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► **To cite this version:**

Catharina A. Goossens Laan, Otto Visser, Michel W.J.M. Wouters, Jan-Willem W. Coebergh, Cornelis J.H. van de Velde, et al. Variation in treatment policies and outcome for bladder cancer in the Netherlands. *EJSO - European Journal of Surgical Oncology*, 2010, 36, 10.1016/j.ejso.2010.06.003 . hal-00612398

HAL Id: hal-00612398

<https://hal.science/hal-00612398>

Submitted on 29 Jul 2011

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Accepted Manuscript

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

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PII: S0748-7983(10)00158-7

DOI: [10.1016/j.ejso.2010.06.003](https://doi.org/10.1016/j.ejso.2010.06.003)

Reference: YEJSO 2991

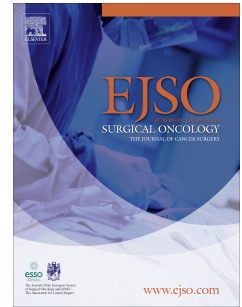
To appear in: *European Journal of Surgical Oncology*

Received Date: 19 April 2010

Accepted Date: 1 June 2010

Please cite this article as: Goossens Laan CA, Visser O, Wouters MWJM, Coebergh JWW, van de Velde CJH, Hulshof CCM, Kil PJ,. Variation in treatment policies and outcome for bladder cancer in the Netherlands, *European Journal of Surgical Oncology* (2010), doi: 10.1016/j.ejso.2010.06.003

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

2

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

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20 Word count: Abstract 248; Total 3188

21

22 **Abstract**

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

25 Methods: All newly diagnosed patients with primary bladder cancers during 2001 –
26 2006 were selected from the Netherlands Cancer Registry (n=29,206). Type of
27 primary treatment was analysed according to Comprehensive Cancer Centre region,
28 hospital type (academic, non-academic teaching or other hospitals) and volume (≤ 5 ,
29 6-10 or >10 cystectomies yearly). For stage II-III patients undergoing cystectomy we
30 analyzed the proportion of lymph node dissections and 30-days mortality.

31 Results: 44% of patients with stage II-III bladder cancer underwent cystectomy, while
32 26% were not treated with curative intent. Cystectomy was the preferred option in
33 three of nine regions, radiotherapy in two, and two regions waived curative treatment
34 more often. Between 2001 and 2006 the number of cystectomies increased with 20%
35 (n=108). Twenty-one percent (n=663) of these procedures were performed in 44 low
36 volume hospitals. In 79% of the cystectomies lymph node dissections were
37 performed, more often in high and medium-volume centers (82% and 81%
38 respectively) than in low-volume hospitals (71%, the odds ratio being 1.5). The
39 overall 30-days postoperative mortality rate was 3.4% and increased with older age.
40 It was significantly lower in high-volume centers (1.2%). Conclusion: Treatment

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

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

48 Introduction

49

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

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

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

65 **Patients and Methods**

66

67 *Cancer registry data.*

68 All patients with primary bladder tumours newly diagnosed in the Netherlands
69 between January 1, 2001 and December 31, 2006 were selected from the
70 population-based Netherlands Cancer Registry, with complete national coverage.

71 Dutch hospitals are served in the nine regions by the largely coordinating and
72 facilitating Comprehensive Cancer Centers (CCC). In the hospitals, registration clerks
73 of the CCCs extract information for the registry from the medical records, notified by
74 the Dutch National Pathology database (PALGA). A variety of data are collected, i.e.
75 on demographics, morphology, stage at diagnosis and primary treatment (planned in
76 the six months following diagnosis) and vital status, date of follow-up or death. Tumor
77 site and morphology were coded according to the International Classification of
78 Diseases for Oncology (ICD-O).(5) Quality of data is generally considered to be high
79 and completeness was estimated to be more than 95%.(6;7)

