Original article

Outcomes with multimodal therapy for elderly patients with rectal cancer

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Background: **Treatment guidelines for stage II and III rectal cancer include neoadjuvant chemoradiotherapy, surgery and postoperative adjuvant chemotherapy. Although data support this recommendation in younger patients, it is unclear whether this benefit can be extrapolated to elderly patients (aged 75 years or older).**

Methods: **This was a retrospective review of patients aged at least 75 years with stage II or III rectal cancer who underwent surgery with curative intent from 1996 to 2013 at the Mayo Clinic. Kaplan–Meier analysis and log rank test were used to compare overall survival between therapy groups. Cox proportional hazards model was used to estimate the independent effect of treatment group on survival.**

Results: **A total of 160 elderly patients (median age 80 years) with stage II (66) and stage III (94) rectal cancer underwent surgical resection. Only 30·0 and 33·8 per cent received neoadjuvant or adjuvant therapy respectively. Among patients with stage II disease, there was no significant difference in 60-month survival between patients who received any additional therapy and those who had surgery alone (55 *versus* 38 per cent respectively; $P = 0{\cdot}184$), whereas additional therapy improved survival in patients with stage III tumours (58 *versus* 30 per cent respectively; $P = 0{\cdot}007$). Multivariable analysis found a survival benefit for additional therapy in elderly patients with stage III disease (hazard ratio 0·58, 95 per cent c.i. 0·34 to 0·98).**

Conclusion: **A multimodal approach in elderly patients with stage III rectal cancer improved oncological outcomes.**

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Introduction

Cancer remains the second most common cause of death in people aged 75 years and over worldwide[1]. Although deaths from colorectal cancer have stabilized in many western and northern European countries, colorectal cancer remains the third most common cancer worldwide, and 37 per cent of all colorectal cancers occur in people aged 75 years or more[2,3]. As the proportion of people aged at least 75 years increases, the number of elderly patients with rectal cancer is likely to continue to increase[4–6]. Healthy individuals over the age of 75 years can expect to live another 10 years, and even those with colorectal cancer can anticipate a life expectancy of more than 5 years[7,8]. Therefore, surgeons are increasingly faced with treating elderly patients with rectal cancer. The drive to treat these patients aggressively is supported by the current US, UK and European national treatment guidelines for locally advanced rectal cancer, which all recommend neoadjuvant chemoradiotherapy followed by surgery with curative intent and postsurgical adjuvant chemotherapy[9–11]. Rectal cancer is predominately a disease of the elderly, and 70 per cent of those affected present with stage II–III disease[12,13]. Therefore, determining the optimal management strategy for elderly patients with stage II and III disease is crucial.

There is a clear survival benefit of neoadjuvant and postresection adjuvant therapy for younger patients with stage II and III rectal cancer[14–16]. However, the median

age in these studies was 58–69 years, and it is unclear whether these findings can be extrapolated to patients aged 75 years or more[17–23]. Studies[24–26] have shown that adjuvant therapies in the elderly can significantly decrease quality of life. Patients aged 75 years and over have an increased risk of morbidity compared with younger patients, probably because they have an average of five other medical conditions at the time of diagnosis of colorectal cancer, and the rate of co-morbidities in this group is increasing[27–30]. This partially explains why only half of elderly patients receive the recommended treatment for stage III rectal cancer[31,32]. Unfortunately, it is often difficult to determine why these patients do not receive additional therapy from national database studies.

As the burden of cancer in the elderly population continues to increase around the world it is important continually to reassess whether current recommended treatment regimens are beneficial[33–35]. This study assessed whether a clinically significant survival was associated with neoadjuvant and/or adjuvant therapy together with potentially curative resection of stage II and III rectal cancer in patients aged at least 75 years.

Methods

As a National Cancer Institute-designated Cancer Center, Mayo Clinic in Rochester, Minnesota, maintains a prospective tumour registry. After obtaining institutional review board approval, all patients aged 75 years and above with stage II and III rectal carcinoma, who underwent surgery with curative intent at this centre between 1996 and 2013, were identified. Patients undergoing palliative surgery were excluded.

