International Surgery Journal
Venogopala K et al. Int Surg J. 2016 Aug;3(3):1360-1363
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: http://dx.doi.org/10.18203/2349-2902.isj20162711

Research Article

Role of neo-adjuvant chemo - radiotherapy in colorectal malignancy

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Received: 19 February 2016
Revised: 12 April 2016
Accepted: 03 June 2016

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ABSTRACT

Background: Adenocarcinoma of the colon and rectum is one among most common site of new cancer cases and deaths in both men (following prostate and lung/bronchus) and women (following breast, cervix and lung/bronchus). The objective of this study was to evaluate the usefulness of neoadjuvant chemo-radiotherapy in colorectal carcinoma.
Methods: This study has been conducted in the department of surgery, Govt. Rajaji hospital, Madurai during 2008-2009. 20 patients were subjected to detailed history, thorough clinical examination of the abdomen, digital rectal examination, proctoscopy, and scopy guided biopsy was taken for histopathological examination.
Results: All patients were subjected to chemo-radiotherapy for 6weeks, followed by surgery. 20% of the patients underwent low anterior resection, 35% of patients underwent anterior resection, 35% of the patients underwent abdomino-perineal resection, 10% had undergone loop colostomy. Out of the 20 patients 2 female patients had posterior vaginal wall fixity which following CRT underwent APR without resection of the posterior vaginal wall.
Conclusions: Neoadjuvant therapy may be considered a rational approach for treatment of curative rectal cancer. Volumetric reduction of neoplasia, mesorectum and lateral pelvic nodes was evident in 90% of the patients.

Keywords: Colorectal malignancy, Neoadjuvant therapy, Chemo-radiotherapy, Abdomino-perineal resection, Loop colostomy

INTRODUCTION

Adenocarcinoma of the colon and rectum is one among most common site of new cancer cases and deaths in both men (following prostate and lung/bronchus) and women (following breast, cervix and lung/bronchus).The lifetime risk for developing invasive colorectal cancer increases with age, with more than 90% of new cases being diagnosed in patients older than 50 years.[1]

Sporadic colorectal cancer occurs in the absence of family history, generally affects an older population (60 to 80 years of age), and usually presents as an isolated colon or rectal lesion. Genetic mutations associated with the cancer are limited to the tumor itself, unlike hereditary disease, in which the specific mutation is present in all cells of the affected individual. Nevertheless, the genetic of colorectal cancer initiation and progression proceed along very similar pathway in both hereditary and sporadic forms of the disease.[2]

The biologic properties of the rectum, combined with its anatomic distance from the small intestine afforded by it retroperitoneal pelvic location, provides an opportunity for treatment by radiation therapy.[3]

The treatment of colorectal cancer has changed significantly during the past 20 years, and there is considerable controversy today concerning the precise

role of surgery, radiation therapy, and chemotherapy, and the ideal timing of each modality with relation to the others. Although information from clinical trials has provided data supporting the multimodality treatment of rectal cancer, the criteria for patient selection remains controversial. According to recent analysis preoperative radiation is superior to postoperative radiation. The best course of neoadjuvant treatment has not yet been determined.[4]

Neoadjuvant chemoradiation may increase the ability of the surgeon to preserve continence by down-staging the cancer, in some instance shrinking the size of the tumor to permit the achievement of a cancer-free margin at the distal extent of the resection, when a clear margin that would permit an anastomosis could not be achieved without such shrinkage.[5]

Finally, to still improve surgical outcomes a further effort was made, since twenty years to now, by employing adjuvant therapies - radiotherapy (RT) and chemotherapy (CT) - resulting in significant reduction of local recurrence rates, however partially improving mortality but exposing patients to high morbidity.

Later on, a continuous change of adjuvant approach has been developed: in short, adjuvant therapy has been replaced, step by step, by neo-adjuvant approach. The present study was undertaken to evaluate the usefulness of neoadjuvant chemo-radiotherapy in colorectal carcinoma.

METHODS

This study has been conducted in the department of surgery, Govt. Rajaji hospital, Madurai during 2008-2009. Patients admitted in general surgery units, surgical gastroenterology and surgical oncology department were selected. All these patients were subjected to detailed history, thorough clinical examination of the abdomen, digital rectal examination, proctoscopy, and scopy guided biopsy was taken for histopathological examination.

All these patient had base line biochemical investigation done and included blood- Hb%, TC, DC, sugar, urea, creatinine, urine - sugar, albumin, microscopy liver function test ultrasonography double contrast barium enema when warranted computed tomogram plain and contrast enhanced, magnetic resonance imaging when feasible.

All patients were counselled with regards to treatment side effects, possible outcome with and without the preoperative chemo-radiotherapy, the side effects during the course. The patients were counselled with regards to colostomy. During the counseling session, a previous ostomate was included.

Indications for neoadjuvant therapy, basing a difference between the absolute and relative one were explained. Dosages of drugs and radiation were taken care. Comparing indicatively of clinical and diagnostic data before neoadjuvant therapy and before surgery was done. Patients were staged according to the TNM classification system using clinical and radiological data.[6]

Radiation therapy

The main reasons for favoring pre-operative radiation have been the desire to reduce their rate of both pelvic recurrence and extra pelvic metastases based on the assumption that some metastases arise from cells released during intra operative manipulation of the cancer, the lower likelihood of late radiation enteritis because small bowel is less likely to be adherent in the pelvis prior to surgery,& the relatively greater radio responsiveness of normally oxygenated cancer cells relative to cells and tissues that may be hypoxic secondary to alteration in vascularity resulting from pelvic surgery.