80

81 *Hospitals and regions.*

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

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

90

91 *Data analysis.*

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

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

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

116

117 *Statistical methods.*

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

124 Results

125

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

131

132 *Treatment of superficial or non muscle-invasive bladder cancer*

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

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

151

152 *Treatment of muscle-invasive bladder cancer*

153 Almost 8,000 patients with MIBC were diagnosed in 2001-2006 (on average 1,300
154 annually). A cystectomy was performed in 36% of all muscle-invasive cases. In stage
155 II 43% underwent a cystectomy, 31% received radiotherapy, <1% chemotherapy and
156 26% of the patients received only local treatment or no treatment. 44% of stage III
157 patients underwent a cystectomy, 31% received radiotherapy, 1% chemotherapy,
158 and 25% received only local treatment or no treatment. 17% of newly diagnosed
159 patients with stage IV underwent cystectomy, while 19% received radiotherapy and
160 16% with chemotherapy. 48% of the stage IV patients received no therapy or only
161 local treatment.

162 An increasing proportion of stage II patients underwent cystectomy, from 39% in
163 2001 to 47% in 2006, but remaining more or less constant in stage III (39%
164 cystectomies in 2001 and 38% in 2006). Utilization of radiotherapy decreased from
165 34% to 27% in stage II and from 36% to 30% in stage III.

166 Figure 2 shows that the proportion of patients undergoing cystectomy for muscle-
167 invasive cancer strongly decreased with age. In a multivariate analysis the OR of
168 patients of 60-74 years versus <60 years was 0.49 ($p= 0.000$) and the OR of ≥ 75
169 years versus <60 was 0.06 ($p= 0.000$). Radiotherapy was more often administered in
170 older patients (60-74 yr OR 2.0, $p= 0.000$; ≥ 75 yr OR 5.2, $p= 0.000$). The chance of
171 having one of both treatments declines with increasing age (60-74 yr OR 0.65, $p <$
172 0.002 ; ≥ 75 yr OR 0.18, $p= 0.000$).

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

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

187 stage II-III disease was lower in region 2, 3, 6, and 8 in comparison to region 1 (OR
188 0.8, $p < 0.016$; OR 0.6, $p = 0.000$, OR 0.8, $p < 0.031$ and OR 0.7, $p < 0.035$,
189 respectively). The differences in radiotherapy mainly followed differences in the
190 application of interstitial radiotherapy (brachytherapy): the regions with a high
191 percentage of radiotherapy were the same as those performing brachytherapy more
192 often (region 1 and 7). In two regions (region 4 and 9) a curative treatment was
193 performed clearly less often (OR 0.7, $p < 0.009$; OR 0.6, $p = 0.000$) than in other
194 regions.

195

196 *Cystectomy*

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

204 Sixty percent of the operations were performed in community hospitals. The
205 contribution of specialized centers was slightly increasing from 13% in 2001 to 18%
206 in 2006. In 44 hospitals five or less cystectomies were done annually, accounting for
207 21% of all patients, 36 hospitals an average of 6-10 operations, together comprising

208 46% of all cystectomies in 2006. More than ten cystectomies annually were
209 performed in another 13 hospitals (Figure 4). The proportion of patients being
210 operated in these high-volume hospitals increased from 32% in 2001 to 36% in 2006.
211 Lymph node dissections were performed in 79% of all cystectomies (Table 3), more
212 often in specialized centers in comparison to the community hospitals (OR 2.7;
213 $p \leq 0,000$), and significantly more often in median and high-volume hospitals (81% and
214 82%) in comparison to low-volume hospitals (71%) (OR 1.47 (6-10/year) and OR
215 1.52 (≥ 10 /year) vs. low-volume hospitals; $p=0,027$, and $p=0,043$).