Data from medical records were used to confirm and update findings from the tumour registry. Follow-up information was also updated through annually mailed surveys. Operative details and information regarding the triage of patients to one therapy group or another was captured when available. The Charlson/Deyo Co-morbidity Index (CCI) score was calculated, with a score of 0 indicating no co-morbid conditions recorded, 1 indicating one co-morbid condition, and 2 or above indicating the appropriate number of co-morbid conditions. The primary outcome was overall survival.

Practice standards at this institution have followed the National Institutes of Health guidelines, which were first reported in 1990[14], and subsequently the National Comprehensive Cancer Network (NCCN) guidelines[36] published in 1996. In accordance with the sixth edition of the American Joint Committee on Cancer (AJCC) TNM system[37], radiotherapy and concomitant 5-fluorouracil chemotherapy are offered routinely to all patients with stage II or III rectal cancer. Patients who do not receive chemoradiotherapy either decline treatment, have medical contraindications to radiotherapy, develop postoperative complications leading to no treatment, or are deemed too ill to tolerate irradiation and chemotherapy. Of note, eight patients in the present study were not offered neoadjuvant radiation because of a history of irradiation to the pelvis, but standard practice is to recommend additional radiotherapy even if the patient has been irradiated previously. Adjuvant chemotherapy is advised in all patients after successful surgical recovery, generally consisting of eight cycles of an oxaliplatin-based regimen.

To evaluate the effect of additional therapy, patients who received any therapy in addition to surgery were grouped and compared with those who received surgery alone. In the additional therapy group, a comparison was made between patients who received neoadjuvant chemoradiotherapy followed by surgery with curative intent, and those who had surgery first followed by postresection adjuvant chemotherapy.

Statistical analysis

Normally distributed data, expressed as mean(s.d.), were examined with the Student's *t* test. Non-normally distributed data, presented as median (i.q.r.), were analysed by means of the Mann–Whitney *U* test. Fisher's exact test was used to examine categorical variables. Survival analysis was performed using the method of Kaplan and Meier, with survival defined as time from diagnosis to death or censoring. Patients were censored at the date of last correspondence or follow-up. Survival curves were compared with the log rank test. To estimate the independent effect of treatment group on survival, a Cox proportional hazards model was developed, which included treatment group, CCI score, tumour location, year of diagnosis, tumour grade and operation type. $P < 0{\cdot}050$ was considered statistically significant for all comparisons. Statistical analysis was performed with R version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall outcomes

The study included 160 patients aged at least 75 years who underwent surgery with curative intent for stage II (66) or III (94) rectal cancer between 1996 and 2013. Median age at diagnosis was 80 (range 75–93, i.q.r. 77–83) years, and 85·6 per cent were Caucasian. Procedures performed were abdominoperineal resection (85, 53·1 per cent), low anterior resection (70, 43·8 per cent) and coloanal anastomosis

Table 1 Characteristics of elderly patients with stage II and III rectal cancer

	Stage II ($n=66$)	Stage III ($n=94$)	P*
Age (years)			0·015
75–80	31 (47)	64 (68)	
81–85	20 (30)	21 (22)	
> 85	15 (23)	9 (10)	
Sex ratio (M : F)	50 : 16	64 : 30	0·380
Caucasian	57 (86)	80 (85)	1·000
CCI score			0·072
0	30 (45)	49 (52)	
1	13 (20)	27 (29)	
≥ 2	23 (35)	18 (19)	
Year of diagnosis			0·062
1996–2002	22 (33)	49 (52)	
2003–2008	32 (48)	33 (37)	
2009–2013	12 (18)	12 (13)	
Tumour extent			< 0·001
T1	–	4 (4)	
T2	–	18 (19)	
T3	61 (92)	65 (69)	
T4	5 (8)	7 (7)	
High tumour grade	51 (77)	76 (81)	0·725
Node status			< 0·001
N0 (no positive nodes)	66 (100)	9 (10)	
N1 (1–3)	–	58 (62)	
N2 (≥ 4)	–	27 (29)	
Tumour location			0·321
Unknown	0 (0)	1 (0)	
Proximal rectum	22 (33)	20 (21)	
Mid rectum	16 (24)	26 (28)	
Distal rectum	28 (42)	47 (50)	
Margin-positive	5 (8)	5 (5)	0·742
Procedure			0·763
APR	35 (53)	50 (53)	
LAR	28 (42)	42 (45)	
Total proctectomy	3 (5)	2 (2)	
Surgical approach			0·926
Open	57 (86)	83 (88)	
Laparoscopic	6 (9)	7 (7)	
Hand-assisted	3 (5)	4 (4)	

Values in parentheses are percentages. CCI, Charlson/Deyo Co-morbidity Index; APR, abdominoperineal resection; LAR, low anterior resection. *Fisher's exact test.

