unfavourable factor (odds ratio 1.4, CI 0.7-2.9). In patients who underwent cystectomy in an oncological centre the LRR was lower than for patients from community hospitals, but the difference was not statistically significant. Figure 2 shows that the SLRR for the various hospitals ranged from 0 to 1.7 (all hospitals combined: 1), but for all hospitals the CI included 1.

Figure 2: Stage standardized local recurrence rate after cystectomy for bladder cancer in Greater Amsterdam, 1988-1997 (hospitals are sorted according to the number of cystectomies; bars represent 95% confidence intervals; reference = 1 for all hospitals combined)

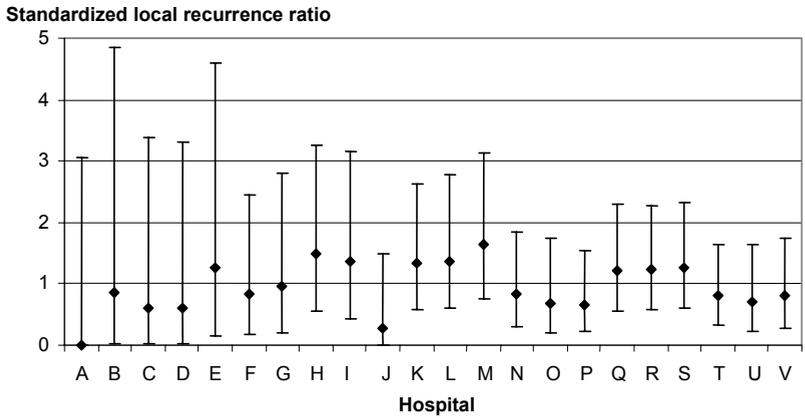


Figure 3 shows survival of patients after cystectomy. Crude 5-year survival of patients with local recurrence was 11% (median 15 months), without local recurrence 63% (log-rank: $p < 0.0001$). The difference in survival between patients with and without local recurrence was mainly caused by the poor survival after local recurrence: median survival after local recurrence was only 2.5 months, while 1-year survival was 19% (figure 4).

Figure 3: Crude survival of patients with or without local recurrence after cystectomy for bladder cancer in Greater Amsterdam, 1988-1997 (excluding cases dying within 3 months after cystectomy)

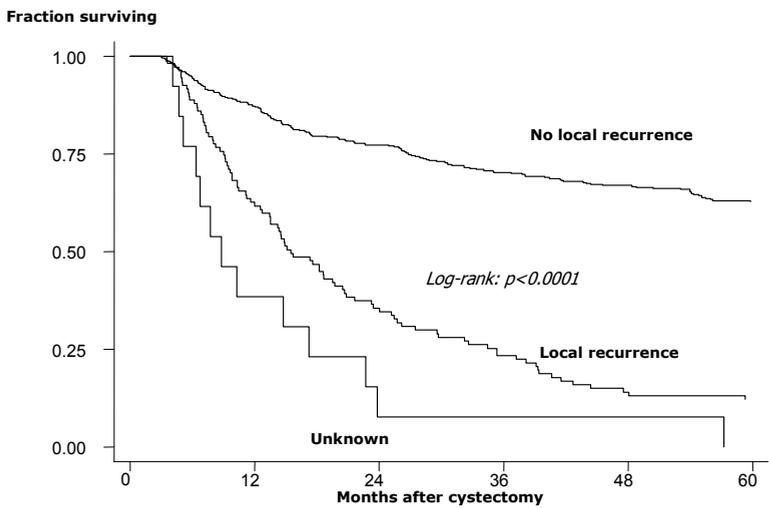


Figure 4: Crude survival after local recurrence following cystectomy for bladder cancer in Greater Amsterdam, 1988-1997

