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ORIGINAL ARTICLE **CME**

Neoadjuvant Treatment of Locally Advanced Rectal Cancer in Elderly Patients: Real-World Experience at a Tertiary Institution

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ABSTRACT

Introduction: *The incidence of rectal cancer increases with age. Neoadjuvant radiotherapy, with or without concurrent chemotherapy, has been shown to improve outcomes. Elderly patients are underrepresented in clinical trials. In Hong Kong, there is a lack of consensus and local data to inform patient selection and formulate optimal treatment strategies for them. We sought to examine the outcomes of elderly patients undergoing neoadjuvant treatment for locally advanced rectal cancer.*

Methods: *Cases of patients with locally advanced rectal cancers who received neoadjuvant treatment in Department of Clinical Oncology, Queen Elizabeth Hospital from 2015 to 2018 were reviewed. 'Elderly patient' was defined as those ≥70 years at diagnosis. The key study endpoints were local relapse-free survival (RFS), regional RFS, distant RFS, overall RFS, and overall survival. Other endpoints included rate of downstaging, rate of conversion from threatened/involved margins to clear margins, and treatment-related toxicities.*

Results: *In all, 74 elderly patients and 142 non-elderly patients were identified. The proportion of patients receiving concurrent chemotherapy during radiotherapy was lower in the elderly patients ($p < 0.001$). Chemoradiation administered to patients of all ages did not result in statistically significant differences in any survival endpoint. Elderly patients deemed unfit for concurrent chemotherapy had a higher incidence of treatment toxicities. Age was not a significant prognostic factor in any categories of survival.*

Conclusion: *Age should not be a deterministic factor in treatment planning in locally advanced rectal cancer. Satisfactory oncological outcomes can be achieved in selected elderly patients. Utilisation of geriatric assessment and consideration of patients' preference are required to optimise treatment outcomes.*

Key Words: *Aged; Chemoradiotherapy; Neoadjuvant therapy; Radiotherapy; Rectal cancers*

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Ethics Approval: This research was approved by the Research Ethics Committee (Kowloon Central/Kowloon East Cluster) of Hospital Authority, Hong Kong (Ref: KC/KE-21-0264/ER-3) and was conducted according to the Declaration of Helsinki. Informed consent of patients was waived because of the retrospective nature of the study.

中文摘要

局部晚期直腸癌年老病人的術前輔助治療：第三層醫療機構的實際經驗

張天俊、祝菀馨、張嘉文、周重行、霍善智、梁海量、羅志清

簡介：直腸癌發病率隨年齡增長而上升。已有研究顯示術前輔助放射治療（不論有否同步進行化學治療）能改善病情。年老病人在臨床測試中的代表性不足。在香港，在選取病人及為該類病人制訂最佳治療策略方面，醫學界尚未達成共識，本地數據亦不足。我們嘗試分析進行局部晚期直腸癌術前輔助治療的年老病人的病情。

方法：本研究回顧了於2015至2018年期間在伊利沙伯醫院臨床腫瘤科接受術前輔助治療的局部晚期直腸癌病人個案。「年老病人」的定義為於確診時年屆70歲或以上的病人。關鍵研究終點為無局部復發存活、無區域復發存活、無遠處轉移存活、整體無復發生存率及總生存率。其他研究終點包括癌症降期率、從受威脅／侵犯切緣轉為陰性切緣率及治療相關毒性。

結果：我們分析了74名年老病人及142名非年老病人。年老病人在接受放射治療期間同時進行化學治療的比例較低（$p < 0.001$）。為所有年齡的病人進行放化療在任何存活終點並沒有出現統計學上的顯著差異。不適合同時接受化學治療的年老病人，其治療毒性發生率較高。年齡並非任何類別存活的重要預後因素。

結論：在規劃局部晚期直腸癌的治療時，年齡不應被視為決定性因素。部分年老病人可以獲得令人滿意的腫瘤治療結果。要達至最佳治療結果，須使用老年評估及考慮病人的偏好。

INTRODUCTION

According to the latest Hong Kong Cancer Statistics 2019, colorectal cancer ranked second in annual incidence of neoplasms in Hong Kong.[1] Within the 5556 new cases in 2019, 2072 were rectal/anal malignancies. Age is an important risk factor for rectal cancers; over half of the newly diagnosed rectal/anal cancer patients in 2019 were >65 years old.[1]

Surgery is the mainstay of curative treatment for rectal adenocarcinomas. Extensive research efforts were made in search of the optimal neoadjuvant therapy modalities to improve outcomes. The German Rectal Cancer Study Group's phase III study published in 2004 set the standard of neoadjuvant chemoradiotherapy for clinical T3/4 or lymph node positive diseases,[2] and the role of concurrent chemotherapy during neoadjuvant radiotherapy (RT) was confirmed in a 2013 Cochrane review in lowering the incidence of local recurrence.[3] Mesorectal fascial involvement threatening the circumferential resection margin (CRM) and distal rectal tumours were included in international treatment guidelines as relative indications for neoadjuvant treatment.[4,5]

Elderly patients were underrepresented in these clinical trials. Ageing is associated with poor performance status, an increased incidence of comorbidities, and suboptimal treatment tolerance. Retrospective studies have investigated the outcomes of elderly patients undergoing rectal cancer treatments,[6-9] but conclusions were divided regarding the adequate methodology of patient selection, the optimal magnitude of neoadjuvant treatment in patients with marginal performance status, and the side-effect profile of this population. There is also a lack of local data specifically for this controversial topic. We therefore performed this study to examine the outcomes of elderly patients undergoing neoadjuvant treatment for locally advanced rectal cancers.

