Guideline versus non-guideline based management of rectal cancer in octogenarians

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RESEARCH PAPER

Guideline versus non-guideline based management of rectal cancer in octogenarians

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Abstract

Purpose The number of octogenarians with rectal adenocarcinoma is growing. Current guidelines seem difficult to apply on octogenarians which may result in non-adherence. The aim of this retrospective cohort study is to give insight in occurrence of treatment-related complications, hospitalisations and survival among octogenarians treated according to guidelines versus octogenarians treated otherwise.

Methods 108 octogenarians with rectal adenocarcinoma were identified by screening of medical records. 22 patients were excluded for treatment process analysis because of stage IV disease or unknown stage. Baseline characteristics, diagnostic process, received treatment, motivation for deviation from guidelines, complications, hospitalisations and date of death were documented. Patients were divided in two groups depending on adherence to treatment guidelines. Differences in baseline characteristics, treatment-related complications and survival between both groups were evaluated.

Results Diagnosis and treatment according to guidelines occurred in 95 and 54% of the patients, respectively. When documented, patient's preference and comorbidities were major reasons to deviate from guidelines. 66% of patients who were treated according to guidelines experienced complications versus 34% of those treated otherwise ($p=0.02$). After adjustment for differences in age and polypharmacy, this association was not significant. Patients treated according to the guideline had better survival 18 months after diagnosis (80 versus 56%, $p=0.02$).

Conclusions Treating octogenarians with rectal cancer according to guidelines seem to lead to better overall survival, but may lead to a high risk of complications. This may jeopardise quality of life. More and prospective studies in octogenarians with rectal cancer are needed to customize guidelines for these patients.

Keywords Rectum · Adenocarcinoma · Octogenarian · Guideline · Complication · Survival

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Introduction

Rectal cancer is one of the most common malignancies globally. Approximately 65% of the patients with newly diagnosed rectal cancer are over 65 years of age and approximately 12% are even over 80 years of age [1–3]. Age is a known risk factor for the development of rectal cancer. One could therefore hypothesize that the ageing of the population and improving of diagnostics will likely lead to an increase in the number of very old (80 years or older) cancer patients [1, 4, 5].

Despite the expected increase of (especially very) old patients with rectal cancer, current guidelines are based on clinical trials which mostly included fit patients and those younger than 65 years of age [6]. Therefore, these guidelines cannot automatically be extrapolated to older and vulnerable

patients. Due to this lack of evidence in current guidelines, non-adherence is likely to occur in clinical practice [7]. This may lead to both under- and overtreatment. Previous studies show patients aged > 75 being at higher risk for treatment-related complications and experience worse survival compared to younger patients [8, 9]. Besides that, older patients may accept certain negative impacts of a treatment, accompanied with loss of quality of life, less likely than younger patients do [10]. A major question is whether deviation from current guidelines is justified in older patients.

The aim of our study was to give insight into current practice and especially into how octogenarians who are treated according to guidelines differ from octogenarians treated otherwise with respect to the occurrence of treatment-related complications, hospitalisations and survival.

Materials and methods

Study population and data collection

This retrospective cohort study was performed in two teaching hospitals (Zuyderland medical centre Heerlen and VieCuri medical centre) in the southern part of the Netherlands. All octogenarians diagnosed between January 2008 and January 2015 with adenocarcinoma of the rectum were included. Data were extracted from medical records using a list of predefined parameters to describe a diagnostic and treatment process as well as complications, hospitalisations and survival. Patients with unknown or stage IV disease were excluded from treatment process analysis.

Diagnostic process description

Parameters used for the diagnostic process description included patient characteristics, disease characteristics and used diagnostics.

Patient characteristics were scored by the physician at time of consultation and retrospectively extracted by two authors (A.v.V. and L.V.) from medical records when present. Patient characteristics included: age, gender, living situation (at home/institutionalized), marital status (married/not married or widowed), comorbidities using the Charlson score (range 0–37; patients scored automatically 2 because of the presence of a solid tumour), the presence of polypharmacy (≥ 5 medications), performance status using the WHO performance score documented by physician (range 0–4), weight (in kg), and length (in m) [11, 12]. When parameters were absent in medical records, these were defined as missing.