216 The overall 30-days mortality rate after cystectomy in 2004-2006 was 3.4%. (Table 3)
217 This rate rose with increasing age of the patient from 1.1% below the age of 60, 3.1%
218 for 60-74 years and 7.4% for patients 75 years or older. In the high-volume centers
219 the mortality rate was significantly lower (1.2%; OR 0.2 vs. low-volume hospitals;
220 $p=0.002$). Mortality rates after 60 and 90 days were higher (all hospitals combined
221 5.7% and 7.7% and high volume 3.1% and 4.9%), but the relative difference in
222 mortality rate between the high, medium and low volume hospitals remained
223 unchanged.

224

225 **Discussion.**

226 This paper summarizes the major variations in treatment policies in the period 2001-
227 2006 for different regions and hospital types in the Netherlands. Remarkable regional
228 differences in the choice of primary treatments were found. Availability of interstitial

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

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

239
240 American and European guidelines indicate that a patient with a pT1G3 tumor should
241 initially receive BCG intravesical therapy, although cystectomy can be considered.
242 (4;9;10). The majority (90%) of patients with the high grade T1-tumours in our study
243 received initially local therapy only (TURBT with BCG-instillations). We may conclude
244 that this is in accordance with the current guidelines.

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

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

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

257 Our study shows that high procedure volume for cystectomy was statistically
258 significantly associated with lower postoperative mortality, especially related to that in
259 hospitals with a procedural annual volume of ≤ 5 cystectomies, where a 30-day
260 mortality of 6.4% was found. In the Netherlands there are 44 of these low volume
261 hospitals and together they perform 111 cystectomies a year (21% of all patients). A
262 third of patients (36%) underwent cystectomy in high volume hospitals, which have a
263 significantly lower mortality (1.2%), while most patients (46%) are operated in
264 medium volume hospitals with annually 6-10 cystectomies and a mortality rate of
265 3.6%.

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

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

274

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

289 In most industrialized countries, medical disciplines, insurance companies and policy
290 makers discuss potential improvements of patient safety and quality of health
291 care.(23) In the literature more and more studies advocate specific volume standards
292 for high risk cancer operations, such as ≥ 11 cystectomies a year. (14;20;21) In the
293 United States the Leapfrog group, a large coalition of insurance companies
294 encourages patients to have their operation in a high volume referral center since
295 2000, but there have been no reports about actual overall improvement in outcome
296 from these volume-based referral initiatives. Apparently, focusing on volume only,
297 which is only a proxy for quality of care, is not enough for improving care-processes
298 and outcome.

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

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

313

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

318

319 Conflict of interest statement:

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

323

324 Acknowledgements: The authors thank the registration teams of the Comprehensive
325 Cancer Centres for the collection of data for the Netherlands Cancer Registry and the
326 investigators of the Netherlands Cancer Registry involved in the analyses of quality of
327 cancer care.

328

329

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403

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.