(5, 3·1 per cent). Overall, 87·5 per cent had an open operation and the remainder underwent minimally invasive approaches. Of 159 tumours with a known location, most were located in the distal rectum (75, 47·2 per cent); the remainder were in the mid (42, 26·4 per cent) or proximal (42, 26·4 per cent) rectum. All patients had pathologically confirmed adenocarcinoma, with two of the signet ring subtype and nine being mucinous. The majority of tumours were high grade (127, 79·4 per cent) with a mean size of 4·21(1·86) cm. A mean of 16·5(10·9) lymph nodes were examined. R0 resections were accomplished in 150 patients (93·8 per cent) and ten had positive radial margins. Of the patients with distal tumours, five had a radial margin of 2 mm or less. The overall 30-day mortality rate was 1·9 per cent and the 90-day mortality rate 3·9 per cent.

Table 2 Characteristics of elderly patients with rectal cancer by therapy type

	Any additional therapy ($n=82$)	Surgery alone ($n=78$)	P*
Age (years)			0·162
75–80	52 (63)	43 (55)	
81–85	22 (27)	19 (24)	
> 85	8 (10)	16 (21)	
Sex ratio (M : F)	60 : 22	54 : 24	0·707
Caucasian	69 (84)	68 (87)	0·748
CCI score			0·329
0	44 (54)	35 (45)	
1	21 (26)	19 (24)	
≥ 2	17 (21)	24 (31)	
Year of diagnosis			0·293
1996–2002	32 (39)	39 (50)	
2003–2008	38 (46)	27 (35)	
2009–2013	12 (15)	12 (15)	
Tumour extent			0·147
T1	4 (5)	0 (0)	
T2	9 (11)	9 (12)	
T3	61 (74)	65 (83)	
T4	8 (10)	4 (5)	
High tumour grade	72 (88)	55 (71)	0·012
Node status			0·347
N0 (no positive nodes)	35 (43)	40 (51)	
N1 (1–3)	30 (37)	28 (36)	
N2 (≥ 4)	17 (21)	10 (13)	
Tumour location			0·483
Unknown	1 (1)	0 (0)	
Proximal rectum	19 (23)	23 (29)	
Mid rectum	20 (24)	22 (28)	
Distal rectum	42 (51)	33 (42)	
Margin-positive	4 (5)	6 (8)	0·683
Procedure			0·066
APR	45 (55)	40 (51)	
LAR	37 (45)	33 (42)	
Total proctectomy	0 (0)	5 (6)	
Surgical approach			0·524
Open	71 (87)	69 (88)	
Laparoscopic	6 (7)	7 (9)	
Hand-assisted	5 (6)	2 (3)	

Values in parentheses are percentages. CCI, Charlson/Deyo Co-morbidity Index; APR, abominoperineal resection; LAR, low anterior resection. *Fisher's exact test.

A higher proportion of patients with stage III disease were aged 75–80 years (68 per cent *versus* 47 per cent for stage II; $P=0·015$), but sex, race, CCI score, year of diagnosis, margin-positive rate, tumour grade, tumour location, procedure and approach were similar in the two stage groups (*Table 1*).

Comparing all patients who received any additional therapy with those who had surgery alone, those in the additional therapy group were more likely to have high-grade tumours (88 *versus* 71 per cent; $P=0·012$). Age, sex, race, CCI score, year of diagnosis, tumour extent, number of positive nodes, tumour location, margin-positive rate, procedure and approach were similar in the two groups (*Table 2*).

