

# LOCAL RECURRENCE AFTER CYSTECTOMY AND SURVIVAL OF PATIENTS WITH BLADDER CANCER: A POPULATION BASED STUDY IN GREATER AMSTERDAM

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## ABSTRACT

**Purpose:** We determined 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 patients with bladder cancer 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 individuals. For all patients who underwent cystectomy between 1988 and 1997 at 18 participating hospitals information on local recurrence and vital status was collected from the medical records.

**Results:** Five-year relative survival in all 8,321 bladder cancer cases combined 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 to IV, respectively. Five-year relative survival after cystectomy was 81%, 44% and 23% for stages II to IV, respectively. The LRR after cystectomy was 19% in all 566 cases and all institutions combined. The LRR increased with higher pT stage and it achieved 11%, 23% and 31% for stages II to IV, respectively. It was slightly lower at oncological centers than at community hospitals (18% vs 20%, not significant).

**Conclusions:** Survival is higher than the European average but below the value in the United States. Only 1 of 3 stages II-III cases was treated with cystectomy. Relatively high stage specific survival is experienced after cystectomy despite local recurrence in 1 of 5 patients.

**KEY WORDS:** bladder; bladder neoplasms; cystectomy; neoplasm recurrence, local; survival

Bladder cancer is the sixth most prevalent cancer in The Netherlands.<sup>1</sup> Compared with other European countries the incidence of bladder cancer is relatively low.<sup>2</sup> In The Netherlands more than two-thirds of all new patients with bladder cancer present with superficial disease,<sup>3</sup> which can be sufficiently treated with repeat local treatments. Cystectomy is usually offered as the treatment of choice in patients presenting with muscle invasive bladder cancer and to patients in whom local treatment of superficial bladder cancer is unsuccessful. Studies of local recurrence after cystectomy are often hospital based and the local recurrence rate (LRR) has been reported to be 7% to 25%.<sup>4–7</sup> In a population based setting we investigated survival in patients with bladder cancer and the LRR after cystectomy in the region of the Comprehensive Cancer Centre Amsterdam (CCCA).

## MATERIALS AND METHODS

**Cancer registry data.** All primary bladder tumors diagnosed in patients with residence in the CCCA region (population 2.84 million) between January 1, 1988 and December 31, 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 treat-

ment. Stage grouping in this study was done according to TNM classification, fifth edition (table 1).<sup>8</sup> cTNM was used for the survival analysis including all patients and pTNM was used for subset analysis of cystectomy cases. We converted older TNM data to those of the fifth edition but all T4 tumors were classified as stage IV because subclassification into T4a/b was not available for all cases.

**Followup.** The vital status of all patients was updated by linking files with deceased individuals to the cancer registry. These electronic data files, covering 1988 to 1999, were made available by the majority of municipal population registries and they included all deceased residents irrespective of the cause of death. Active followup at the hospitals was performed in patients residing in the remaining municipalities and if electronic data did not fully cover 1988 to 1999. Subsequently the vital status of all patients still alive at last followup was updated until September 1, 2003 by linkage to

TABLE 1. TNM, 5th edition stage grouping

Stage	Tumor	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

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the electronic death registry at the Central Office for Genealogy (COG), which contains all deceased Dutch residents beginning October 1, 1994. This registry is updated on a daily basis with data from all municipal population registries in The Netherlands. Patients in whom followup ended before October 1, 1994 were checked in the personal record card registry of the COG, which contains all Dutch residents deceased before October 1, 1994. Finally, patients not known at the COG were assumed to be alive at September 1, 2003. The completeness of followup was estimated to be greater than 99.5%.<sup>9</sup>

**Cystectomy.** A subset of patients was defined by selecting patients from the cancer registry who underwent cystectomy during 1988 to 1997. Data from 2 small hospitals of 20 could not be included because staff at 1 hospital refused permission to extract data from the medical records and because many patient files had been destroyed at the other. Patients referred to the oncological centers from outside of the CCCA region were excluded to maintain data population based. Patients in whom cystectomy was not the primary treatment were included but at several hospitals they could not be included because of missing data in the medical records department.

