A Phase II Study of Concurrent Preoperative Chemotherapy and Radiotherapy in Locally Advanced Rectal Cancer

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Abstract: **Background:** Colo-rectal cancer is the third most common cancer in the western world; rectal cancer comprises about one-third of these cases. The increasing life expectancy in this population adds to the importance of evaluating long-term results of curative treatment. Purpose: Preoperative chemo-radiotherapy can lead to pathologic complete response. Fluorouracil-based preoperative chemo-radiation is the current standard of care for locally advanced rectal cancer. This study was designed to determine clinical response rate in locally advanced rectal cancer treated with preoperative regimen followed by surgical resection. Also it studies the effect of this regimen on increasing resection rate in those patients and to evaluate the validity of the technique of abdominally assisted trans-anal pull through as a sphincter preserving procedure in such patients. Secondary Objective: to determine the toxicity of this preoperative regimen. **Methods:** Clinical and pathological data from 2008 to 2011 of a prospectively maintained thirty three patients of locally advanced rectal cancer database were examined. Inclusion criteria were patients with previously untreated either inoperable or locally advanced rectal cancer and not suitable for primary sphincter sparing surgery. These patients received preoperative concurrent chemo-radiotherapy by using Oral flouropyramidines (Capecitabine). **Results:** Thirty-three patients were identified (54.5%) male and (45.5%) females with median age of 40 yrs. old (range 17–80 y)). Data regarding preoperative chemo-radiotherapy were available for 33 patients (100%). The dose of radiotherapy was 5040 cGy/28ttt, and Capecitabine chemotherapy schedule is 850mg/m^2 daily concurrent with radiotherapy. As regard tumor response to neo-adjuvant therapy; 18/33 patients (54.5%) achieved complete response, 8/33 patients (24%) achieved partial response and 7/33 patients (21%) had no response. Trans-anal abdominally assisted colo-anal pull-through was performed in 27 patients (81.8%) and 6 patients (18 %) underwent abdomino-perineal resection. About the toxicity in this study; for chemotherapy, deep venous thrombosis developed in 5 patients (15 %) and hand-foot syndrome developed in 7 patients (21%). For radiotherapy 19 patients (57.5%) developed wet desquamation. The main post-operative complications were fistula in 2 cases (6%) and partial stump ischemia in 3 (9%). We had a median disease free survival of 9.5 months and reported a 93% local control rate and 6.6% local failure rate after a maximum follow up period of 15 months. **Conclusion:** Preoperative chemo-radiotherapy by using Capecitabine improves down staging in locally advanced rectal cancers. It is safe, effective, convenient and well tolerated by the patients. The study assumes that the surgical technique of Trans-Anal Abdominally Assisted Colo-Anal Pull Through for rectal cancer has many advantages as a sphincter-preserving technique; it is efficient and safe procedure providing acceptable oncological and functional results while minimizing local infection and avoiding the diverting stoma with its negative impact on the quality of life.

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Key Words: Locally advanced rectal cancer, Sphincter-sparing surgery, combined modality therapy, Capecitabine.

Introduction

Surgery is the primary treatment for rectal cancers. In locally advanced stages; it is supported by combined-modality therapy (chemotherapy and/or radiation) to reduce the risk of local recurrence. Chemo-radiotherapy can be administered before surgery or after tumor resection; however, the timing is still a matter of controversy {**1**}.

Recently, surgical techniques for sparing rectal function after radical resection of low rectal cancer have changed significantly by; improved knowledge of the biologic behavior of rectal cancer, advanced technology and improved surgical skills. However, even with this advanced techniques there are a significant postoperative complications that may affect the outcome such as; pelvic abscess, fistulae, anastomotic leak and stricture **{2, 3, 4}**. Many variations of the pull-through concept have been introduced and modified by different workers during the last decades and its main principle is to have an anastomotic line totally diverted from fecal contamination **{5}**. The rationale for preoperative concurrent chemo-radiotherapy is based on less acute toxicity, increases the resection rate and/or sphincter preservation rate. The most significant disadvantage is that a fraction of patients unnecessarily treated due to

the inaccurate clinical staging, which results in treatment failure and thereby treatment resistance **{6}**. Furthermore, the Swedish Rectal Trial Group have shown benefits in both pelvic control and overall survival with preoperative radiotherapy alone but the technical difficulties related to surgical access to the lower rectum, particularly in the narrow male pelvis, may increase the risks of incomplete tumor clearance down to the levator ani muscle**{7}**. Hence, neo-adjuvant combined therapeutic strategies are gaining increasing importance **({8, 9}**.