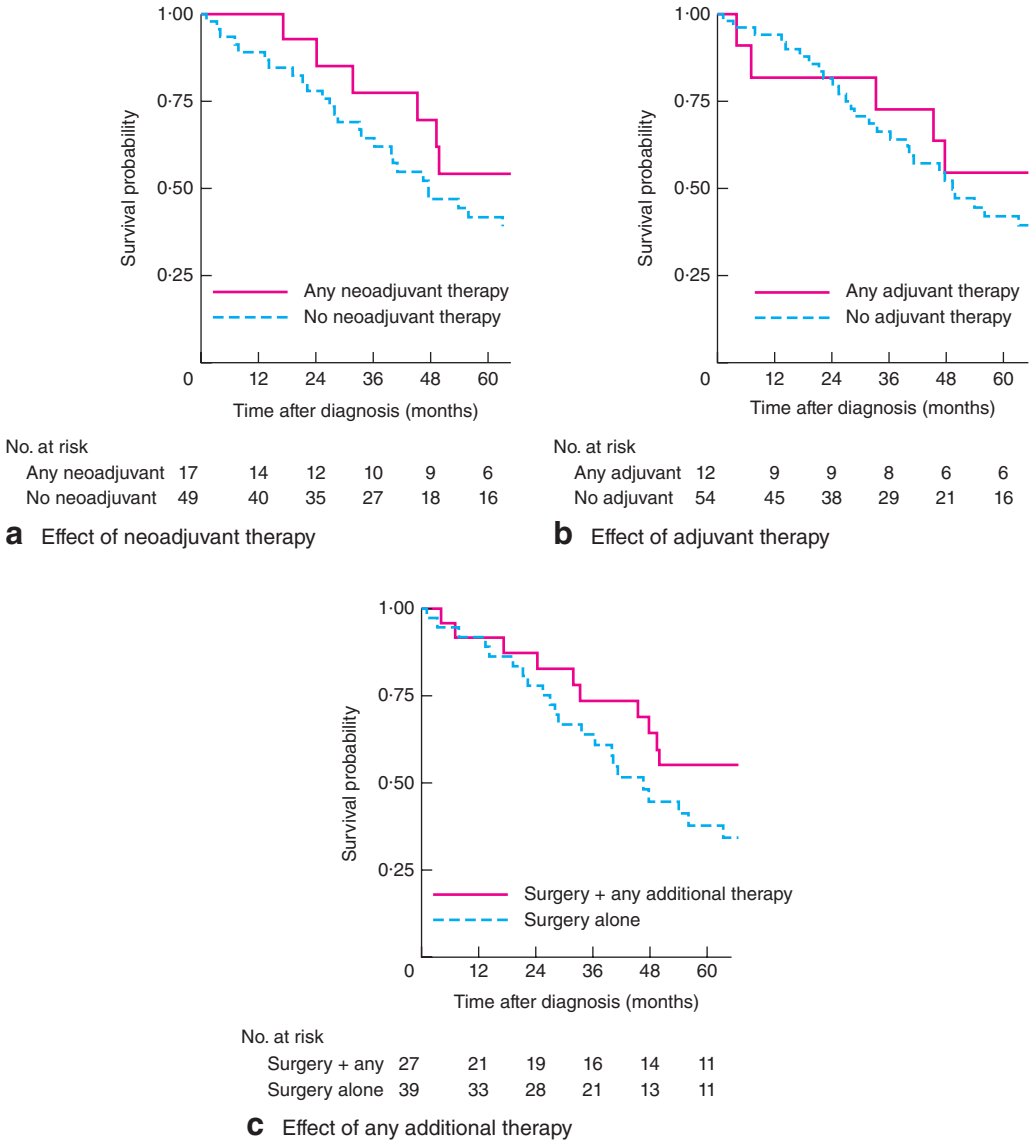

Fig. 1 Survival of patients with stage II rectal cancer, comparing effect of **a** neoadjuvant therapy *versus* no neoadjuvant therapy, **b** adjuvant therapy *versus* no aduvant therapy and **c** any additional therapy *versus* surgery alone. **a** $P = 0{\cdot}398$, **b** $P = 0{\cdot}375$, **c** $P = 0{\cdot}184$ (log rank test)

Stage II rectal cancer outcomes

Kaplan–Meier analysis showed no significant difference in survival distribution curves for elderly patients with stage II disease who received neoadjuvant therapy compared with those who did not have preoperative treatment (*Fig. 1a*), or for patients who received post-resection adjuvant therapy compared with those who did not (*Fig. 1b*). Any additional therapy, regardless of type or timing, did not show a statistically significant survival benefit, but the survival curves did separate (60-month survival 55 *versus* 38 per cent respectively for any additional therapy *versus* surgery alone; $P = 0{\cdot}184$) (*Fig. 1c*). A conditional survival analysis excluding patients who died within 12 months of surgery also failed to show a benefit of any additional therapy (*versus* surgery alone) in patients with stage II disease ($P = 0{\cdot}163$).