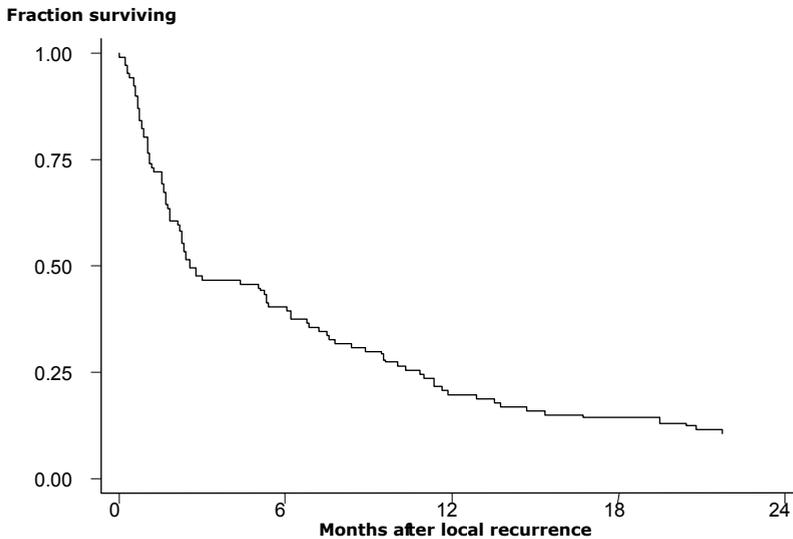
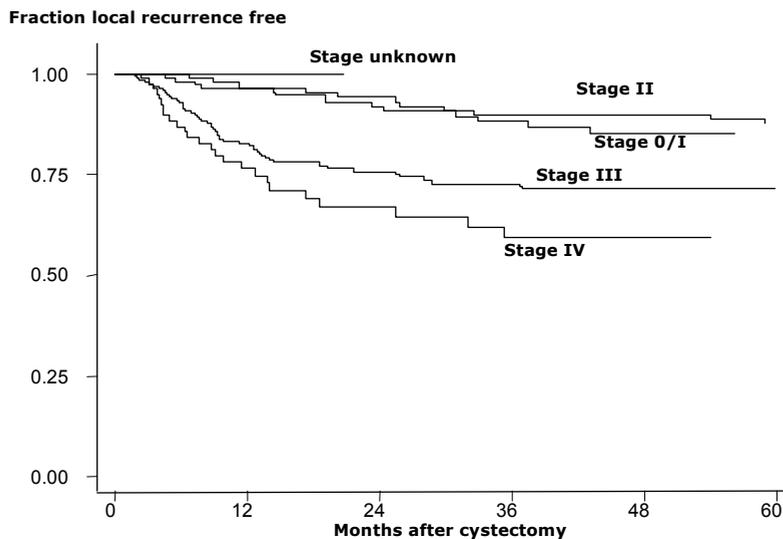


Figure 5: Local recurrence free survival according to pathological stage after cystectomy for bladder cancer in Greater Amsterdam, 1988-1997. Log-rank test: stage III versus stage 0-II: $p < 0.0001$; stage IV versus stage 0-II: $p < 0.0001$; stage III versus stage IV: $p = 0.07$



Local recurrence free survival decreased with increasing stage (figure 5). There was little difference between the lower stages (stage 0-II). However, in stage III (log-rank versus stage 0-II: $p < 0.0001$) and stage IV (log-rank versus stage 0-II: $p < 0.0001$) the risk of local recurrence was higher than in lower stages.

The stage-specific RSR of patients who underwent a cystectomy (table 5) was higher than for the total group of bladder cancer patients, which comprises all treatments (table 3), with the exception of superficial bladder cancer. For stage II, the 5-year RSR was 81% for cystectomy patients (pTNM), compared to 44% for all patients combined (cTNM). For stage III, these rates were 44% and 28%, respectively.

Table 5: Local recurrence free survival according to pathological stage after cystectomy for bladder cancer in Greater Amsterdam, 1988-1997. Log-rank test: stage III versus stage 0-II: $p < 0.0001$; stage IV versus stage 0-II: $p < 0.0001$; stage III versus stage IV: $p = 0.07$

TNM stage*	Number of Cases	Years after diagnosis (95% confidence interval)		
		1	5	10
0 / I	96	91 (82-96)	81 (68-92)	78 (59-95)
II	123	92 (84-96)	81 (70-89)	69 (54-82)
III	261	67 (61-73)	44 (37-51)	25 (17-35)
IV	91	60 (49-70)	23 (14-34)	22 (12-33)
TOTAL**	577	76 (72-79)	55 (50-60)	44 (37-50)

* Stage grouping according to the 5th edition of the TNM Classification⁸, but T4 classifies as stage IV

**Including 6 cases with unknown stage

Discussion

In this study we evaluated survival and treatment outcomes of patients with bladder cancer. The five-year RSR of patients diagnosed with bladder cancer between 1988-2001 was 75%. Survival after five years for patients with non-invasive papillary bladder cancer equals survival in the general population (RSR 99%). Between five and ten years after diagnosis survival figures decreased (10-year RSR 92%), but this should be interpreted with caution. These patients are at higher risk to develop invasive bladder cancer than the general population and other factors (e.g. smoking with associated co-morbidity) may also be of importance.

