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ORIGINAL ARTICLE

The Value of Using Short Course Radiotherapy (SCRT) Versus Short Course Radiotherapy Followed by Delayed Surgery (SCRT-DS) For Management of Patients with Locally Advanced Rectal Cancer (LARC); A Comparative Study

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General Surgery [1,2,8], Anesthesia and Intensive care[3], Medical Oncology[4], Clinical Oncology[5], Pathology[6] & Internal Medicine[7]

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ABSTRACT

Background: Management of patients with locally advanced rectal carcinoma (LARC) is different than early stage rectal carcinoma, as only surgical management of this cancer is related to higher incidence of cancer recurrence, whether distant or local recurrence.

Using SCRT in addition to immediate surgery is another valid management option. But there are still some patients too frail for chemo-radiation and promising results were found with the strategy of using radiotherapy followed by delayed surgery performance for a better management of LARC patients.

Aim of the present report was to assess the feasibility, toxicity, short and long term outcome in addition to assessing the ability to produce pathological complete response to therapy of using a SCRT and SCRT followed by delayed surgical resection, in patients with a middle and/or low LARC.

Patients and methods: we prospectively assessed 60 patients who were diagnosed with middle and/or low LACR we divided them into; 35 patients underwent SCRT only and 25 patients underwent SCRT followed by delayed surgical resection (SCRT-DS group). We compare between both included groups regarding; short term, long term, surgical and survival outcomes.

Results: All included patients showed disappearance of cancer-related hemorrhage. Cancer-related pelvic pain disappearance happened in 80% of patients.

In patients who underwent SCRT alone; complete pathologic respons e was reported in 15% of patients, partial response was reported in 15% of patients and no response was reported in 70% of patients. In patients who underwent SCRT-DS complete pathologic response was reported in 30% of patients, partial response was reported in 40% of patients and no response was reported in 30% of patients. All the patients have R0 resection margin.

In all included patients down-staging of cancer occurred 78.9% of patients without statistically significant differences between both included groups of patients.

Median OS rate and DFS rate were better in the SCRT-DS group than in SCRT group (p =0.049 and 0.036 respectively).

Conclusions: we demonstrated that using SCRT followed by a delayed surgery in patients with a low/middle LARC which were considered “unfit” for LCRT is a feasible and safe management strategy regarding both surgical and oncologic outcomes.

Keywords: Short course radiotherapy (SCRT), delayed surgery, locally advanced rectal cancer (LARC).

INTRODUCTION

Management of patients with locally advanced rectal carcinoma (LARC) is different than early stage rectal carcinoma, as only surgical management of this cancer is related to higher incidence of cancer recurrence, whether distant or local recurrence, so multidisciplinary management approaches are needed **[1, 2].** It was found that using

neoadjuvant therapy (NAT), long-course chemoradiotherapy (LCRT) and/or short-course radiotherapy (SCRT), might lead to reduction of LARC local recurrence rate [**3, 4**].

NAT then performing total mesorectal excision (TME) is the usual management of LARC patients. In those patients the preferred option is LCRT [**5**].

Using SCRT in addition to immediate surgery is another valid management option that might reduce recurrence risk by 60-70%. But in case of presence of high-risk features during radiological evaluation the use of chemoradiotherapy (CRT) will be more beneficial because adding chemotherapy to conventional fractionated radiotherapy was found to improve local control and cancer-specific survival rates [**6, 7**]. But there are still some patients too frail for chemo-radiation and promising results were found with the strategy of using radiotherapy followed by delayed surgery performance for a better management of LARC patients [**8, 9**].

Due to high rates of toxicity; chemoradiotherapy (CRT) and radiotherapy (RT) efficacy and benefits in frail patients with LARC are still controversial [**10, 11**].

Additionally there is increasing number of old patients who were diagnosed with CRC, most of them over 60 years of age at diagnosis and LAC form one third of all diagnosed CRC cases [**12, 13**]. These patients have high liability of chronic diseases that inversely affects overall health and well-being.