Disease characteristics were assessed by clinical tumour-node-metastasis (TNM) classification (version 5) [13, 14].

The used diagnostics were assessed by documentation of the use of colonoscopy, MRI, endoscopic ultrasonography, CT-abdomen, and chest X-ray as defined in prevailing guidelines.

Treatment process description

Parameters used for the treatment process description included received treatment, treatment-related complications/hospitalisations and survival.

Received treatment was extracted from medical records and compared to Dutch guidelines at time of presentation. Reasons for deviation from the guidelines were extracted from medical records when documented. Due to an update of the Dutch colorectal guidelines in 2014, two versions were used (2008 and 2014) [13, 14]. A summary of treatment recommendations is shown in Table 1. Patients with unknown or stage IV disease were excluded from treatment process analysis, since treatment recommendations for these patients are not included in detail in the applied guidelines.

The occurrence of complications due to radiotherapy, chemotherapy or surgery and unplanned hospitalisation due to these complications were registered.

Overall survival was assessed 18 months after diagnosis. When medical records showed patients being still alive 18 months after diagnosis, patients were censored. When survival status was inconclusive in the medical records, the patient's general practitioner was consulted.

Statistical analyses

SPSS version 23 was used for statistical analyses. Significance level was set at $p < 0.05$.

Differences in baseline characteristics between those treated according to guidelines and those treated otherwise were analysed using Chi-square test, Fisher's exact test and Mann–Whitney *U* test.

The association between baseline characteristics and treatment-related complications was analysed with the Chi-square and Mann–Whitney *U* test. Variables with a *p* value of < 0.05 in the univariate analysis were implemented in a multivariate analysis, with the maximum of one variable per ten events taken into account, using a logistic regression analysis. Besides that, differences of percentages in treatment-related complications and hospitalisations per treatment modality were compared between patients treated according to the guideline and patients treated otherwise.

Survival differences between patients who were treated according to the guideline and those treated otherwise were evaluated with a Kaplan–Meier plot and log rank test. Because of low power, multivariate survival analyses were not performed.

Table 1 Dutch national guidelines used as references

Stage		TNM	Neoadjuvant treatment	Surgical treatment	Adjuvant treatment
Dutch national guidelines 2008					
I		T1–N0–M0 (low risk)[a]	No	TME	No
		T1–N0–M0 (high risk)	5×5 RT	TME	No
		T2	5×5 RT	TME	No
II		T3–N0–M0	5×5 RT	TME	No
		T4–N0–M0	5×5 RT	TME	No
III		N1	5×5 RT	TME	No
		N2	18×2 RT + chemotherapy[b]	TME	No
IV		M1	No recommendation		
Stage	Distance MRF	TNM	Neoadjuvant treatment	Surgical treatment	Adjuvant treatment
Dutch national guidelines 2014					
I		T1–N0–M0	No	TME	No
		T2–N0–M0	No	TME	No
II	>1 mm				
		T3–N0–M0 < 5 mm EI[c]	No	TME	No
		T3–N0–M0 > 5 mm EI	5×5RT	TME	No
	<1 mm				
		T3	RT + chemotherapy	TME	No
	Any				
		T4	RT + chemotherapy	TME	No
III		T1–N1–M0	5×5 RT	TME	No
		T2–N1–M0	5×5 RT	TME	No
		T3–N1–M0	5×5 RT		
		N2	RT + chemotherapy	TME	No
IV		M1	No recommendation		

MRF mesorectal fascia

[a]Low risk: G1 or G2 (good tumour differentiation) and no lymphatic or venous invasion

[b]Often used: capecitabine 825 mg/m^2 during RT

[c]Extramural invasion

Ethics

The study was approved by the ethics review board of Zuyderland MC Heerlen (16-N-148) and VieCuri Medical Centre.

Results

Patients

108 patients aged 80 or older were diagnosed with rectal cancer and were eligible for evaluation of the diagnostic process. 17 patients were diagnosed with stage IV and therefore excluded from treatment process analyses. Another five patients were excluded because of an unknown tumour stage, leaving 86 patients for evaluating treatment efficacy and toxicity (Fig. 1).