METHODS

We retrospectively reviewed the medical records of consecutive patients that received neoadjuvant treatment for rectal cancer in Department of Clinical Oncology, Queen Elizabeth Hospital during the period from 1 January 2015 to 31 December 2018. Patients were considered for neoadjuvant treatment if they satisfied the following inclusion criteria: (1) biopsy-proven adenocarcinoma of rectum (located ≤12 cm from anal verge); (2) staging by pelvic magnetic resonance imaging, and either computed tomography scan covering thorax, abdomen and pelvis, or positron emitted tomography/computed tomography of the

whole body, showing non-metastatic disease that was at local stage T3 or above by American Joint Committee on Cancer's Cancer Staging Manual 7th edition, or with involved or threatened mesorectal fascia; and (3) deemed fit for neoadjuvant treatment and subsequent surgery by the attending physician based on performance status, age, and comorbidities. The diagnostic scans and the decision to institute neoadjuvant treatment were discussed in a multidisciplinary team meeting involving clinical oncologists, colorectal surgeons, and diagnostic radiologists.

Neoadjuvant treatment consisted of pelvic RT with or without concurrent chemotherapy. For RT, gross tumour volume was determined from clinical data (physical examination, colonoscopy and imaging findings). Clinical target volume included gross tumour volume plus a 2-cm circumferential margin, the entire mesorectum, and high-risk nodal areas including presacral, mesorectal, obturator, and internal iliac nodes. A 1-cm circumferential margin was added to clinical target volume to form the planning target volume. Patients were treated with long-course RT with conformal, intensity-modulated radiotherapy or volumetric modulated arc therapy techniques. A minimum dose of 45 Gy in 25 fractions was prescribed to the 100% isodose line; an optional boost to the gross disease was allowed up to a total equivalent dose of 54 Gy in 30 fractions, either with two-phase techniques (in conformal RT) or simultaneous integrated boost (in intensity-modulated radiotherapy/volumetric modulated arc therapy).

Similar to reported local practice,[10] two regimens of concurrent chemotherapy were adopted: intravenous bolus 5-fluorouracil at 500 mg/m^2 on Days 1-3 and Days 29-31, or oral capecitabine at 825 mg/m^2 twice daily, 5 days per week. Omission of concurrent chemotherapy due to advanced age, comorbidities, or patient preference was allowed.

Cross-sectional imaging was repeated at around 4-6 weeks after completion of RT to evaluate treatment response after neoadjuvant treatment and to assess operability. If operable, total mesorectal excision was performed ideally 6-10 weeks after RT completion. Based on our institution protocol, further adjuvant chemotherapy was not routinely offered due to the lack of evidence supporting benefit of adjuvant chemotherapy in randomised controlled trials and meta-analyses.

After treatment, surveillance was performed with regular history taking, physical examination, carcinoembryonic antigen monitoring, and surveillance colonoscopy. Cross-sectional imaging with computed tomography or positron emitted tomography/computed tomography scan was arranged when clinically indicated.

In this study, we defined elderly patients as those ≥70 years old at the time of histological diagnosis. The key endpoints of this study were local relapse-free survival (RFS), regional RFS, distant RFS, overall RFS, and overall survival (OS). Other endpoints included rate of downstaging (both T and N stages) and rate of conversion from threatened/involved CRM to clear margins. Treatment-related toxicities were assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and 30-day postoperative mortality. Data were analysed using commercial software SPSS (Windows version 24.0; IBM Corp, Armonk [NY], United States). Baseline characteristics between groups were tabulated and compared using the Mann-Whitney *U* test for continuous data and the Chi squared test for categorical data. Survival endpoints were estimated by the Kaplan-Meier method. Prognostic significance of clinical predictors was analysed using the log-rank test in simple analysis and the Cox proportional hazards model in multivariable regression analysis.

RESULTS

A total of 238 cases of patients with rectal cancer who received neoadjuvant therapy were identified. Twenty-two cases were excluded for Stage IV disease at baseline. A total of 74 of the remaining 216 patients were elderly patients. Median ages of elderly patients and non-elderly patients were 76.0 and 61.2 years, respectively. In total, 91.7% of the patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-1; a higher proportion of ECOG PS score of 2 was noted in the elderly population (18.9% vs. 2.8%, $p = 0.011$). Elderly patients had a significantly higher prevalence of comorbidities (hypertension: 66.2% vs. 26.8%, $p < 0.001$; ischaemic heart disease: 16.2% vs. 4.9%, $p = 0.019$). No statistically significant difference was noted between elderly and non-elderly groups in clinical stage or CRM status. The full baseline demographics and comorbidities before treatment initiation are shown in Table 1.