Aim of the present report was to assess the feasibility, toxicity, short and long term outcome in addition to assessing the ability to produce pathological complete response to therapy of using a SCRT and SCRT followed by delayed surgical resection, in patients with a middle and/or low LARC.

PATIENTS AND METHODS

In the current study we prospectively assessed 60 patients who were diagnosed with middle and/or low LACR who underwent SCRT in both Faculty of Medicine Benha University and Zagazig University hospitals in the period from March 2015 to December 2019. The clinical, pathological, surgical and oncological data were prospectively acquired. Included patients were followed up in the outpatient clinics in Departments of General Surgery, Medical Oncology and Clinical Oncology and Nuclear Medicine in both Benha University and Zagazig University.

We defined low LARC as tumors located <6 cm from anus and middle LARC as tumors located >6e11 cm from the anus.

Clinical and radiological staging was done by using computed tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography/CT (PET/CT) if needed.

American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) system was used for staging of all [**14**].

We chose patients treatment type according to TNM stage, age, general patient's condition, disability, and preexisting comorbidity.

After application of inclusion criteria of the study we randomly divided patients into 2 groups the first group includes 35 patients underwent SCRT (SCRT group) only and the second group include 25 patients underwent SCRT followed by delayed surgical resection (SCRT-DS group).

Treatment

Radiotherapy was done according to the standard protocol of using CT-based 3D- conformal management planning. The volume of clinical targets included; malignant tissue, mesorectal tissues (that include perirectal lymph nodes, presacral lymph nodes and internal iliac lymph nodes.

SCRT included single doses of 5.0 Gy in 5 fractions within 1 week up to a total dose of 25 Gy.

To assess adverse factors of radiation therapy we used Common Terminology Criteria for Adverse Events (CTCAE) [**15**].

After finishing radiotherapy we restaged included patients with CT scan of the whole body, pelvic MRI and endoluminal ultrasound.

Surgical management includes; low anterior rectal resection in 16 cases (64.0%), Hartmann's resection, abdomino-perineal rectal resection or procto-colectomy 6e8 weeks after radiotherapy coarse completion. We performed all surgeries in an open technique.

We recorded any post-operative complications and graded them according to classifications of Clavien-Dindo [**16**].

We evaluated post-treatment pathological response using Dworak regression scoring system [**17**].

In-patient and outpatient monitoring patients for occurrence of perioperative complications was done by colorectal surgical team for about 1 month and 3 months after the operations and then returned with the pathology report, to radiation oncology department.

Loperamide was prescribed for patients presented with proctitis but we prescribed 5-aminosalicilates (5ASA) tablets or hydrocortisone suppository for cases presented with bloody discharge. Additionally, we evaluated patients for occurrence of perioperative complications as anastomosis leakage, delayed wound healing or dehiscence, formation of rectovaginal, rectovesical or enterocutaneous fistulae.

Evaluation of pathologic response to radiotherapy was assessed depending on the pathology report by evaluation of degree of tumor invasion (pT) and positive lymph nodes number (pN) in addition to number of nodes down-staging.

Survival rate evaluation using Kaplan-Meyer curves was started from time of ending radiotherapy. None of included patients received post-operative chemotherapy.

Patients with recurrent CRC after performing former surgery, patients with synchronous occurrence of distant metastasis, patients with previous history of irradiation to the pelvis, patients with past history another cancer, patients with renal function impairment and patients with medical unfitness for surgery were excluded from the study.

Written informed consent was obtained from all participants after informing them about advantage and complications of the study. The study was approved by the research ethical committee of Faculty of Medicine, Zagazig and Benha University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical methods

The statistical analysis was done using SPSS 22.0 (IBM Corp., Armonk, NY) software.

Quantitative data were expressed as mean ± standard deviation (SD) or median and qualitative data were expressed as frequency and percentage. Chi 2 test was used for categorical data. Fisher exact test was used for frequency, and Student's test in the case of continuous data.