Chemotherapy

5-fluorouracil (5-FU) - Antimetabolite ,it's a pyrimidine antagonists is converted in the body to the corresponding nucleotide 5-fluoro-2-deoxyuridine monophosphate, which inhibits thymidylate synthase and blocks the conversion of deoxyuridic acid to deoxythymidylic acid. Selective failure of DNA synthesis occurs due to non-availability of thmidylate. Thymidine can partially reverse its toxicity. Fluorouracil itself get incorporated into nucleic acid and this may contribute to it toxicity. Even resting cells are affected, though rapidly multiplying ones are more susceptible.

Efforts have been made to enhance the activity O 5-FU by co-administration with other agent. The potency of 5-FU can be enhanced by the administration of reduced folate- leucovorin when 5-FU is given in combination with leucovorin response rates range from 21% to 48%. A randomized prospective trail compared 5-FU alone, sequentially methotrexate plus 5-FU and leucovorin plus 5-FU among patients with untreated colorectal cancer. Response rates of 11%, 5% and 49.8% respectively were achieved.

All patients in the study, after thorough clinical, radiological, histopathological and baseline investigation and counseling underwent radiotherapy 4500 to 6000cGy in 150 to 200cGy fractions for 5 days a week and concurrent 5-FU 10 mg/kg and leucovorin 30 mg infusion every 21 days for 6 cycles and restaged after the completion of the therapy clinically and radiologically.

RESULTS

Total numbers of cases were twenty among them 14 were male and 6 were female. Out of 20 cases, 4 (20%) were well differentiate adenocarcinoma, 8 (40%) moderately differentiated adenocarcinoma, 5 (25%) poorly differentiated adenocarcinoma, 2 (10%) infiltrating type

of adenocarcinoma and 1 (5%) mucinous adenocarcinoma (Figure 1).

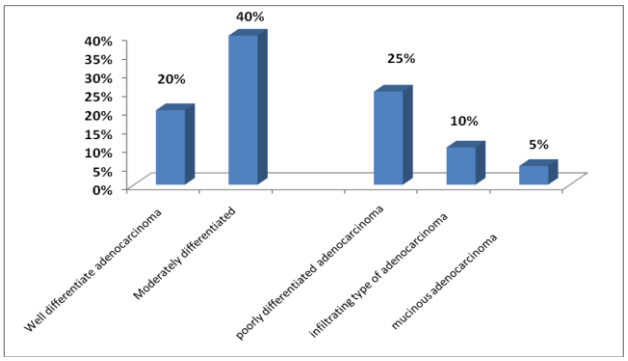

Figure 1: The distribution of cases according to their histopathology.

Table 1: Distance of lower extent of lesion from the anal verge.

	pre-CRT	post-CRT
4 to 6 cm	+7	3
6 to 8 cm	-5	6
8 to 12 cm	-6	8
12 to 15 cm	-1	2
More than 15 cm	-1	1

Table 1: Type of surgery done following neo adjuvant therapy.

Surgery	No. of patients	Percentage
Low anterior resection	4	20%
Anterior resection	7	35%
APR	7	35%
Loop colostomy	2	10%

All patients were subjected to chemo-radiotherapy for 6 weeks, followed by surgery. 20% of the patients underwent low anterior resection, 35% of patients underwent Anterior Resection, 35% of the patients underwent abdomino-perineal resection, and 10% had undergone loop colostomy (Table 2).

Out of the 20 patients 2 female patients had posterior vaginal wall fixity which following CRT underwent APR without resection of the posterior vaginal wall.

Total number of patients who underwent APR was 35% which without the neo-adjuvant therapy would have been 60% i.e., 25% patients were benefited from a sphincter saving procedure.

DISCUSSION

90% of the patients underwent definitive surgery. Abdomino perineal resection and anterior resection was the commonest surgery performed in the study constituting about 70%. 55% of total patients had undergone a spincter preserved procedure.

Table 3: Results of trials comparing surgery versus neoadjuvant therapy.

	Surgery	RT+Surgery
Stockolm II trial (S)[6]	56%	62%
Swedish trial (S)[7]	48%	58%
MRCRCWP (L)[8]	46%	52%

RT alone; S: Short term; L: Long term

In 35% of patients, tumor regression of ≥2 cm, ≤3 cm was noted followed neoadjuvant therapy. On digital rectal examination. Among 7 patients who underwent APR, 4 patients (55.5%) had perineal wound infection, which was treated with appropriate dressing and antibiotics after obtaining culture and sensitivity reports. Out of 18 patients, who underwent definitive surgery 6 patients constituting 33.33% had abdominal wound infection and were treated with daily dressing and appropriate antibiotics. 2 patients had died post-operatively, one patient on 1st POD due to pulmonary embolism and the other on 8th POD due to ARDS.

CONCLUSION

Goals of neoadjuvant are varied, had advantages over adjuvant therapy neoadjuvant therapy may be considered a rational approach for treatment of curative rectal cancer. Volumetric reduction of neoplasia, mesorectum and lateral pelvic nodes was evident in 90% of the patients. There was 25% improved surgical feasablity for a sphincter saving procedure in the study. There was a definite reduction of side effect on close organ, mainly on small bowel, which is not displaced into pelvis by post-operative adhesions. There was no local recurrence in patients who underwent surgery during the 2 year follow up period. All Non-Metastatic patients are candidates for pre-operative neoadjuvant therapy. Patient selection by detailed pre-op staging very important. Radiation total dose/fraction/fields are not uniformly agreed upon. Neoadjuvant therapy needed in many cases.

ACKNOWLEDGEMENTS

Authors would like to sincerely thanks to all patients involved in this study for their kind co-operation and allowing me to complete the study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Venogopala K, Venkatappa SK, Karepgol B. Role of neo-adjuvant chemo - radiotherapy in colorectal malignancy. Int Surg J 2016;3:1360-3.