STAGE DISTRIBUTION AND PATIENT RESPONSE POST NEO-ADJUVANT SHORT COURSE RADIOTHERAPY IN RECTAL CANCER, SINGLE CENTER STUDY

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ABSTRACT

Background

Colorectal cancer (CRC) is one of the leading causes of mortality and morbidity in the world. It is the third most common malignancy and the fourth leading cause of cancer-related deaths worldwide, accounting for approximately 1,400,000 new cases and about 700,000 deaths worldwide.

Objectives

The objective of this study is to assess patients' response and developments of complication, after the use of neo-adjuvant short course radiotherapy in addition to the effect of this treatment modality on pathological response, local control and distant metastasis.

Methods

Forty six patients, who were histopathologically proven to have colorectal carcinoma, were randomly assigned to receive 25 Gy of radiation, in a short period of time prior to surgical resection of tumor. Local control, distance metastasis and post operative signs and symptoms measured over a period of 5 years (2013-2018). The treatment period ranged between 3-327 days.

Results

The overall survival of patients and their experience with post operative toxicity was improved; there was statistically significant correlation between spread of the tumor and duration of radiotherapy, p value was less than 0.05.In addition 84% of cases had no recurrence. Overall survival was about 76% of cases at the end of this research. The rate of post operative complication decreased. But the duration of radiotherapy had no significant effect on the mortality. (p value=0.2)

Conclusion

Preoperative short-course radiotherapy before colorectal surgical intervention favors better local control and distant metastasis in addition to less complication, more comfort for patients and favorable survival rate.

Keywords: *Neo-adjuvant Short Course Radiotherapy, Rectal Cancer.*

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INTRODUCTION

Colorectal cancer (CRC) is one of the leading causes of mortality and morbidity in the world [1]. It is the third most common malignancy and the fourth leading cause of cancer-related deaths worldwide, accounting for approximately 1,400,000 new cases and about 700,000 deaths worldwide [2]. There is a large geographic difference in the global distribution of colorectal cancer [3] . In recent years, the incidence and mortality rates of CRC in Eastern Europe, Latin America and Asia have grown higher than other countries [4] .

The current treatment of locally advanced rectal adenocarcinoma (lower and middle tumors with a distance of less than 12 cm from the anal verge) is based on neo-adjuvant radiotherapy then chemotherapy or not, followed by a surgical excision.

There are two approaches for preoperative radiation therapy. The first, developed in Northern Europe and Scandinavia, is short-course (hypo-fractionation) radiation (25 Gy in 5 fractions), which is associated with significant local control LC improvement and more tolerable in contrast to long course post operative radiotherapy [5]. The other approach (long course) is a standard course (50.4 Gy in 28 fractions) combined with concurrent chemotherapy (chemo-radiation) [6] . Based on this experience we started short course (hypo fractionated) pre operative radiotherapy. This is due to acceptable toxicity and comparable efficacy to long course chmoradiation [7-9].

PATIENTS AND METHODS

This interventional study included 45 patients pathologically proven to have resectable rectal cancer (resection of the tumor and associated lymph nodes with negative margins) that were treated in Zhinawa Cancer Center, from May 2013 until September 2017. It was conducted to study patient response and satisfaction after the use of neo-adjuvant short course radiotherapy and its effect on pathological response, local control, and systemic recurrence; this is in addition to post operative patients' experience of complications. All the patients were recruited randomly based on their diagnosis and they had no prior treatment for these diseases.

Ethical considerations and methods were employed during the research. This research was allowed to be conducted after compliance with all ethical considerations of Kurdistan Board of High Medical Specialties in collaboration with the scientific committee by University of Sulaimani College of Medicine. Prior to any procedure and treatment informed consent was taken from the patients, the risks and outcomes that may issue form methods employed, were explained and patients were informed about consequences and complications of each of the stages of treatment.

The patients who received other modalities of treatment prior to this research were excluded from the study.

The entire participants received preoperative short-course irradiation (25 Gy delivered in five fractions over 5 days). The clinical target volume CTV included the primary tumor, (GTV) gross tumor volume with mesorectum, internal iliac lymph node, presacral lymph nodes, and obturator lymph nodes. The treatment delivered by using four beam techniques with the patient lying down either Prone or in supine position [10,11] followed by receiving neo-adjuvant courses of Chemotherapy XELODA, FOLFOX for some of them. Capecitabine tab and CAPOX were used then they underwent total Mesorectal excision (TME), Abdomino perineal resection (APR) and Low Anterior Resection (LAR). Some of them refused operation; others did not want to receive Chemotherapy. Some of the patients have received adjuvant courses of chemotherapy at the discretion of the treating physician, depending on the pathological stage.

All patients underwent surgical treatment. The most common types of surgery were lower anterior resection (61.9%) and abdominoperineal resection (29%); in 14 (6.7%) patients, Hartman's procedure was carried out. In two cT1N0 cases (1%), local tumor excision was performed after radiotherapy. In another patient, because of large intestine polyposis, total proctocolectomy was performed. Due to the locally advanced and un-resectable tumor, two patients underwent palliative surgery with colostomy formation after neo adjuvant short course radiotherapy.