Stage III rectal cancer outcomes

For elderly patients with stage III rectal cancer, there was improved overall survival for those who received neoadjuvant therapy compared with those who did not (*Fig. 2a*). A similar survival benefit was noted for patients

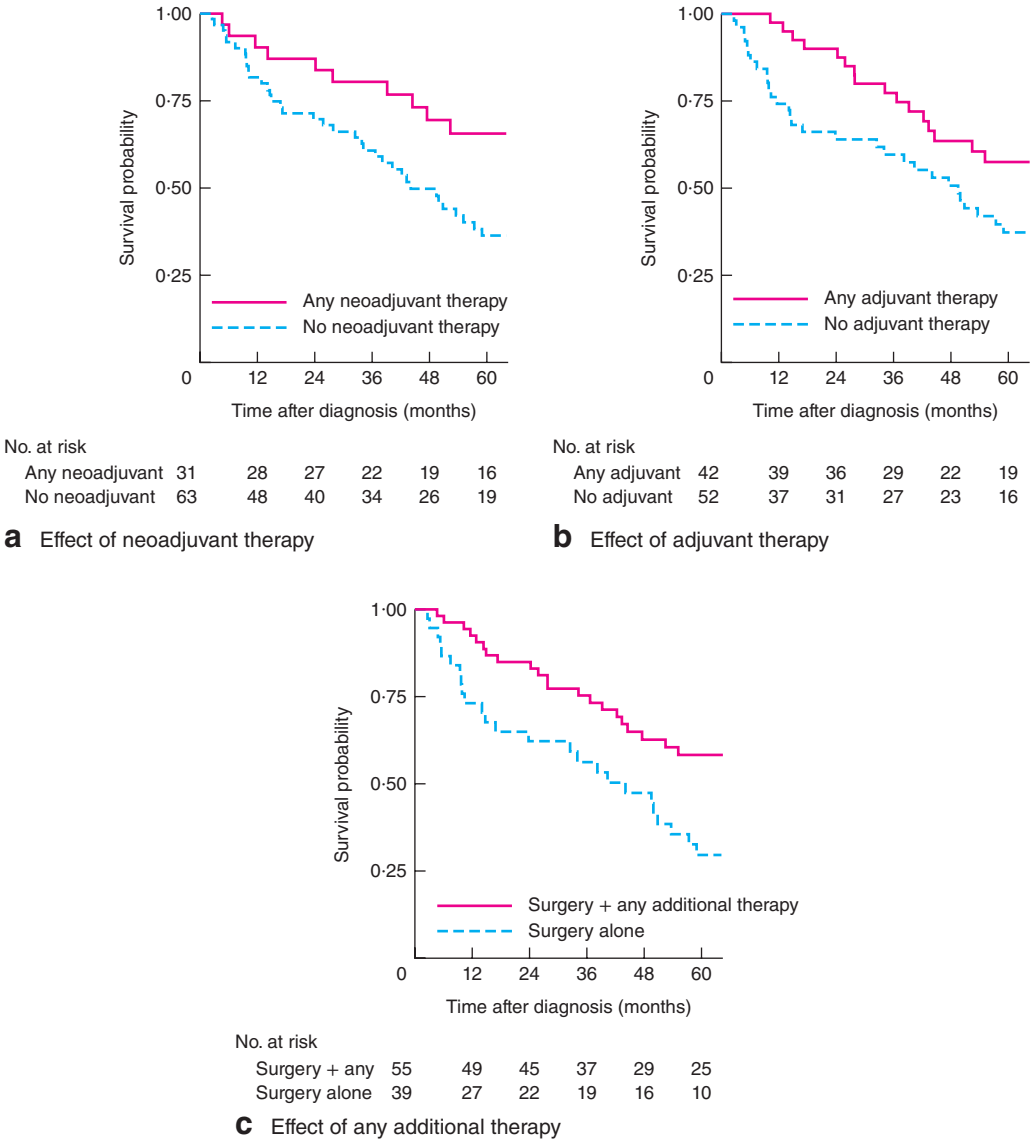

Fig. 2 Survival of patients with stage III rectal cancer, comparing effect of **a** neoadjuvant therapy *versus* no neoadjuvant therapy, **b** adjuvant therapy *versus* no aduvant therapy and **c** any additional therapy *versus* surgery alone. **a** $P = 0{\cdot}017$, **b** $P = 0{\cdot}009$, **c** $P = 0{\cdot}007$ (log rank test)

with stage III who received adjuvant therapy compared with those who did not have postresection therapy (*Fig. 2b*). Patients who received any adjuvant therapy, regardless of type or timing, had significantly better survival than those who underwent surgery alone (60-month survival 58 *versus* 30 per cent respectively; $P = 0{\cdot}007$) (*Fig. 2c*).

Multivariable analysis

Multivariable analysis including all elderly patients, regardless of stage, showed that receiving any additional therapy was associated with improved survival, and a CCI score of 2 or more was an independent predictor of worse survival (*Table 3*). Increasing age also appeared to confer worse survival, but this did not reach statistical significance. The survival benefit of additional therapy was not significant in analysis of patients with stage II disease; however, increasing age was predictive of decreased survival in this subgroup (*Table 4*). The survival benefit conferred by additional therapy in patients with stage III tumours was confirmed by multivariable analysis.

Table 3 Multivariable cox proportional hazards survival analysis for stage II and III rectal cancer combined

	Hazard ratio	*P*
Therapies		
Surgery alone	1·00 (reference)	
