Urothelial Cell Carcinoma

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chapter 4

Effects of age and comorbidity on treatment and survival of patients with muscle-invasive bladder cancer

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Abstract

This study assessed whether rising age, socioeconomic status (SES) and presence of serious comorbidity affected treatment choice and survival in a population-based series of patients with muscle-invasive bladder cancer (MIBC) in the Netherlands. Therefore a consecutive series was studied, including all patients diagnosed with MIBC between 1995-2009 in the Eindhoven cancer registry, preceding centralisation of cystectomy. The independent effects of age, SES and serious comorbidity on therapy choice and their effects on overall survival were estimated by multivariate logistic regression and multivariate Cox proportional hazard analyses, respectively.

Of the 2,445 patients, 38% were aged ≥75 years at diagnosis and 63% had at least one serious comorbid condition. Higher age and serious comorbidity were independent predictors for abstaining from cystectomy, where SES was not (61-74 versus <=60: OR:0.8; 95%CI:0.6-1.0; ≥75 versus ≤60: OR:0.1; 95%CI:0.1-0.2; one comorbid condition versus none: OR:0.7; 95%CI:0.5-0.9; two versus none: OR:0.6; 95%CI:0.5-0.8). Patients undergoing cystectomy, external beam radiotherapy (EBRT) or interstitial radiotherapy (IRT) survived longer independent of age, SES, and serious comorbidity (HR:0.4; 95%CI:0.4-0.5; HR:0.8; 95%CI:0.7-0.9; HR:0.4; 95%CI:0.3-0.5, respectively).

Consequently, preceding centralisation of cystectomy, higher age and serious comorbidity were independent predictors for abstaining from cystectomy due to an expected high rate of short term medical problems. As cystectomy is associated with a better survival, independently from age, SES and serious comorbidity, it can be questioned whether cystectomy has been underutilized in elderly and in patients with serious comorbidity. Centralisation might be a solution for this suggested underutilization.

4 Effects of age and comorbidity on treatment and survival of patients with muscle-invasive bladder cancer

Introduction

In the Netherlands, patients aged ≥65 years represent more than 80% of all cases of mortality.[1] In 2008 the most important cause of death was cancer, which accounted for 30% of all deaths. As expected, the prevalence of registered comorbidity in newly diagnosed cancer patients increased with age: 48% for patients aged 50-64 years and up to 80% for those ≥80 years[2].

In the Netherlands, bladder cancer was the seventh most common cancer in 2010 {www.cijfersoverkanker.nl} and has a peak incidence in the seventh decade of life.[3] Serious comorbidity may complicate surgical treatment of bladder cancer. Especially patients with prior cardiac history who undergo radical cystectomy are more likely to develop complications.[4] Cystectomy as high risk, low volume operation shows a volume-outcome relationship; less postoperative mortality and longer survival are reported for patients treated by high volume providers.[5] The management of bladder cancer in this growing group of elderly is an increasing challenge. About 20-40% of all patients with bladder cancer will present with or progress to MIBC. [6] For patients with MIBC, radical cystectomy remains the preferred treatment.[6] This procedure appears to be safe for elderly patients and is even feasible for patients of older age with serious comorbidity.[3, 7-8] Although radical cystectomy has been suggested to have a survival benefit for selected elderly patients[9], these patients generally do not undergo this type of surgery due to the higher risk of morbidity and postoperative mortality.[10-15] Furthermore, there is a role for bladder-preserving approaches, either IRT for selected patients[16] or EBRT as alternative to radical cystectomy[17-18]; aiming

to maintain quality of life for the elderly while maintaining comparable local control and survival. High SES is also known to affect choice of treatment and have better survival rates for instance prostate cancer.[19]
The aim of this study is to assess whether rising age, SES and presence of serious comorbidity affected treatment choice and survival in a population-based series of patients with MIBC in the Netherlands, preceding centralisation of cystectomy.

