



# Neoadjuvant chemoradiation using either oral capecitabine or bolus 5-FU in locally advanced rectal cancer: Long-term survival and prognostic factors

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## Purpose

This retrospective study evaluated the long-term survival and prognostic factors in locally advanced rectal cancer (LARC) treated with neoadjuvant chemoradiation using either oral capecitabine or bolus 5-FU.

## Materials and Methods

Between July 1993 and May 2002, 195 consecutive patients with LARC (cT3/T4 or N+) were enrolled in this study. Preoperative TNM stage was II in 40 (20%) and III in 155 (80%).

The patients received neoadjuvant concurrent chemoradiation using either two cycles of i.v. bolus 5-FU (500 mg/m<sup>2</sup>/day) plus leucovorin (LV, 20 mg/m<sup>2</sup>/day) (Arm I, 105 patients) or two cycles of oral capecitabine (1,650 mg/m<sup>2</sup>/day) plus leucovorin (20 mg/m<sup>2</sup>/day) (Arm II, 90 patients).

Radiation of 45 Gy in daily fractions of 1.8 Gy was delivered to the pelvis, followed by a 5.4 Gy boost to the primary tumor site. Definitive surgery was performed 6 weeks after the completion of chemoradiation.

Univariate and multivariate analyses were performed using a log-rank test and Cox proportional hazard model to evaluate the prognostic factors.

Variables	Group		P
	Arm I	Arm II	
Sex			
Male	67 (64)	57 (63)	0.532
Female	38 (36)	33 (37)	
Age			
<65	77 (73)	61 (68)	0.244
≥65	28 (27)	29 (32)	
ECOG			
0	3 ( 3)	1 ( 1)	0.386
1	95 (90)	86 (96)	
2	7 ( 7)	3 ( 3)	
Tumor mobility			
Mobile & partially fixed	73 (71)	46 (53)	0.008
Totally fixed	30 (29)	41 (47)	
Distance from anal verge			
≤5 cm	57 (54)	36 (40)	0.032
> 5cm	48 (46)	54 (60)	
cT stage			
T2		1 ( 1)	0.297
T3	98 (93)	79 (88)	
T4	7 ( 7)	10 (11)	
cN stage			
N0	22 (21)	18 (20)	0.372
N1	30 (29)	34 (38)	
N2	53 (50)	38 (42)	
cTNM stage			
II	22 (21)	18 (20)	0.507
III	83 (79)	72 (80)	

## Results

The median follow-up was 70 months in Arm I and 54 months in Arm II. The 5-years overall survival (OS) and disease-free survival (DFS) were 73% and 64%, respectively (Fig.1 and Fig. 2). No significant differences were observed in OS and DFS in either arm ( $p=0.098$ ,  $0.582$ , respectively) (Fig.2 and Fig. 3). In addition, there were no significant local recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) (Fig. 4 and Fig. 5).

Poor prognostic factors for OS were totally fixed tumor ( $p=0.003$ ), advanced cTNM stage ( $p=0.007$ ), and advanced pTNM stage ( $p<0.001$ ) in the univariate analyses. Prognostic factors for decreased DFS were less than 65 years old ( $p=0.039$ ), totally fixed tumor ( $p=0.008$ ), advanced cTNM stage ( $p=0.022$ ), advanced pTNM stage ( $p<0.001$ ), and no pathologic complete response ( $p=0.022$ ) (Table 1).

In the multivariate analysis, significant favorable prognostic factors for OS were female ( $p=0.036$ ), less fixed tumor ( $p=0.016$ ), and less advanced pTNM ( $p<0.001$ ) (Table 2). For DFS, favorable prognostic factors were less fixed tumor and less advanced pTNM ( $p=0.031$ ,  $p<0.001$ , respectively) (Table 3).

