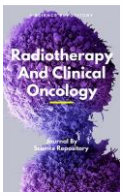

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Research Article

Local Recurrence in Patients with Upper Third Rectum Cancer Treated with Surgery Alone Compared with Surgery Plus Chemoradiotherapy

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ABSTRACT

Background: Colorectal cancer is the third most common neoplasm in Mexico, rectal cancer is the 16th most common neoplasm [1]. Due to the different behavior and prognostic factors of locally advance disease, manage should be tailored by a multidisciplinary approach. In tumors that rise in the upper third rectum cancer scenario there are no studies comparing the oncological results of multimodal treatment vs surgery alone.

Objective: To compare the disease-free survival in patients with upper third rectal cancer treated with surgery alone vs multimodal treatment.

Material and Methods: We conducted a descriptive, retrospective, longitudinal study using an historical cohort. Analysis was based from the information in patient`s records from diagnosed with cancer of the upper third rectum from 2011 to 2016. All patients with diagnosis of upper third rectum cancer were set in to two groups according to the treatment modality recited: Surgery alone and neoadjuvant chemotherapy. The records of patients diagnosed with cancer of the upper third rectum were reviewed and divided into two groups: with and without neoadjuvant chemoradiotherapy, both treated with surgery.

Results: A total of 64 patient`s record were eligible, 48 of them were treated with surgery alone and 16 with a multimodal approach. The mean age was 65.5 years in those treated with surgery and 69 in the multimodal management group. The most frequent procedure was anterior resection, 45 cases (70.3%) in the group treated with surgery and 12 cases (18.7%) in the multimodal group. A case of complete pathological response was reported after a follow up of two years.

Conclusion: The data suggests that there are no statistically significant differences in the local recurrence and disease-free survival with the use of neoadjuvant chemoradiotherapy.

Introduction

Colorectal cancer is a frequent disease and represented in 2018 the third most common neoplasm in males and the second in females, with 1.8 million new cases and almost 861,000 deaths in 2018, according to the World Health Organization [1]. In the United States, 145,600 new cases are diagnosed annually, of which 44,180 correspond to the rectum. This disease accounts for approximately 8 percent of all cancer deaths [2]. The rectum is anatomically defined as the last 16 cm of large intestine from the anal canal and is covered by a fatty tissue that contains its closest regional lymph nodes. It is richly vascularized and is surrounded by a thin membrane that corresponds to the mesorecta fascia, whose

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surgical resection must be complete to achieve adequate regional lymphadenectomy and thus ensure a microscopic margin free of neoplastic cells. From the clinical point of view the rectum is divided into thirds by its length, the lower third extends from the pectineal line to 5 cm, the middle 5 to 10 cm and the upper 10 to 15 cm.

The fascia of the upper rectum limits the locoregional spread of cancer, unlike the middle and lower third of the rectum that lacks this anatomical limit and therefore have predisposition for locoregional spread. Treatment of colorectal cancer is dictated by the clinical stage, which is the most important prognostic factor of survival in patients with colorectal cancer. Currently, the TNM classification (Tumor, Nodule, Metastasis) is the most frequently used to assess the extent of the tumor, the lymph node status and the presence of metastases. Stages I and II are defined as early stages confined to the organ (T1-T4bN0M0), while stage III is considered being locoregional spread of the disease to the regional lymph nodes [3, 4]. The preferred modality of treatment for locoregional disease is surgery, however, those with T3, T4 tumors and nodal disease are candidates for preoperative chemoradiotherapy, intending to sterilize the circumferential margin, after which the clinical response of the tumor is assessed, defining the extent of the surgical treatment [5, 6].

As a result of multidisciplinary management and the perfecting of the surgical techniques during the past two decades, there have been a significant improvement in the control rate of the rectal cancer in clinical stages II and III, by decreasing the locoregional recurrence rate of the disease [7]. This has been proved by several clinical trials that demonstrated the benefit of adding chemoradiotherapy to the surgical treatment this has increased local control of the disease allowing higher rates of anal sphincter preservation, in the absence of more complications [8-11].

However, it is worth mentioning that in these studies patients with upper rectal cancer were underrepresented in final analysis, particularly in the German study and the Dutch study (currently governing international treatment guidelines), did not reveal any benefit in the control of the disease [9, 10]. Surgical experts propose that, due to its anatomical characteristics, upper rectal cancer, has a biological behavior similar to descending colon cancer, and it could be treated as sigmoid cancer with surgery without the need for complementary treatments [11]. Although the upper third rectum has a different biological behavior, it has not been classified as an independent entity, and acceptance of the same modality treatments as the lower and middle thirds of rectum had been used, this observation promts to conduct studies to evaluate the efficacy of different treatment options for this location of rectal tumors [12, 13].

Materials and Methods

We reviewed the records of an historical cohort from the HGO XXI Century Oncology Research Unit, Oncology Hospital, Siglo XXI Medical Center IMSS, that included the patients diagnosed with cancer of the upper third rectum from 2011 to 2016 [14-16]. The patients incorporated in the analysis were those with cancer of the upper rectum (tumors from 10 to 16 cm of the anal margin measured by preoperative colonoscopy) as long as a complete resection of the tumor (R0) was reported in the final pathologic assessment. The patients with a histology other than adenocarcinoma, with synchronous and/or metachronous colorectal cancer as well as hereditary cancer were not considered for the study.

