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Original Research Article

Impact of neoadjuvant chemoradiotherapy on post-operative outcome in patients with rectal cancer

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ABSTRACT

Background: Neoadjuvant chemoradiotherapy not only helps in downstaging the rectal cancer, it also reduces the rate of local recurrence but it has its own attendant risk factors. Our aim is to look into the implications of neoadjuvant chemoradiotherapy in patients with rectal cancer in our hospital.
Methods: Retrospective data was collected from the infoflex system of database for the patients who underwent neoadjuvant chemoradiotherapy between January 2016-December 2019 in our DGH. The data was analysed for demographics, type of surgery, histology, length of stay, complications and stoma reversal rates.
Results: Total 27 patients with rectal cancer during the study period underwent neoadjuvant chemoradiotherapy. 16 were male and 11 females. Age range was 33-82 year. 13 patients underwent APER, 8 Hartmann's and 6 anterior resection with covering loop ileostomy. 5 patients initially required defunctioning sigmoid loop colostomy and one loop ileostomy prior to the start of neoadjuvant treatment. Histology showed 26 adenocarcinoma, and 1 squamous cell cancer. 3 patients had complete pathological response (cPR). Post-operative stay was from 5-32 days. 12 patients developed pelvic collection, 5 wound infection (4 perineal+1 abdominal), 5 had paralytic ileus, 1 patient had PR bleed, 2 anastomotic leak and 2 patients had chest related complications. Only 4 out of 6 loop ileostomies were reversed.
Conclusions: Neoadjuvant treatment benefits come with its attendant complications. The tissue response to radiotherapy and chemotherapy and advanced tumor stage may contribute for the increased morbidity. Hopefully in future with the advent of new armamentarium, the degree of morbidity may come down.

Keywords: Rectal cancer, Neoadjuvant chemoradiotherapy, Pathological complete response, Complete clinical response

INTRODUCTION

Rectal cancer accounts for approximately 30% of colorectal cancers. The incidence is increasing, and the treatment is complex. Albeit surgery is the mainstay with Total mesorectal excision (TME) being the standard operative technique since it was first described by Professor Bill Heald from Basingstroke Hospital in 1982, neoadjuvant treatment plays a significant role in the management of these patients.[1,2] In UK neoadjuvant chemoradiotherapy is the standard practice for managing locally advanced rectal cancers.

The rationale of neoadjuvant long course chemoradiotherapy (LCCRT) is based on the evidence from predominantly the EORTC, FFCD and German trials. The EORTC radiotherapy group trial demonstrated that long-course preoperative radiotherapy with chemotherapy given either preoperatively or postoperatively reduced local recurrence rate significantly but no improvement in overall survival.[3]

FFCD 9203 trial concluded that preoperative chemoradiotherapy despite a moderate increase in acute toxicity and no impact on overall survival significantly improves local control and is recommended for T3-4, N0-2, M0 adenocarcinoma of the middle and distal rectum.[4]

The German rectal cancer study group showed that preoperative chemoradiotherapy (CRT) compared with postoperative CRT conferred better local control and was associated with reduced toxicity.[5]

All these trials demonstrated a significant reduction is local recurrence but no difference in overall survival. LCCRT is used in locally advanced rectal cancers to downstage the tumours so they are amenable for R0 resection– the gold standard of oncological resection or sphincter preserving surgery.

Surgery is performed after 6-8-week interval from completion of LCCRT and it became the standard practice since the results of Lyons R90-01 study were published. This trial showed increased tumor down staging if surgery was performed after 6 weeks as compared to 2 weeks post chemoradiotherapy.[6]

LCCRT increases the chances of downstaging or downsizing but it comes with attendant risks. The chemotherapy agents predominantly act as radiosensitizer.

Our aim was to look into the post-operative outcome of patients with rectal cancers who underwent LCCRT at our East and North Hertfordshire Trust.

METHODS

It is a retrospective observational study. All the patients who had LCCRT for rectal cancer between January 2016-December 2019 at East and North Hertforshire NHS Trust were included in the study. Data was collected from the infoflex database. Infoflex provides the data management system for various NHS Trusts, and operates by bringing together patient data so that all healthcare workers can access up-to-date patient data easily, at one central point.

All patients had staging workups including digital rectal examinations, colonoscopy, CT scan of chest, abdomen and pelvic, MRI pelvis (rectum), complete blood counts, liver enzyme assays, and serum CEA analysis. If further workup was needed, MRI liver or PET scan was performed. Clinical and pathologic stages were determined according to the American joint committee on cancer staging.