Baseline patient characteristics are presented in Table 2. Median age of the total population was 83 years (range 80–94 years) and 50% of patients was male. At least 74% of the patients were non-institutionalized patients. The Charlson score was ≥ 3 in 62% of the population. Unfortunately, the WHO performance score was not documented in 52% of the medical records and body mass index was not documented in 36% of the records. 55% of the patients used more than five medications at the time of diagnosis of rectal cancer.

Diagnostic process description

103 of 108 patients (95%) received diagnostic evaluation according to applicable guidelines leading to a clinical TNM stage (Table 2). Two patients refused diagnostic evaluation and one patient was evaluated and treated in another hospital. In one patient, the T-stage was inconclusive. The fifth

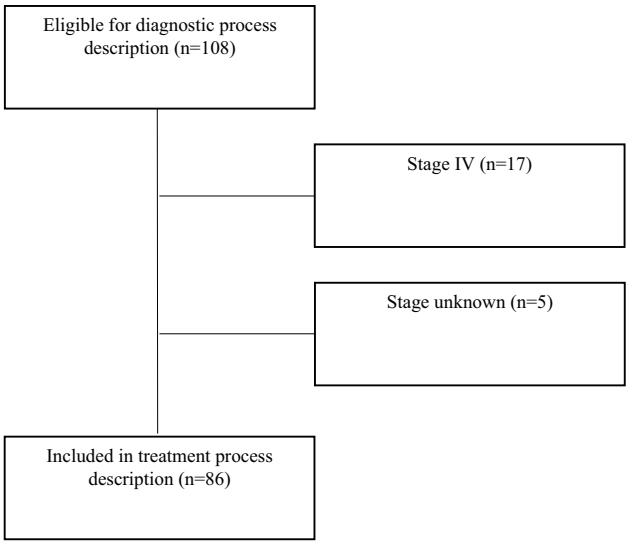

Fig. 1 Selection process

patient did not receive further diagnostics due to a present mild cognitive impairment, diagnosed by a geriatrician several years before the adenocarcinoma, and cognition was not re-evaluated due to a stroke at time of rectal bleeding. Most patients were diagnosed with stage III disease (30%), followed by stage II (29%), stage I (21%) and stage IV (16%).

Almost all patients ($n=104$, 96%) were discussed in a multidisciplinary team presenting a medical oncologist, gastroenterologist, surgeon, pathologist, radiologist, specialized nurse and sometimes a geriatrician. Three patients were not discussed multidisciplinary since they did not receive diagnostic evaluation as mentioned above. One patient was not discussed after successful removal of a malignant polyp.

Treatment process description

Of the 86 patients eligible for the treatment process description, 46 patients (54%) were treated according to the guideline, while 40 (46%) were not. A Charlson score of ≥ 3 and polypharmacy were significantly more often documented in patients not treated according to the guidelines ($p<0.05$, Table 2).

Of the 40 patients not treated according to guidelines, 11 (27%) preferred treatment other than recommended by guidelines. In 10 patients (25%), the physician decided to treat otherwise because of comorbidities ($n=5$), poor general condition ($n=2$), poor cognition subjectively described by the physician ($n=1$) or questionable staging ($n=2$).

For the remaining 19 patients (48%), no obvious motive could be detected from the medical charts for the decision not to treat according to guidelines.

Treatment outcome

44 patients (51%) experienced adverse events due to treatment (surgery, chemotherapy and/or radiotherapy), being significantly higher in patients treated according to the guidelines (66 versus 40%, $p=0.02$, Table 3) and in those with stage III disease (48 versus 26%, $p=0.04$). Furthermore, patients who experienced adverse events were younger (median age of 82 versus 84.5 years, $p=0.01$) and presented less often with polypharmacy (43 versus 67%, $p=0.03$). There was no significant association between adverse events and Charlson score. After adjustment for differences in age and polypharmacy, there was no significant difference found in the presence of adverse events in patients who were treated according to the guidelines when compared to those treated otherwise (OR 2.3, 95% CI 0.88–6.07). In this multivariable analysis, only age was significantly associated with the presence of adverse events (OR 0.8, 95% CI 0.72–0.98).

Complications led to hospitalisation in 36% of the patients treated according to guideline and in 38% of the patients treated otherwise.