Capecitabine is an orally bio-available fluoropyrimidine (i.e. anti-metabolite) pro-drug, which uses a complex enzymatic activating pathway to convert it to the cytotoxic agent 5-FU. The primary cytotoxic action of 5-FU is inhibition of the enzyme thymidilate synthase, thereby preventing DNA synthesis prior to cell division. The final part of this pathway generates 5-FU within the tumor itself by exploiting the activity of thymidine phosphorylase (TP), which is expressed more in tumor tissue than normal tissues. Theoretically high levels of TP in tumor would offer an advantage for Capecitabine. In contrast, a high level of expression of TP appears associated with a poorer response to 5FU in colorectal cancer. Ionizing radiation also increases TP levels directly, as well as indirectly, through an increase in levels of tumor necrosis factor a **{6, 10, 11, 12}**.

The preclinical data suggests that prolonged exposure to 5FU is responsible for the radio-sensitizing effect. Because of the short half-life of bolus 5FU, prolonged or continuous venous infusions (CVI) of 5FU have frequently been used to maintain adequate levels, and minimize toxicity. In the clinical setting CVI is accepted to be more effective in chemo-radiation than bolus 5FU. However, CVI either require admission with repeated daily intravenous administrations, or a portable infusion device, which may increase the risk of catheter related infections and thrombosis. Hence, a twice daily dosing schedule using oral Capecitabine offers an alternative **{6, 13}**.

Methods

This is a phase II trial to study the effectiveness of combining Capecitabine chemotherapy and external –beam radiotherapy followed by surgery in locally advanced rectal cancer patients. It is carried out in Asyut University Hospital, Faculty of Medicine and South Egypt Cancer Institute, Asyut University.

Study Type: Interventional, Study Design; Treatment, Single Non-Randomized, Open Label, Uncontrolled.

Eligibility criteria: Histo-pathologically proved rectal carcinoma which is non-metastatic and previously untreated. The tumor was inoperable and /or locally advanced and not suitable for primary sphincter sparing surgery. Other criteria were, age 18 yrs. old and over and Performance status 60 and above.

Work up

All patients were subjected to complete history and physical examination including digital rectal examination to asses tumor distance from anal verge. Complete laboratory investigations were performed including tumor marker CEA. Radiological studies; CXR, pelvi-abdmoinal MSCT and/or MRI and double contrast enema were done for all patients. More also, all patients had proctoscopic and full colonoscopy survey and in some cases examination under anesthesia was taken. After complete work up, Patients were staged before treatment according to TNM Clinical Staging according to the 2001 AJCC staging system.

Treatment

Radiotherapy: The target volume included the rectum and the draining lymph node chains (Para-rectal, hypo-gastric and pre-sacral lymph nodes) up to S1-S2 junction. It was defined using the simulator and localization was performed while the patient in the prone position with a full bladder to displace the small bowel anteriorly and superiorly. The contour of pelvis was marked on CT transverse section and the superior border was marked at L5/S1 inter-space and the inferior border at or just distal to the obturator foramen. The lateral borders were 1.5 cm outside true bony pelvis. All patients were treated by photon either 6 or 15 MV generated from linear accelerator, with a total dose of 5040 cGy in 28 fractions over 6 weeks.

Chemotherapy: Capecitabine 850 mg /m2 was given in divided doses twice daily during radiotherapy settings 5 days a week.

RE-assessment: All patients were re-evaluated after neo-adjuvant therapy by CBC, CEA, digital rectal examination, MSCT or MRI and proctoscopy.