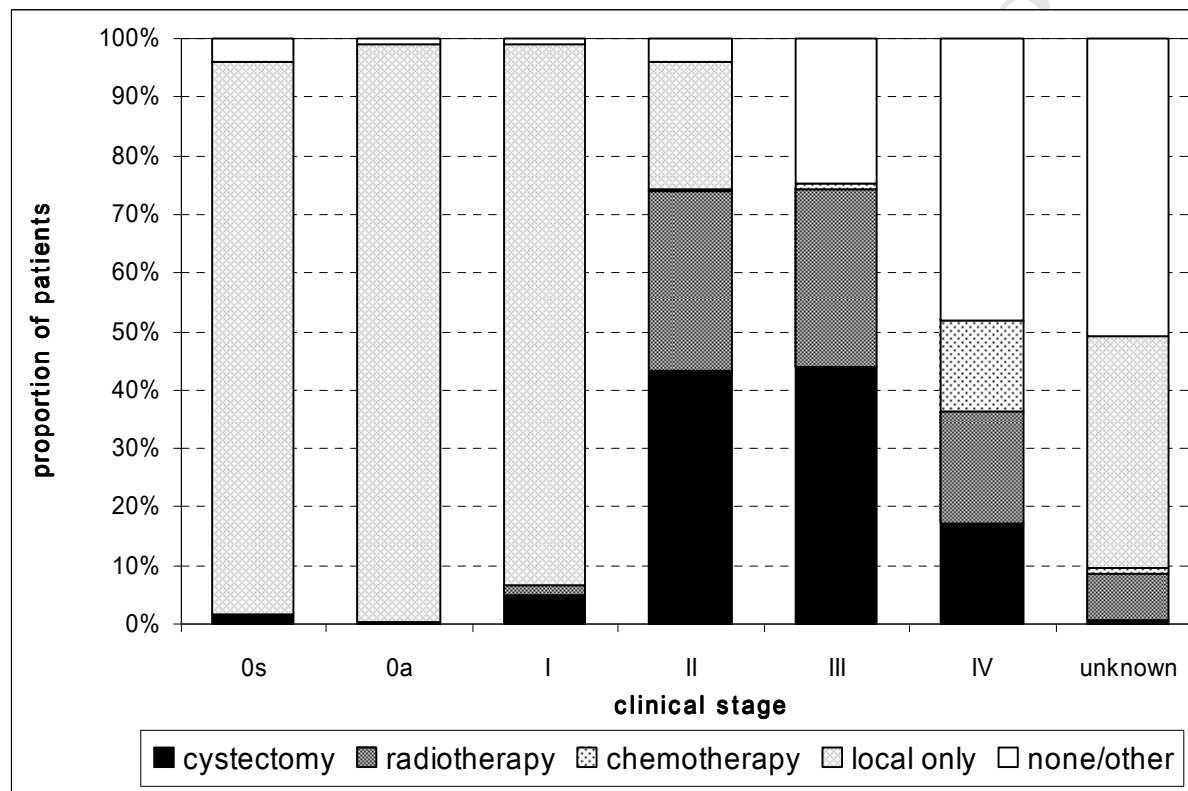
Average volume	Proportion of lymph node dissections	30 day (60 day) mortality rate
<= 5 per year	71%	6.4% (8.6%)
> 5-10 per year	81%	3.6% (6.4%)
> 10 per year	82%	1.2% (3.1%)
Total	79%	3.4% (5.7%)

413

414 Figure 1

415 Treatment of newly diagnosed patients with bladder cancer according to clinical

416 stage, the Netherlands 2001-2006.



417

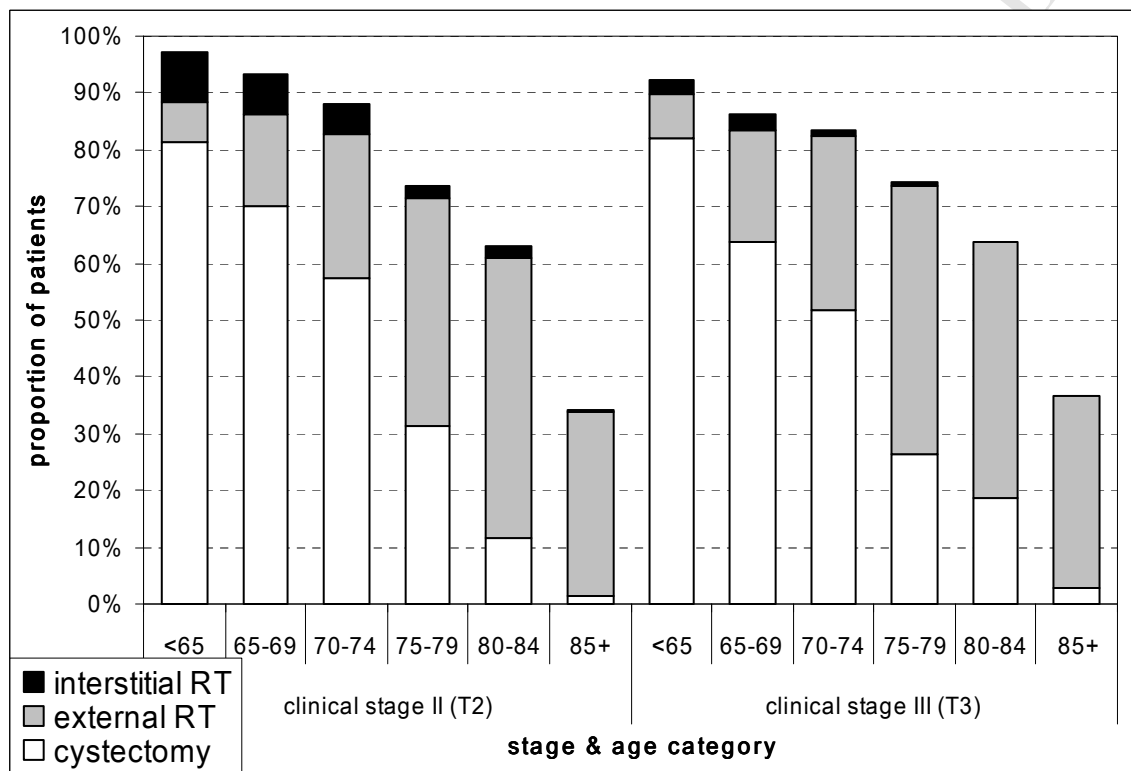
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419 Figure 2