A total of 53 elderly patients and six non-elderly patients had neoadjuvant RT alone; the proportion of patients who received concurrent chemotherapy was

Table 1. Baseline demographics by age-group and treatment.*

	Elderly patients (n = 74)			Non-elderly patients (n = 142)		
	Whole cohort	CRT (n = 21)	RT alone (n = 53)	Whole cohort	CRT (n = 136)	RT alone (n = 6)
Median age at diagnosis, y (range)	76.0 (70.0-89.4)	71.2 (70.2-75.3)	78.8 (70.0-89.4)	61.2 (39.1-69.8)	61.1 (39.1-69.8)	67.1 (53.7-69.2)
Gender						
Male	50 (67.6%)	18 (85.7%)	32 (60.4%)	102 (71.8%)	99 (72.8%)	3 (50.0%)
Female	24 (32.4%)	3 (14.3%)	21 (39.6%)	40 (28.2%)	37 (27.2%)	3 (50.0%)
Tobacco use						
Never	40 (54.1%)	9 (42.9%)	31 (58.5%)	69 (48.6%)	66 (48.5%)	3 (50.0%)
Active	11 (14.9%)	5 (23.8%)	6 (11.3%)	41 (28.9%)	40 (29.4%)	1 (16.7%)
Ex-user	22 (29.7%)	7 (33.3%)	15 (28.3%)	29 (20.4%)	27 (19.9%)	2 (33.3%)
Unknown	1 (1.4%)	0	1 (1.9%)	3 (2.1%)	3 (2.2%)	0
Alcohol use						
Never	54 (73.0%)	11 (52.4%)	43 (81.1%)	97 (68.3%)	91 (66.9%)	6 (100%)
Active	11 (14.9%)	6 (28.6%)	5 (9.4%)	30 (21.1%)	30 (22.1%)	0
Ex-user	6 (8.1%)	4 (19.0%)	2 (3.8%)	12 (8.5%)	12 (8.8%)	0
Unknown	3 (4.1%)	0	3 (5.7%)	3 (2.1%)	3 (2.2%)	0
Comorbidities						
Ischaemic heart disease	12 (16.2%)	1 (4.8%)	11 (20.8%)	7 (4.9%)	6 (4.4%)	1 (16.7%)
Diabetes mellitus	19 (25.7%)	2 (9.5%)	17 (32.1%)	31 (21.8%)	27 (19.9%)	4 (66.7%)
Hypertension	49 (66.2%)	11 (52.4%)	38 (71.7%)	38 (26.8%)	36 (26.5%)	2 (33.3%)
Hyperlipidaemia	23 (31.1%)	3 (14.3%)	20 (37.7%)	29 (20.4%)	26 (19.1%)	3 (50.0%)
ECOG PS score						
0-1	60 (81.1%)	21 (100%)	39 (73.6%)	138 (97.2%)	135 (99.3%)	3 (50.0%)
2	14 (18.9%)	0	14 (26.4%)	4 (2.8%)	1 (0.7%)	3 (50.0%)
Tumour distance from anal verge, cm						
0-5.0	39 (52.7%)	11 (52.4%)	28 (52.8%)	67 (47.2%)	64 (47.1%)	3 (50.0%)
5.1-10.0	35 (47.3%)	10 (47.6%)	25 (47.2%)	70 (49.3%)	67 (49.3%)	3 (50.0%)
10.1-15.0	0	0	0	5 (3.5%)	5 (3.7%)	0
Overall stage						
II	9 (12.2%)	3 (14.3%)	6 (11.3%)	13 (9.2%)	12 (8.8%)	1 (16.7%)
III	65 (87.8%)	18 (85.7%)	47 (88.7%)	129 (90.8%)	124 (91.2%)	5 (83.3%)
Clinical T staging						
2	3 (4.1%)	0	3 (5.7%)	6 (4.2%)	6 (4.4%)	0
3	61 (82.4%)	18 (85.7%)	43 (81.1%)	102 (71.8%)	98 (72.1%)	4 (66.7%)
4	10 (13.5%)	3 (14.3%)	7 (13.2%)	34 (23.9%)	32 (23.5%)	2 (33.3%)
Clinical N staging						
0	9 (12.2%)	3 (14.3%)	6 (11.3%)	13 (9.2%)	12 (8.8%)	1 (16.7%)
1	15 (20.3%)	3 (14.3%)	12 (22.6%)	25 (17.6%)	25 (18.4%)	0
2	50 (67.6%)	15 (71.4%)	35 (66.0%)	104 (73.2%)	99 (72.8%)	5 (83.3%)
CRM status						
Clear	16 (21.6%)	5 (23.8%)	11 (20.8%)	34 (23.9%)	34 (25.0%)	0
Involved/threatened	58 (78.4%)	16 (76.2%)	42 (79.2%)	108 (76.1%)	102 (75.0%)	6 (100%)
Carcinoembryonic antigen						
Normal	28 (37.8%)	9 (42.9%)	19 (35.8%)	44 (31.0%)	44 (32.4%)	0
Elevated	45 (60.8%)	12 (57.1%)	33 (62.3%)	97 (68.3%)	92 (67.6%)	5 (83.3%)
Unknown	1 (1.4%)	0	1 (1.9%)	1 (0.7%)	0	1 (16.7%)

Abbreviations: CRM = circumferential resection margin; CRT = chemoradiotherapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; RT = radiotherapy.
* Data are shown as No. (%), unless otherwise specified.

lower in elderly patients than non-elderly patients (28.4% vs. 95.8%, $p < 0.001$). The most common reasons for chemotherapy omission in elderly patients were advanced age (n = 44, 83%), poor performance status (n = 4, 7.5%), and patient refusal (n = 4, 7.5%). Technique of RT, boost dose frequency, and time of RT completion were similar between elderly and non-elderly groups.

After neoadjuvant treatments, 58 elderly cases (78.4%) and 128 non-elderly (90.1%) cases went on to undergo radical surgery as planned; 16 elderly patients (21.6%) and 14 non-elderly patients (9.9%) did not undergo radical surgery. The reasons are shown in Table 2. These patients were excluded from survival analyses but were included in toxicity and safety analyses.