Treatment in the guideline group included surgery more frequently compared to the non-guideline treated group (89 versus 53%, $p=0.00$) (Table 3). Surgery consisted in all but one case of total mesorectal excision (TME). In this one patient, a deviating stoma was made because of cT4N0M0 rectal cancer. No significant difference was found in method of total mesorectal excisions (initial open versus laparoscopic) between the guideline group and the non-guideline group. A total of ten laparoscopic surgeries were converted to an open surgery (eight in the guideline group and two in the non-guideline group). Reasons for conversion were exposure difficulties or tumour characteristics which needed open surgery ($n=7$), complications during surgery ($n=2$), and patients related characteristics/problems due to comorbidities ($n=1$). Most conversions took place within the first 2 years after the introduction of laparoscopic rectal surgery in the presenting hospitals (2011 and 2012).

Adverse events due to surgery, although nonsignificant, were reported more frequently in the guideline treated group (66 versus 48%, $p=0.17$). In five (12.2%) of all patients who underwent surgery, a second surgical procedure was needed during hospitalisation due to complication of the initial surgery. Four of these were treated according to the guideline and four of the five initial surgeries were open procedures. Besides that, three (7.3%) of all patients who underwent surgery died during hospitalisation of initial surgery. Two of these patients were treated according to the guideline, while one did not receive neoadjuvant chemotherapy although advised by guideline. Nine surgical procedures according to the guideline (22%), led to an unplanned hospitalisation due to adverse events, while this occurred in three surgical

Table 2 Baseline characteristics

	Total	Guideline	Non-guideline	*p* value[a]	Stage unknown/IV
N (%)	108 (100)	46 (42.6)	40 (37.0)		22 (20.4)
Male, *n* (%)	54 (50.0)	23 (50.0)	18 (45.0)	0.643	13 (59.1)
Median age, years (range)	83 (80–94)	83 (80–93)	84 (80–94)	0.250	82.5 (80–93)
Living situation, *n* (%)				0.714	
At home	80 (74.1)	30 (65.2)	32 (80.0)		18 (81.8)
Institutionalized	10 (9.3)	3 (6.5)	5 (12.5)		2 (9.1)
Missing	18 (16.7)	13 (28.3)	3 (7.5)		2 (9.1)
Marital status, *n* (%)				0.511	
Married	54 (50.0)	16 (34.8)	23 (57.5)		15 (68.2)
Not married/widowed	22 (20.4)	10 (21.7)	10 (25.0)		2 (9.1)
Missing	32 (29.6)	20 (43.5)	7 (17.5)		5 (22.7)
Charlson score, *n* (%)				**0.047***	
2	41 (38.0)	21 (45.7)	10 (25.0)		10 (45.5)
≥ 3	67 (62.0)	25 (54.3)	30 (75.0)		12 (54.5)
Polypharmacy, *n* (%)				**0.031***	
Yes	59 (54.6)	19 (41.3)	28 (70.0)		10 (54.5)
No	42 (38.9)	22 (47.8)	12 (30.0)		8 (36.4)
Missing	7 (6.5)	5 (10.9)	0 (0.0)		2 (9.1)
WHO score, *n* (%)					
0	27 (25.0)	11 (23.9)	10 (25.0)		6 (27.3)
1	17 (15.7)	8 (17.4)	6 (15.0)		3 (13.6)
2	8 (6.5)	2 (4.3)	3 (7.5)		3 (9.1)
Missing	56 (51.9)	25 (54.3)	21 (52.5)		10 (45.5)
Body mass index, *n* (%)				0.522	
< 20	6 (5.6)	2 (4.3)	2 (5.0)		2 (9.1)
20–30	51 (47.2)	23 (50.0)	19 (47.5)		9 (40.9)
> 30	12 (11.1)	9 (19.6)	3 (7.5)		0 (0.0)
Missing	39 (36.1)	12 (26.1)	16 (40.0)		11 (50.0)
Stage, *n* (%)				0.382	
I	23 (21.3)	12 (26.1)	11 (27.5)		–
II	31 (28.7)	14 (30.4)	17 (42.5)		–
III	32 (29.6)	20 (43.5)	12 (30.0)		–
IV	17 (15.7)	–	–		17 (77.3)
Missing	5 (4.6)	–	–		5 (22.7)
Received diagnostics, *n* (%)					
Colonoscopy	107 (99.1)	46 (100)	39 (97.5)	0.465	22 (100)
MRI rectum	93 (86.1)	42 (91.3)	36 (90.0)	1.000	15 (68.2)
Endoscopic ultrasound	3 (2.8)	3 (6.5)	0 (0.0)	0.245	0 (0.0)
CT-abdomen[b]	68 (63.0)	23 (50.0)	29 (72.5)	**0.033***	16 (72.7)
MRI liver[b]	35 (32.4)	22 (47.8)	10 (25.0)	0.029	3 (13.6)
X-thorax	101 (93.5)	44 (95.7)	38 (95.0)	1.000	19 (86.3)
Discussed multidisciplinary, *n* (%)	104 (96.3)	45 (97.8)	40 (100)	1.000	19 (86.4)