420 Proportion of clinical stage II-III bladder cancer patients treated with cystectomy or

421 radiotherapy according to age category, the Netherlands 2001-2006

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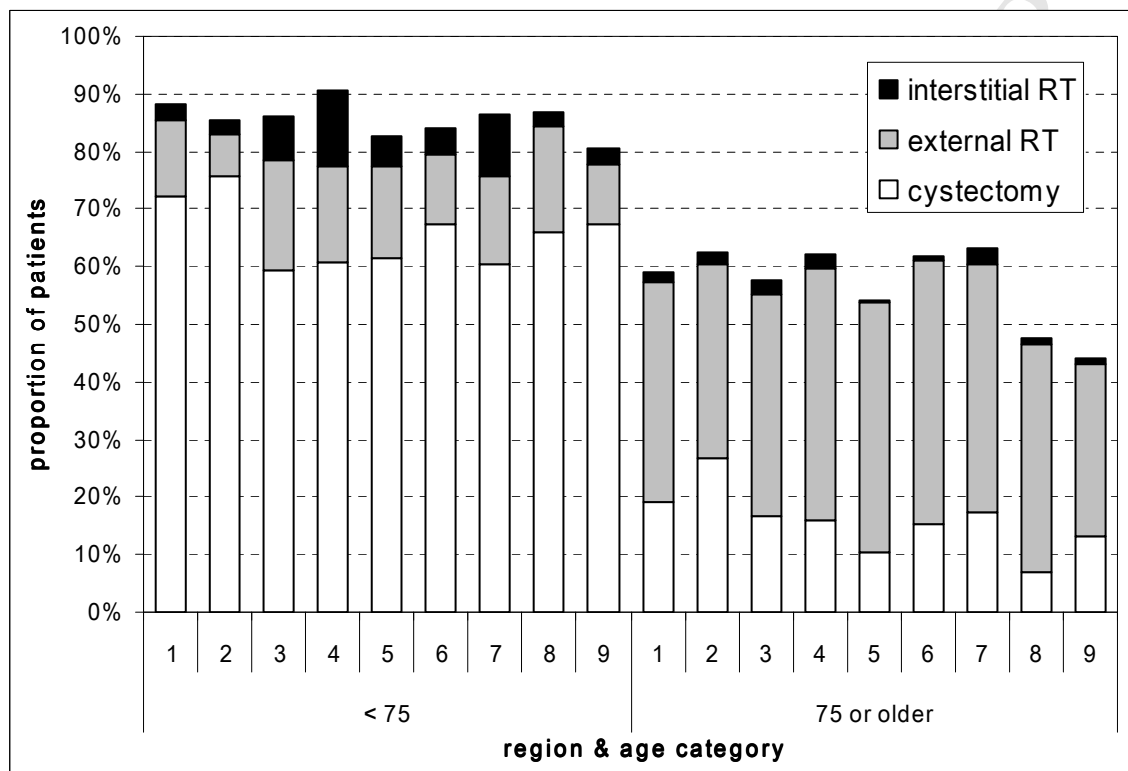
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424 Interstitial radiotherapy may also be preceded by a short external radiotherapy session.