Surgery: After re-staging, all patients were subjected to surgery in the form of abdominally assisted trans-anal colo-anal pull through as a sphincter preserving procedure or to abdomino-perineal resection. The former technique includes two parts abdominal part and anal one; the abdominal part follows the standard oncologic resection steps of high ligation and total meso-rectal excision. The trans-anal part begins by putting the patients in a lithotomy position and dilating of the anal canal by placing self retaining retractors. Thorough examination and mapping of the anal canal and lower rectum was performed and the distal safety margin was marked under direct vision. A circumferential full thickness resection of the rectal wall above the ano-rectal junction was done. In ultra-low rectal cancer, the anal mucosa above the dentate

line and the internal sphincter were either partially or totally resected as well. After procto-sigmoidectomy, a healthy part of colon was pulled out through the anus (Designed Colo-Anal Intussusceptions) and fixed in place by 4 to 6 stay sutures (2/0 Vicryl). The stitches were full thickness at the ano-rectal sphincter and sero-muscular in the dragged colon, being careful to avoid any kind of stitch or compression at the mesenteric border. A length of 5 to 8 cm of pulled stump was left outside the anal verge and its edge was fixed to the peri-anal skin by another 4 stay sutures. In all patients we didn't do any diverting stoma. Steps of caring of the pulled stump were simple, so that it can be carried out by the patients themselves after discharge. The patient was advised to put pads till the time of trimming, and the stump was kept wet and clean by frequent saline wash and Vaseline gauze, and by applying an antiseptic cream twice daily. Stump trimming was performed after a minimum of 2 weeks and the patient was readmitted for one day surgery and started his evaluation for the functional out come after 3 months. According to the post-operative TNM pathological staging, adjuvant chemotherapy was given whenever indicated.

Follow-up

The outcome of the sphincter sparing surgery was assessed as regard to anal continence, frequency of motions and complications. Functional outcome evaluation was undertaken at the 3rd and 6th months post-operatively. Incontinence was scored using Kirwan's grading score: (1) no incontinence; (2) incontinence of flatus and liquids; (3) occasional incontinence of solids; (4) frequent incontinence of solids; (5) incontinence requiring a colostomy **{5}**.
Local recurrence was defined as recurrence around anastomotic line and pelvic floor. Colonoscopy and a whole-body 3D CT were done six months after surgery, and then annually or more frequently in cases of abnormal symptoms or findings.

Toxicity: Acute and chronic toxicity was evaluated according to WHO Common Toxicity Criteria (2006) assessment of efficacy and complications.

Statistical methods: For comparing of percentage was used (chi- square test). Disease – Free and Over-all Survival rates were calculated according to Kaplan-Meier actuarial method and comparison between survivals rates were done by Long Rank test.

Results

Patient's characteristics are summarized in table (1). Thirty three patients were classified according to pretreatment variables (age, gender, performance, residence, T stage, N stage and tumor localization).

Table (1): Demonstrates patients and tumor characteristics.

Item	No (%) "n=33"
1- Age:	
≤ 40ys.	19 (57.6%)
≥ 40ys.	14 (42.4%)
Mean ± S.D	42.48 ± 16.30
2- Sex:	
Male	18 (54.5%).
Female	15 (45.5%)
3- P.S:	
70%	6 (18.2%)
80%	8 (24.2%)
90%	10 (30.3%)
100%	9 (27.3%)
4- Residence:	
Rural.	14 (42.4%)
Urban.	19 (57.6%)
5-T stage	
cT2	7
cT3	12
cT4	14
6-N stage	
cN0	7
cN+	26
7-Tumour localization (cm from anal verge)	
0–5	8
>5 – 10	15
>10-15	10

Table (2): Illustrates response to neo-adjuvant treatment.

Item	No (%)
Response:	
●C.R	18(54.5%)
●P.R	8(24.2%)
●STATIONARY	7(21.21%)

Final evaluation of response to preoperative chemo-radiotherapy showed that the number of patients whom achieved CR were (54.5 %), while (24.2 %) had PR and (21.21%) had Stationary response table (2).

Table (3): Illustrates link between response to neo-adjuvant chemo-radiotherapy and type of surgery.

Surgery	**Response**			
	C.R "n=8" CR= 18	**P.R "n=8"**	**Stationary "n=7"**	P-value
AP	0 (0%)	2 (25%)	4 (22.22%)	P= 0.03 Sig.
SP	14(77.8%)	6(75.0%)	7 (100%)	

There is significant relationship between preoperative chemo-radiotherapy and the degree of response (Figure 1), especially when being translated into sphincter preservation in 27/33 patients (Table 3) and 14 patients (77.78%) achieves complete response (Table 2).
The relation between surgical approach and tumor distance from the anal verge is illustrated in table (4).

Table (4): Illustrates the link between surgical approaches and tumor distance from anal verge.