Figure 1 illustrates the treatment scheme with number of cases involved. The time to radical surgery and the

Table 2. Reasons for radical surgery not being performed.*

	Elderly patients (16/74)			Non-elderly patients (14/142)		
	Whole cohort	CRT (3/21)	RT alone (13/53)	Whole cohort	CRT (13/136)	RT alone (1/6)
Inoperable disease	5 (6.8%)	1 (4.8%)	4 (7.5%)	9 (6.3%)	8 (5.9%)	1 (16.7%)
General condition deterioration thus unfit for operation/anaesthesia	5 (6.8%)	1 (4.8%)	4 (7.5%)	1 (0.7%)	1 (0.7%)	0
Patient refusal	6 (8.1%)	1 (4.8%)	5 (9.4%)	4 (2.8%)	4 (2.9%)	0

Abbreviations: CRT = chemoradiotherapy; RT = radiotherapy.
* Data are shown as No. (%), unless otherwise specified.

rate of sphincter preservation were similar between elderly and non-elderly patients. A total of 27 patients subsequently received further adjuvant chemotherapy after surgery. Treatment details are listed in the online supplementary Appendix.

No statistically significant difference in treatment outcomes was observed between elderly and non-elderly cases, or between the CRT and RT-alone arms. Eleven patients achieved a pathological complete response after neoadjuvant treatment, with all of them had received neoadjuvant CRT; the incidence was similar in the elderly and non-elderly CRT cohorts. Detailed treatment outcomes are listed in Table 3.

The 5-year local RFS, regional RFS, distant RFS, overall RFS and OS of the entire cohort were 88.0%, 88.7%, 63.9%, 57.1% and 70.2%, respectively. Elderly and non-elderly patients who underwent CRT did not demonstrate a statistically significant difference in any survival endpoints. Five patients in the elderly RT-alone subgroup died of non-cancer causes (12.5% of the subgroup; 3 due to infection, 1 due to acute myocardial infarction, and 1 due to cerebrovascular accident); no non-cancer mortality was documented in the elderly CRT subgroup. The Kaplan-Meier curves of the survival endpoints are demonstrated in Figure 2.

Elderly patients who underwent neoadjuvant CRT had noninferior toxicities and safety profiles in both neoadjuvant treatment and surgery when compared to their non-elderly counterparts. The incidence of grade ≥3 toxicities in neoadjuvant treatment in elderly and non-elderly CRT arms were 4.8% and 14.0%, respectively. Postoperative 30-day morbidities were 16.7% and 24.4%, respectively. Elderly patients who underwent neoadjuvant RT alone had higher incidence of significant treatment toxicities, with 7.5% having grade ≥3 RT toxicities, and 32.5% having significant morbidities after operation. No treatment-induced mortality was observed in this cohort. Table 4 shows the incidence of significant treatment toxicities.

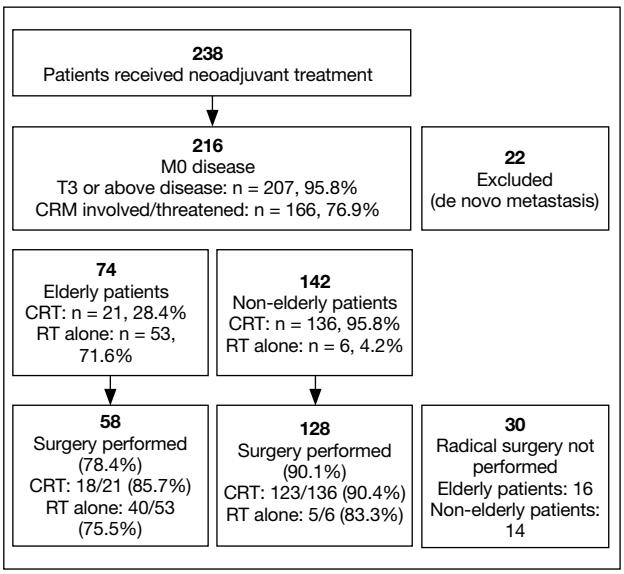

Figure 1. Treatment flowchart and number of patients involved.
Abbreviations: CRM = circumferential resection margin; CRT = chemoradiotherapy; RT = radiotherapy.

Analyses of prognostic factors indicated that older age was not a significant prognostic factor in any of the categories of survival on simple and multivariable analyses. After multivariable regression analysis, resection margin involvement and intramesorectal plane of excision were significantly associated with shorter local RFS. Presence of lymphovascular invasion and intramesorectal plane of excision were significantly associated with shorter distant RFS. Lymphovascular invasion, margin involved, and intramesorectal plane of excision were significantly associated with shorter overall RFS. Absence of concurrent chemotherapy, poorly differentiated histology, lymphovascular invasion, and intramesorectal plane of excision were significantly associated with shorter OS. The simple and multivariable analyses results are shown in Table 5.