The inclusion criteria were any rectal cancer with threatened or breached circumferential resection margin, cancers encroaching intersphincteric plane, involving levator ani muscle or demonstrating high risk features for local recurrence. The exclusion criteria were T1/T2 rectal cancers, cancers with widespread metastatic disease, patients unfit for surgery and recurrent rectal cancers. Individual notes were looked into for type of operation, type of stoma, length of hospital stay, post-operative complications, histology and stoma reversal rates. All cases were discussed in the multidisciplinary team meeting.

The statistical analysis was done using MedCalc®. Data is expressed as percentages, mean and range. This study does not require ethical approval.

RESULTS

Total 581 colorectal cancers were diagnosed during the study period i.e. January 2016- December 2019, of which 386 were colon cancers and 195 were rectal cancer. Of these 195 patients with rectal cancer 27 patients (14%) underwent LCCRT.

Here, 16 patients were male and 11 females. The mean age was 65 years (33-82 years). 13 patients had abdominoperineal excision of rectum (APER) of them 2 patients had vertical rectus abdominis muscle (VRAM) myocutaneous flap reconstruction of the perineum. 8 patients had Hartmann's procedure and 6 patients underwent anterior resection with covering loop ileostomy. 5 patients were defunctioned by loop sigmoid colostomy and 1 with loop ileostomy before the start LCCRT. The patient who underwent defunctioning loop ileostomy had synchronous cancer in transverse colon (Table 1).

Table 1: Types of surgical intervention in patients undergone LCCRT.

Type of surgical intervention	Number of patients
Abdomino perineal excision of rectum (APER)	13
Hartmann's procedure	08
Anterior resection with loop ileostomy	06

The average length of stay was 9 days with the range being 5-32 days.

Total 12(44%) patients had pelvic collection, 10 patients were treated conservatively and 2 patients required CT guided drainage. 2 (33%) patients had anastomotic leak. These leaks were radiological leaks confirmed on CT scans. The anastomotic leaks were treated conservatively as the patients had defunctioning loop ileostomies. 5 (18%) patients developed wound infection of which 4 were perineal and 1 was abdominal, all of them were treated conservatively. 5 (18%) developed paralytic ileus following the surgical intervention. 1 patient developed hospital acquired pneumonia, 1-gram negative sepsis and 1 rectal bleeding (Table 2).

Table 2: Post-operative complications in patient undergone LCCR.

Complications	Number of patients/ percentage
Pelvic collection	44
Anastomotic Leak	33
Wound infection	18
Paralytic ileus	18
Hospital Acquired Pneumonia	03
Gram negative sepsis	03
Rectal bleeding	03

Total 21 (77%) patients had end colostomy and 6 (23%) has loop ileostomy as a stoma after the definitive surgical procedure. Only 4 patients out of 6 i.e. 66% had their defunctioning ileostomy reversed. The two patients whose defunctioning ileostomies could not be reversed were the patients who had anastomotic leak.

The histological analysis of the rectum post operatively demonstrated 26 (96%) had adenocarcinoma, 1 had squamous cell cancer (4%). 3 (11%) patients had complete pathological response (Figure 1).

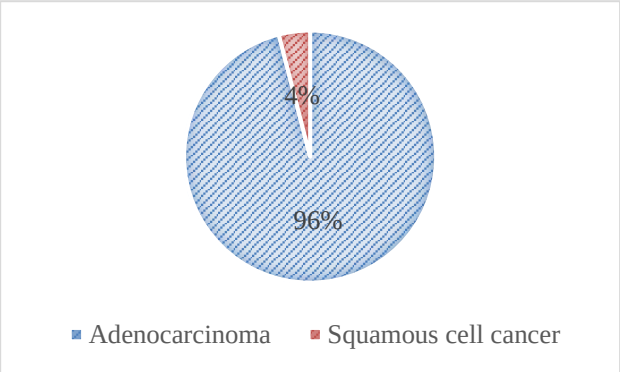

Figure 1: Post-operative histology results.

DISCUSSION

Colorectal cancer is the third most common malignancy worldwide with approximately 900,000 deaths annually. Left sided cancers account for roughly two third of the total colorectal cancers with rectum being the most common site (30%). The treatment of rectal cancer is multi modal including surgery, radiotherapy and chemotherapy. Though surgery is the mainstay it is supported by neoadjuvant radiotherapy and chemotherapy and this has improved the survival over the past few decades.