Overall survival (OS) was defined as the interval between the date of first biopsy until either death or last follow-up. Disease free survival rate (DFS) was defined as the interval between the date of surgical intervention to recurrence date or date of the last follow-up visit. Survival results were estimated using the curves of Kaplan-Meier. Findings were considered statistically significant if $p < 0.05$.

RESULTS

Patient characteristics

We included a total of 60 patients with LARC divided into 25 patients underwent SCRT-DS and 35 patients only treated by SCRT.

The median age of all included patients was 65 (ranged from 50 - 78) we found no significant differences in age of both included patients groups.

LARC in middle rectum was present in 90% of patients who underwent SCRT-DS and 93%, of patients who only treated by SCRT. The distance from anal verge was 5.9 ± 3.22 cm.

No significant differences between both included groups of patients regarding; tumor size, grade, stage, histopathological subtype or nodal status.

In patients who underwent SCRT-DS we performed surgical resection at about 6-8 weeks after finishing the course of radiotherapy. We performed low anterior resection (LAR) in most patients.

Short-term results

All included patients who completed the course of SCRT showed disappearance of cancer-related hemorrhage. Cancer-related pelvic pain disappearance happened in 80% of patients, while the remaining 20% of patients needed analgesic therapy up to 10 days after completion of SCRT.

Adverse effects which were caused by radiotherapy were found in 15% of all patients.

We haven't performed surgical excision in SCRT group due to anesthesia's contraindication or due to patients' refusal of surgery.

Overall rate of morbidity was 25%. Rate of Clavien-Dindo grade 3 was 12%.

Anastomotic leakage happened in 8% of patients.

No evidence of immediate postoperative mortality.

The median duration from radiotherapy ending to performing surgery was about ten months.

Pathologic response

In patients who underwent SCRT alone; complete pathologic response was reported in 15% of patients, partial response was reported in 15% of patients and no response was reported in 70% of patients.

In patients who underwent SCRT-DS complete pathologic response was reported in 30% of patients, partial response was reported in 40% of patients and no response was reported in 30% of patients. All the patients have R0 resection margin.

Long-term outcomes

In all included patients down-staging of cancer occurred 78.9% of patients without statistically significant differences between both included groups of patients.

The median follow-up was 18 months and 30 months for the SCRT and SCRT-DS groups, respectively.

Median OS rate and DFS rate were better in the SCRT-DS group than in SCRT group (p =0.049 and 0.036 respectively).

Table1: Clinicopathological findings of both groups of patients

Variable		SCRT N=35		SCRT-DS N=25		Total N=60		P value
		N	%	N	%	N	%	
Age (years)		68	58 - 78	64	52 - 77	65	50 - 78	0.192
Sex	female	12	34.3%	8	32.0%	20	33.3%	0.853
	male	23	65.7%	17	68.0%	40	66.7%	
histopathological subtype	conventional adeno carcinoma	29	82.9%	21	84.0%	50	83.3%	0.907
	mucoid carcinoma	6	17.1%	4	16.0%	10	16.7%	
Site in the rectum	Mid	29	82.9%	21	84.0%	50	83.3%	0.907
	Low	6	17.1%	4	16.0%	10	16.7%	
Stage	II	15	42.9%	10	40.0%	25	41.7%	0.825
	III	20	57.1%	15	60.0%	35	58.3%	
Grade	Low	15	42.9%	10	40.0%	25	41.7%	0.825
	High	20	57.1%	15	60.0%	35	58.3%	
Type of primary operation	LAR	14	40.0%	16	64.0%	30	50.0%	0.306
	APR	11	31.4%	5	20.0%	16	26.7%	
	Proctocolectomy	4	11.4%	1	4.0%	5	8.3%	
	Hartman	6	17.1%	3	12.0%	9	15.0%	
LN metastases	Absent	15	42.9%	10	40.0%	25	41.7%	0.825
	Present	20	57.1%	15	60.0%	35	58.3%	