According to the EURO CARE-study on survival of cancer patients in Europe, survival of bladder cancer patients in the Netherlands is among the highest in Europe.¹¹ The EURO CARE-study reports equally high rates for Germany, Austria, Spain and Sweden. In the EURO CARE-study no data are available on stage distribution, so it is unknown whether this result is due to a more favourable stage distribution or to other factors.

In the USA, the reported bladder cancer survival rates from the SEER-Program are higher than in Europe.¹² Five-year relative survival rates from the SEER-Program for 1990-1999 are 97%, 65%, 56% and 22% for stage I, II, III and IV, respectively, compared to 82%, 44%, 28% and 9% in our study. Although the lower survival in our study may be influenced by differences in staging procedures between the USA and the Netherlands, differences in treatment practices may also have influenced the results. Of all patients who initially presented with clinical stage II-III bladder cancer only 30% underwent a cystectomy. Of the patients <75 years old (probably appropriate candidates) only 44% underwent

cystectomy. These percentages are remarkably low in view of the consensus in the Netherlands that cystectomy is the preferred treatment for stage II-III bladder cancer. In our study, survival of patients with stage II-III bladder cancer who underwent a cystectomy was much higher than for all patients combined, but comparison between these patient groups is biased by factors such as age, comorbidity, and physician's preference.

Development of local recurrence in patients undergoing cystectomy has been reported at rates from 7% to 25%.⁴⁻⁷ Sengelov already demonstrated that intensified examination resulted in more sites of metastases,¹³ and local recurrence rates are probably under-reported, as the finding of distant metastases decreases the need for intensified local follow up when local recurrences are asymptomatic. After cystectomy, the tumour recurred locally in one out of five patients in our study, so our results are not among the most favourable when compared to other studies. This might be related to the fact¹⁷ that many other studies were performed in oncological centres, while our study comprised a large number of community hospitals in addition to three oncological centres. No statistically significant difference in SLRR between the various hospitals, nor a relation between the number of cystectomies per hospital and the SLRR could be demonstrated. The LRR in the oncological centres combined was lower, but the difference was not statistically significant. However, the annual number of cystectomies by hospital was rather low in all hospitals. For oncological centres this was due to the exclusion of referred patients from outside the CCCA region. In recent years, a tendency towards centralization of cystectomies has occurred in our region and future studies should demonstrate whether this has improved the results.

Stage and grade are known prognostic indicators for local failure.^{14,15} In contrast to what we expected, no significant difference was found between LRRs after a R0-dissection (no residual tumour after cystectomy) and R1-dissection (microscopic residual tumour). This might be explained by the higher death rates shortly after resection for patients with residual microscopic disease. These patients might not have lived long enough to develop clinical detectable local recurrences. In other series, margin status was a predictor for local recurrence, although no distinction between microscopic or macroscopic residual tumour was made.¹⁶ Furthermore, the use of peri-operative chemotherapy might be of influence. In the time period of our study however, peri-operative chemotherapy was not standard practice. Consequently, only 17 patients underwent this multimodality treatment, and this small number does not enable separate analysis and conclusions.

Patients who recur locally usually do so within the first 2 years after treatment, which is consistent with our findings.^{7,14,17,18} Differences in LRRs may be influenced by differences in definition. Mostly, local recurrence is defined as bladder cancer recurrence in the soft tissue within the true pelvis, while tumour outside the pelvis is considered as distant metastases. Some authors, however, define a combination of both local and distant recurrence as distant recurrence only, as patient outcome appears to be dictated by concomitant systemic metastases.^{17,19} Urethral or upper tract recurrences are sometimes considered as a local recurrence also. However, they represent a different biological process of

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recurrence, and both treatment and prognosis differ greatly from true pelvic recurrences.²⁰

The aggressive natural behaviour of local recurrences after cystectomy results in poor prognosis in many series,^{14,18} and our data confirm this experience. No data were available about the therapy following local recurrences, but the final outcome of patients with a local recurrence appears to be poor, regardless of treatment. Despite the availability of chemotherapeutic regimens long-term survival is achieved in less than 10% of these patients.^{17,18}

Conclusions

The five-year RSR of all patients combined was 75%, which is slightly better than European figures, but the stage-specific rates are worse than American figures.

Of all patients with stage II-III bladder cancer, only 30% underwent cystectomy. Cystectomy patients experienced a relatively high stage-specific survival. After cystectomy, a local recurrence occurred in one out of five patients, and prognosis for these patients is poor. We found no difference in the LRR between the various hospitals.

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