Patients and methods
Data from all patients primary diagnosed with histologically proven urothelial cell carcinoma (transurethral resection or bladder biopsy) with invasion of the detrusor muscle between 1995 and 2009 were obtained from the population-based database of the Eindhoven Cancer Registry (ECR). The ECR covered about 10 medium to large community hospitals in which the number of practising urologists increased from 30 to 40. The nationwide Dutch network and registry of histopathology and cytopathology (PALGA) submits reports of all diagnosed malignancies to the ECR. In addition, the national hospital discharge databank completes case ascertainment up to ≥95%.[20] Registration clerks collect data on diagnosis, staging, treatment and comorbidity (diabetes, hypertension, cardiovascular disease, pulmonary disease and any other significant comorbidity) from the medical records, including pathology and surgery reports, and letters from the general practitioner plus current medication data, using a strict registration and coding manual. These data are entered into the ECR.

Data
Data on vital status (available until 31 December 2011) were obtained from the hospital records and the mortality register of the Central Office for Genealogy (that registers all deaths in the Netherlands via the municipal population registries). Tumor stage was based on pathological information; if pathological information was missing the clinical information was used. A modified Charlson score was used to assess comorbidity.[2] When comorbidity was not mentioned in the medical file of the patient, it was registered as not recorded, and these patients were analyzed as not having comorbidity. If patients were treated in a hospital outside the region of the ECR, comorbidity was also missing, (n=114), these patients were excluded from all analyses. Comorbidity was categorized into none, one, and two or more comorbidities per patient. Next to that, subgroups of patients with the comorbid conditions of diabetes, hypertension, and cardiovascular or pulmonary diseases were analysed. An indicator for SES as developed by Statistics Netherlands was used, in which SES is defined at a neighbourhood level (based on six-digit postal code). On average each postal code area contains 17 households, thus covering a very small geographic area. Postal codes were assigned to four SES categories, low, intermediate, high and institutionalized. This latter category contains the postal codes of care-providing institutions, such as a nursing home. Patients for whom SES was missing (n=41) were excluded from the analyses.
Data were entered into a separate, anonymous, password-protected database. According to Dutch laws on data protection and patient-provider agreement no official approval from an Institutional Review Board was needed. {http://www.federa.org/codes-conduct}

Statistics
The characteristics of all patients with MIBC were described according to primary treatment. 6-month, 1-, 3- and 5-year cohort based relative survival (RS) was calculated, according to patient, tumor characteristic and given treatment. Multivariate logistic regression models were used to assess whether age, SES and comorbidity were independent predictors of the choice for either cystectomy, EBRT or IRT in MIBC patients. The models were adjusted for sex, period of diagnosis, and tumor stage. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. In addition, the impact of various comorbid conditions was assessed in separate models on the probability of undergoing cystectomy, after adjustment for age, stage, sex and period of diagnosis. To assess whether age, SES, comorbidity and therapy choice affected overall survival, a multivariate Cox proportional hazard was used to estimate hazard ratios (HR), and 95% CIs. The models were adjusted for sex, tumor stage and period. All analyses were performed in SAS version 9.3.

Results
Patient characteristics
Overall, 2,455 patients with MIBC were included; their characteristics are presented in table 1. The majority was male (75%), the mean age was 70 and 38% were aged ≥75 years at diagnosis. Overall, 63% of these patients suffered from at least one comorbid condition and 32% had at least two concomitant comorbid conditions. For 14% of the patients without comorbidity no information on comorbidity was recorded in the medical files. In patients aged ≤60, 61-74 years and ≥75 years, the percentage