Table2: Oncological findings of both groups of patients

Variable		SCRT N=35		SCRT-DS N=25		Total N=60		P value
		N	%	N	%	N	%	
T	Stable disease	12	34.3%	8	32.0%	20	33.3%	0.053
	Down stage	23	65.7%	17	68.0%	40	66.7%	
N	Stable disease	5	14.3%	4	16%	9	15%	0.825
	Down stage	15	42.8%	6	24%	21	35%	
Stage	Stable disease	29	82.9%	21	84.0%	50	83.3%	0.907
	Down stage	6	17.1%	4	16.0%	10	16.7%	
Recurrence pattern after therapy	Local	8	34.8%	5	50.0%	13	39.4%	0.411
	Distant	15	65.2%	5	50.0%	20	60.6%	
Death	Alive	14	40.0%	16	64.0%	30	50.0%	0.047
	Dead	21	60.0%	9	36.0%	30	50.0%	
Relapse*	Free	12	44.4%	15	75.0%	27	57.4%	**0.036**
	Relapse	15	55.6%	5	25.0%	20	42.6%	

Table 3: Survival rates of both groups of patients

	Total N	N of Events	Censored		Survival time in Months				Survival rate%	Sig.
					Mean		Median			
					Estimate ±SE	95% CI	Estimate ±SE	95% CI		
Overall Survival										
SCRT	35	21	14	40.0%	18.9±0.8	17.4-20.4	18.0±0.5	17.0-19.0	11.0%	0.049
SCRT-DS	25	9	16	64.0%	21.1±1.0	19.1-23.1	23.0±2.8	17.5-28.5	0.0%	
Overall	60	30	30	50.0%	19.8±0.6	18.6-21.0	18.0±1.5	15.0-21.0	41.0%	
Relapse-Free Survival										
SCRT	27	15	12	44.4%	18.3±1.0	16.2-20.3	17.0±1.0	15.0-19.0	30.5%	**0.036**
SCRT-DS	20	5	15	75.0%	18.8±0.4	17.9-19.6	NR		57.3%	
Overall	47	20	27	57.4%	19.6±0.8	18.0-21.2	18.0±0.6	16.8-19.2	8.8%	

NR: Not reached. 95%CI: 95% confidence interval, Sig.: significance, SE: standard error

Table 4: Univariate and multivariate analyses of overall survival rate of included patients

Co-variate	***Overall Survival***			
	Univariate		***Multivariate***	
	Sig.	HR (95% CI)	Sig.	HR (95% CI)
Age (years)	0.199	1.03 (0.99-1.07)		
sex	0.792	0.88 (0.35-2.23)		
histopathological subtype	0.978	1.01 (0.41-2.52)		
Initial site	Ref.			
Initial site(low)	0.458	1.52 (0.50-4.63)		
Initial site(Mid)	0.896	1.09 (0.31-3.87)		
DUKE stage	Ref.			
DUKE stage(II)	0.998	1.00 (0.30-3.32)	0.959	1.04 (0.25-4.32)
DUKE stage(III)	0.173	0.47 (0.16-1.39)	0.961	1.04 (0.23-4.66)
LN metastases	0.029	2.61 (1.10-6.17)	0.079	2.48 (0.90-6.82)
Size of largest LN mm	0.211	0.91 (0.79-1.05)		
Type of primary operation	0.204	1.66 (0.76-3.63)		
SCRT-SD	0.002	0.21 (0.08-0.57)	0.003	0.01 (0.00-0.23)
SCRT	0.037	4.65 (1.10-19.62)	0.205	2.72 (0.58-12.76)
Relapse	0.011	3.37 (1.32-8.63)	0.004	0.01 (0.001-0.26)
Downstaging	<0.001	0.54 (0.39-0.75)	0.023	0.59 (0.38-0.93)

HR: hazard ratio, 95%CI: 95% confidence interval, Sig.: significance.