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

**Statistical methods.** Because cause of death is not available in the population registries, we were unable to calculate disease specific survival. Instead, we calculated relative survival using STATA (StataCorp, College Station, Texas) according to Dickman et al.<sup>10</sup> This method corrects crude survival for expected mortality according to annual life tables of the general population.

To compare LRRs among hospitals a standardized LRR was calculated. Based on the stage specific LRR for all hospitals combined and the stage distribution at a specific hospital an expected number of local recurrences was calculated per hospital. The expected numbers were compared with the observed numbers and a stage standardized LRR (SLRR) was calculated as the ratio between the observed and expected numbers. Exact 95% CIs based on the Poisson distribution of 0 and Kaplan-Meier survival curves were calculated using STATA.

## RESULTS

**Primary treatment in patients with primary bladder cancer.** A total of 8,321 patients with primary bladder cancer

were diagnosed between 1988 and 2001. About three-quarters of all patients received local treatment only as primary treatment (table 2). Of patients presenting with clinical stages II and III 33% and 24%, respectively, received local treatment only. For stages II and III more patients underwent radiotherapy (36% and 40%) than cystectomy (30% and 30%, respectively). Patients 75 years and older underwent cystectomy less often than younger patients (chi-square test  $p < 0.001$ ).

**Survival in all patients.** One and 5-year crude survival in all patients combined was 83% and 58%, respectively. Figure 1 shows crude survival according to stage. The 1 and 5-year relative survival rate (RSR) was 87% and 75%, respectively (table 3). The 10-year RSR was 67% (95% CI 65 to 70). RSRs decreased with increasing age.

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

Up to 5 years after diagnosis patients with stage 0-a bladder cancer experienced survival that was almost equal to that in the general population (RSR 99%, CI 97 to 101) but the 10-year RSR was 92% (CI 88 to 95). In patients with stages 0-is and I 5-year (85% and 82%) and 10-year (78% and 73%, respectively) RSRs were almost equal.

Patients with muscle invasive bladder cancer experienced 5-year survival that decreased from 44% for stage II to 28% for stage III and 9% for stage IV. The 10-year RSR was 36%, 21% and 6% for stages II to IV. Adenocarcinoma, squamous cell carcinoma and undifferentiated carcinoma of the bladder resulted in lower survival rates than transitional cell carcinoma (table 3). The 5-year RSR for grade I tumors was 101%, which decreased to 88% for grade II, 52% for grade III and 26% for grade IV.

**Local recurrence after cystectomy.** A total of 577 patients underwent cystectomy between 1988 and 1997 (0 to 12 cystectomies per hospital yearly), of whom 11 had macroscopic residual disease, including stage III in 3 and stage IV in 8. In 110 of the remaining 566 patients (19%) local recurrence developed (table 4). For 13 patients medical records were not available and it could not be established whether local recurrence had developed. Most of them died within a year after cystectomy.

There was little difference in the LRR between males and females (19% and 21%, respectively). The LRR was decreased for squamous cell carcinoma compared with transitional cell

TABLE 2. Primary treatment of primary bladder cancer in Greater Amsterdam, 1988 to 2001

cTNM Stage* (age group)	No. Pts	% Primary Treatment			
		Local Only	Cystectomy With/Without Radiotherapy	Radiotherapy	Other
0-a	3,698	98	Less than 1	Less than 1	2
0-is	191	88	2	1	9
I	1,914	90	3	5	2
II:	1,170	33	30	36	1
Younger than 75	711	22	44	33	Less than 1
75 or Older	459	51	6	41	1
III:	457	24	30	40	7
Younger than 75	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
Overall	8,321	76	8	11	5

\* According to TNM classification, fifth edition,<sup>8</sup> but T4 classified as stage IV.