* Statistical significance

[a]Patients treated according to guideline versus patients not treated according to guideline

[b]Distant metastasis was recommended to be investigated by MRI of the liver or by CT-abdomen

procedures in patients who were treated otherwise (14%) (Table 3). This difference was not statistically significant ($p = 0.38$).

Patients treated according to the guideline also experienced adverse events due to radiotherapy more often, although not significant (12 versus 3%, $p = 0.39$). Adverse

Table 3 Adverse events and hospitalisation due to cancer therapy

	Patients characteristics related to adverse events, univariate analysis		
	Adverse event	No adverse event	*p* value
Total, *n* (%)	44 (51)	42 (48.9)	
Guideline treatment, *n* (%)			
Yes	29 (65.9)	17 (40.5)	**0.02***
No	15 (34.1)	25 (59.5)	
Age, median (range)	82 (80–93)	84.5 (80–94)	**0.01***
Stage, *n* (%)			
I–II	23 (52.3)	31 (73.8)	**0.039***
III	21 (47.7)	11 (26.2)	
Polypharmacy, *n* (%)			
Yes	19 (43.2)	28 (66.7)	**0.031***
No	22 (50.0)	12 (28.5)	
Missing	3 (6.8)	2 (4.8)	
Charlson score, *n* (%)			
2	18 (41.0)	13 (31.0)	0.336
≥3	26 (59.1)	29 (69.0)	

	Adverse events and hospitalisations per treatment modality					
	Guideline (*n* = 46)			Non-guideline (*n* = 40)		
	Received treatment, *n*	Adverse events, *n* (%)	Hospitalisations, *n* (%)	Received treatment, *n*	Adverse events, *n* (%)	Hospitalisations, *n* (%)
Total treatments	90	33 (36.7)	12 (36.4)	59	16 (27.1)	6 (37.5)
Radiotherapy	41	5 (12.2)	3 (7.3)	29	1 (3.4)	0 (0.0)
Chemotherapy	8	1 (12.5)	0 (0.0)	9	5 (55.6)	3 (33.3)
Surgery	41	27 (65.9)	9 (22.0)	21	10 (47.6)	3 (14.3)

* Statistical significance

events due to radiotherapy led to hospitalisation in three cases, which were all patients treated according to the guideline.

Controversially, patients treated otherwise experienced adverse events due to chemotherapy more often (56 versus 13%, $p = 0.13$) which led to an unplanned hospitalisation in three cases, who were all patients treated otherwise.

Figure 2 shows that 18 months after diagnosis 20% of the patients who were treated according to the guideline were deceased compared to 44% of those treated otherwise ($p = 0.02$). It is notable that the Kaplan–Meier curves cross around 150 days after diagnosis, showing more deaths occur in the guideline group in the first 150 days.

Discussion

The aim of our study was to evaluate efficacy of diagnosis and treatment according to guidelines among octogenarians with rectal cancer. Our study shows that almost all patients were diagnosed according to guidelines and were discussed in a multidisciplinary board. In the past, the diagnostic process (especially full visualisation of the colon) was not always adequate, although improvements were yet described [15, 16].