Characteristic		Total	%	Mean age at diag-nosis (yrs)	Cystec-tomy (%)†	EBRT (%)¡	IRT (%)	TUR only (%)	Other treat-ment (%)
Gender	Male	1829	75	70	34	35	7	17	12
	Female	616	25	71	32	33	5	20	15
Age group	≤60 years	444	18		52	15	10	10	22
	61-74 years	1062	44		43	31	9	12	11
	≥75 years	939	38		13	48	3	28	10
Period	1995-1999	704	29	70	29	43	8	18	12
	2000-2004	858	35	71	32	35	7	19	13
	2005-2009	883	36	71	39	27	7	18	14
TNM	Stage II	1402	57	72	25	43	10	23	6
	Stage III	503	21	69	59	24	3	8	12
	Stage IV	540	22	68	30	23	1	16	33
Comorbidity	None#	919	37	67	38	32	8	13	14
	One	748	31	71	32	35	6	19	14
	Two or more	778	32	74	27	37	6	23	11
Type of comorbidity	Diabetes	285	12	74	26	39	7	24	9
	Hypertension	472	19	73	34	35	8	17	12
	Cardiovascular	753	31	74	26	39	7	22	11
	Pulmonary	315	13	73	27	39	5	23	9
SES	Low	643	26	72	30	38	6	18	13
	Intermediate	1002	41	69	38	34	6	16	12
	High	624	26	69	36	33	9	16	13
	Institutionalized*	176	7	77	12	35	6	36	15
Total		**2445**		**70**	**33**	**35**	**7**	**18**	**13**

(EBRT= External Beam Radiation Therapy; IRT=Interstitial Radiation Therapy; TUR=Trans Urethral Resection; SES= Socio Economic Status)

$ As more than one treatment can be offered to a patient, % can be higher than 100%

Patient with unrecorded comorbidity included. * Patients in care-providing institutions.

† 20 patients treated with neo-adjuvant chemotherapy included.

¡ 32 patients treated with neo-adjuvant chemotherapy included.

Source: Eindhoven Cancer Registry.

Table 1: Patient and tumor characteristics of patients with muscle invasive bladder cancer according to primary treatment, diagnosed between 1995 and 2009 (n=2,445) in the south of the Netherlands.

Characteristic		N (mean age at diagnosis)	6-month RS	1-year RS	3-year RS	5-year RS
Gender	Male	1829	0.83	0.68	0.43	0.36
	Female	616	0.73	0.53	0.31	0.27
Age group	≤60 years	444	0.86	0.71	0.46	0.41
	61-74 years	1062	0.84	0.70	0.44	0.39
	≥75 years	939	0.73	0.53	0.30	0.21
Period	1995-1999	704	0.81	0.64	0.43	0.37
	2000-2004	858	0.79	0.61	0.37	0.32
	2005-2009	883	0.81	0.67	0.40	0.32
TNM	Stage II	1402	0.86	0.74	0.52	0.46
	Stage III	503	0.81	0.63	0.34	0.27
	Stage IV	540	0.66	0.40	0.14	0.09
Treatment	Cystectomy	810 (65 yrs)	0.93	0.79	0.53	0.48
	EBRT	846 (74 yrs)	0.87	0.67	0.36	0.29
	IRT	168 (66 yrs)	0.95	0.92	0.77	0.70
	Only TUR	442 (76 yrs)	0.55	0.39	0.23	0.19
	Other treatment	315 (68 yrs)	0.63	0.45	0.24	0.16
Total		**2445**	**0.80**	**0.64**	**0.40**	**0.33**

(EBRT= External Beam Radiation Therapy; IRT=Interstitial Radiation Therapy; TUR=Trans Urethral Resection)

Table 2: Relative survival (RS) according to patient, tumor characteristic and treatment

of patients without comorbidity decreased from 61% to 36% to 28%, respectively (data not in table). The percentage of patients with two or more comorbid conditions was 13%, 33% and 40% for those aged ≤60, 61-74 and ≥75 years, respectively (data not in table).
33% of all 2,455 patients underwent cystectomy being 13% in patients aged ≥75 years, 43% among those aged 61-74, and 52% among those aged ≤60 (Table 1). Of the patients aged ≥75 years with no, one, and two comorbid conditions 13%, 10% and 15% underwent cystectomy, respectively (data not in table).
One third of all patients underwent neither cystectomy, EBRT nor IRT. Of this group, 442 patients underwent only a TUR, having the highest mean age (76 years), having more than two comorbid conditions, and having T2 tumor. Neo-adjuvant chemotherapy was performed in 52 patients (2.1%); in 20 patients prior cystectomy and in 32 patients prior radiotherapy. Among the group with other treatments, patients merely had higher stage disease. (Table 1 and 2)
The 6-month, 1-, 3- and 5-year relative survival rates according to treatment were 0.93, 0.79, 0.53 and 0.48 for patients who underwent cystectomy. The EBRT group showed poorer relative survival compared to the cystectomy patients, but patients categorized in the groups of TUR only or other treatment exhibited the poorest relative survival. (Table 2)

