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Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: A population-based study

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ABSTRACT

It is likely that the shift from post- to pre-operative radiotherapy and the introduction of total mesorectal excision (TME) surgery have contributed to the observed improved survival of rectal cancer in the south of the Netherlands. However, no improvement was seen for patients aged 70 or older. To investigate possible causes of this lack of improvement, we examined the risk of treatment-related complications and overall survival. Therefore, a random sample of 455 patients with rectal cancer aged 60 years or older, diagnosed between 1995 and 2001 was extracted from in the Eindhoven Cancer Registry database. Fifty-one percent of patients aged 60–69 years-old had any complication within one year of diagnosis compared to 65% of patients aged 70 or older ($p = 0.007$). Older patients were at higher risk of developing treatment-related complications (odds ratio (OR) 1.8; $p = 0.01$), as were patients with comorbidity (OR 1.7; $p = 0.07$), and those who received pre-operative radiotherapy (OR 1.8; $p = 0.02$). In a multivariable analysis, age older than 70 (hazard ratio (HR) 2.2; $p < 0.0001$), comorbidity (HR 1.7; $p = 0.03$), and having two or more complications (HR = 2.2; $p = 0.0002$) had a negative effect on survival. The lack of improvement in the prognosis of elderly patients with rectal cancer after a shift from post- to pre-operative radiotherapy might partially be explained by a higher risk of treatment-related complications. In order to optimise the risk/benefit ratio of elderly patients, individualisation of treatment by means of a comprehensive geriatric assessment will be of critical importance.

1. Introduction

The treatment of rectal cancer has changed during the last two decades. In the south-east Netherlands, the shift from post-operative towards pre-operative radiotherapy (5 × 5 Gy) and the introduction of total mesorectal excision (TME) surgery have been the most important changes. It is very likely that these developments have contributed to the improved survival of patients with rectal cancer that was observed in this region.[1] The decline in the relative risk of death in the

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period 1995–2000 *versus* 1980–1989 of patients with rectal cancer appeared to be related to age. Comparing both periods, the relative risk of death was 0.45 for patients under 60 years of age and 0.62 for those 60–74 years-old. However, no improvement in risk of death was found for patients over 74 years of age.[1]

Current treatment guidelines for patients with rectal cancer include pre-operative radiotherapy (5×5 Gy) for cT1-3 tumours, and prolonged chemoradiotherapy followed by resection and intraoperative radiotherapy (IORT) for cT4 tumours. Elderly patients are more likely to suffer from other chronic illnesses (comorbidity) which may contra-indicate the standard treatment because of the fear of an increased risk of complications and death.[2–4] The results of a systematic review examining the outcome of surgery for colorectal cancer in elderly patients showed a progressive increase of post-operative morbidity and mortality with advancing age.[5] The contribution of age to this increased morbidity and mortality in elderly patients is not clear. The increased proportion of patients undergoing emergency surgery, together with more frequent comorbidity could contribute significantly to the increased risk of an adverse outcome in the elderly.[5–7] In this study, we investigated the influence of age and comorbidity on treatment-related complications and survival of elderly patients with rectal cancer in the south-east of the Netherlands.

2. Patients and methods

2.1. Eindhoven cancer registry

The Eindhoven Cancer Registry has been collecting data on patients with newly diagnosed cancer in a large part of southern Netherlands with a population of 2.3 million inhabitants. The registry is notified by six pathology departments, 10 community hospitals and two radiotherapy institutes. Despite the lack of access to death certificates, the infrastructure of and good access to Dutch health care facilities in combination with the notification procedures used have made it possible to establish a completeness of the registry exceeding 95%.[8]

Information on diagnosis, staging, comorbidity at time of diagnosis and treatment is routinely extracted from the medical records by the registrars usually 6–18 months after diagnosis. Prognostically relevant concomitant conditions are recorded from the medical records according to a slightly adapted version of the Charlson index (Table 1).[9] In the original version used by Charlson and colleagues, not only the number but also the seriousness of the comorbid condition was taken into account. Within the framework of the cancer registry it was not feasible to register severity of comorbidity, but we only recorded serious comorbid conditions with possible prognostic impact. We also included hypertension, which has been shown to be a prognostic factor in some previous studies. In the analyses we classified comorbidity as no comorbidity, one comorbid condition, or two or more comorbid conditions.

