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Catharina A. Goossens Laan, Otto Visser, Michel W.J.M. Wouters,
Jan-Willem W. Coebergh, Cornelis J.H. van de Velde, Maarten. C.C.M.
Hulshof, Paul J.M. Kil

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Authors: Catharina A. Goossens Laan, MD Otto Visser, MD, PhD Michel W.J.M. Wouters, MD Jan-Willem W. Coebergh, MD PhD Cornelis J.H. van de Velde, MD PhD Maarten. C.C.M. Hulshof, MD, PhD Paul J.M. Kil, MD PhD

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Variation in treatment policies and outcome for bladder cancer in the Netherlands

Catharina A. Goossens – Laan MD¹, Otto Visser MD, PhD², Michel W.J.M. Wouters MD³, Jan-Willem W. Coebergh, MD PhD⁴, Cornelis J.H. van de Velde, MD PhD⁵, Maarten. C.C.M. Hulshof, MD, PhD⁶, Paul J.M. Kil, MD PhD⁷

On behalf of the 'Quality of cancer care' task force of the Signalling Committee Cancer of the Dutch Cancer Society (the committees full report is available on www.kwfkankerbestrijding.nl)".

¹St. Elisabeth Hospital, department of Urology, Tilburg, The Netherlands, affiliated with Utrecht University Medical Center, department of Urology; ²Comprehensive Cancer Centre Amsterdam, Amsterdam, The Netherlands; ³Department of Surgical Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; ⁴Comprehensive Cancer Centre South, Eindhoven, The Netherlands ⁵Leiden University Medical Center, Surgery, Leiden, The Netherlands; ⁶Department of Radiotherapy, Academic Medical Center Amsterdam, Amsterdam; ⁷ St. Elisabeth Hospital, department of Urology, Tilburg, The Netherlands.

Corresponding author: C.A. Goossens - Laan,

Department of Urology, University Medical Centre Utrecht; HP:C04.236

PO Box 85500, 3508 GA Utrecht, Tel: +31-88-755 80 79 Fax:+31-30- 254 05 32

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Abstract

Aim: To describe the population-based variation in treatment policies and outcome for bladder cancer in the Netherlands.

Methods: All newly diagnosed patients with primary bladder cancers during 2001 – 2006 were selected from the Netherlands Cancer Registry (n=29,206). Type of primary treatment was analysed according to Comprehensive Cancer Centre region, hospital type (academic, non-academic teaching or other hospitals) and volume (≤ 5 , 6-10 or >10 cystectomies yearly). For stage II-III patients undergoing cystectomy we analyzed the proportion of lymph node dissections and 30-days mortality.

Results: 44% of patients with stage II-III bladder cancer underwent cystectomy, while 26% were not treated with curative intent. Cystectomy was the preferred option in three of nine regions, radiotherapy in two, and two regions waived curative treatment more often. Between 2001 and 2006 the number of cystectomies increased with 20% (n=108). Twenty-one percent (n=663) of these procedures were performed in 44 low volume hospitals. In 79% of the cystectomies lymph node dissections were performed, more often in high and medium-volume centers (82% and 81% respectively) than in low-volume hospitals (71%, the odds ratio being 1.5). The overall 30-days postoperative mortality rate was 3.4% and increased with older age. It was significantly lower in high-volume centers (1.2%). **Conclusion:** Treatment

policies for muscle-invasive bladder cancer in the Netherlands showed regional preferences and a gradual increase of cystectomy. Cystectomy albeit considered as golden standard, was performed in a minority of the muscle-invasive cases. In high-volume institutions, lymph node dissection rates were higher and post-operative mortality rates were lower.

Keywords: Bladder cancer, mortality rate, treatment, volume surgery, population-based.