Additional therapies	0·58 (0·38, 0·88)	0·011
Age (years)		
75–80	1·00 (reference)	
81–85	1·57 (0·99, 2·50)	0·056
> 85	1·68 (0·96, 2·94)	0·070
CCI score		
0	1·00 (reference)	
1	1·33 (0·81, 2·17)	0·260
≥ 2	2·11 (1·29, 3·46)	0·003
Year of diagnosis		
1996–2002	1·00 (reference)	
2003–2008	1·07 (0·70, 1·65)	0·749
2009–2013	1·19 (0·56, 2·53)	0·656
Tumour location		
Distal	1·00 (reference)	
Mid	0·90 (0·57, 1·42)	0·654
Proximal	0·97 (0·60. 1·57)	0·913
Tumour grade		
Low	1·00 (reference)	
High	1·45 (0·87, 2·42)	0·148
Tumour stage		
II	1·00 (reference)	
III	1·14 (0·76, 1·70)	0·539

Values in parentheses are 95 per cent c.i. CCI, Charlson/Deyo Co-morbidity Index.

Reasons for no additional therapy

Across stage II and III rectal cancers, 48 patients (30·0 per cent) received neoadjuvant chemotherapy and/or radiation (2 neoadjuvant chemotherapy only, 3 neoadjuvant radiation only, 43 both). Of the 112 patients who did not receive any neoadjuvant therapy, 69 had sufficient documentation regarding why this decision was made (*Table 5*). Not recommended was the most common reason (45 per cent) to explain why patients with stage II (14 of 32) and III (17 of 37) did not receive neoadjuvant therapy before surgical resection.

For stage II and stage III disease, 54 patients (33·8 per cent) received adjuvant chemotherapy and/or radiation (28 adjuvant chemotherapy only, 1 adjuvant radiation only, 25 both). Of the patients who did not have adjuvant therapy, the reasons were documented sufficiently for 65 (*Table 5*). Co-morbidity, perioperative morbidity and patient preference accounted for 27 of 34 patients with stage II disease, and all 31 patients with stage III disease not receiving any additional therapy. When considering any therapy regardless of timing, only 82 (51·3 per cent) of the patients had chemotherapy or radiation therapy.