To treat a patient with neoadjuvant chemoradiotherapy is a multidisciplinary team (MDT) decision though it depends upon the clinical stage of the tumor at presentation. This involves a thorough medical history and clinical examination, including digital rectal examination (DRE), and radiological examinations. MRI pelvis and EUS rectum are used for local staging of the tumor. MRI provides detailed images of the pelvis allowing for accurate staging of the tumour and facilitating pre-operative planning. MRI aids in assessing the circumferential resection margin (CRM) status, a very important determinant in planning surgery. In a prospective observational study of 408 patients, 87% (95%CI: 83-90%) had clear margins on MRI. Surgical resection specimens of this cohort demonstrated clear margins in 94% (95%CI: 93-96%). Specificity was found to be 92% (95%CI: 90-95%).[7] EUS is effective at measuring the depth of tumour invasion in early rectal cancers.[8] Accuracy in assessing T stage for EUS has been quoted in the range of 85%- 90%.[9] Computed tomography (CT) of the thorax, abdomen, and pelvis is useful for both local and distant staging. CT has an accuracy rate of 85.1%, a positive predictive value of 96.1% and a negative predictive value of 3.9% in detecting hepatic metastases.[10]

NICE stratifies rectal cancer according to risk of local pelvic recurrence into three groups, low risk, moderate risk and high risk.

Low risk group includes cT1 or cT2 or cT3 cancers with no lymph node involvement. Moderate risk group includes any cT3 or above cancer in which surgical resection margin is not threatened, any rectal cancer with suspicious lymph nodes not threatening surgical resection margin or the presence of extramural venous invasion (EMVI). High risk group involves either the threatened or involved circumferential resection margin (CRM) or low tumors encroaching onto the inter-sphincteric plane or with levator involvement. A threatened margin is where the cancer is within 1mm of the circumferential resection margin.

In our study also the anastomotic leak rate was higher along with the wound infection rates and these results echo with the results of trans-tasman oncology group in 2017 which analysed the differences in immediate post-operative outcomes between short course and long course neoadjuvant patients11. The patients in the TROG group who were administered radiotherapy over a longer course were at higher risk of developing an anastomotic leak (7.1 vs 3.5%) and perineal wound breakdown (50 vs 38.3%), however, neither of these were found to be statistically significant.

Approximately 20% of patients treated with neoadjuvant chemoradiotherapy for locally advanced rectal cancer achieve a pathological complete response (pCR) while the remainder derive the benefit of improved local control and downstaging and a small proportion show a minimal response.[12] Our study showed a complete pathological response in approximately 11% patients, it is possible that ours was a small study.

There has been a growing interest in watch and wait policy initially propounded by Habr Gama in 1998. There could be complete clinical response(cCR) or complete pathological response. Complete clinical response means where there is no objective evidence of tumour on clinical examination or on endoscopy at least after 4 weeks of completion of neoadjuvant treatment. Complete pathological response means there is no evidence of malignancy in the specimen. The tumor is replaced by fibrous tissue. In their paper Habr-Gama et al proposed that those patients who have achieved complete clinical response can be managed by regular observation only. It was observed that 30.5% patients exhibited a (cCR) after a follow up of 36 months.[13]

A retrospective study in Sweden of 3564 patients with loop ileostomies outlined a 9-mo reversal rate of 68.4%. Risk factors for prolonged interval to reversal and for conversion to permanent stoma included, post-operative complications (HR=0.67, 0.62-0.73), adjuvant chemotherapy (0.63, 0.57-0.69) and advanced cancer stage (stage III 0.74, 0.66-0.83 and stage IV 0.38, 0.32-0.46)14. In our study we had reversal of loop ileostomy rate of 66% which is similar to the Swedish study.

Emmanuel et al published a study in 2018 investigating outcomes for rectal cancer patients with diverting stomas.[15] The authors found that those with such stomas experienced a higher rate of post-operative complications (57.1 vs 34.9%, P=0.003) and an increased average length of hospital stay (13 d vs 6.9 d, P=0.005). Our study also shows increased rate of post op complications and increased length of stay.

Limitations

It is a single centre study with small study group and no comparative arm. Comorbidities of the patients were not taken into account which could be one of the factors contributing in the post-operative outcome. Patients undergoing APER resection have increased morbidity due to perineal dissection on top of the abdominal surgical intervention which can skew some of the results of the whole cohort.

CONCLUSION

In our study a proportion of patients had complete pathological response, it underlines the potential for further exploration of organ preservation in selected cases who had complete clinical response post LCCRT. Our study also highlights the need for the search of better chemotherapeutic agents and regimens which could potentially reduce the degree of morbidity in future. However, to draw conclusions from a single centre, retrospective small group study would not be appropriate and international, multi centre large group studies in future may give us better answers.

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