Table 3. Treatment outcomes.*

		Elderly patients (n = 58)			Non-elderly patients (n = 128)		
		Whole cohort	CRT (n = 18)	RT alone (n = 40)	Whole cohort	CRT (n = 123)	RT alone (n = 5)
Pathological response							
ypT	0	2 (3.4%)	2 (11.1%)	0	11 (8.6%)	11 (8.9%)	0
	In situ	2 (3.4%)	0	2 (5.0%)	2 (1.6%)	2 (1.6%)	0
	1	2 (3.4%)	1 (5.6%)	1 (2.5%)	5 (3.9%)	5 (4.1%)	0
	2	9 (15.5%)	2 (11.1%)	7 (17.5%)	20 (15.6%)	19 (15.4%)	1 (20.0%)
	3	42 (72.4%)	12 (66.7%)	30 (75.0%)	81 (63.3%)	78 (63.4%)	3 (60.0%)
	4	1 (1.7%)	1 (5.6%)	0	9 (7.0%)	8 (6.5%)	1 (20.0%)
ypN	0	38 (65.5%)	11 (61.1%)	27 (67.5%)	77 (60.2%)	75 (61.0%)	2 (40.0%)
	1	14 (24.1%)	6 (33.3%)	8 (20.0%)	33 (25.8%)	31 (25.2%)	2 (40.0%)
	2	6 (10.3%)	1 (5.6%)	5 (12.5%)	18 (14.1%)	17 (13.8%)	1 (20.0%)
Resection margin	Clear	44 (75.9%)	12 (66.7%)	32 (80.0%)	101 (78.9%)	96 (78.0%)	5 (100%)
	Involved	14 (24.1%)	6 (33.3%)	8 (20.0%)	27 (21.1%)	27 (22.0%)	0
Pathological CR		2 (3.4%)	2 (11.1%)	0	9 (7.0%)	9 (7.3%)	0
T downstaging		18 (31.0%)	6 (33.3%)	12 (30.0%)	48 (37.5%)	47 (38.2%)	1 (20.0%)
N downstaging		43 (74.1%)	13 (72.2%)	30 (75.0%)	95 (74.2%)	91 (74.0%)	4 (80.0%)
CRM clearance from involved/threatened		32/43 (74.4%)	10/13 (76.9%)	22/30 (73.3%)	76/96 (79.2%)	71/91 (78.0%)	5/5 (100%)
Survival data							
3-year	Local RFS	88.5%	94.4%	85.7%	91.1%	90.8%	100%
	Regional RFS	94.5%	94.4%	94.5%	90.7%	90.3%	100%
	Distant RFS	69.8%	77.8%	66.2%	72.0%	71.1%	100%
	Overall RFS	65.0%	77.8%	59.3%	66.2%	65.6%	80.0%
	OS	77.5%	88.9%	72.3%	86.4%	86.7%	80.0%
5-year	Local RFS	85.3%	94.4%	80.6%	89.0%	88.6%	100%
	Regional RFS	94.5%	94.4%	94.5%	86.4%	86.0%	100%
	Distant RFS	64.7%	77.8%	58.4%	63.7%	62.6%	100%
	Overall RFS	60.1%	77.8%	51.9%	55.8%	55.0%	80.0%
	OS	62.5%	83.3%	52.4%	73.8%	73.6%	80.0%

Abbreviations: CR = complete response; CRM = circumferential resection margin; CRT = chemoradiotherapy; OS = overall survival; RFS = relapse-free survival; RT = radiotherapy; ypN = pathological nodal staging following therapy; ypT = pathological tumour staging following therapy.

* Data are shown as No. (%), unless otherwise specified.

DISCUSSION

Elderly rectal cancer patients were a heterogenous group with diverse outcomes after neoadjuvant treatment, as demonstrated by our study, which is to date the largest reported Hong Kong cohort, and with neoadjuvant CRT outcomes comparable to local and international data.[2,10-12]

Elderly patients deemed fit for neoadjuvant CRT had comparable outcomes compared to their non-elderly counterparts, including pathological complete response rate, rate of tumour downstaging, probability of conversion from involved/threatened CRM, survival endpoints, and adverse events. On simple and multivariable analyses, it was demonstrated that old age was not an independent prognostic factor in any categories of survival. This echoes the findings of Kang et al,[7] demonstrating an elderly subgroup treated with trimodality therapy with survival outcomes similar to those of younger patients.

Whereas less fit patients in this study underwent neoadjuvant RT alone, they tolerated the whole treatment course less well, despite treatment de-escalation, with 30.2% experiencing significant treatment toxicities, and 17.0% not completing treatment due to frailty and non-compliance. A total of five out of 40 patients (12.5% of the subgroup) that completed treatment died due to non-cancer causes. Our RT-alone cohort — mostly elderly patients — had poorer OS, which was in contrast to published data that suggested concurrent chemotherapy omission was not detrimental to RFS or OS.[3,13] The reason behind poorer OS in our RT-alone cohort was likely due to selection bias, as the patients were of more advanced age, with more comorbidities and a higher incidence of non-cancer mortalities, with limited choices for palliative systemic treatment of disease recurrence.