2.2. Patient population

The total number of patients with rectal adenocarcinoma aged 60 years or older diagnosed between 1995 and 2001 in the Eindhoven Cancer Registry area amounted to 2094. Patients presenting with distant metastases ($N = 322$) were excluded. Of the remaining patients, we randomly selected 455 patients, since the total patient population was too extensive to gather the additional information from the medical files (see below). The random selection procedure was carried out using SAS statistical software (SAS Institute Inc., Cary, NC, USA, 1999). From the sample of 455 rectal cancer patients, 29 clinical records could not be found in the hospitals due to migration, death or an unexplained reason. These 29 patients were excluded from the study. Fourteen of these patients (48%) died during the follow-up period completed on January 1st, 2005.

Table 1 – Classification of comorbidity, according to an adapted version of Ref. [9]

Previous malignancies (except basal skin carcinoma and carcinoma *in situ* of the cervix)
Chronic obstructive pulmonary diseases (COPD)
Cardiovascular diseases (myocardial infarction, cardiac decompensation, angina pectoris, intermittent claudication, abdominal aneurysm, peripheral arterial disease)
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Hypertension
Diabetes mellitus
Digestive tract diseases (stomach diseases, Crohn's disease, ulcerative colitis, liver cirrhosis, hepatitis)
Other (connective tissue diseases, severe rheumatoid arthritis, kidney diseases, dementia, tuberculosis, chronic infections)

2.3. Pre-operative findings/social status

Additional information on performance status, urgency of surgery, pre-operative radiotherapy, and haemoglobin level, was recorded by two researchers (an epidemiologist and an experienced surgeon), with the approval and under supervision of the treating physicians. Performance status of patients was extracted from the medical record using the Karnofsky scale. For patients who underwent surgery we also recorded the American Society of Anesthesiologists (ASA) score. However, since 45% of the ASA score and 49% of the Karnofsky score were not mentioned in the medical files, we did not include these variables in our analyses. Patients with haemoglobin levels below 6.5 mmol/l (before treatment or any transfusion) were assigned to the low haemoglobin group.

Socio-economic status (SES) of the patient was defined at neighbourhood level (based on postal code of residence area, 17 households on average) combining mean household income (in 1998) and mean value of the house/apartment (in 2000), derived from individual fiscal data made available at an aggregated level. Postal codes were assigned to 3 SES categories: low (1st–3rd decile), intermediate (4th–7th decile), and high (8th–10th decile). Postal codes of institutions, such as nursing homes, were assigned to a separate category and were excluded from the logistic regression and survival analysis (19 patients, all aged 70 or older).

2.4. Post-operative findings

Serious complications occurring within one year of diagnosis were recorded. These were defined as minor infections (e.g. wound infections, urinary tract infections), major infections (e.g. abscess, peritonitis, anastomotic leakage), pulmonary complications (e.g. pneumonia), haemorrhage (requiring blood transfusion or surgery), thrombo-embolic events, cardiac complications (e.g. cardiac failure, ischaemic heart disease), haematological complications, complications typically due to radiotherapy (e.g. radiation enteritis), stoma problems, death due to complications (stated in the medical file), and other complications (e.g. kidney failure, lymphoedema, fatigue, cerebral problems, ileus, incontinence, urine retention).

Also the date of a local tumour recurrence was recorded.

2.5. Follow-up

Information on vital status of the patients was obtained from the hospital records, the civil municipal registries and the death register of the Central Bureau for Genealogy. The latter is an institution that registers all deceased Dutch citizens via the municipal civil registers. In this way, information on patients who had moved outside the registry area was also obtained. In total 201 (47%) colorectal cancer patients died during follow-up, which was completed on January 1st, 2005. The median follow-up in months was 48.5 (range 0–119).

2.6. Statistical analyses

The prevalence of complications was analyzed according to age (dichotomised into <70 and $\geqslant$70 years); significance was tested by means of a χ^2 test. The independent influence of age, gender, stage, comorbidity, socioeconomic status, haemoglobin level and treatment on development of complications was analysed in a logistic regression analysis. Crude survival was computed with date of diagnosis as the starting point and death or end of study as end-point. The log-rank test was used to compare univariable survival rates between groups of patients. Univariable survival analyses were stratified according to age at diagnosis (<70 and $\geqslant$70 years). Multivariable proportional hazards regression methods were used to discriminate independent risk factors for death. The likelihood ratio method was used to determine hazard ratios. The SAS computer package (version 8.2) was used for all statistical analyses (SAS Institute Inc., Cary, NC, USA, 1999).