Table5: Univariate and multivariate Cox regression analyses for Relapse-free survival rate of included patients

Co-variate	*Relapse-free Survival*			
	Univariate		***Multivariate***	
	Sig.	HR (95% CI)	Sig.	HR (95% CI)
Age (years)	0.87	1.00 (0.95-1.04)		
sex	0.033	1.63 (1.04-2.56)	0.034	1.62 (1.04-2.52)
histopathological subtype	0.339	0.49 (0.11-2.12)		
Initial site	Ref.			
Initial site(low)	0.824	0.86 (0.23-3.25)		
Initial site(Mid)	0.948	1.05 (0.25-4.39)		
DUKE stage	Ref.			
DUKE stage(II)	0.375	1.89 (0.46-7.70)		
DUKE stage(III)	0.667	0.75 (0.20-2.83)		
LN metastases	0.04	2.72 (1.05-7.10)		
Size of largest LN mm	0.043	0.83 (0.68-0.99)	0.145	0.86 (0.70-1.05)
Type of primary operation	0.062	0.38 (0.14-1.05)		
SCRT-SD	0.653	1.43 (0.30-6.72)		
SCRT	0.08	4.11 (0.85-20.00)		
Relapse	<0.001	7.32 (2.43-21.99)	0.001	6.16 (2.02-18.78)
Downstaging	0.108	32.28 (0.46-2240.74)		

HR: hazard ratio, 95%CI: 95% confidence interval, Sig.: significance.

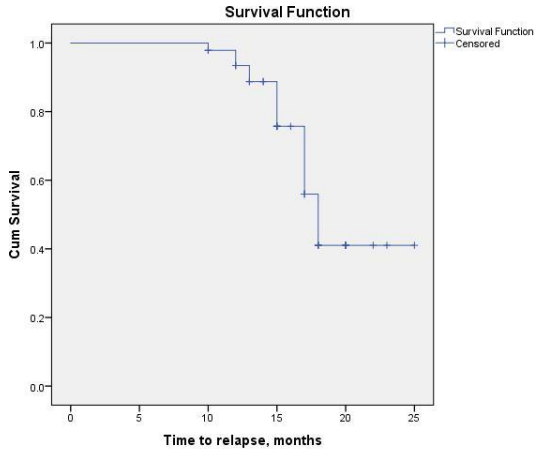

Fig.1 A

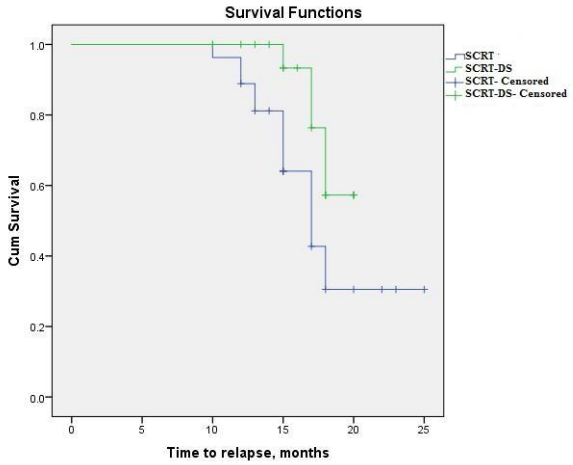

Fig.1 B

Figure 1: Kaplan– Meier survival curves illustrating the recurrence -free survival rate (A) RFS rate of all included patients (B) RFS rate correlating between both included groups of patients.