In our institution, patients' fitness for treatment was assessed based on ECOG PS score, age, and comorbidities. Inter-observer variability is inevitable,

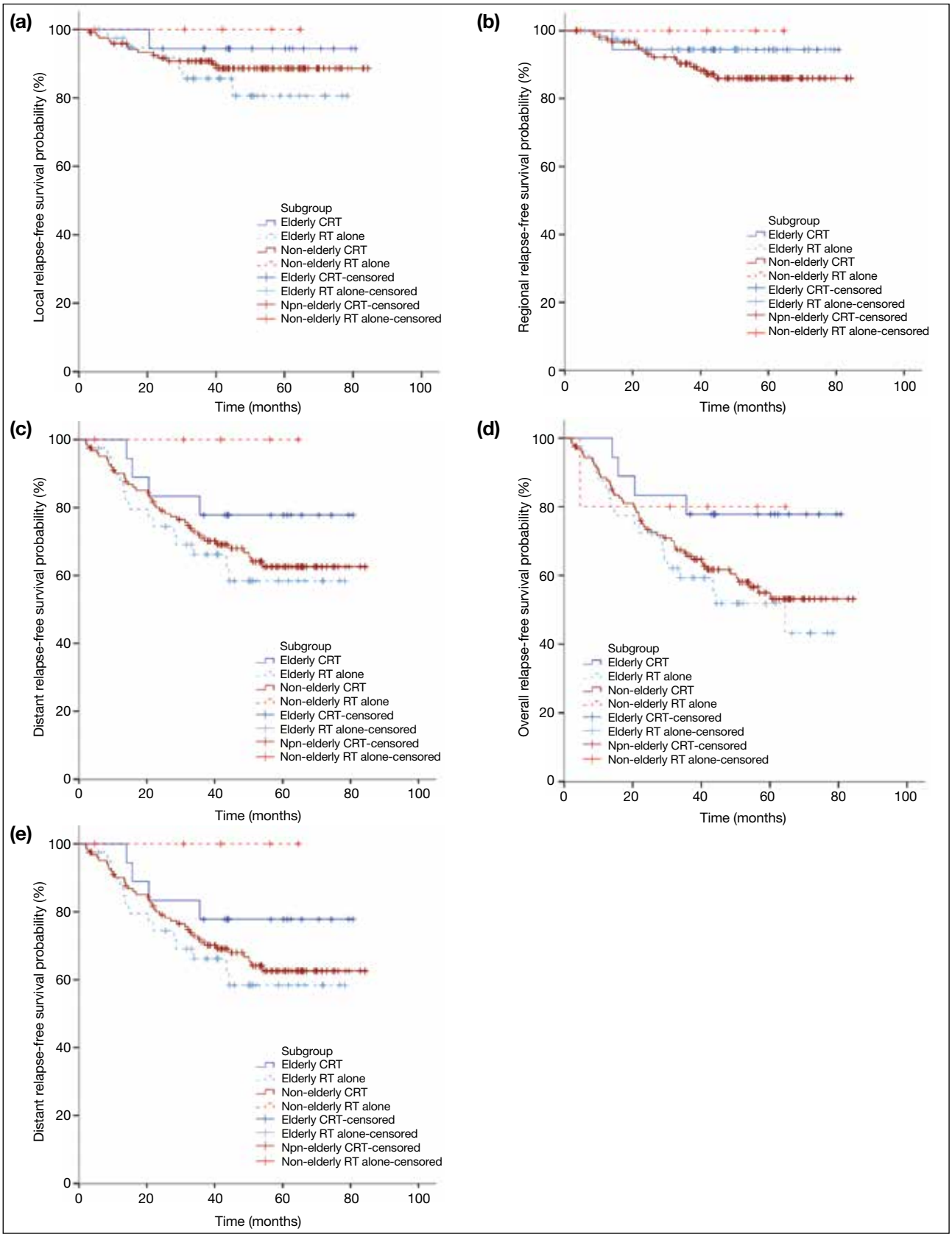

Figure 2. Kaplan-Meier curves illustrating different survival endpoints of elderly patients and non-elderly patients receiving chemoradiotherapy and radiotherapy alone: (a) local relapse-free survival, (b) regional relapse-free survival, (c) distant relapse-free survival, (d) overall relapse-free survival, and (e) overall survival.
Abbreviations: CRT = chemoradiotherapy; RT = radiotherapy.

Table 4. Significant treatment toxicities.*

		Elderly patients (n = 74)			Non-elderly patients (n = 142)		
		Whole cohort	CRT (n = 21)	RT alone (n = 53)	Whole cohort	CRT (n = 136)	RT alone (n = 6)
No. of patients who suffer from any significant treatment toxicities in any phase of treatment		20 (27.0%)	4 (19.0%)	16 (30.2%)	49 (34.5%)	48 (35.3%)	1 (16.7%)
		Neoadjuvant therapy (grade ≥3 toxicities)					
		Elderly patients (n = 74)			Non-elderly patients (n = 142)		
		Whole cohort	CRT (n = 21)	RT alone (n = 53)	Whole cohort	CRT (n = 136)	RT alone (n = 6)
All		5 (6.8%)	1 (4.8%)	4 (7.5%)	20 (14.1%)	19 (14.0%)	1 (16.7%)
RT toxicities	All categories	5 (6.8%)	1 (4.8%)	4 (7.5%)	10 (7.0%)	10 (7.4%)	0
	Dermatitis	2 (2.7%)	1 (4.8%)	1 (1.9%)	7 (4.9%)	7 (5.1%)	0
	Gastrointestinal	3 (4.1%)	0	3 (5.7%)	2 (1.4%)	2 (1.5%)	0
	Urinary	0	0	0	1 (0.7%)	1 (0.7%)	0
	Other	1 (1.4%)	0	1 (1.9%)	0	0	0
Chemo toxicities	All categories	-	0	-	-	10 (7.4%)	-
	Haematologic	-	0	-	-	6 (4.4%)	-
	Renal	-	0	-	-	2 (1.5%)	-
	Infection	-	0	-	-	2 (1.5%)	-
	Hand-foot syndrome	-	0	-	-	1 (0.7%)	-
		Surgery (30 days post-operation)					
		Elderly patients (n = 58)			Non-elderly patients (n = 128)		
		Whole cohort	CRT (n = 18)	RT alone (n = 40)	Whole cohort	CRT (n = 123)	RT alone (n = 5)
All		16 (27.6%)	3 (16.7%)	13 (32.5%)	31 (24.2%)	30 (24.4%)	1 (20.0%)
Wound healing >30 days		9 (15.5%)	1 (5.6%)	8 (20.0%)	17 (13.3%)	16 (13.0%)	1 (20.0%)
Abscess/collection requiring intervention		3 (5.2%)	1 (5.6%)	2 (5.0%)	7 (5.5%)	7 (5.7%)	0
Ileus/adhesive intestinal obstruction		4 (6.9%)	1 (5.6%)	3 (7.5%)	8 (6.3%)	8 (6.5%)	0
Second operation		4 (6.9%)	0	4 (10.0%)	1 (0.8%)	1 (0.8%)	0
Mortality		0	0	0	0	0	0