The median time between the end of radiotherapy and the operation was 13 days. In 16 (34.7%) patients, surgery was performed within 10 days after radiotherapy; for the remaining 30 patients (65.2%), the break between radiotherapy and surgery was above 10 days.

A histo-pathological evaluation of the postoperative material revealed adenocarcinoma in 40 (86.9%) cases. In the remaining 6 (13%) patients, a complete regression of cancer was confirmed.

All the patients post operatively ,have been assessed for any signs and symptoms of complication as diarrhea, bleeding per rectum, nausea and any other discomforts that might be due to the treatment.

"IBM SPSS statistics version 22" was used for computation and analysis of the data. In addition, a P- Value of (≤ 0.05) was considered as statistically significant.

RESULTS

The demographic features of the population under study were variable, 19 cases of the participants were males and 27 cases were females, 35 cases were from the city center, but 11 cases were living in the rural area and other suburbs, Table 1.

In regard to age distribution of the patients under observation the results appears here in the table below. Patients from variable age groups were included; the range was 24-80 years of age. The highest groups were people in their 6th and 7th decade of their lives. Only about 28.2% of the patients were under 50 years of age the rest of them were above this age in which incidence of colorectal carcinoma is high, Table 2 .

The staging for the tumor performed using TNM staging; AJCC American Joint Committee on cancer 8th edithion TNM staging system, before operation with help of histo-pathologist and a group of specialized oncologist. N+ve: positive Lymph nodes without mention the number of it, Table 3.

Then grading for each individual case was performed with the help of general surgeons, Table 4.

In addition histo-pathological types of carcinoma was classified as it appears in the following table, the commonest being rectal adenocarcinoma which constitute about 76.1% of cases, the rest of them are recto-sigmoid adenocarcinoma and rectal adenocarcinoma(intestinal type) ,each 8.7% and 4.3% subsequently, Table 5.

All the patients underwent chemotherapy treatment and the dosing appears in the table below, this includes; Capecitabine, Capox, 5 Fluorouracil, Table 6. 69% of the cases received Neo-Adjuvant chemotherapy, Table 7.

Different methods of surgical treatment were employed; Low anterior resection for 13 cases (28.2%), Low anterior resection and colostomy for another 6 cases(13%) , but majority of them 23(50%), underwent abdominoperineal resection and colostomy. (information can be retrieved from table in the appendix), 2 (4.3%) of them no operation and other 8(17.3%) no information about the type of operations.

After treatment with short period radiotherapy and surgical resection, incidence of local recurrence was 4.35% and distant metastasis was 10.9% ,Table 8.

The survival of the patients after five years was about 56.5 % as 26 cases were still alive. Eleven cases passed away, Table 9.

Post operative complications due to radiation and operation is common undergoing such procedures this includes bleeding per rectum, abdominal pain, change in bowel habit and etc….However the most common presenting symptoms were bleeding per rectum,(52%) followed by bleeding per rectum and abdominal pain in combination(26%), but after the treatment experience of the patients changed , Table 10.

The relation between histo-pathological examination and after radiotherapy and development of metastasis was not significant too, (p value= 0.074).

Type of pathological examination after radiotherapy and operation in relation to mortality was not significant, Table 11.

TNM staging after radiotherapy and treatment had no significant relation with development of metastases and overall mortality of the cases. P values were (0.96) and (0.5) subsequently.

Table 1. The demographic features of the study participants

Demographic features		Frequency	Range
Age in year (Mean ± SD)		57.2 ± 13.9	24 to 80
Gender (%)	Male	19 (41.3%)	
	Female	27 (58.7%)	
Residency (%)	Inside city	35 (76.1%)	
	Outside city	11 (23.9%)	

Table 2. The age distribution of the study participants

Age groups (year)	Frequency	Percent (%)
21-30	2	4.3
31-40	2	4.3
41-50	9	19.6
51-60	12	26.08
61-70	10	21.7
71- and above	11	23.9
Total	46	100

Table 3. TNM grading of the colorectal carcinoma among the study participants before radiotherapy treatment

TNM (before radiotherapy)	Frequency	Percent (%)
T2-3N0M0	1	2.2
T2N+veM0	1	2.2
T2N0M0	2	4.3
T2N1M0	1	2.2
T3N+veM0	8	17.4
T3N0M0	7	15.2
T3N1M0	17	36.9
T3N2M0	1	2.2
T4bN1M0	1	2.2
T4N+veM0	1	2.2
T4N0M0	1	2.2
T4N1M0	2	4.3
Undefined	3	6.5
Total	46	100

Table 4. Grading of the colorectal cancer that defined by surgeon before radiotherapy

Grade of the tumor	Frequency	Percent (%)
Undefined	40	87
I	1	2.2
II	4	8.7
III	1	2.2
Total	46	100

Table 5. Histoapthological findings of colorectal cancer among the patients before radiotherapy