Impact of age, SES and comorbidity on treatment choice
After adjustment for sex, period of diagnosis and stage, higher age and serious comorbidity, were independent predictors of abstaining from cystectomy, where SES was not (61-74 versus ≤60 years: OR:0.8; 95%CI:0.6-1.0; ≥75 versus ≤60 years: OR:0.1; 95%CI:0.1-0.2; one comorbid condition versus none: OR:0.7; 95%CI:0.5-0.9; two comorbid conditions versus none: OR:0.6; 95%CI:0.5-0.8). (Table 3)
Patients with cardiovascular disease, diabetes and pulmonary disease significantly less often underwent a cystectomy (OR: 0.6; 95%CI:0.5-0.8; OR:0.6; 95% CI:0.5-0.9; OR:0.6; 95%CI:0.4-0.8, respectively; data not in table). Older patients were more often referred for EBRT. Patients aged ≥75 and patients between age 61 - 74 more often underwent EBRT than patients under 60 (OR:5.1; 95%CI:3.8-6.9, OR:2.4; 95%CI:1.8-3.4 respectively). Patients aged ≥75 years received less often IRT than younger patients (OR:0.2; 95%CI:0.1-0.3). There is no independent effect of comorbidity on the option of being referred for these latter two treatments.

Impact of age, SES, comorbidity and treatment choice on overall survival
Table 4 shows that age, SES and comorbidity were independently associated with overall survival. These effects were adjusted for sex, tumor stage and period, where female sex and higher stage were also independent predictors of survival (HR: 1.2; 95%CI:1.1-1.3; HR:3.3; 95% CI:2.9-3.7, respectively). These effects remained significant after adding treatment to the model, although the effects of age decreased. Overall, older age, female sex, advanced stage, more comorbidity and not undergoing treatment with curative intent (cystectomy, EBRT or IRT) were associated with a lower survival. Patients undergoing cystectomy, EBRT or IRT lived longer independent of age, SES, and serious comorbidity (HR:0.4; 95%CI:0.4-0.5; HR:0.8; 95%CI:0.7-0.9; HR:0.4; 95%CI:0.3-0.5, respectively).
When assessing the effect of various comorbid conditions on survival (corrected for sex, age, period of diagnosis, stage, SES and cystectomy) in separate models, the presence of diabetes (HR 1.5.95% CI 1.3-1.8), cardiovascular disease (HR 1.3, 95% CI 1.2-1.5), hypertension (HR 1.1, 95% CI 1.0-1.3) and pulmonary disease (HR 1.5, 95% CI 1.3-1.7) significantly decreased survival.

Discussion
Of the 2,445 patients, 38% were aged ≥75 years at diagnosis; and 63% had at least one serious comorbid condition. Higher age and serious comorbidity were independent predictors for abstaining from cystectomy, where SES was not (61-74 versus <= 60: OR:0.8; 95%CI:0.6-1.0; >=75 versus <=60: OR:0.1; 95%CI:0.1-0.2; one comorbid condition versus none:OR:0.7; 95%CI:0.5-0.9; two comorbid conditions versus none:OR:0.6; 95%CI:0.5-0.8).
Patients treated with cystectomy, EBRT or IRT had a better survival independent of age, SES, and serious comorbidity (HR:0.4; 95%CI:0.4-0.5; HR:0.8; 95%CI:0.7-0.9; HR:0.4; 95%CI:0.3-0.5, respectively).
We found the usual association between age and comorbidity, i.e. the percentage of patients with ≥2 comorbid conditions was a threefold higher for patients aged ≥ 75 years (40%) compared to patients aged <60 years (13%). Although this association is well established, the impact of these factors on cancer survival is not unequivocal. For bladder cancer it has been shown that patients with low SES have more risk of suffering from, especially cardiovascular, comorbidities.[26] Patients who are smoking have a common risk factor for the development of both cardiovascular or lung disease and bladder cancer.[3;17] As these patients are in poorer health than bladder cancer patients without these comorbidities, the chance on the best treatment, cystectomy, is diminished.