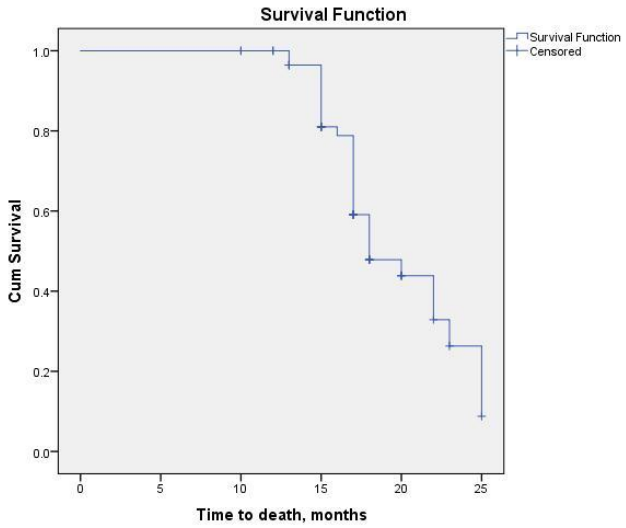

Fig.2 A

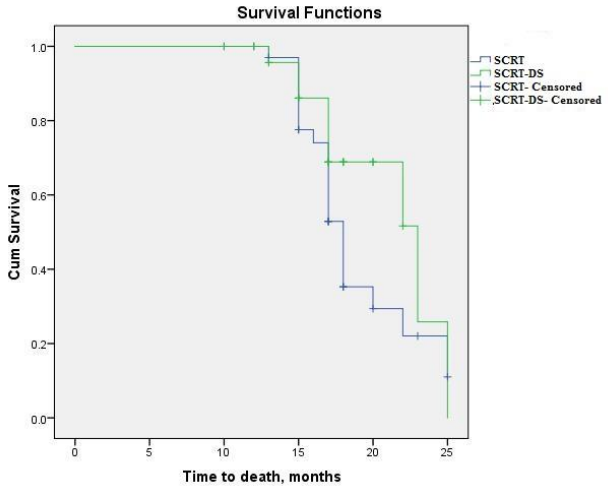

Fig.2 B

Figure 2: Kaplan– Meier survival curves illustrating the overall survival rate (A) OS rate of all included patients (B) OS rate correlating between both included groups of patients.

DISCUSSION

In the current study we showed that frail patients who were diagnosed with a LARC that was located in the middle or the lower rectum and underwent SCRT-DS have better outcomes than patients who underwent SCRT.

Our results were similar to results of **Lancellotti et al., [2]**.

Long coarse radiotherapy (LCRT), followed by total mesorectal excision with clear safety margins is the standard management for patients with LARC that was located in the middle or the lower rectum [**18**].

Using preoperative LCRT was found to have several advantages to patents with LARC as it lead to reduction in tumor size, increase chances of surgery with free safety margins and ability to reduce local cancer recurrence risks [**Wyrwicz Glynne-Jones L et al. 2017**], but LCRT had many adverse events than SCRT [**19**], without significantly reported differences between LCRT and SCRT in oncological and surgical outcomes [**20**],

Which support our results about values of SCRT use in LARC.

In our study we reported overall rate of down staging in most patients, who underwent SCRT-DS with an accepted control of cancer related symptoms after treatment ending.

Our findings are in line with results of previous studies [**7, 21**], proving benefits and advantages of performing rectal surgery in frail patients.

Standard management approach of LARC was LCRT in addition to surgery was found to be associated with low rates of local recurrence but without reducing rate of distant metastases.

Our results showed that using SCRT as a neoadjuvant therapy resulted in little morbidity, symptoms improvement mainly decreasing rectal hemorrhage in addition to tumor down-staging. After finishing SCRT course; patients were re-evaluated to be fit for delayed surgery, with better postoperative outcomes.

SCRT-DS has better oncologic outcomes than patients who only treated by SCRT **[22]**. Moreover we showed that outcomes of patients underwent SCRT-DS could be better than standard LCRT followed by surgery [**23, 24**], suggesting that SCRT-DS in patients with LARC is feasible option for them.

Points of strengths of the study; we overcome previous studies limitations [2] which was a retrospective study and performed this prospective study, we included patients managed in two institutions.

CONCLUSIONS

patients with a low/middle LARC which were considered "unfit" for LCRT, because of its toxicity, adverse effects and postoperative morbidity, we demonstrated that using SCRT followed by a delayed surgery in these patients is a feasible and safe

management strategy regarding both surgical and oncologic outcomes.

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