Although the diagnostic process was performed accurate, only 54% of the patients were treated according to the guidelines. This implicates that current guidelines seem not applicable enough for octogenarians. When documented, comorbidities are one of the main reasons for physicians to deviate from the guidelines. Furthermore, this study confirms that octogenarians often decide to deviate from guidelines. This was also seen in the previous studies [7, 17, 18]. However, since this was a retrospective study, one cannot be certain that patients were well informed before making a decision. Besides that, in almost half of the patients not treated by guideline, no reasons for deviation could be detected at all. This implicates that documentation, and subsequently our knowledge, of reasons to deviate from guidelines is still lacking,

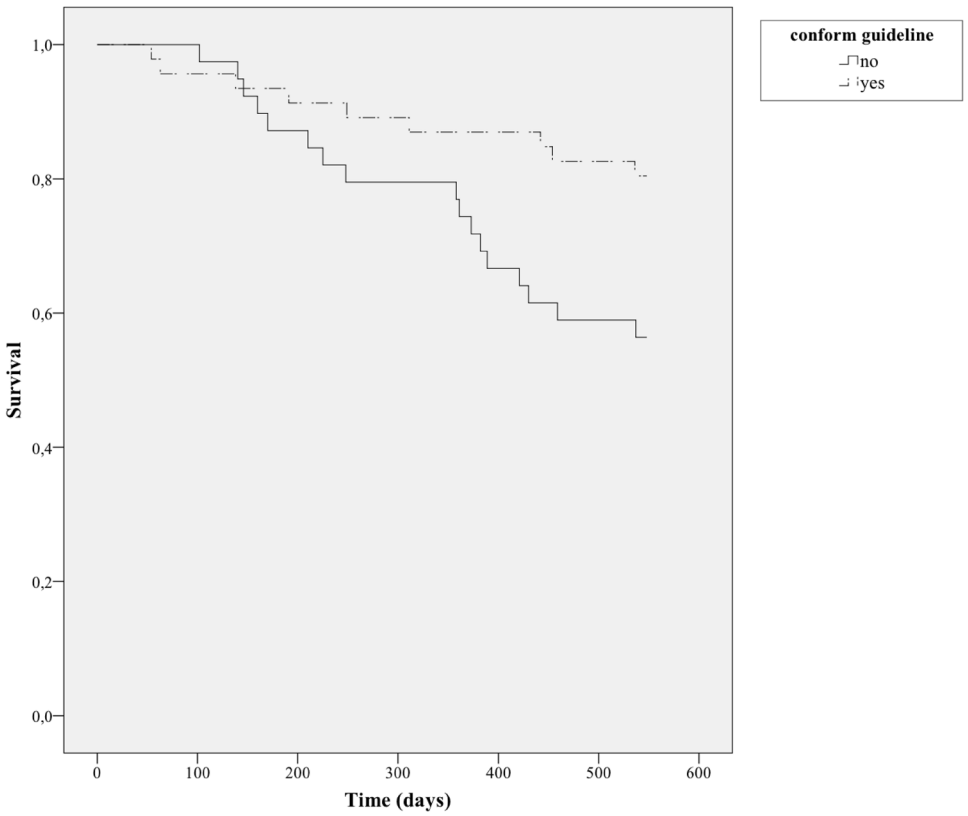

Fig. 2 Kaplan–Meier survival analyses

which makes it difficult to review current guidelines for octogenarians.

Patients who did receive treatment according to the guideline experienced better 18-month survival than patients who were treated otherwise (after a slightly worse survival in the first 150 days after diagnosis, which might be due to treatment-related complications). A better long-term survival for older persons who were treated according to the guidelines was also seen in previous studies [19, 20]. Unfortunately, we could not adjust for factors such as comorbidities and age in a multivariate analysis because of low power. In addition, since the cause of death was not a study outcome, recorded mortality may have been due to other causes than rectal cancer-related causes. However, Dekker et al. showed the 1-year mortality in patients aged > 75 years with colorectal cancer is mainly attributed to colorectal cancer itself, and less common to other causes [21]. Nevertheless, we could not confirm treatment according to guideline as independent predictor for survival.

Although treatment according to the guideline seems to lead to a better survival, this study shows that a substantial number of complications occurred in octogenarians (51%), with treatment according to the guideline as a predictor in univariate analysis. However, after adjustment for age and polypharmacy, treatment according to the guideline was no longer significantly associated with complications. It was remarkable that the multivariate analysis showed high age as a protective factor for the occurrence of complications in octogenarians, while most studies show high age as risk factor for occurrence of complications [9, 22, 23]. We hypothesize that age was taken into account when treatment choice was made by physicians. This may have led to more intensive treatment in younger octogenarians, which may have had obscured frailty.