Table 1. Univariate analysis for prognostic factors

Variables	OS	p	DFS	p
Treatment group				
Arm I	68	0.098	61	0.582
Arm II	79		68	
Age				
<65	72	0.295	60	0.039
≥65	75		75	
Sex				
Male	67	0.138	60	0.319
Female	82		70	
Tumor mobility				
Mobile & partially fixed	78	0.003	69	0.008
Totally fixed	85		54	
Distance from anal verge				
≤ 5 cm	70	0.308	57	0.185
> 5cm	75		70	
Clinical stage				
II	87	0.007	83	0.022
III	69		59	
Pathological stage				
0-II	85	0.000	79	0.000
III-IV	49		33	
pCR				
Yes	87	0.068	84	0.022
No	70		60	

Abbreviations: Arm I= bolus 5-FU + leucovorin; Arm II= oral capecitabine; pCR= Pathological complete response

Table 2. Multivariate analysis for overall survival

Variables	Hazard ratio	95 % confidence interval	P
Treatment group			
Arm I	1.783	0.300-0.885	0.182
Arm II			
Age			
<65	0.080	0.300-0.885	0.777
≥65			
Sex			
Male	1.858	1.042-3.313	0.036
Female			
Tumor mobility			
Mobile & partially fixed	0.515	0.300-0.885	0.016
Totally fixed			
Distance from anal verge			
≤5 cm	0.746	0.300-0.885	0.388
> 5cm			
Clinical stage			
stage II	0.161	0.300-0.885	0.688
stage III			
Pathological stage			
< stage III	0.218	.126-.380	0.000
≥ stage III			
pCR			
Yes	0.057	0.300-0.885	0.811
No			

Abbreviations: Arm I= bolus 5-FU + leucovorin; Arm II= oral capecitabine; pCR= Pathological complete response

## Conclusion

The long-term survival with neoadjuvant chemoradiation using oral capecitabine was comparable to that with bolus 5-FU. Preoperative tumor mobility and postoperative pTNM stage were the most significant prognostic factors for overall and disease-free survival in locally advanced rectal cancer patients treated with neoadjuvant chemoradiation.