Introduction

In the Netherlands, bladder cancer is the fifth common tumor in men, and the seventh in women.(1) While the incidence of non-invasive bladder cancer in the Netherlands has been increasing, it is decreasing for invasive bladder cancer. In recent years, the mortality rates from bladder cancer decreased among males, contrasting females.(2;3)

A patient with newly diagnosed non muscle-invasive disease may be cured with local treatment only; i.e. one or multiple transurethral resections of the tumor(s)(TUR-BT) with or without subsequent bladder instillations. Cystectomy is the preferred therapy, for patients with muscle-invasive bladder cancer (MIBC) and for patients who underwent unsuccessful local treatment of non muscle-invasive bladder cancer. When a patient is not eligible for a cystectomy due to co-morbidity, or old age or patient preference, radiotherapy is the second best option.(4)

Increasing evidence for a positive association between quality of care in cancer treatment in relation to volume and infrastructure (5-7) led us to explore variations in staging and treatment policies and its outcome for bladder cancer in the Netherlands.

Patients and Methods

Cancer registry data.

All patients with primary bladder tumours newly diagnosed in the Netherlands between January 1, 2001 and December 31, 2006 were selected from the population-based Netherlands Cancer Registry, with complete national coverage. Dutch hospitals are served in the nine regions by the largely coordinating and facilitating Comprehensive Cancer Centers (CCC). In the hospitals, registration clerks of the CCCs extract information for the registry from the medical records, notified by the Dutch National Pathology database (PALGA). A variety of data are collected, i.e. on demographics, morphology, stage at diagnosis and primary treatment (planned in the six months following diagnosis) and vital status, date of follow-up or death. Tumor site and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O).⁽⁵⁾ Quality of data is generally considered to be high and completeness was estimated to be more than 95%.^(6;7)

Hospitals and regions.

Patients of all (N=97) hospitals in the Netherlands were included in this study. Hospitals were grouped into three categories, i.e. 1) 9 academic hospitals 2) non-academic hospitals with teaching facilities for urology residents 3) other hospitals (community hospitals). The influence of a radiotherapy department on the

choice of treatment was also investigated. Type of primary treatment was analysed according to geographic region (subdivided according to age and stage), hospital type and annual volume (≤ 5 , $>5-10$ or >10 cystectomies yearly). Variations in treatment policies, according to age and stage were assessed in the nine regions.

Data analysis.

Data analysis was done with anonymised data. Stage grouping in this study was done according to the UICC TNM classification, 6th edition.(8) cTNM was used for the diagnosis and general treatment policies including all patients and pTNM for subset analysis of cystectomy cases. Excluded from analysis were bladder tumors without histology proven diagnosis, sarcomas, lymphomas, bladder cancer only found postmortem, incomplete registrations, and tumour recurrence (except when stage 0 progressed into stage I or higher). Local treatment is defined as one or multiple transurethral resections of the tumor often followed by bladder installations. Only the initial treatment (within six months after diagnosis) for every new tumour was registered, thereby disregarding cystectomy for an initial non muscle-invasive tumour that progressed to muscle-invasive disease more than six months after the first diagnosis or a salvage cystectomy after radiotherapy. When the initial treatment took more than six months to complete, for example in case neo-adjuvant chemotherapy preceded the cystectomy, the whole treatment was registered.

Primary treatment was grouped according to local resection or no treatment (local treatment), cystectomy, radiotherapy or chemotherapy. A patient who underwent cystectomy and radiotherapy or chemotherapy was classified as cystectomy. A patient receiving radiotherapy as well as chemotherapy was classified as radiotherapy. Curative and palliative cystectomy or radiotherapy could not be distinguished.

A subset of patients was analyzed for the proportion of lymph node dissections according to surgical volume and the 30 and 60 day-mortality rate after cystectomy. For this category the years of analysis were restricted from 2004 until 2006 as the date of cystectomy was not available for all cases in earlier years.

Statistical methods.

Logistic regression analysis was performed to examine the influence of age at diagnosis (< 60, 60-74, ≥75 years), gender, stage, type of hospital, hospital volume, CCC-region on the odds of receiving surgery (cystectomy), radiotherapy, and on either surgery or radiotherapy. All analyses, including the logistic regression analyses, were performed in STATA, version 10. Results were considered statistically significant for $p < 0.05$.

Results

During 2001-2006, 29,206 patients (78% male) were diagnosed with primary bladder cancer. Six percent of all new patients were diagnosed in academic hospitals, 23% in non-academic hospitals with a teaching facility for urology and 71% in the other hospitals. Patient, hospital, regional and treatment characteristics are presented in Table 1.