	Cystectomy		EBRT		IRT	
Factor	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Age (years)						
≤60	1.0		1.0		1.0	
61-74	0.8	(0.6 – .0.9)	2.4	(1.8 – 3.3)	0.8	(0.5 – 1.2)
≥75	0.1	(0.1 – 0.2)	5.1	(3.8 – 6.9)	0.2	(0.1 – 0.3)
Male	1.0		1.0		1.0	
Female	0.9	(0.7 – 1.2)	0.9	(0.7 – 1.1)	0.9	(0.6 – 1.3)
Period						
1995-1999	1.0		1.0		1.0	
2000-2004	1.3	(1.0 – 1.6)	0.7	(0.6 – 0.9)	1.0	(0.7 – 1.5)
2005-2009	1.9	(1.5 – 2.4)	0.5	(0.4 – 0.6)	0.9	(0.6 – 1.4)
Stage						
II	1.0		1.0		1.0	
III	4.3	(3.4 – 5.4)	0.5	(0.4 – 0.6)	0.2	(0.1 – 0.4)
IV	0.8	(0.6 – 1.0)	0.5	(0.4 – 0.6)	0.1	(0.0 – 0.2)
Comorbidity						
None	1.0		1.0		1.0	
One	0.8	(0.6 – 1.0)*	1.0	(0.8 – 1.2)	0.8	(0.5 – 1.2)
Two or more	0.7	(0.5 – 0.9)*	1.0	(0.8 – 1.2)	0.9	(0.6 - 1.3)
Socioeconomic status						
Low	1.0		1.0		1.0	
Intermediate	1.2	(1.0-1.6)	0.9	(0.8-1.2)	1.0	(0.6-1.6)
High	1.1	(0.8-1.4)	0.9	(0.7-1.1)	1.6	(1.0-2.5)
Institutionalized	0.4	(0.2-0.7)	0.6	(0.4-0.9)	1.2	(0.6.-2.5)

(EBRT= External Beam Radiation Therapy; IRT=Interstitial Radiation Therapy; TUR=Trans Urethral Resection)

^ Other treatment options not included in analysis

* Estimate of odds ratio (OR) is significant, 95% confidence interval does not include 1.0

Patient with unrecorded comorbidity included. Source: Eindhoven Cancer Registry.

Table 3: Multivariate logistic regression analyses of determinants of cystectomy and EBRT or IRT in patients with muscle-invasive bladder cancer. (n= 2,445)

Variable		Model with age, sex, period and stage		Model with age, sex, period, stage and comorbidity		Model with age, sex, period, stage, comorbidity and treatment	
Factor		**HR**	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**
Age (years)	≤60	1.0		1.0		1.0	
	61-74	1.4	(1.2 – 1.6)	1.3	(1.2 – 1.5)	1.3	(1.1 – 1.5)
	≥75	2.9	(2.5 – 3.4)	2.7	(2.3 – 3.1)	2.0	(1.7 – 2.4)
Sex	Male	1.0		1.0		1.0	
	Female	1.2	(1.1 – 1.3)	1.2	(1.1 – 1.3)	1.2	(1.1 – 1.3)
Period	1995-1999	1.0		1.0		1.0	
	2000-2004	1.0	(0.9 – 1.1)	1.0	(0.9 – 1.1)	1.0	(0.9 – 1.1)
	2005-2009	0.9	(0.8 – 1.0)	0.9	(0.8 – 1.0)*	0.9	(0.8 – 1.0)
Stage	II	1.0		1.0		1.0	
	III	1.5	(1.4 – 1.7)	1.5	(1.4 – 1.7)	1.8	(1.6 – 2.0)
	IV	3.2	(2.9 – 3.6)	3.3	(2.9 – 3.7)	3.0	(2.6 – 3.3)
Socioeconomic status							
	Low	1.0		1.0		1.0	
	Intermediate	0.9	(0.8 - 1.0)	0.9	(0.8 - 1.0)	0.9	(0.8 - 1.0)
	High	0.8	(0.7 - 0.9)*	0.8	(0.7 - 0.9)*	0.8	(0.7 - 0.9)*
	Institutionalized	1.4	(1.1 - 1.6)	1.4	(1.1 - 1.6)	1.3	(1.1 -1.5)
Comorbidity	None			1.0		1.0	
	One			1.2	(1.1 – 1.3)	1.1	(1.0 – 1.2)
	Two or more			1.4	(1.2 – 1.6)	1.4	(1.1 - 1.5)
Cystectomy	No					1.0	
	Yes					0.4	(0.4 - 0.5)
EBRT	No					1.0	
	Yes					0.8	(0.7 - 0.9)
IRT	No					1.0	
	Yes					0.4	(0.3 - 0.5)