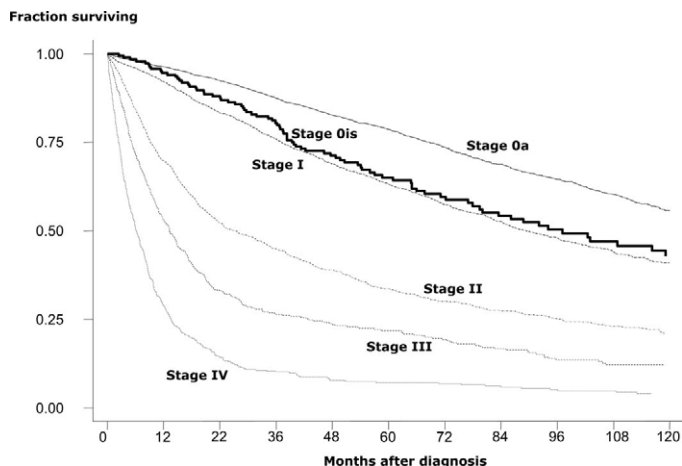


FIG. 1. Crude survival according to clinical stage after bladder diagnosis cancer in Greater Amsterdam, 1988 to 2001.

carcinoma. For adenocarcinoma and undifferentiated carcinoma the LRR was increased (not significant). For lower stages the LRR was 5% in stage 0-a/0-is, 15% in stage I and 11% in stage II. For stages III (LRR 23%, OR 2.2, CI 1.1 to 4.4) and IV (LRR 31%, OR 3.0, CI 1.4 to 6.7) bladder cancer LRRs were significantly increased. Microscopic residual disease after cystectomy was an unfavorable factor (OR 1.4, CI 0.7 to 2.9). In patients who underwent cystectomy at an oncological center the LRR was lower than in patients at community hospitals but the difference was not statistically

significant. Figure 2 shows that the SLRR at the various hospitals was 0 to 1.7, that is 1 for all hospitals combined, but for all hospitals the CI included 1.

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

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

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

#### DISCUSSION

In this study we evaluated survival and treatment outcomes in patients with bladder cancer. The 5-year RSR in patients diagnosed with bladder cancer between 1988 and 2001 was 75%.

Survival after 5 years in patients with noninvasive papillary bladder cancer equals survival in the general population

TABLE 3. Relative survival in patients with bladder cancer in Greater Amsterdam, 1988 to 2001

Parameter	No. Pts	% Yrs After Diagnosis (95% CI)		
		1	5	10
Diagnosis period:				
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)		
Sex:				
M	6,560	89 (88–90)	76 (75–78)	69 (66–71)
F	1,761	80 (78–82)	70 (67–73)	63 (58–67)
Age group:*				
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 or Older	2,733	80 (78–82)	66 (63–70)	56 (49–63)
cTNM stage:†				
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)
Morphological type:				
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)
Adenoca	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)
Morphological grade:				
1	1,626	101 (99–101)	101 (98–103)	94 (89–99)
2	2,594	96 (95–97)	88 (86–90)	80 (76–84)
3	2,858	75 (73–77)	52 (50–55)	43 (39–47)
4	191	44 (37–52)	26 (19–34)	19 (11–29)
Unknown	1,052	84 (82–87)	73 (69–77)	66 (61–72)
Overall	8,321	87 (86–88)	75 (74–76)	67 (65–70)

\* Four 0 to 14-year-old patients.

† According to TNM classification, fifth edition,<sup>8</sup> but T4 classified as stage IV.

‡ No pathological confirmation.