Treatment of superficial or non muscle-invasive bladder cancer

At first diagnosis, 71% of the patients had non muscle-invasive primary bladder cancer, 73% in males and 64% in females. Seventy percent of the non muscle-invasive cancers were non-invasive papillary carcinomas (Ta or stage 0a), while 30% were cancers invading the subepithelial connective tissue only (T1 or stage I). Flat tumours (carcinoma in situ or stage Tis) represented five percent of the non-muscle invasive cancers. Initial treatment of bladder cancer in the Netherlands according to stage is shown in figure 1. The vast majority of patients with non muscle-invasive cancers received TUR-BT (with or without instillations) (Tis 94%, Ta grade 1-2 99%, Ta grade 3 97%, Ta grade unknown 96%; T1 grade 1-2 96%, T1 grade 3 90%, T1 grade unknown 91%). Cystectomy was performed in 1.5% of the patients in stage Tis, <0.5% in stage Ta and 2% in low and medium grade T1-tumours. The treatment remained unknown in 4% of patients (Tis 4%, Ta grade 1-2 1%, Ta grade 3 1%, Ta

grade unknown 4%; T1 grade 1-2 1%, T1 grade 3 1%, T1 grade unknown 3%). High grade T1-tumors were diagnosed in 3,043 patients (53% of all T1 tumors). Seven percent of T1G3 tumors underwent a cystectomy, and 2% received radiotherapy. A multivariate regression analysis revealed cystectomy to be performed significantly less in older patients (≥ 75 years; OR 0.2, $p = 0.000$) and more frequent in region 7 (OR 1.82, $p < 0.0035$) in stage T1G3.

Treatment of muscle-invasive bladder cancer

Almost 8,000 patients with MIBC were diagnosed in 2001-2006 (on average 1,300 annually). A cystectomy was performed in 36% of all muscle-invasive cases. In stage II 43% underwent a cystectomy, 31% received radiotherapy, <1% chemotherapy and 26% of the patients received only local treatment or no treatment. 44% of stage III patients underwent a cystectomy, 31% received radiotherapy, 1% chemotherapy, and 25% received only local treatment or no treatment. 17% of newly diagnosed patients with stage IV underwent cystectomy, while 19% received radiotherapy and 16% with chemotherapy. 48% of the stage IV patients received no therapy or only local treatment.

An increasing proportion of stage II patients underwent cystectomy, from 39% in 2001 to 47% in 2006, but remaining more or less constant in stage III (39% cystectomies in 2001 and 38% in 2006). Utilization of radiotherapy decreased from 34% to 27% in stage II and from 36% to 30% in stage III.

Figure 2 shows that the proportion of patients undergoing cystectomy for muscle-invasive cancer strongly decreased with age. In a multivariate analysis the OR of patients of 60-74 years versus <60 years was 0.49 ($p = 0.000$) and the OR of ≥ 75 years versus <60 was 0.06 ($p = 0.000$). Radiotherapy was more often administered in older patients (60-74 yr OR 2.0, $p = 0.000$; ≥ 75 yr OR 5.2, $p = 0.000$). The chance of having one of both treatments declines with increasing age (60-74 yr OR 0.65, $p < 0.002$; ≥ 75 yr OR 0.18, $p = 0.000$).

Patients were more likely to undergo a curative treatment in stage III than for stage II (OR 1.6, $p = 0.000$). More cystectomies were performed in comparison to radiotherapy (stage III: OR cystectomy 1.5, $p = 0.000$ vs. radiotherapy 0.99, $p < 0.9$) (Figure 3). Women more often underwent cystectomy (OR cystectomy 1.2, $p < 0.016$; OR radiotherapy 0.75 ($p = 0.000$)), contrasting radiotherapy for men.