Survival was determined by survival curves with log Rank and Cox models for the case of multivariate analysis whereas impact measures were used to determine the risk using a bivariate model such as the multiple logistic regression model and survival analysis [14, 15, 17, 18]. For statically purposes a value of $p < 0.05$ was considered significant. The analysis was carried out with SPSS systems version 24.0.

Results

We analysed the records of 100 patients diagnosed with rectal cancer of the upper third in the period from January 2011 to December 2016. Twenty-six cases were excluded due to lack of complete patient follow-up, incomplete records and tumoral location within their rectum misclassification. Patients were assigned into two groups; those who received neoadjuvant chemoradiotherapy and those who did not receive such treatment. From a total of 64 patients; forty-eight were treated with surgery alone and 16 with neoadjuvant treatment followed by surgery. The average age of the patients was 65.5 years in the surgery only group and 69 years in the multimodal treatment group. The type of surgical procedure was based on intraoperative findings (previous resection, low anterior resection, posterior and total exenteration). Low anterior resection was the most frequent surgical procedure, performed in 45 cases (70.3%), while three patients underwent partial cystectomy (4.7%), one patient had a total pelvic exenteration (1.6%). Postoperative morbidity was 29.7%. After treatment, the 29 cases (45.3%) were classified with pathologic stage III, in 7 cases (10.9%) as stage I and in one a complete pathological response was reported (1.6%). Adjuvant chemotherapy was offered to patients with stage IIB-IIIC; a total of thirty-six patients (56.3%) received adjuvant chemotherapy with the aim of increasing disease-free survival (Tables 1 & 2).

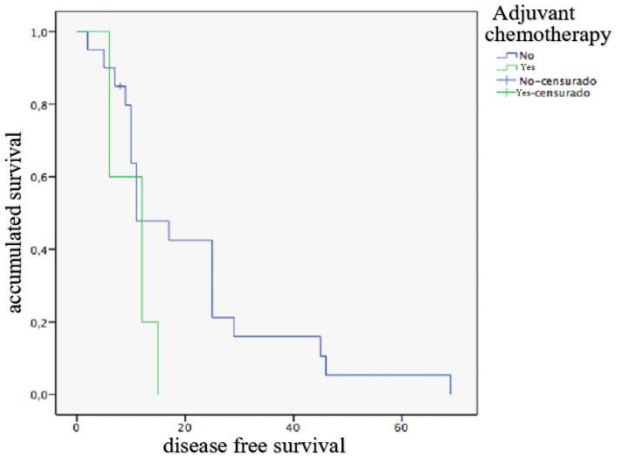

Figure 1: Recurrence with and without QT/RT.

Both groups were treated with surgical resection and were followed for a period of 24 months the use of neoadjuvant chemoradiotherapy was stablished based on surgeon's preference (Figure 1). In patients that received preoperative chemoradiotherapy, surgery was performed between 10 and 12 weeks after the end of radiotherapy. Recurrence was defined as evidence of disease after at least 6 months since surgery. The

follow-up evaluation was performed on a four-month basis and included clinical exploration, chest x-rays, carcinoembryonic antigen (CAE) measurement, and imaging studies such as MRI and CT scan as well as a liver ultrasonography in cases with CAE measurement elevation. Global recurrence rate was 37.5% and a mortality rate of 7.8% were reported at 2 years of follow-up (Table 1).

Table 1: General characteristics of patients with upper rectal cancer.

Variable	**N (%) 64**
Sex	
Male	32 (50 %)
Female	32 (50 %)
Edad años	65.1 (±12)
CT/RT neoadyuvant	
No	16 (19.8 %)
Yes	48 (59.3 %)
Surgical Procedure	
Lower anterior resection	45 (70.3 %)
Anterior resection	8 (12.5 %)
Posterior exenteration	6 (9.4 %)
Lower anterior resection with bowel resection	1 (1.6 %)
Lower anterior resection with partial cistectomy	3 (4.7 %)
Total pelvic exenteration	1 (1.6 %)
Pathological clinical stage	1 (1.6 %)
I	7 (10.9 %)
IIA	14 (21.9 %)
IIB	10 (15.6 %)
IIC	3 (4.7 %)
III	29 (45.3 %)
Ajuvant Chemotherapy	
No	28 (43.8 %)
Yes	36 (56.3 %)
Postoperative Complication	
No	45 (70.3 %)
Yes	19 (29.7 %)
Recurrence	
No	40 (62.5 %)
Yes	24 (37.5 %)
Mortality	
No	59 (92.2 %)
Yes	5 (7.8 %)

Table 2: Bivariate analysis of patients without CT/RT and with CT/RT.