Length	SP (n=27)	AP (n=6)	P-value
0 -5	4 (14.81%)	4 (66.67%)	P < 0.001**
>5 – 10	13 (48.14%)	2 (33.33%)	
>10 - 15	10 (37.03%)	-------	

Functional outcome including anal continence and frequency of motions as well as surgical complications were evaluated starting from the 3rd month postoperatively, table (5).

Table (5): Illustrates functional outcome and complications after sphincter preservation.

Post surgical F.U:	
At 3 months interval	
Kirwan grade 1	20/27 (74%)
Kirwan grade 2	7/27 (25.9%)
At 6 months interval	
Kirwan grade 1	23/27 (85.1%)
Kirwan grade 2	4/27 (14.8%)
•	
Frequency of motions:	
At 3 months interval	
1 - 2 per day	14/27 (50%)
3 – 5 per day	6/27 (22.2%)
> 5 per day	7/27 (25.9%)
At 6 months interval	
1 - 2 per day	21/27 (77.7%)
3 – 5 per day	6/27 (22.2%)
> 5 per day	0/27 (0%)
Partial stump ischemia	3/27 (11.1%)
Fistula	2/27 (7.4%)

As regard the toxicity in this study, for chemotherapy 5 patients (15.15%) developed deep venous thrombosis and 7 patients (21.2%) developed hand and foot syndrome. For the radiotherapy 19 patients (57.5%) developed wet desquamation, table (6).

Table (6): Illustrates post treatment complications.

Item	No. (%)
DVT:	
• Yes.	5 (15.15%)
• No.	28 (84.84%)
Wet desquamation:	
• Yes.	19 (57.57%)
• No.	14 (42.42%)
Hand and Foot syndrome:	
• Yes.	7 (21.21%)
• No.	26 (78.78)

The study achieved a mean overall survival of eleven months and a median disease free survival of 9.5 months, table (7). We reported a 93% local control rate and 6.6% local failure rate after a maximum follow up period of 15 months.

Table (7): Shows the survival outcome.

Item	No
Overall survival(Mean ± S.D)	11.00 ±8.18
Disease free survival(Mean ± S.D)	9.25±6.37

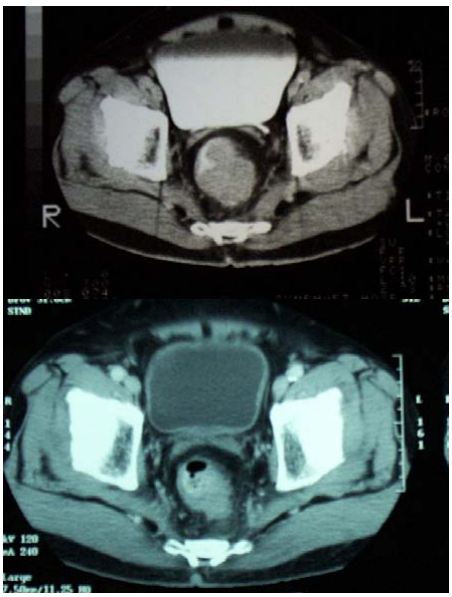

Figure (1): Pelvic MSCT scan of a patient; before and after neo-adjuvant chemo-radiotherapy. The tumor down staging (PR) is demonstrated.

Discussion

Established data from several clinical trials have reveled that local recurrence can be reduced by up to 40% with adjuvant radiotherapy and even further if combined with chemotherapy **{14}**. More recent data showed that preoperative chemo-radiotherapy as compared with postoperative chemo-radiotherapy improves local control and reduces treatment toxicity which is important as well as improves disease-free survival **{15}.** The main goal for neo-adjuvant chemo-radiotherapy is to improve local cancer control, sphincter preservation and overall survival. Thus it has gained wide acceptance and has replaced other adjuvant treatment protocols.

This effect is clearly obvious in this study as (54.5%) of patients had CR, (21.2%) had stable disease and none of them showed disease progression. These figures comparable to those reported by **Valintini et al**, who showed that partial response was achieved for (77%) of the patients, (23%) for stable disease and (0%) for disease progression **{16}**. But it is better than **G´erard et al**, who reported complete response in (19.2%) of the patients, incomplete response in

(40.4%), no response in (36.6%) and disease progression in (5.8%) **{13}**.

Randomized trials and a meta-analysis have shown that Capecitabine is at least as effective as 5-FU as systemic therapy for metastatic colorectal cancer or as adjuvant therapy for high-risk colon cancer **{17, 18}**.