The likelihood for receiving a specific kind of treatment is not dependent on the type of hospital where the initial diagnosis was made. The availability of a radiation department in the hospital of diagnosis did not affect the likelihood for receiving radiotherapy. However, there are strong regional preferences for specific treatments as shown for patients with stage II disease (figure 3). Among patients below 75 years of age 60 to 77% underwent cystectomy in the various regions, and 10 to 28% underwent radiotherapy. The chance of undergoing a cystectomy in stage II-III disease was higher in region 2, 3 and 6 in comparison to region 1 (OR 1.4, $p < 0.005$; OR 1.9, $p = 0.000$ and OR 1.3, $p < 0.024$). The chance of undergoing radiotherapy in

stage II-III disease was lower in region 2, 3, 6, and 8 in comparison to region 1 (OR 0.8, $p < 0.016$; OR 0.6, $p = 0.000$, OR 0.8, $p < 0.031$ and OR 0.7, $p < 0.035$, respectively). The differences in radiotherapy mainly followed differences in the application of interstitial radiotherapy (brachytherapy): the regions with a high percentage of radiotherapy were the same as those performing brachytherapy more often (region 1 and 7). In two regions (region 4 and 9) a curative treatment was performed clearly less often (OR 0.7, $p < 0.009$; OR 0.6, $p = 0.000$) than in other regions.

Cystectomy

Between 2001 and 2006 the total annual number of cystectomies increased 23% (from 472 to 585). Eleven percent of the cystectomies were performed in clinically non-muscle invasive disease, 77% were in clinical stage II or III (T2-T4a). Twelve percent were clinical stage IV. The proportion of clinically potentially understaged patients ranged from 44% in clinical stage I, 48% in stage II and 22% in stage III (table 2). The proportion of clinically overstaged patients ranged from 12% in clinical stage III and 21% in clinical stage IV (Table 2).

Sixty percent of the operations were performed in community hospitals. The contribution of specialized centers was slightly increasing from 13% in 2001 to 18% in 2006. In 44 hospitals five or less cystectomies were done annually, accounting for 21% of all patients, 36 hospitals an average of 6-10 operations, together comprising

46% of all cystectomies in 2006. More than ten cystectomies annually were performed in another 13 hospitals (Figure 4). The proportion of patients being operated in these high-volume hospitals increased from 32% in 2001 to 36% in 2006. Lymph node dissections were performed in 79% of all cystectomies (Table 3), more often in specialized centers in comparison to the community hospitals (OR 2.7; $p \leq 0.000$), and significantly more often in median and high-volume hospitals (81% and 82%) in comparison to low-volume hospitals (71%) (OR 1.47 (6-10/year) and OR 1.52 (≥ 10 /year) vs. low-volume hospitals; $p=0.027$, and $p=0.043$).

The overall 30-days mortality rate after cystectomy in 2004-2006 was 3.4%. (Table 3) This rate rose with increasing age of the patient from 1.1% below the age of 60, 3.1% for 60-74 years and 7.4% for patients 75 years or older. In the high-volume centers the mortality rate was significantly lower (1.2%; OR 0.2 vs. low-volume hospitals; $p=0.002$). Mortality rates after 60 and 90 days were higher (all hospitals combined 5.7% and 7.7% and high volume 3.1% and 4.9%), but the relative difference in mortality rate between the high, medium and low volume hospitals remained unchanged.

Discussion.

This paper summarizes the major variations in treatment policies in the period 2001-2006 for different regions and hospital types in the Netherlands. Remarkable regional differences in the choice of primary treatments were found. Availability of interstitial

radiotherapy (brachytherapy) explained much of the variation in frequency of radiotherapy use in both stage II and III disease, with subsequent lower cystectomy rates in these regions (Figure 3). Nevertheless, in two regions curative treatment options (radiotherapy or cystectomy) were clearly used less often than in other regions, suggesting disparities in the chance of receiving optimal treatment for patients with bladder cancer.

No difference in choice of treatment was found in the three different types of hospitals (academic hospital, training hospital or community hospital). Lymph node dissection and mortality rates in cystectomy procedures differed with hospital volumes. Patients in high volume centers exhibited lower mortality rates than in low volume centers.

American and European guidelines indicate that a patient with a pT1G3 tumor should initially receive BCG intravesical therapy, although cystectomy can be considered (4;9;10). The majority (90%) of patients with the high grade T1-tumours in our study received initially local therapy only (TURBT with BCG-instillations). We may conclude that this is in accordance with the current guidelines.