Abbreviations: CRT = chemoradiotherapy; RT = radiotherapy.
* Data are shown as No. (%), unless otherwise specified.

and discrepancies between physiological and chronological ages exist. Despite multidisciplinary team meeting endorsement, the treatments for a portion of less fit patients were futile on retrospective review, ranging from incapability to tolerate the whole treatment course to short lifespan after treatment completion. There is therefore a need for more accurate and objective tools to stratify patients' fitness for different intensities of neoadjuvant treatments, or even radical treatment at all.

Multidisciplinary participation in comprehensive geriatric assessment is recommended by the International Society of Geriatric Oncology when assessing frailty for tailoring the treatment plan in colorectal cancers.[14] However, it is a time- and resource-consuming process which hinders its routine use. Specific to rectal cancer, an international expert panel recommends patients aged ≥70 years to receive mandatory office-based frailty screening tests before being considered for usual care[15]; any presence of a frailty predictor requires a formal geriatric assessment and a geriatrician's presence in multidisciplinary decision making.

After careful assessment of fitness and frailty, treatment intent and its intensity should be adjusted accordingly. A review by Wang et al[16] proposed a treatment algorithm for locally advanced rectal cancer in elderly/comorbid patients based on degree of frailty. Elderly patients that are fully fit should undergo neoadjuvant treatment, either long-course CRT or short-course RT alone, before radical surgery. For less fit patients, different emerging nonsurgical treatment approaches, e.g., watch and wait approach or brachytherapy boost after CRT, should be considered. Palliative RT, or even symptomatic care, should be considered if patients are deemed frail. The adaptation of the abovementioned approaches will likely screen out unfit patients, avoid futile treatments in patients with limited life expectancies due to comorbidities, and

Table 5. Simple and multivariable analyses of prognostic factors.