425 Figure 3

426 Regional variation in treatment of clinical stage II bladder cancer patients according

427 to age and comprehensive cancer centre region, the Netherlands 2001-2006.



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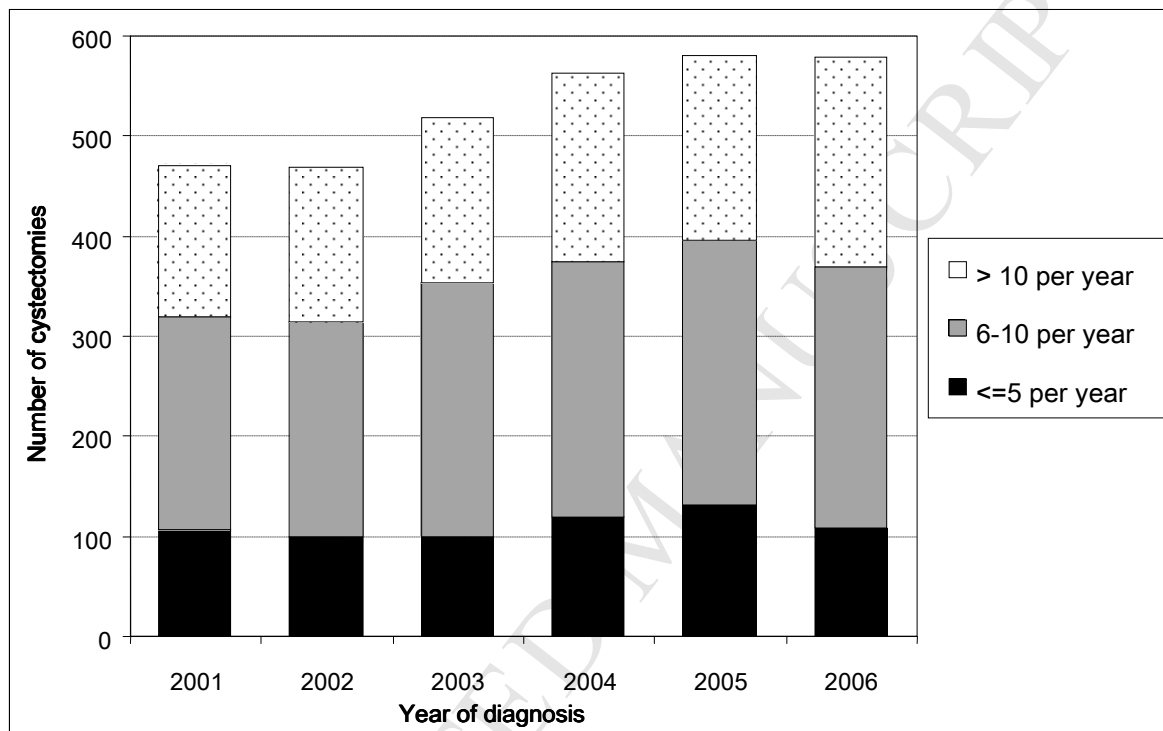
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435 Figure 4

436 Number of patients who underwent cystectomy according to average annual number

437 of cystectomies per hospital, the Netherlands 2001-2006.



438

439