Radical cystectomy is considered the 'golden standard' for stage II and III (muscle-invasive) bladder cancer, being reinforced by recent updates of European and Dutch guidelines.(4;11) In view of these guidelines the low number of cystectomies for MIBC cancer patients (36%) was remarkable. Even in MIBC patients below 75 years

the number of cystectomies was low (stage II 65%; stage III 68%), but seems to increase over time.

However, our data are similar to a recent Swedish population-based study. The curative intent for patients with clinical stage T2_T4 bladder cancer was 41% (by means of radiotherapy (8%) or cystectomy (33%)). For patients younger than 75 years, the curative intent of total treatment arm was 62%.(12) In comparison to the Sweden, the Dutch percentage of cystectomy was slightly higher, moreover increasing with 8% over this study period.

Our study shows that high procedure volume for cystectomy was statistically significantly associated with lower postoperative mortality, especially related to that in hospitals with a procedural annual volume of ≤ 5 cystectomies, where a 30-day mortality of 6.4% was found. In the Netherlands there are 44 of these low volume hospitals and together they perform 111 cystectomies a year (21% of all patients). A third of patients (36%) underwent cystectomy in high volume hospitals, which have a significantly lower mortality (1.2%), while most patients (46%) are operated in medium volume hospitals with annually 6-10 cystectomies and a mortality rate of 3.6%.

Mounting evidence suggests that high procedure volume of complex operations is related with lower operative mortality after high-risk cancer surgeries (cystectomy, esophagectomy, pancreatectomy, etc).(13;14), but the difference might partly be affected by selective referral of relatively healthy patients of higher SES. Only one

Dutch study compared post-operative mortality of patients undergoing cystectomy for low-volume hospitals with an oncologic center.(15) The postoperative mortality was unsignificantly lower in the oncologic center (1.8% versus 3.5%). The present national population-based study is more suggestive because of its power.

Nevertheless, our study has several limitations. Though data on age and gender were available, our study lacks information on co-morbidities and performance status of patients. Though several studies have shown that radical cystectomy is a safe option in elderly fit patients, a poor performance status of patients might jeopardize surgical treatment and lead to a choice for radiotherapy or palliative treatment only.(16-19). A study in two CCC-regions showed co-morbid conditions in elderly patients to affect the choice of treatment (submitted). There could also be the patient preference to choose for a bladder sparing approach, although there is no such differential information available within the Netherlands. Then, only the cystectomies six months after first diagnoses were taken into account, so the real cystectomy volume per hospital may be larger. Up to 30% of patients with superficial tumors involves in $\geq$ T1-tumors,(11) of which an unknown percentage will undergo cystectomy. Though a re-biopsy is planned within 6 weeks after local resection for T1 tumors, and will be take place within the six months interval after first diagnosis.

In most industrialized countries, medical disciplines, insurance companies and policy makers discuss potential improvements of patient safety and quality of health care.(23) In the literature more and more studies advocate specific volume standards for high risk cancer operations, such as ≥ 11 cystectomies a year. (14;20;21) In the United States the Leapfrog group, a large coalition of insurance companies encourages patients to have their operation in a high volume referral center since 2000, but there have been no reports about actual overall improvement in outcome from these volume-based referral initiatives. Apparently, focusing on volume only, which is only a proxy for quality of care, is not enough for improving care-processes and outcome.

Moreover, complex surgical procedures like radical cystectomy have more dimensions than mortality and depend on more than hospital volume alone. Other factors include surgeon's competence, the hospitals infrastructure e.g. quality of critical care units and broad consultant expertise, the implementation of standard pathways and protocols.(22) Most important, the surgical team should be capable to handle all postoperative complications. In addition to post-operative mortality rates, patient outcome can also be measured using complication and recurrence rates, number of resected lymph nodes, surgical margins, survival rate and last but not least by the impact on quality of life.(23) To provide optimal quality of care for patients with muscle-invasive bladder cancer, quality of care indicators could be used for measuring and monitoring one's own performance.(24) The facilitating cancer

registries of the Comprehensive Cancer Centers could greatly assist by independently collecting extra clinical data at regional or national scale and provide feedback to attending physicians and possible specific audits undertaken by them.