2.7. Results

The general characteristics are shown in Table 2; 182 patients were between 60- and 69 years-old and 244 were aged 70 years or older. The male–female ratio was 1.8 among patients aged 60–69 and 1.0 among the elderly ($p = 0.004$). Patients aged 70 years or older were more likely to have rectal cancer in an

Table 2 – General characteristics of patients with rectal cancer diagnosed in 1995–2001 in the southern Netherlands, by age

	60–69 years (N = 182)	70+ years (N = 244)	p-Value[a]
	N (%)	N (%)	
Gender			
Male	116 (64)	121 (50)	0.004
Female	66 (36)	123 (50)	
Stage (TNM)			
I	56 (31)	69 (28)	0.3
II	58 (32)	81 (33)	
III	55 (30)	64 (26)	
Unknown	13 (7)	30 (12)	
Comorbidity			
No comorbidity	61 (34)	41 (17)	<0.0001
One comorbid condition	55 (30)	64 (26)	
Two or more comorbid conditions	62 (34)	134 (55)	
Unknown comorbidity	4 (2)	5 (2)	
Socio-economic status			
High	63 (35)	81 (33)	0.0006
Intermediate	61 (34)	88 (36)	
Low	58 (32)	56 (23)	
Institutionalised	0 (0)	19 (8)	
Haemoglobin level			
Normal (>6.5 mmol/l)	161 (89)	197 (81)	0.02
Low ($\leqslant$6.5 mmol/l)	13 (7)	34 (14)	
Unknown	8 (4)	13 (5)	
Treatment			
Surgery alone	78 (43)	115 (47)	0.004
Pre-operative radiotherapy	89 (49)	87 (36)	
Other/none	15 (8)	42 (17)	

a χ^2 test for equal proportions, the null hypothesis specifies equal proportions of the total sample size for each class.

unknown stage than patients aged 60–69 (12% *versus* 7%, respectively), although there was no trend for older patients to be diagnosed in a more advanced stage of disease ($p = 0.3$). Eighty-one percent of the patients aged 70 or older had one or more concomitant diseases compared to 64% of patients aged 60–69 ($p < 0.0001$). Fourteen percent of patients aged 70 or older had low haemoglobin levels, in contrast to 7% of patients aged 60–69 ($p = 0.02$). Of patients aged 70 or older, 36% underwent pre-operative radiotherapy, compared to 49% of younger patients ($p = 0.004$); the proportion receiving other or no treatment was higher among the elderly. Four percent of patients underwent emergency surgery (2% of patients aged 60–69 *versus* 5% of patients 70 or older, $p = 0.2$; data not shown).

Fifty-one percent of patients aged 60–69 years-old had any complication within one year of diagnosis compared to 65% of patients aged 70 or older ($p = 0.007$) (Fig. 1). The most frequent complications within one year of diagnosis were minor infections, major infections, and pneumonia. Elderly patients suffered more from cardiac complications (8% *versus* 2%, $p = 0.01$) and pneumonia (12% *versus* 7%, $p = 0.13$) than younger patients, and there were also more deaths due to treatment complications (especially cardiac) among these patients (9% *versus* 3%, $p = 0.01$).

According to the results of the logistic regression analysis, the risk of developing complications was almost twice as high for patients aged 70 or older compared to younger patients ($p = 0.01$, Table 3). Females appeared to have a lower risk of developing complications than males, whereas patients with stage III disease had a higher risk than those with stages I or II. The risk of developing complications was higher for patients with comorbidity compared to those without comorbidity, although not significantly (OR = 1.7 for one concomitant disease; OR = 1.5 for two or more concomitant diseases). This effect was more pronounced among patients aged 70 or older (OR = 2.3, $p = 0.04$ for one concomitant disease; OR = 2.3, $p = 0.03$ for two or more concomitant diseases; data not shown). Patients who underwent surgery plus radiotherapy had a significantly higher risk of developing complications (OR = 1.8, $p = 0.02$) compared to those who underwent surgery alone.