There was no difference in receipt of neoadjuvant therapy by stage (74 per cent of patients with stage II and 67 per cent with stage III disease did not have neoadjuvant

Table 4 Multivariable cox proportional hazards survival analysis for stage II and III rectal cancer

	Stage II		Stage III	
	Hazard ratio	*P*	Hazard ratio	*P*
Therapies				
Surgery alone	1·00 (reference)		1·00 (reference)	
Additional therapies	0·59 (0·28, 1·24)	0·164	0·58 (0·34, 0·98)	0·043
Age (years)				
75–80	1·00 (reference)		1·00 (reference)	
81–85	2·56 (1·12, 5·89)	0·026	1·23 (0·62, 2·45)	0·551
> 85	2·71 (1·15, 6·36)	0·022	1·49 (0·62, 3·55)	0·371
CCI score				
0	1·00 (reference)		1·00 (reference)	
1	2·12 (0·86, 5·25)	0·103	1·21 (0·65, 2·26)	0·549
≥ 2	3·04 (1·45, 6·38)	0·003	2·08 (0·95, 4·57)	0·068
Year of diagnosis				
1996–2002	1·00 (reference)		1·00 (reference)	
2003–2008	1·80 (0·85, 3·81)	0·125	0·89 (0·51, 1·56)	0·683
2009–2013	2·07 (0·65, 6·60)	0·218	0·83 (0·27, 2·55)	0·751
Tumour location				
Distal	1·00 (reference)		1·00 (reference)	
Mid	1·63 (0·69, 3·87)	0·266	0·79 (0·44, 1·43)	0·441
Proximal	2·13 (0·96, 4·73)	0·063	0·69 (0·35, 1·37)	0·292
Tumour grade				
Low	1·00 (reference)		1·00 (reference)	
High	1·50 (0·60, 3·73)	0·382	1·37 (0·70, 2·66)	0·358

Values in parentheses are 95 per cent c.i. CCI, Charlson/Deyo Co-morbidity Index.

Table 5 Reasons why additional therapy was not given

	All patients	Stage II	Stage III
No neoadjuvant therapy	(*n* = 69)	(*n* = 32)	(*n* = 37)
Not recommended	31 (45)	14 (44)	17 (46)
Co-morbidity	18 (26)	8 (25)	10 (27)
Patient declined	20 (29)	10 (31)	10 (27)
No adjuvant therapy	(*n* = 65)	(*n* = 34)	(*n* = 31)
Not recommended	7 (11)	7 (21)	0 (0)
Co-morbidity	14 (22)	5 (15)	9 (29)
Patient declined	34 (52)	17 (50)	17 (55)
Perioperative morbidity	10 (15)	5 (15)	5 (16)

Values in parentheses are percentages. Forty-one patients without sufficient documentation on reason are excluded.

Table 6 Factors affecting the odds of having additional therapy compared with surgery alone

	Odds ratio	*P*
Age (years)		
75–80	1·00 (reference)	
81–85	0·97 (0·51, 1·86)	0·938
≥ 85	0·58 (0·27, 1·24)	0·162
CCI score		
0	1·00 (reference)	
1	0·78 (0·40, 1·52)	0·463
≥ 2	0·63 (0·32, 1·24)	0·180
Year of diagnosis		
1996–2002	1·00 (reference)	
2003–2008	1·82 (0·99, 3·48)	0·053
2009–2013	1·48 (0·69, 3·20)	0·313
Tumour location		
Distal	1·00 (reference)	
Mid	0·80 (0·41, 1·54)	0·501
Proximal	0·75 (0·39, 1·46)	0·403
Tumour stage		
II	1·00 (reference)	
III	1·72 (0·95, 3·10)	0·072

Values in parentheses are 95 per cent c.i. CCI, Charlson/Deyo Co-morbidity Index.

therapy; $P = 0{\cdot}427$) but there was a significant difference in receipt of adjuvant therapy (82 *versus* 55 per cent respectively had no adjuvant therapy; $P = 0{\cdot}005$). Age, CCI score, year of diagnosis, tumour location and tumour stage were not predictive of receiving additional therapy on multivariable analysis (*Table 6*). Although there was a trend towards receiving additional therapy in patients operated on between 2003 and 2008 in the adjusted analysis (odds ratio 1·82, 95 per cent c.i. 0·99 to 3·48; $P = 0{\cdot}053$), the proportion receiving any additional therapy did not appear to change over the course of the study (*Fig. 3*). The rate of neoadjuvant therapy increased from 19·7 per cent in in 1996–2002 to 33·3 per cent in 2009–2013. Over the same interval the rate of adjuvant therapy remained stable (35·2 to 33·3 per cent).