TABLE 4. Local recurrence rates after cystectomy for bladder cancer in Greater Amsterdam, 1988 to 1997

Parameter	No. Cystectomies	Local Recurrence			
		No. Yes (%)	OR	No. No (%)	No. Unknown (%)
Sex:					
M	448	85 (19)	1 (referent)	355 (79)	8 (2)
F	118	25 (21)	1.0 (0.6–1.8)	88 (75)	5 (4)
Morphological type:					
Transitional cell Ca	214	97 (19)	1 (referent)	406 (79)	11 (2)
Squamous cell Ca	27	3 (11)	0.4 (0.1–1.4)	22 (81)	2 (7)
Adenoca	18	7 (39)	2.4 (0.8–6.7)	11 (61)	–
Undifferentiated Ca	7	3 (43)	2.4 (0.5–11)	4 (57)	–
TNM stage:*					
0 (Ta/Tis)	22	1 (5)		21 (95)	–
I	74	11 (15)	1 (referent)	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:					
None	490	90 (18)	1 (referent)	395 (81)	5 (1)
Microscopic	42	13 (31)	1.4 (0.7–2.9)	27 (64)	2 (5)
Unknown	34	7 (21)	1.0 (0.4–2.3)	21 (62)	6 (18)
Hospital:					
Community	458	91 (20)	1 (referent)	354 (77)	13 (3)
Oncological center	108	19 (18)	0.8 (0.5–1.5)	89 (82)	–
Totals	566	110 (19)		443 (78)	13 (2)

Excluding cystectomies done for palliative intent and/or with residual disease.

\* According to TNM classification, fifth edition,<sup>8</sup> but T4 classified as stage IV.

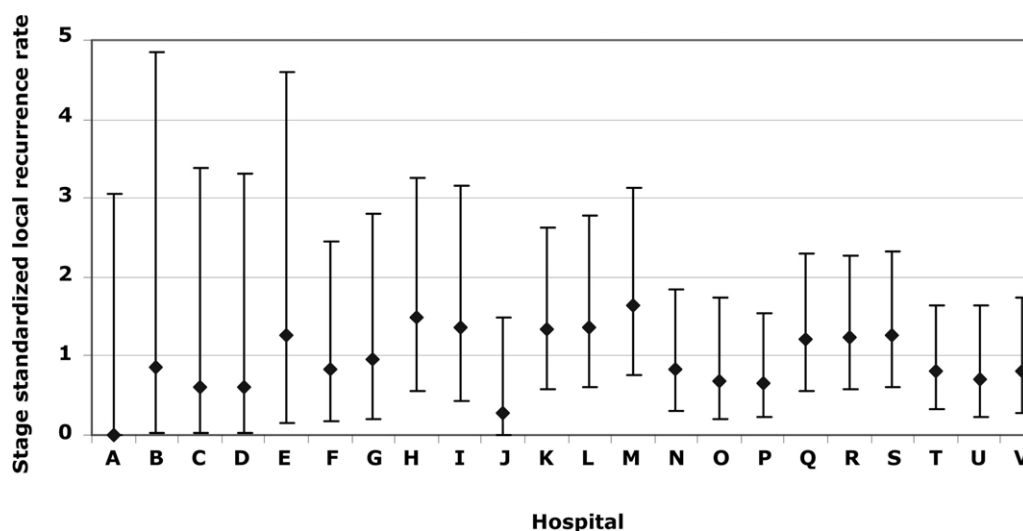


FIG. 2. Stage standardized local recurrence rate after cystectomy for bladder cancer in Greater Amsterdam, 1988 to 1997, with hospitals (A to V) sorted according to number of cystectomies. Referent = 1 for all hospitals combined. Bars represent 95% CI.

(RSR 99%). Between 5 and 10 years after diagnosis survival rates decreased (10-year RSR 92%) but this should be interpreted with caution. These patients are at higher risk for invasive bladder cancer than the general population and other factors, eg smoking with associated comorbidity, may also be of importance.

According to the European Cancer Registries Study on Cancer Patients' Survival and Care (EUROCARE) survival in patients with bladder cancer in The Netherlands is among the highest in Europe.<sup>11</sup> The EUROCARE study shows equally high rates in Germany, Austria, Spain and Sweden. In the EUROCARE study no data are available on stage distribution, and so it is unknown whether this result is due to more favorable stage distribution or to other factors.