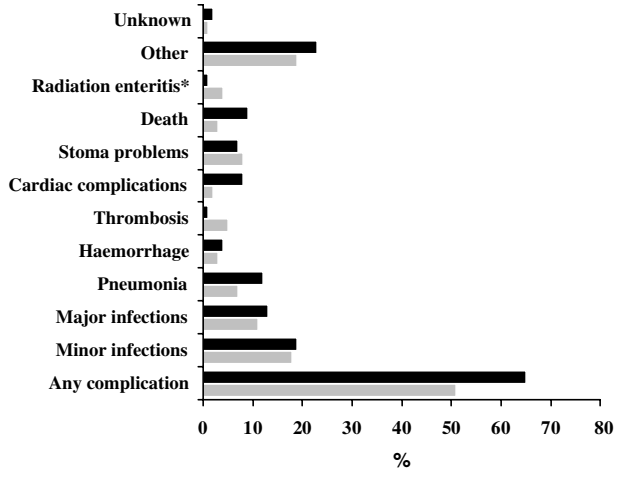

Fig. 1 – Age-specific prevalence of complications during the first year after diagnosis among rectal cancer patients diagnosed between 1995 and 2001. *Percentage of patients receiving radiotherapy. □, 70+ years (N = 244). ■, 60–69 years (N = 182).

Table 3 – Risk of developing complications within one year after diagnosis for patients who underwent elective surgery for rectal cancer diagnosed between 1995 and 2001 in the southern Netherlands; multivariable logistic regression model including all variables listed[a]

	Odds ratio	*p*-Value
Age		
60–69 years[b]	1.0	
70+ years	1.8	0.01
Gender		
Male[b]	1.0	
Female	0.7	0.08
Stage (TNM)		
I[b]	1.0	
II	1.1	0.7
III	1.8	0.04
Comorbidity		
No comorbidity[b]	1.0	
One comorbid condition	1.7	0.07
Two or more comorbid conditions	1.5	0.2
Socio-economic status		
High[b]	1.0	
Intermediate	0.8	0.4
Low	1.0	0.9
Haemoglobin level		
Normal (>6.5 mmol/l)[b]	1.0	
Low (⩽6.5 mmol/l)	1.1	0.3
Treatment		
Surgery alone[b]	1.0	
Surgery + radiotherapy	1.8	0.02

a Cases with missing values for any of the covariates were left out of the analyses.
b Reference category.

The rate of local recurrence was similar for patients who underwent surgery plus pre-operative radiotherapy and for those who underwent surgery alone (6% *versus* 8%, $p = 0.4$; no difference by age).

The crude 5-year survival rate was 70% for patients aged 60–69 years old and 44% for patients aged 70 or older ($p < 0.0001$, Table 4). These rates increased to 79% for patients aged 60–69 years without comorbidity and 60% for patients aged 70 or older without comorbidity. For both age groups the crude survival decreased with an increasing number of comorbid conditions, higher stage and number of complications. For patients aged 70 or older crude survival was also worse for those with a low haemoglobin level and for those receiving adjuvant radiotherapy or other/none treatment. In a multivariable analysis, higher age (hazard ratio (HR) = 2.2), comorbidity (HR = 1.7) and the development of 2 or more complications had a negative effect on survival. The receipt of pre-operative radiotherapy had a borderline significant negative influence on survival (HR = 1.4, $p = 0.10$).

Table 4 – Uni- and multivariable analyses for overall survival of patients with rectal cancer diagnosed between 1995 and 2001 in the southern Netherlands[a]

	Univariable				Multivariable	
	60–69 years		70+ years		All ages	
	5 years (%)	*p*-Value	5 years (%)	*p*-Value	Hazard ratio	*p*-Value
Age						
60–69 years[b]	70				1.0	
70+ years			44	<0.0001	2.2	<0.0001
Gender						
Male[b]	67		46		1.0	
Female	76	0.2	42	0.2	1.0	0.8
Stage (TNM)						
I[b]	82		63		1.0	
II	68		45		1.3	0.3
III	59	0.03	30	0.001	2.0	0.002
Comorbidity						
No comorbidity[b]	79		60		1.0	
One comorbid condition	71		47		1.7	0.05
Two or more comorbid conditions	63	0.03	38	0.09	1.7	0.03
Socio-economic status						
High[b]	79		42		1.0	
Intermediate	65		52		0.7	0.10
Low	66	0.3	42	0.6	0.9	0.6
Haemoglobin level						
Normal (>6.5 mmol/l)[b]	71		46		1.0	
Low (⩽6.5 mmol/l)	58	0.7	34	0.01	1.1	0.2
Treatment						
Surgery alone[b]	70		56		1.0	
Surgery + radiotherapy	71		42		1.4	0.10
Other/none	[c]		18	0.002	[c]	
Complications						
No complication[b]	81		58		1.0	
One complication	69		50		1.1	0.8
Two or more complications	54	0.007	29	0.0003	2.2	0.0002

a Cases with missing values for any of the covariates were left out of the analyses.
b Reference category.
c Analyses could not be completed due to small numbers.