In this study, complications occurred more often in patients treated according to the guideline, especially surgery-related complications (although this was not significant when adjusted for age and polypharmacy). In addition, more hospitalisations due to surgical complications were documented in the patients treated according to the guideline. These hospitalisations implicate that treatment-related complications can have a substantial impact in octogenarians. Although our study did not show statistical significance in this matter, this finding is in concordance with previous studies which showed that treatment-related complications in patients aged > 70 years lead to more extensive results, such as worse survival rates, when compared to younger patients [7, 9, 21]. Besides that, previous studies have shown that surgical complications increase the risk of failure to returning to premorbid functioning [24]. Therefore, based on this retrospective study, the effect of surgery on the remaining quality of life should not be underestimated in an octogenarian. However, one should take into account that a possible learning curve of laparoscopic surgery was seen in

this study. The fact that most conversions to open surgery took place in the first 2 years after implementation of laparoscopic rectal surgery supports this theory.

In contrast with surgery, our study shows that chemotherapy led to more complications and hospitalisations in patients who were not treated according to the guideline. The presence of polypharmacy in this group might be a reason for this effect, since some previous studies have shown that polypharmacy leads to a greater risk of toxicity and readmission [25, 26], although others did not [27, 28]. Another reason may be the selection bias of more fragile patients in this group.

Nevertheless, a good estimation of the occurrence of complications should be made before start of the treatment. The International Society of Geriatric Oncology (SIOG) recommended that a form of a geriatric assessment may help in the prediction of treatment-related complications and decision-making [29, 30]. Studies have shown that a geriatric assessment (GA) can reveal obscured frailty and leads to changes in treatment plan or to optimisation of geriatric domains, which contribute to frailty, prior to treatment [31, 32]. In addition, there are some studies which show that certain geriatric domains, such as nutritional status and comorbidity, appear to be predictive for mortality and other factors, such as a summary frailty score based on a comprehensive GA, appear to be predictive for mortality and toxicity in older cancer patients [33]. The amount of missing data on nutritional status and WHO performance score in this retrospective cohort study shows that geriatric domains which could affect treatment outcomes were not standard documented in our hospitals. A geriatric assessment could have contributed in this. However, geriatric assessments are time consuming and there is no hard evidence for the effect of a GA-based treatment decision on mortality and toxicity yet. Therefore, it is recommended to perform a prospective study to assess the effect of a (abbreviated) GA, as a treatment decision-making tool, on patients survival and toxicity.

The fact that this was a retrospective study is the main weakness of this study. It could have led to misinterpretations of the data. As said, the design of our study led to missing data which could have been important, such as nutritional status and WHO performance status, because these domains were not standard documented by the physicians. Second, our study population was quite small which led to only partial adjustment for the presence of selection bias. The strength of this study was the description of the diagnostic and treatment process in an unselected population which is underrepresented in the present literature and guidelines, the octogenarians. In addition, we specifically described patients with adenocarcinoma of the rectum. Most previous studies described patients with colon and rectal carcinoma, while these require a different approach [11, 12].

Conclusion

In conclusion, based on this retrospective cohort study, the value of current guidelines is questionable since they seem to be used for only a selected number of (very) old patients with rectal cancer. Treating octogenarians according to the guidelines seems to improve overall survival 18 months after diagnosis, but seems also to be accompanied with a higher risk of complications, which may jeopardise quality of life. More, and preferable prospective, studies with very old people are needed to fine-tune current guidelines and to create a guideline applicable for octogenarians, taking both survival time and quality of life into account, which helps in shared clinical decision-making.

Author contributions Study concept: FB, AV. Study design: FB, AV, MLJ-H. Data acquisition: AV, LV. Quality control of data and algorithms: AV, MLJ-H. Data analysis and interpretation: AV, FB, YW, EB, FJV, MLJ-H. Statistical analysis: AV, MLJ-H. Manuscript preparation: AV, FB, YW, MLJ-H. Manuscript editing: AV, FB, YW, EB, FJV, MLJ-H. Manuscript review: AV, FB, YW, EB, FJV, MLJ-H.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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