In the United States reported bladder cancer survival rates in the Surveillance, Epidemiology, and End Results program are higher than in Europe.<sup>12</sup> Five-year RSRs in the Surveillance, Epidemiology, and End Results program for 1990 to 1999 are 97%, 65%, 56% and 22% for stages I to IV compared with 82%, 44%, 28% and 9%, respectively, in our study.

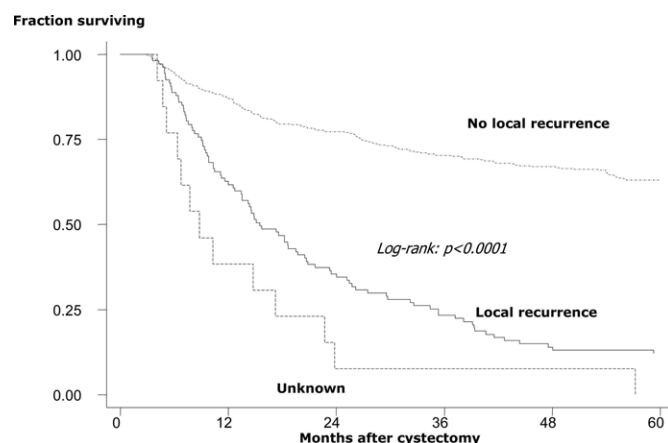


FIG. 3. Crude survival in patients with or without local recurrence after cystectomy for bladder cancer in Greater Amsterdam, 1988 to 1997, excluding those dying within 3 months after cystectomy.

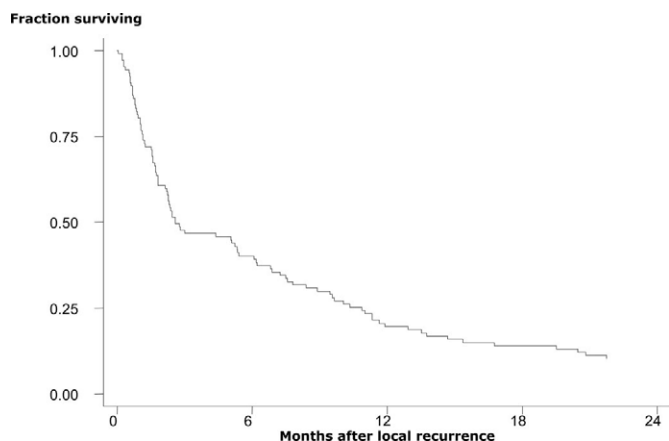


FIG. 4. Crude survival after local recurrence following cystectomy for bladder cancer in Greater Amsterdam, 1988 to 1997.

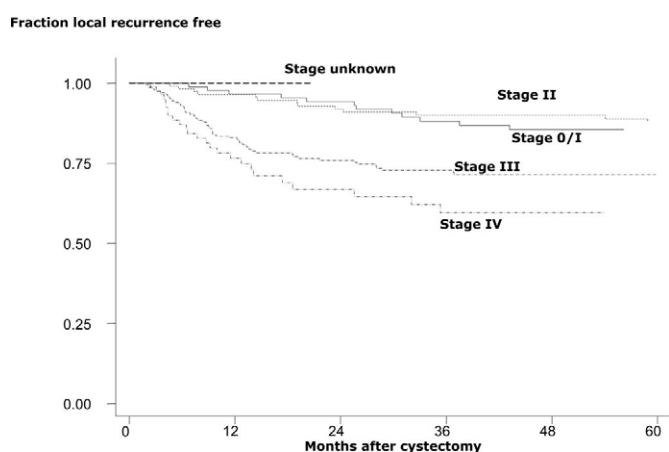


FIG. 5. Local recurrence-free survival according to pathological stage after cystectomy for bladder cancer in Greater Amsterdam, 1988 to 1997. Stage III vs 0-II log rank test  $p < 0.0001$ . Stage IV vs 0-II log rank test  $p < 0.0001$ . Stage III vs IV log rank test  $p = 0.07$ .