(EBRT= External Beam Radiation Therapy; IRT=Interstitial Radiation Therapy; TUR=Trans Urethral Resection)

^ Other treatment options not included in analysis

* Estimate of hazard ratio (HR) is significant, 95% confidence interval does not include 1.0

Patient with unrecorded comorbidity included. Source: Eindhoven Cancer Registry.

Table 4: Multivariate Cox regression model of risk on death for patients with new diagnosed muscle-invasive bladder cancer, in the South of the Netherlands, 1995 - 2009 (based on overall survival)

MIBC is an aggressive malignancy; if left untreated its course is usually fatal with ≥85% of patients dying from their disease in 24 months.[17;21] As compared to earlier population-based studies, the 35% of our patients treated with EBRT for MIBC is relatively high, whereas the 34% undergoing cystectomy, is similar to the results of other series.[22] With increasing age and comorbidity treatment will be progressively less invasive. This is in contrast to our study, where IRT was less used in the elderly although it is a bladder preserving, and therefore a less aggressive but still an invasive treatment. No conclusions can yet be drawn on the group of patients who received neo-adjuvant chemotherapy because of small numbers and probably marked selection.

As expected in this retrospective study, undergoing a cystectomy was significantly associated with longer survival in comparison to ERBT and IRT, also after adjustment for differences in age, comorbidity and stage, these results might have been affected by referral bias. After adjustment for cystectomy, high age and comorbidity were also independently associated with shorter survival. The negative impact of comorbidity on overall survival was also reported in two other retrospective studies including 210 and 1,121 patients.[24,25] In the first study, age was not an independent predictor of overall survival. Another study in a population-based radical cystectomy cohort including 11,260 patients showed age to be the main determinant of other-cause mortality and cancer-specific mortality.[23] However, in this study comorbidity was not assessed.

The critical factor for success of any treatment for MIBC in the elderly is patient selection.[26] The question then remains whether the patients having good prognosis after cystectomy would have had the same good result after treatment with IRT or EBRT. A Dutch study on IRT showed that at 1, 3 and 5 years, the disease-free probability was 85%, 68% and 61% and overall survival probability was 91%, 74% and 62%, respectively. This concerns a selected patient population (solitary, T1G3 -T3 bladder tumors, diameter<5 cm.).[16] Despite the apparent benefits of radical cystectomy in selected elderly patients, to date no guidelines are available for patient selection.[10] Although several validated geriatric assessment scales and indicators are used for the elderly referred for chemotherapy, these tools are rarely applied to patients treated with other modalities.[27] It is reasonable to assume that for fit elderly patients radical cystectomy offers the best form of disease control.[9] Screening tools to distinguish between fit and frail patients will increase their chance of survival or prevent early death and treatment can be individualised for frail elderly patients in order to maintain optimal quality of life.[28]

Another factor, which has not been observed in this study, that can contribute positively to the survival of the cystectomy patients is the relationship between the volume of operations performed in a center and survival after cystectomy.[29] Though not examined in our study, the possible benefit of additional chemotherapy to EBRT or surgery is another issue that must be subject of the discussion on patient selection. Moreover, EBRT concurrently combined with chemotherapy offers comparable results with those of surgery.[18]