Histopathological examination	Frequency	Percent (%)
Rectal adenocarcinoma	35	76.1
Rectal adenocarcinoma and signet ring	1	2.2
Signet ring carcinoma	1	2.2
Rectal adenocarcinoma (Intestinal type)	2	4.3
Rectal adenocarcinoma (poorly differentiated)	1	2.2
Recto-sigmoid adenocarcinoma	4	8.7
Anorectal mucinous carcinoma	1	2.2
Undifferentiated carcinoma	1	2.2
Total	46	100

Table 6. The distribution of the neo-adjuvant chemotherapy treatment used for the study participants

Neo-Chemotherapy before radiotherapy (day)	Frequency	Percent (%)
100 tab of Capecitabine	1	2.2
13 cycles of chemotherapy every 5 days (Capecitabine)	1	2.2
3 cycles of chemotherapy every 7 days	1	2.2
4 cycles of chemotherapy	2	4.3
4 cycles of chemotherapy (CAPOX)	2	4.3
4 cycles of chemotherapy then radiotherapy(Oxaliplain& 5fU)	1	2.2
5 cycles of chemotherapy (CAPOX)	1	2.2
6 cycles of chemotherapy every 21 days	1	2.2
8 cycles of chemotherapy	3	6.5
8 cycles of chemotherapy (FOLFOX)	1	2.2
Modified FOLFOX6 (1 cycle/14 days)	1	2.2
No chemotherapy	28	60.8
No file	3	6.5
Total	46	100

Table 7. Neo-adjuvant chemotherapy in the participants before radiotherapy

Neo-Chemotherapy before radiotherapy	Frequency	Percent (%)
Yes	32	69.6
No	14	30.4
Total	46	100

Table 8. The distribution of the local recurrence and distant metastasis among the study participants after radiotherapy

Local recurrence and/or distant metastasis	Frequency	Percent (%)
Local recurrence	2	4.3
Distant metastasis	5	10.9
No	39	84.8
Total	46	100

Table 9. Outcome of the study participants after radiotherapy

Outcome	Frequency	Percent (%)
Alive	26	56.5
Died	11	23.9
Missed because of the loss of follow up	9	19.6
Total	46	100

Table 10. Presenting the clinical features of the study participants

Presenting symptoms	Frequency	Percent (%)
Bleeding per rectum	24	52.2
Bleeding per rectum and abdominal pain	11	23.9
Change in bowel habit	1	2.2
Bleeding per rectum and pain at Perineum	1	2.2
Bleeding per rectum, pain and constipation	3	6.5
Bleeding per rectum and constipation	4	8.7
Bleeding per rectum and diarrhea	1	2.2
Bleeding per rectum, pain and diarrhea	1	2.2
Total	46	100

Table 11. Shows statistically insignificant relationships between the histopathological types of the tumor and the study participants' outcome

Histopathological examination (before radiotherapy)	Outcome		Total	P-value (Pearson Chi-Square)
	Alive	Died		
Rectal adenocarcinoma	25	10	35	
Rectal adenocarcinoma and signet ring	1	0	1	
Signet ring carcinoma	0	1	1	
Rectal adenocarcinoma (Intestinal type)	2	0	2	
Rectal adenocarcinoma (poorly differentiated)	1	0	1	0.583
Rectosigmoid adenocarcinoma	4	0	4	
Anorectal mucinous carcinoma	1	0	1	
Undifferentiated carcinoma	1	0	1	
Total	35	11	46	

DISCUSSION

This study signifies that the use of short term pre operative radio therapy is of importance to decrease mortality and improve overall survival of patients with colorectal carcinoma. Studies conducted in other centers also identifies this concepts to be true for example, in a study conducted in Sweden by Cede mark and et al. ; 849 patients were randomized to evaluate the role of preoperative radiotherapy in patients who were undergoing surgery for colorectal cancer, the incidence of pelvic recurrence were significantly lower than in patients who did not have this short term radio therapy prior to operation , p:0.001.

But for the overall survival and distant metastasis there was no significant change p-value was more than 0.05. In the current study, even for survival and distant metastasis this can be concluded that there is better out come. The Swedish study was conducted in a time that medicine was not advanced as today. How ever in the current study missed patients and lack of compliance of the patients with regular follow up outweighs some of the results of this study. But post operative morbidity was significantly higher in the irradiated group [12].

Other studies have been conducted by other researchers elsewhere, in one of other studies that have been conducted recently by Skora et al. On 210 patients between 2001 and 2013, the local control and distant metastasis had significant reduction with the use of neo adjuvant therapy, (p value less than 0.01) [13]. In addition to that less chances of toxicity were observed. The results of these studies are comparable to the study under observation. Patients in the current study experienced less signs and symptoms compared to the patients without neo-adjuvant therapy. We can conclude that the short-course preoperative radiotherapy is of significant importance for colorectal cancer management. It improves the results of treatment in patients with locally advanced rectal cancer and provides acceptable post operative complication and improves overall patients out come and survival.

In conclusion, neoadjuvant radiotherapy prior to surgical resection of tumor can have favorable effect on both local control and distant metastasis, when performed for patients with colorectal carcinoma. It has effect on the quality of patient's life; as it can reduce the signs and symptoms experienced by patients.

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