The significance of using Capecitabine as a neo-adjuvant arises from its pharmacokinetic characteristics; it is a pro-drug with a complex enzymatic activation pathway and which in its final part generates 5-FU within the tumor cells itself, thus has the advantage of reducing systemic toxicity. Capecitabine was associated with a significantly lower incidence of diarrhea (which represent the main dose limiting toxicity when pelvic radiotherapy is administered) and grade 3/4 neutropenia when compared to bolus 5FU and leucovorin **{10, 18 and 19}**. The radio-sensitizing effect of Capecitabine was enhanced when it was taken at 1 hour before radiotherapy **{19}**. The results of this study confirm theses above results regarding equal efficacy of capecitabine to 5-FU in local control as (81.8%) of patients in this work had sphincter preservation and 15 to 21% showed signs of treatment toxicity that didn't interfere with the irradiation course.

Total proctectomy with colo-anal anastomoses (CAA) with or without J pouch is considered the gold standard of conservative surgery. Colonic J-pouches appear to be associated with a better quality of life than straight anastomoses **{20}**. However, even with this advanced techniques there are a significant postoperative complications rate that may affect the out come such as; pelvic abscess, fistulae, anastomotic leak and delayed and even in ability to close the diverting stoma especially in patients having neo-adjuvant chemo-radiation therapy or inter-sphincteric resection**{2, 4}**.

Many variations of the trans-anal colonic pull through concept have been introduced and modified by different workers during the last decades **{5}**. Its main concept is the creation of a clean anastomotic line giving the chance for sound healing thus minimizing risk of anastomotic leaks or fistulae formation which are the common morbidities in sphincter preserving procedures.

In this work, we used this technique for sphincter preservation group of patients without any diverting stoma. We found that this technique posses many advantages; simple with a rapid progressing learning curve, needs less equipped centers than other sphincter preserving procedures and the positive psychological impact of having no cutaneous stoma. More also and despite of no comparative study have been done, we can assume that this technique is cost effective in comparison with some other sphincter preserving procedures; as we only make a 2 rows of stay sutures at the ano-rectal complex and at the peri-anal skin about 6 and 4 stitches respectively, this beside we have no cutaneous stoma to be closed, which will increase the cost. Also hospitalization was minimized until the patient became stable and regained his GIT motility which takes an average of 3 to 5 days postoperatively. There is no special care for the prolapsed stump and can be carried out as an out patient. Lastly, the trimming procedure was carried out as one day surgery.

As regard surgical complications; we had partial stump ischemia (11%) that resulted in minor leakage and was successfully managed by conservation. The fistula rate (7.4%) was iatrogenic, as one of the stitches we had was full thickness in both the vaginal wall and the pulled colonic wall, and it was managed by colostomy reconstruction and closure after 2 months.

In the present study, we had 93% local control rate which is comparable to that reported by **Chua et al {21}**, but it was higher than what was reported by **Roh et al {19}**, who reported local failure (17.9%), this variance may be due to long duration of follow up as it was median follow up of 32 months, while we had a follow up period around 15 months only. The local failure rate was 6.6% which is less than that reported by North Central Cancer Treatment Group protocol (NCCTG), they had 13.5% and 17% respectively **{22}**, and slightly less than that reported **Hu-Lieskovanet al** as 11% and that variance mostly due to different protocol of treatment **{23}**.

Conclusions

We found that the use of Capecitabine in conjunction with radiotherapy as a neo-adjuvant therapy has many advantages; achieving the same oncologic goals of management as other 5FU based regimens, simpler, cost effectiveness as there is no hospitalization, which gives positive psychological impact on the patient. Capecitabine is associated with a significant radio-sensitizing effect and a lower incidence of toxicity, which does not interrupt radiotherapy course. We found also that the technique of Trans-Anal Abdominally Assisted Colo-Anal Pull Through for rectal cancer has many advantages as a sphincter-preserving technique; it is efficient and safe procedure providing acceptable oncological and functional results while minimizing local infection and avoiding the diverting stoma, with its negative impact on the quality of life. A comparative study including outcomes and cost is in processing in our institute between this technique and colo-anal anastomoses and results will be available in the near future. Lastly, the only significant prognostic factor affecting disease free survival and overall survival in this study was staging.

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