Strengths and weaknesses

The present study has both strengths and limitations. A main strength is that our results are based on a large unselected population of patients with diverse treatment policies in about 10 hospitals, rather than from a single institution or clinical trial series in which patients are carefully selected, making the results applicable to a general population of patients with bladder cancer. A second main strength is the availability of the comorbidity status for assessment because of special efforts undertaken by the registry. A limitation includes the impossibility to examine disease-specific survival, and the use of a modified Charlson comorbidity index which may hamper comparison to other studies where the standard Charlson comorbidity index is used.[2] Further limiting aspect of this study is that due to its retrospective character, registration of the exact treatment in the group "other treatment" and the motivation for patient selection for treatment is lacking which may have affected the results. Then, with respect to the observational design of this study we could have utilized the propensity score methods for the correction of confounding factors. However, given the common incidence of the outcome, the regression analyses yielded same results and the propensity score methods were not applied.[30]

Conclusions

Higher age and serious comorbidity were independent predictors for abstaining from cystectomy. Cystectomy is associated with a better survival, independently from age, SES and serious comorbidity. As it is the preferred treatment[6], also in elderly and in patients with serious comorbidity, it can be questioned whether cystectomy was underutilized in elderly and in patients with serious comorbidity. As with the increasing diversity in fit versus frail elderly patients, the need for awareness for good counselling of the patient and choosing the best treatment for the individual patient is becoming more important. Nowadays with the standardized multidisciplinary meetings

between urologist, oncologist and radiation oncologist before treatment for MIBC, the awareness has increased and shared decision making on treatment plan is being done. Reasonably, regionalisation for cystectomy, as in 2010 a volume-based proposal was introduced in the Netherlands, may not only contribute to better outcome of cystectomy but as well to development of selection tools to help decision-making in individualized treatment. Then, referral to IRT or EBRT could be inferior to cystectomy in patients with good prognosis. Thereby the status of alternative treatment options for patients with MIBC is an ongoing debate.

References

1. Olden TE, Schols JM, Hamers JP, Van De Schans SA, Coebergh JW, Janssen-Heijnen ML. Predicting the need for end-of-life care for elderly cancer patients: findings from a Dutch regional cancer registry database. Eur J Cancer Care. 2012; 21:477-84.
2. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and comorbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol 2005;55:231-40.
3. Clark PE, Stein JP, Groshen SG, Cai J, Miranda G, Lieskovsky G, et al. Radical cystectomy in the elderly: Comparison of survival between younger and older patients. Cancer. 2005;103:546-52.
4. Fisher MB, Svatek RS, Hegarty PK, McGinniss JE, Hightower C, Grossman HB, et al. Cardiac history and risk of post -cystectomy cardiac complications. Urology. 2009;74:1085-9.
5. Goossens-Laan CA, Gooiker GA, van Gijn W, Post PN, Bosch JL, Kil PJ, et al. A systematic review and meta-analysis of the relationship between hospital/surgeon volume and outcome for radical cystectomy: an update for the ongoing debate. Eur Urol. 2011;59(5):775-83.
6. Stenzl A, Cowan NC, De Santis M, Kuczyk MA, Merseburger AS, Ribal MJ, et al. Treatment of muscle-invasive and metastatic bladder cancer: update of the EAU guidelines. Eur Urol. 2011;59:1009-18.
7. Clark PE. Bladder cancer. Curr Opin Oncol. 2007;19:241-7.
8. Chang SS, Alberts G, Cookson MS, Smith JA Jr. Radical cystectomy is safe in elderly patients at high risk. J Urol. 2001;166:938-41.
9. Hollenbeck BK, Miller DC, Taub D, Dunn RL, Underwood W 3rd, Montie JE, et al. Aggressive treatment for bladder cancer is associated with improved overall survival among patients 80 years old or older. Urology. 2004;64:292-7.
10. Weizer AZ, Montie JE, Lee CT. Aggressive management of elderly patients with muscle-invasive bladder cancer. Nat Clin Pract Urol. 2006;3:346-7.
11. Basso U, Bassi P, Sava T, Monfardini S. Management of muscle-invasive bladder cancer in the elderly. Expert Rev Anticancer Ther. 2004;4:1017-1035.
12. Chamie K, Hu B, Devere White RW, Ellison LM. Cystectomy in the elderly: does the survival benefit in younger patients translate to the octogenarians? BJU Int. 2008;102:284-90.
13. Farnham SB, Cookson MS, Alberts G, Smith JA Jr, Chang SS. Benefit of radical cystectomy in the elderly patient with significant comorbidities. Urol Oncol. 2004;22:178-81.
14. Lance RS, Grossman HB. Cystectomy in the elderly. Semin Urol Oncol. 2001;19:51-5.
15. Konety BR. Sickness and survival in bladder cancer: is comorbidity the crystal ball? Eur Urol. 2008;53:465-7.
16. Koning CC, Blank LE, Koedooder C, van Os RM, van de Kar M, Jansen E, et al. Brachytherapy after external beam radiotherapy and limited surgery preserves bladders for patients with solitary pT1-pT3 bladder tumors. Ann Oncol. 2012;