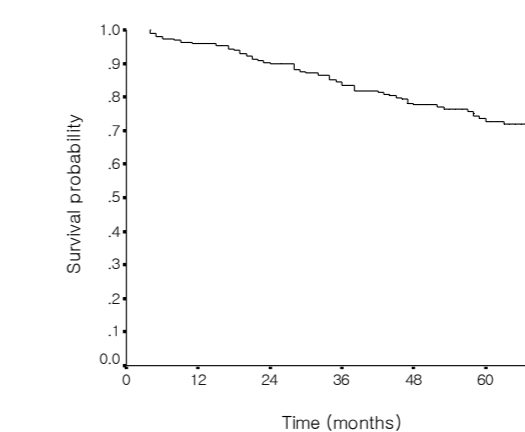


Fig. 1. Overall survival of all patients

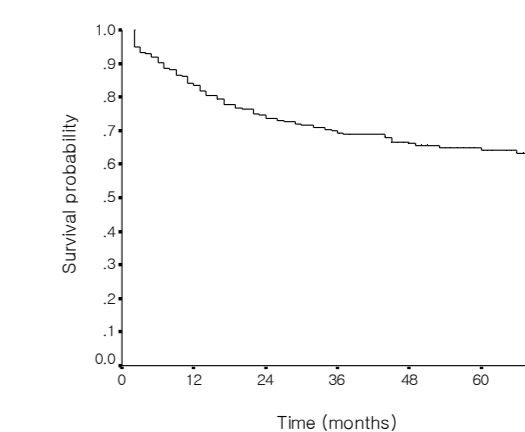


Fig. 2. Disease free survival of all patients

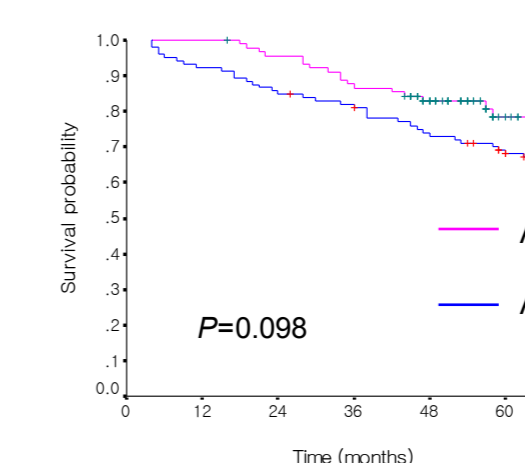


Fig. 3. Overall survival between Arm I and II

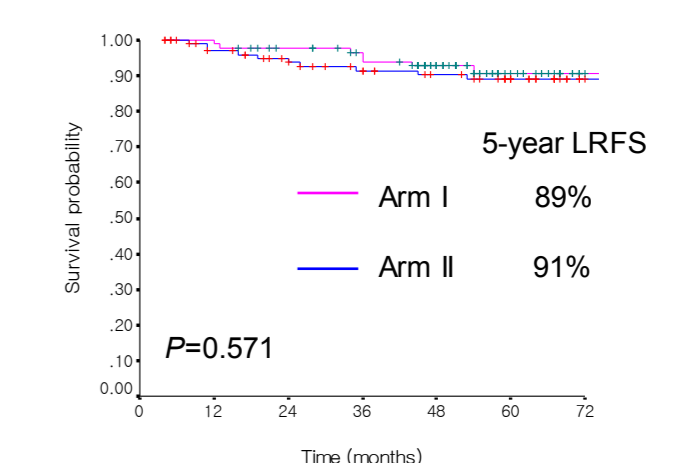


Fig. 5. Local recurrence-free survival between Arm I and II

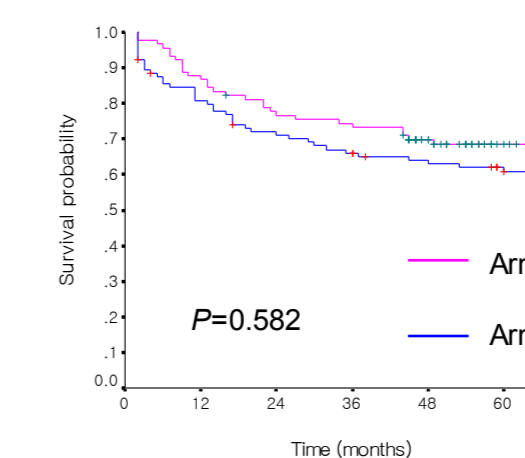


Fig. 4. Disease-free survival between Arm I and II

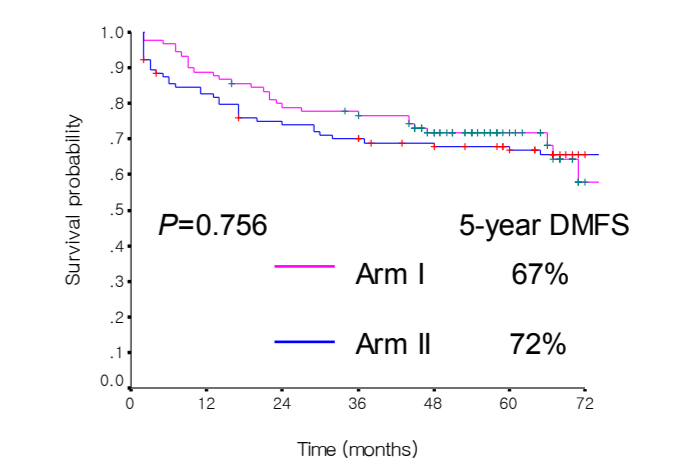


Fig. 6. Distant metastasis-free survival between Arm I and II

Table 3. Multivariate analysis for disease-free survival

Variables	Hazard ratio	95 % confidence interval	P
Treatment group			
Arm I	0.000	0.371-0.954	0.987
Arm II			
Age			
<65	2.503	0.371-0.954	0.114
≥65			
Sex			
Male	3.311	0.371-0.954	0.069
Female			
Tumor mobility			
Mobile & partially fixed	0.595	0.371-0.954	0.031
Totally fixed			
Distance from anal verge			
≤5 cm	1.340	0.371-0.954	0.247
> 5cm			
Clinical stage			
stage II	.115	0.13-0.342	0.734
stage III			
Pathological stage			
< stage III	.210	0.13-0.342	0.000
≥ stage III			
pCR			
Yes	.107	0.13-0.342	0.744
No			

Abbreviations: Arm I= bolus 5-FU + leucovorin; Arm II= oral capecitabine; pCR= Pathological complete response