This paper summarizes the population-based variation in treatment policies for bladder cancer in the Netherlands in the period 2001-2006. Exploring population based cancer registries for differences in patterns of care can give insight in opportunities for improvement and could lead to a change in treatment strategies.

Conflict of interest statement:

C.J.H. van de Velde, president of the ESSO and M.W.J.M. Wouters are both guest-editors of this special issue of the EJSO. O. Visser and J.W. Coebergh both work at a Comprehensive Cancer Center.

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404 Table 1 Characteristics of bladder cancer in the Netherlands, 2001-2006

	Number of cases	%
all cases	29,206	
<u>Year of diagnosis</u>		
2001	4,473	15.3%
2002	4,591	15.7%
2003	4,740	16.2%
2004	4,992	17.1%
2005	5,154	17.6%
2006	5,256	18.0%
<u>Sex</u>		
Males	22,727	77.8%
Females	6,479	22.2%
<u>Age category</u>		
< 60	5,745	19.7%
60-74	12,780	43.8%
75 or older	10,681	36.6%
<u>Clinical TNM-stage</u>		
Tis	973	3.3%
Ta	13,582	46.5%
I	6,267	21.5%
II	4,505	15.4%
III	1,126	3.9%
IV	2,349	8.0%
Unknown	404	1.4%
<u>Morphological classification</u>		
squamous cell carcinoma	343	1.2%
transitional cell carcinoma	28,369	97.1%
adenocarcinoma	195	0.7%
undifferentiated carcinoma	107	0.4%
neuro-endocrine carcinoma	192	0.7%
<u>Hospital of first diagnosis</u>		
university hospital/oncological centre	1,779	6.1%
non-academic teaching hospitals	6,679	22.9%
other hospitals (community)	20,745	71.0%
<u>Radiotherapy facilities in the hospital</u>		
No	23,629	80.9%
Yes	5,577	19.1%
<u>Comprehensive cancer centre</u>		
1	4,020	13.8%
2	2,351	8.0%
3	2,188	7.5%
4	5,292	18.1%
5	2,764	9.5%
6	4,436	15.2%
7	4,169	14.3%
8	1,827	6.3%
9	2,156	7.4%

406 Table 2

407 Pathological stage after cystectomy according to clinical stage of patients with
408 bladder cancer in the Netherlands 2001-2006.

Clinical stage	Pathological stage														Total
	Tis		Ta		I		II		III		IV		unknown		
	n	%	n	%	N	%	n	%	n	%	n	%	n	%	
Tis	13	87%	-	-	2	13%	-	-	-	-	-	-	-	-	15
Ta	1	2%	35	85%	1	2%	2	5%	0	0%	1	2%	1	2%	41
I					173	56%	61	20%	49	16%	27	9%	-	-	310
II					48	2%	958	49%	643	33%	299	15%	-	-	1,948
III					5	1%	57	11%	340	66%	112	22%	-	-	514
IV					2	1%	23	6%	52	14%	291	79%	-	-	368
unknown					-	-	-	-	-	-	-	-	3	100%	3

409 Table 3

410 Relation of average annual volume of cystectomy with lymph node dissection and 30
 411 day-mortality rate in newly diagnosed patients with bladder cancer in the
 412 Netherlands, 2004-2006.

Average volume	Proportion of lymph node dissections	30 day (60 day) mortality rate
<= 5 per year	71%	6.4% (8.6%)
> 5-10 per year	81%	3.6% (6.4%)
> 10 per year	82%	1.2% (3.1%)
Total	79%	3.4% (5.7%)

413

414 Figure 1

415 Treatment of newly diagnosed patients with bladder cancer according to clinical
416 stage, the Netherlands 2001-2006.

419 Figure 2

420 Proportion of clinical stage II-III bladder cancer patients treated with cystectomy or
 421 radiotherapy according to age category, the Netherlands 2001-2006

422

423

424 Interstitial radiotherapy may also be preceded by a short external radiotherapy session.

Figure 3

Regional variation in treatment of clinical stage II bladder cancer patients according to age and comprehensive cancer centre region, the Netherlands 2001-2006.

435 Figure 4

436 Number of patients who underwent cystectomy according to average annual number
437 of cystectomies per hospital, the Netherlands 2001-2006.