	Simple analysis			Multivariable analysis		
	p Value	Hazard ratio	95% CI	p Value	Hazard ratio	95% CI
Local relapse-free survival						
Elderly patient (Yes vs. No)	0.658	1.23	0.49-3.09	0.727	0.77	0.18-3.38
Concurrent chemotherapy (No vs. Yes)	0.416	1.49	0.57-3.88	0.491	1.71	0.37-7.92
Poorly differentiated (Yes vs. No)	0.826	1.25	0.17-9.40	0.817	1.29	0.15-10.98
ypT4 disease (Yes vs. No)	0.041	3.61	1.06-12.32	0.396	1.83	0.45-7.37
yp node positive (Yes vs. No)	0.704	1.19	0.49-2.91	0.425	0.66	0.23-1.84
Lymphovascular invasion (Yes vs. No)	0.105	2.21	0.85-5.76	0.174	2.16	0.71-6.53
Margin involved (Yes vs. No)	0.001	4.42	1.84-10.63	0.032	3.06	1.10-8.54
Intramesorectal plane of excision (Yes vs. No)	<0.001	7.86	3.12-19.76	0.001	6.40	2.22-18.45
Regional relapse-free survival						
Elderly patient (Yes vs. No)	0.212	0.45	0.13-1.57	0.313	0.40	0.07-2.37
Concurrent chemotherapy (No vs. Yes)	0.268	0.44	0.10-1.89	0.614	0.63	0.10-3.87
Poorly differentiated (Yes vs. No)	0.480	1.75	0.37-8.29	0.952	1.07	0.14-8.41
ypT4 disease (Yes vs. No)	0.153	2.92	0.67-12.73	0.171	2.98	0.62-14.23
yp node positive (Yes vs. No)	0.002	5.13	1.83-14.40	0.052	3.15	0.99-10.02
Lymphovascular invasion (Yes vs. No)	0.006	3.94	1.49-10.38	0.090	2.56	0.86-7.59
Margin involved (Yes vs. No)	0.001	5.99	2.09-17.19	0.864	1.10	0.37-3.33
Intramesorectal plane of excision (Yes vs. No)	0.844	0.82	0.11-6.14	0.827	0.79	0.10-6.50
Distant relapse-free survival						
Elderly patient (Yes vs. No)	0.926	1.03	0.60-1.77	0.724	0.87	0.40-1.90
Concurrent chemotherapy (No vs. Yes)	0.663	1.14	0.63-2.04	0.648	1.21	0.53-2.76
Poorly differentiated (Yes vs. No)	0.048	2.53	1.01-6.36	0.378	1.61	0.56-4.62
ypT4 disease (Yes vs. No)	0.413	1.53	0.55-4.21	0.549	0.138	0.48-3.93
yp node positive (Yes vs. No)	<0.001	2.72	1.63-4.55	0.066	1.74	0.96-3.13
Lymphovascular invasion (Yes vs. No)	0.001	2.70	1.54-4.73	0.019	2.13	1.13-3.99
Margin involved (Yes vs. No)	<0.001	3.89	1.93-7.85	0.144	1.57	0.86-2.88
Intramesorectal plane of excision (Yes vs. No)	0.028	2.31	1.09-4.87	0.022	2.55	1.14-5.69
Overall relapse-free survival						
Elderly patient (Yes vs. No)	0.862	0.96	0.59-1.56	0.182	0.61	0.30-1.26
Concurrent chemotherapy (No vs. Yes)	0.419	0.81	0.49-1.35	0.203	1.62	0.77-3.39
Poorly differentiated (Yes vs. No)	0.010	2.85	1.28-6.14	0.115	2.03	0.84-4.89
ypT4 disease (Yes vs. No)	0.328	1.57	0.63-3.91	0.651	1.24	0.49-3.18
yp node positive (Yes vs. No)	0.001	2.09	1.33-3.30	0.607	1.15	0.68-1.94
Lymphovascular invasion (Yes vs. No)	0.025	2.03	1.09-3.77	0.003	2.33	1.32-4.09
Margin involved (Yes vs. No)	<0.001	2.74	1.70-4.42	0.016	1.97	1.14-3.44
Intramesorectal plane of excision (Yes vs. No)	0.016	2.28	1.17-4.45	0.011	2.54	1.24-5.20
Overall survival						
Elderly patient (Yes vs. No)	0.115	1.57	0.90-2.76	0.956	1.03	0.42-2.51
Concurrent chemotherapy (No vs. Yes)	0.012	2.09	1.17-3.71	0.046	2.47	1.02-6.00
Poorly differentiated (Yes vs. No)	0.001	4.42	1.87-10.43	0.002	5.07	1.83-14.09
ypT4 disease (Yes vs. No)	0.165	1.93	0.76-4.88	0.256	1.78	0.66-4.80
yp node positive (Yes vs. No)	0.003	2.33	1.34-4.05	0.311	1.39	0.73-2.65
Lymphovascular invasion (Yes vs. No)	<0.001	3.48	1.94-6.24	0.001	2.96	1.52-5.77
Margin involved (Yes vs. No)	0.001	2.65	1.50-4.69	0.189	1.58	0.80-3.13
Intramesorectal plane of excision (Yes vs. No)	0.004	2.89	1.40-5.97	0.001	4.10	1.79-9.41

Abbreviations: CI = confidence interval; T = tumour staging; yp = pathological staging following therapy.

minimise unbearable treatment toxicities.

Besides fitness for treatment, elderly patients' goals and preferences in treatment outcomes should be carefully respected during treatment planning. In our study, 9.4% of the elderly patients subsequently refused radical surgery after receiving neoadjuvant treatment. The specific reasons of treatment refusal were not documented in clinical notes, yet potential reasons may be due to fear of surgical/anaesthetic risk, or the subsequent inconvenience with a temporary/permanent stoma. Thorough counselling, before and during treatment, would be helpful to formulate a tailor-made treatment plan in respect of patients' preferences, and ensure compliance with treatment.

The concept of total neoadjuvant therapy for rectal cancers was introduced in recent years, with two phase III trials showing that such approach provided a superior pathological complete response rate and outcomes at 3 years (3-year disease-free survival in the UNICANCER-PRODIGE 23 trial, disease-related treatment failure at 3 years in the RAPIDO trial).[17,18] Although OS data were immature to demonstrate superiority of total neoadjuvant

therapy,[19] adding neoadjuvant chemotherapy is being increasingly adopted as a treatment option worldwide. This approach, however, will lead to more systemic chemotherapy exposure and may pose extra toxicities to patients. He et al[20] reported that the addition of neoadjuvant chemotherapy to neoadjuvant CRT in the elderly patients gave rise to similar disease-related survival rates and oncological outcomes with that of younger patients, but geriatric assessments and complications data were lacking in the study. It is expected that as we intensify the magnitude of our neoadjuvant treatment, there will be a growing importance in proper patient selection to balance the risk and benefits of treatment.

There were limitations to this study. The study data was collected retrospectively, limiting the completeness of data and introducing potential bias during data collection. There was selection bias during referral and initiation of neoadjuvant treatment, thus epidemiological data were limited. There was also selection bias when patients were assigned to different neoadjuvant treatment arms (i.e., with or without concurrent chemotherapy), thus confounding factors that were not identified in this study may be present. A short-course RT scheme was not adopted in this cohort, limiting our scope of analysis and subsequent recommendations. Absence of detailed parameters of elderly patients' conditions and the small sample size of this study limit the ability to identify prognostic factors to predict tolerance to treatment, and to derive further recommendations.

CONCLUSION

Age alone should not be a deterministic factor in treatment intensity consideration in locally advanced rectal cancer. Satisfactory oncological outcomes can be achieved in selected elderly patients with locally advanced rectal cancers who undergo standard neoadjuvant treatment and radical surgery, while the risk of shorter survival and toxicities is higher in less fit candidates. Utilisation of geriatric screening and assessment tools, and consideration of patients' preference and treatment objectives are required to achieve tailor-made treatment schemes and optimise treatment outcomes.

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