Although the lower survival in our study may have been influenced by differences in staging procedures between the United States and The Netherlands, differences in treatment practices may also have influenced the results. Of all patients who initially presented with clinical stages II-III bladder cancer only 30% underwent cystectomy. Of the patients younger than 75 years, who were probably appropriate candidates, only 44% underwent cystectomy. These percents are remarkably low in view of the consensus in The Netherlands that cystectomy is the preferred treatment for stages II-III bladder cancer. In our study survival in patients with stages II-III bladder cancer who underwent cystectomy was much higher than that in all patients combined but comparison between these patient groups is biased by factors such as age, comorbidity and physician preference.

The rate of local recurrence in patients undergoing cystectomy has been reported to be 7% to 25%.<sup>4-7</sup> Sengelov et al reported that intensified examination resulted in more sites of metastases<sup>13</sup> and local recurrence rates are probably under reported because the finding of distant metastases decreases the need for intensified local followup when local recurrences are asymptomatic. After cystectomy tumor recurred locally in 1 of 5 patients in our study, and so our results are not among the most favorable when compared with those in other studies. This might be related to the fact that many other studies were performed at oncological centers, while our study comprised a large number of community hospitals, in addition to 3 oncological centers. No statistically significant difference in SLRRs among the various hospitals and no relationship between the number of cystectomies per hospital and the SLRR could be demonstrated. The LRR at the oncological centers combined was lower but the difference was not statistically significant. However, the annual number of cystectomies per hospital was rather low at all hospitals. At oncological centers this was due to the exclusion of referred patients from outside of the CCCA region. In recent years a tendency toward the centralization of cystectomy 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.<sup>14,15</sup> In contrast to what we expected, no significant difference was found between LRRs after R0 dissection (no residual tumor after cystectomy) and R1 dissection (microscopic residual tumor). This might be explained by the higher death rates shortly after resection in patients with residual microscopic disease. These patients might not have lived long enough to have clinically detectable local recurrences. In other series margin status was a predictor for local recurrence, although no distinction between microscopic or macroscopic residual tumor was made.<sup>16</sup> Furthermore, perioperative chemotherapy might be of influence. However, during our study period perioperative 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 have local recurrence usually do so within the first 2 years after treatment, which is consistent with our findings.<sup>7,14,17,18</sup>

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 tumor outside of the pelvis is considered distant metastasis. However, some groups define a combination of local and distant recurrence as distant recurrence only since patient outcome appears to be dictated by concomitant systemic metastases.<sup>17,19</sup> Urethral or upper tract recurrences are sometimes also considered local recurrence. However, they represent a different biological process of recurrence, and treatment and prognosis differ greatly from those of true pelvic recurrences.<sup>20</sup>

The aggressive natural behavior of local recurrences after cystectomy results in poor prognosis in many series<sup>14,18</sup> and our data confirm this experience. No data were available on

TABLE 5. Relative survival after cystectomy in patients with bladder cancer in Greater Amsterdam, 1988 to 1997

TNM Stage*	No. Pts	% Yrs After Diagnosis (95% CI)		
		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)
Overall†	577	76 (72-79)	55 (50-60)	44 (37-50)

\* According to TNM classification, fifth edition,<sup>8</sup> but T4 classified as stage IV.

† Including 6 patients with unknown stage.

therapy following local recurrences but the final outcome in patients with 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.<sup>17,18</sup>

# CONCLUSIONS

The 5-year RSR in all patients combined was 75%, which is slightly better than European values, but stage specific rates are worse than American rates. Of all patients with stages II-III bladder cancer only 30% underwent cystectomy. Patients with cystectomy experienced relatively high stage specific survival. After cystectomy local recurrence occurred in 1 of 5 patients and prognosis in these patients is poor. We found no difference in the LRR among the various hospitals.

A. B. Kraus and J. H. M. M. H. Kramer assisted with data collection and evaluation.

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