23:2948-5.
17. Tran E, Souhami L, Tanguay S, Rajan R: Bladder conservation treatment in the elderly population: results and prognostic factors of muscle-invasive bladder cancer. Am J Clin Oncol. 2009;32:333-7.
18. James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C, et al. Radiotherapy with or without chemotherapy in muscle- invasive bladder cancer. N Engl J Med. 2012;366:1477-1488.
19. Aarts MJ, Koldewijn EL, Poortmans PM, Coebergh JW, Louman M. The Impact of Socioeconomic Status on Prostate Cancer Treatment and Survival in the Southern Netherlands. Urology. 2013;81:593-9.
20. Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. Int J Epidemiol. 1993;22:369-76.
21. Prout GR, Marshall VF. The prognosis with untreated bladder tumors. Cancer. 1956; 9:551-8.
22. Prout GR Jr, Wesley MN, Yancik R, Ries LA, Havlik RJ, Edwards BK: Age and comorbidity impact surgical therapy in older bladder carcinoma patients: a population-based study. Cancer. 2005;15:1638-47.
23. Lughezzani G, Sun M, Shariat SF, Budäus L, Thuret R, Jeldres C, et al. A population-based competing-risks analysis of the survival of patients treated with radical cystectomy for bladder cancer. Cancer. 2011;117:103-9.
24. Megwalu II, Vlahiotis A, Radwan M, Piccirillo JF, Kibel AS. Prognostic impact of comorbidity in patients with bladder cancer. Eur Urol. 2008;53:581-9.
25. Koppie TM, Serio AM, Vickers AJ, Vora K, Dalbagni G, Donat SM, et al. Age adjusted Charlson comorbidity score is associated with treatment decisions and clinical outcomes for patients undergoing radical cystectomy for bladder cancer. Cancer. 2008;112:2384-92.
26. Louwman WJ, Aarts MJ, Houterman S, van Lenthe FJ, Coebergh JW, Janssen-Heynen M. A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. BrJ Cancer. 2010;103:1742-48.
27. Extermann M. Studies of comprehensive geriatric assessment in patients with cancer. Cancer Control. 2003;10:463-8.
28. Kristjansson SR, Nesbakken A, Jordhøy MS, Skovlund E, Audisio RA, Johannessen HO, et al. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: a prospective observational cohort study. Crit Rev Oncol Hematol. 2010;76:208-17.
29. Goossens - Laan CA, Visser O, Hulshof MC, Wouters MW, Bosch JL, Coebergh JW, et al. Survival after treatment for carcinoma invading bladder muscle: a Dutch population-based study on the impact of hospital volume. BJU Int. 2012 Jul;110(2):226-32.
30. Shah BR, Laupacis A, Hux JE, Austin PC. Propensity score methods gave similar results to traditional regression modeling in observational studies: a systematic review. J Clin Epidemiol. 2005;58:550-9.

Chapter 4

Part 2
Urothelial cell carcinoma of the upper urinary tract
- The role of urography