3. Discussion

Patients aged 70 years or older underwent surgery in combination with pre-operative radiotherapy (36%) less often than patients aged 60–69 years (49%). Elderly patients and those who underwent surgery plus radiotherapy had a significantly higher risk of developing complications, especially pneumonia, cardiac complications and death due to complications. Independent prognostic factors were higher age, comorbidity, higher stage, and having two or more complications.

Previous population-based studies already described the influence of age on the receipt of adjuvant radiotherapy for rectal cancer patients.[3,10] The physician might decide not to refer elderly patients for radiotherapy because of advanced age or serious comorbidity, but other factors might also play a role, such as a decreased general mental and physical condition, refusal of the patient, the absence of caregivers in the family situation, and distance to the radiotherapy institute.[3,10] It is likely that the influence of these factors is more important in the longer-term post-operative setting than in the relatively short (5×5 Gy) pre-operative setting. Since 1995, post-operative radiotherapy has been largely replaced by pre-operative radiotherapy in the south of the Netherlands; the rate of post-operative radiotherapy has dropped to 4%.[1]

The current study showed that elderly patients developed more treatment related complications, especially pneumonia and cardiac complications, and were at a higher risk of dying due to a complication. The effect of age on post-operative morbidity and mortality has already been described in a number of other studies.[11–14] A recent prospective multicenter study in France found age older than 70 years and neurologic and cardiorespiratory comorbidity to be independent risk factors of morbidity after colorectal surgery, and age older than 70 years and neurological comorbidity were pre-operative risk factors of mortality.[15] In a review of 28 studies on colorectal cancer surgery in the elderly, an increased frequency of post-operative morbidity and mortality with

advancing age was reported.[5] Pooled data suggested an age-related increase for pneumonia/respiratory failure, cardiovascular complications, cerebrovascular accident, and thromboembolism. There was no increased frequency of anastomotic leaks in the elderly. Overall 5-year survival decreased by age, although there was only little difference in cancer-specific survival between patients who underwent cancer-specific surgery. Unfortunately, in this retrospective population-based study we did not have data on cause of death at our disposal.

Pre-operative radiotherapy reduces the risk of a local recurrence; it tends however to increase the risk of developing complications, including impaired wound healing and bowel dysfunction.[11,16–20] Some authors considered pre-operative radiotherapy as a risk factor for anastomotic leakage.[21,22] Also in our study, patients who underwent surgery plus pre-operative radiotherapy developed more complications than patients undergoing surgery alone. Minor infections such as delay of wound healing were the most frequent complications after adjuvant radiotherapy (18%). Prognosis was negatively affected by age and comorbidity, in line with previous studies.[5,23–26] The Stockholm II Trial reported that both the increase in post-operative mortality and the higher incidence of intercurrent death after radiotherapy were mainly caused by cardiovascular disease.[27] The cause of the increased cardiovascular mortality is not known. One explanation is that, in addition to a local effect on the vascular bed, there is also a systemic effect that may result in thromboembolic and cardiovascular complications developing with time.[28,29] In the current study the risk of local recurrence for the group as a whole was low and was similar for patients receiving pre-operative radiotherapy and for those undergoing surgery alone. However, regardless of having recurrence or survival as an end-point, comparison of treatment outcome in a retrospective population-based study may be biased due to selection of patients by the treating physician.

Unfortunately, ASA and performance score were not mentioned in the majority of the medical files, so that these important variables could not be included in our study. Performance score is found to have a prognostic impact, independent of comorbidity.[30] On the other hand, performance score is often amenable to the malignant disease and its treatment, in contrast to comorbidity. ASA score was found to be a predictor of mortality following surgery for colorectal cancer in some studies[31,32]; however, others did not find an independent effect of ASA on perioperative mortality or morbidity.[7,15] This may be due to the considerable interobserver inconsistency of classification of ASA score.[33,34]

In a previous study it was shown that survival of rectal cancer patients aged 75 or older did not improve in the south of the Netherlands between 1980 and 2000, whereas there was a clear improvement for the younger patients.[1] This observation seems to be partly explained by the results of the current study: elderly patients were at higher risk of developing treatment-related complications. Also the high prevalence of comorbidity is likely to contribute to the lack of improvement for the elderly patients. In order to optimise the risk/benefit ratio of elderly patients, individualisation of treatment by means of a comprehensive geriatric assessment will be of critical importance.

Conflict of interest statement

None declared.

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