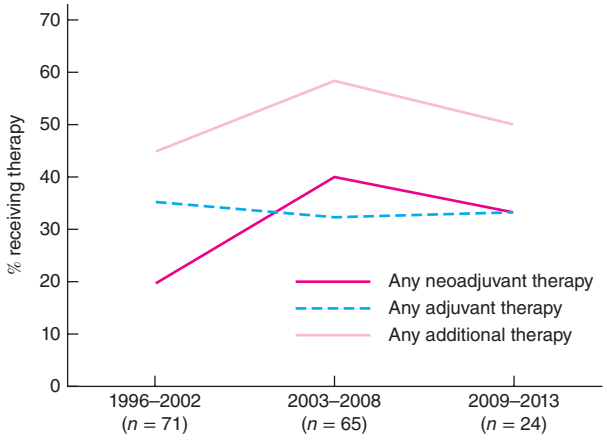

Fig. 3 Changes in utilization rates of additional therapies over time

Discussion

Although standard therapy for locally advanced non-metastatic rectal cancer under most international guidelines is neoadjuvant chemoradiotherapy followed by resection with curative intent and postresection adjuvant therapy, the data presented here suggest that neoadjuvant and postresection adjuvant chemotherapy are rarely achieved in patients aged 75 years or over. Despite this finding, the results clearly support the use of neoadjuvant chemoradiotherapy and/or postoperative adjuvant chemotherapy over surgery alone in elderly patients with stage III rectal cancer.

The data for patients with stage II rectal cancer are less clear. Although no statistically significant improvement in overall survival was observed for neoadjuvant chemoradiotherapy, postoperative chemotherapy, or any therapy *versus* surgery alone, the survival curves are strikingly different. Adjusting for other variables in a multivariable model, the hazard ratio for additional therapy *versus* surgery alone is almost identical for stage II and stage III groups, suggesting that the lack of statistical significance is due to a lack of power and not a lack of clinical significance. Many studies have compared elderly with younger patients[8,25,31,38–40], but this is the largest single-institution study of elderly patients with stage II and III rectal cancer. A national study[32] of elderly Medicare patients showed that only a complete course of both adjuvant radiation and chemotherapy for both stage II and stage III rectal cancer decreased 5-year cancer mortality risk. However, the data presented here suggest that any adjuvant therapy is beneficial in elderly patients with stage III rectal cancer.

Interestingly, the most common reason for patients with stage II and stage III disease not receiving neoadjuvant

therapy was it not being recommended by their providers. Although it is the present authors' practice to offer neoadjuvant therapy to all patients with stage II or III disease, including the elderly, they believe that undocumented frailty and concerns regarding quality of life may have contributed to this finding. More importantly, patient choice appeared to be the most common driver of not receiving postresection adjuvant therapy. Co-morbidities were the least commonly cited reason for not receiving neoadjuvant therapy. However, co-morbidity combined with perioperative morbidity accounted for nearly 40 per cent of the patients who did not receive additional postresection therapy. This, combined with the high rates of patients declining postresection therapy, highlights the importance of offering neoadjuvant therapy in elderly patients with locally advanced rectal cancer because, regardless of provider recommendation, it appears that many are unlikely to receive postresection chemotherapy.

This study has some limitations, including its retrospective and single-institution design. Although detailed charts were available for most patients, it was not possible to ascertain the precise reason for omission of additional therapies in over half of the patients who had surgery alone. Even though multiple confounders were controlled for, selection bias is a significant limitation of the study. Subtle differences in survival in the stage-specific analysis were limited owing to the sample size. Finally, higher-risk patients and those with multiple co-morbidities tend to be referred to the authors' centre and this may limit the applicability of the findings to community practices. Regardless, age alone should not be a reason to deny patients potentially helpful neoadjuvant or adjuvant therapy.

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