Variable	**Without QT/RT (n =48)**	**With QT/RT (n=16)**	**Test**	**IC**
Sex				
Male	24 (50 %)	8 (50 %)	X2	NO .754-1.327
Female	24 (50 %)	8 (50 %)		SI .428-2.337
Age years			p .000	
Median	65.5 (25-90)	69 (54-75)	t -31.5	-68.9 – (- 60.6)
Rank				
Albumin gr/dl	3.56 (± 0.51)	3.43 (± 0.44)	p .000	1.3 – 1.7
			t-36.6	
Preoperative lymphocytes 1,000/mm^3	1.98 (± 0.41)	2.0 (± 0.6)	p .000	1.0-1.8
			t 7.8	
CAE preoperative ng/L	5.7 UI/dl	5.4 UI/dl		
	(0.91-21.2)	(1.01-26.9)		
Surgical Procedure				
Lower anterior resection	33 (68.7 %)	12 (75 %)	RR 6.2	

Anterior resection	7 (14.5 %)	1 (6.2 %)	p 0.49	
Posterior exenteration	3 (6.2 %)	3 (18.7 %)		
Lower anterior resection with bowel resection	1 (2 %)	0		
Lower anterior resection with partial cystectomy	3 (6.2 %)	0		
Total pelvic exenteration	1 (2 %)	0		
Pathological clinical stage				
complete	0	1 (6.2 %)	RR 6.2	
I	7 (14.5 %)	0	p 0.284	
IIA	11 (22.9 %)	3 (18.7 %)		
IIB	8 (16.6 %)	2 (12.5 %)		
IIC	2 (4.1%)	1 (6.2 %)		
III	20 (41.6 %)	9 (56.2 %)		
Complication				
No	31 (64.5 %)	14 (87.5 %)	X2 < 0.082	.743-11.762
yes	17 (35.5 %)	2 (12.5 %)	RR 3	
Postoperative complication				
No	31 (64.5 %)	12 (75 %)	RR 2.6	
Dehicience of the anastomosis	11 (22.9 %)	2 (12.5 %)	P 0.856	
Postoperative bleeding	1 (2 %)	0		
Bowel lesion	1 (2 %)	1 (6.2 %)		
ureteral lesion	2 (4.1%)	0		
Intrabdominal abscess	2 (4.1 %)	1 (6.2 %)		
Recurrence				
No	29 (60.4 %)	11 (68.7 %)	RR 6.1	
Local	4 (8.3 %)	1 (6.2)	P 0.409	
Liver	7 (14.5 %)	0		
Lung	4 (6.25 %)	2 (12.5 %)		
Bone	1 (1.56 %)	0		
Retroperitoneal and liver	1 (1.56 %)	2 (12.5 %)		
Liver and lung	1 (1.56 %)	0		
Mortality				
No	44 (91.6 %)	15 (93.7 %)	0.753	0.76-7.086
Yes	4 (8.4 %)	1 (6.3 %)		

Table 3: Median and median survival.

Neoadjuvant chemoradiotherapy	**Mean**				**Median**			
	Estimate	Typical Error	95% IC		Estimate	Typical Error	95% IC	
			Lower limit	Upper limit			Lower limit	Upper limit
No	20,781	3,924	13,090	28,472	11,000	3,775	3,602	18,398
yes	10,200	1,800	6,672	13,728	12,000	2,683	6,741	17,259
Global	18,598	3,237	12,254	24,942	12,000	,958	10,122	13,878

The estimate is limited to the longest survival time if it has been censored.

Discussion

The anatomical characteristics of tumors located in the upper third of the rectum suggest that the biological behavior of the disease is different from those located in the middle and lower third of the rectum [7, 19]. Several studies show that the local recurrence of patients with tumors originating in the upper third of the rectum before the standard use of concomitant chemoradiotherapy is similar to the use of multimodal treatment [20]. On the other hand, classic studies demonstrate superiority in local control of rectal cancer treated with chemoradiotherapy. However, the analysis of these studies was made regardless of the tumor location within the rectum. In the subgroup analysis, patients with upper third rectal cancer do not benefit in terms of disease-free survival with neoadjuvant therapy versus surgery alone [8-10].

However, it appears that is a non-significative trend towards complication in the no neo-adjuvant treatment group perhaps derived from the intent of ensuring a negative margin [9]. One of the drawbacks in clinical practice with regard to patients with tumors originating in the upper rectum is that due to their anatomical characteristics it is difficult to identify them by endoscopy or imaging studies, due to the weight of the tumor, can cause it to descend into the pelvis. This can result in an overtreatment with concomitant chemotherapy. Although there is a tendency in the current literature to omit chemoradiotherapy in this

group of patients, there are difficulties carry out a clinical trial they can demonstrate the difference between these two treatments.

Conclusion

This study suggests a non-difference in adding neo-adjuvant chemoradiotherapy to patients with upper third rectal tumors, nevertheless, larger studies are needed to confirm the non-inferiority of surgery against the multimodal treatment in patients with upper third rectal cancer. In this study, the local recurrence rate was similar in both treatments which propose that surgery is the main prognostic factor. Another factor to take into account is that the possibility of achieving a complete clinical response exist only within the multimodal treatment.

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