A Study on the Influence of Pre-operative Chemo-radio therapy in cases of Locally Advanced Rectal Cancer

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Abstract

Rectal cancer is one of the common causes contributing to cancer related disease burden. Although surgery is the main line of treatment in rectal cancer the advent of neo-adjuvant therapy has significantly changed the treatment of the disease as well as the quality of life of patients after treatment.

Introduction

Although surgery is still the mainstay of treatment but the compliance is poor due to fear of living with permanent colostomy associated with APR (abdomino-perinealresection).The larger and omized trial from the Netherlands evaluated the benefit of preoperative radiation therapy leading to significantly lower rates of pelvic relapse. Follow-up analyses of this trial further showed that node-positive patients undergoing total mesorectal resection (TME) alone experience pelvic failure rates exceeding 20%. More recently, the German Rectal Cancer Study demonstrated that preoperative chemo radiotherapy (vs.post operative therapy) leads to superior pelvic control and sphincter preservation ,as well as lower rates of a cute and chronic toxicity. The results of this trial contributed to a paradigm shift and preoperative or neo-adjuvant therapy has been widely adopted as the standard of care forlocallyadvancedrectalcancer.OtherEuropeantrialshaverecentlyestablished the value of concurrent chemotherapy with preoperative radiation therapy in optimizing local disease control. It is important to remember that chemotherapy is used in radio sensitizing doses in this setting.

There are few phase II studies which compared 5-FU/LV and Capecitabine in CRT setting,

and the recent German randomized trial by H of heinzetal. Proved the non-inferiority of Capecitabine compared to 5-FU/LV in neo-adjuvant CRT setting. In this study, we have evaluated the response and outcomes of patients with LARC who received neo-adjuvant CRT with either 5-FU/LV or capecitabine in our center. CRT with 5-fluorouracil (5-FU) and leucovor in (LV) has been the standard of careinthe LARC. Capecitabine, an orally administered fluoropyrimidines carbamate, a pro drug of 5-FU, was developed for prolonged and continuous anti tumoractivity of 5-FU which mimics continuous infusion. Conversion to 5-FU involves three steps with thymidine phosphorylase (TP) used in the final step. Drugnotonly exhibitstumor selective activity, as TP is high in tumor cells, but also has a synergistic effect with radiation treatment (RT),which was confirmed by Sawada etal (RT up-regulates TP levels in the tumor). There are few phase II studies which compared 5-FU/LV and capecitabine in CRT setting, and the recent German randomized trial by Hofheinz et al. proved the non-inferiority of Capecitabine compared to 5-FU/LV in neo-adjuvant CRT setting. Literature regarding its tolerability and equivalence in CRT setting is sparse from our continent.

Aim: To study the patients diagnosed with locally advanced rectal cancer for their response to chemo-radiotherapy.

Objective: To study the rate of radiation enteritis after preoperative chemo-radiotherapy followed by adjuvant chemo-radiotherapy.

Review of Literature

Background

"Colorectal cancer (CRC) is the third most commonly diagnosed malignancy in both the sexes combined. CRC has both strong environmental associations and genetic risk factors. The incidence of new cases and mortality has been steadily declining for the past years, except for younger adults (younger than 50 years), possibly related to an increase in cancer screening and better therapy modalities. Approximately 5% of all CR Care attributed to two inherited syndromes, Familial Adenomatous Polyposis, and Lynchsyndrome. The change of the normal epithelium to a precancerous lesion and ultimately an invasive carcinoma requires an accumulation of genetic mutations either somatic (acquired) and/or germ-line(inherited)inanapproximately10to15-year period.[1][2][3] Chromosomal instability, mismatch repair, and Cp Ghypermethylation are the major path ways to CRC. The most important prognostic indicator is the pathological stage at presentation. All new CRC cases

should be universally screened for DNA mismatch repair/micro satellite status, and RAS/BRAF mutational testing when considering for prognosis and prediction of chemotherapy efficacy. In almost all patients, a diagnostic or screening colonoscopy is required for tissue biopsy pathological confirmation of colon carcinoma. Base line computed tomography (CT) of the chest, abdomen, and pelvis with contrast and carcino embryonic antigen (CEA) are the preferred cost-effective, staging studies done before surgical resection. Surgical resection is the main treatment modality for localized early-stage cancer. Adjuvant therapy could augment the chance of cure on high-risk patients. Oligo-metastatic, liver and lung, and local-recurrence patients are potential curable candidates with multimodality therapies. Palliative systemic therapy is reserved for non-surgical candidates aiming to improve quality of life and prolong life expectancy."

Evaluation

"Initial evaluation may involve barium enemaor CT colonography, but ultimately a colonoscopy is required for tissue biopsy.[14][15][16] Colonoscopy sensitivity is about 94.7% (95% CI 90% to 97%) and may miss from 2% to 6% of cases, mostly right-sided, pending on preparation quality and hands experience. Flexible sigmoidoscopy is no replacement for a complete diagnostic colonoscopy, still is a screening modality that reduces CRC mortality. The Federal Drug Administration (FDA) has approved PILLCAM2 for those non-obstructed patients with incomplete colonoscopy, and not for routine screening. Routine laboratory workup with complete blood count, iron studies, basic metabolic panel, liver function test and coagulation tests are not diagnostic but often useful. CEA greater than5 ng/mL has a poor prognostic value when present, but lacks diagnostic sensitivity 46% (95% C I0.45 to 0.47) and has limited specificity 89% (95% CI 0.88 to 0.92). Pre-operative CEA is indicated on all newly diagnosed rectal cancer, normalization after surgical resection is expected and serial as says to be monitored on follow up visits."

Stage0 (Carcinomain Situ)

"In stage 0, abnormal cells are found in the mucosa (innermost layer) of the rectal wall. These abnormal cells may become cancer and spread into nearby normal tissue. Stage 0 is also called carcinoma insitu."

Stage I:

"In stage I rectal cancer, cancer has formed in the mucosa (innermost layer) of the rectal wall and has spread to the sub mucosa (layer of tissue next to the mucosa)or to the muscle layer of the rectal wall"

Stage II:

"Stage II rectal cancer is divided into stages IIA, IIB ,and IIC."

Stage IIA: "Cancer has spread through the muscle layer of the rectal wall to the serosa (outermost layer) of the rectal wall."

Stage IIB: "Cancer has spread through the serosa (outermost layer) of the rectal wall to the tissue that lines the organs in the abdomen (visceral peritoneum)."

Stage IIC: "Cancer has spread through the serosa (outermost layer) of the rectal wall to nearby organs."

Stage III

"Stage III rectal cancer is divided into stages IIIA, IIIB, and IIIC."

In stage III A, cancer has spread:

- "through the mucosa (inner most layer) of the rectal wall to the sub-mucosa (layer of tissue next to the mucosa) or to the muscle layer of the rectal wall. Cancer has spread to one to three nearby lymph nodes or cancer cells have formed in tissue near the lymph nodes; or"
- "through the mucosa(inner most layer)of the rectal wall to the sub mucosa (layer of tissue next to the mucosa). Cancer has spread to four to six nearby lymph nodes."

Instage IIIB, cancer has spread:

- "through the muscle layer of the rectal wall to the serosa (outermost layer) of the rectal wall or has spread through the serosa to the tissue that lines the organs in the abdomen (visceral peritoneum). Cancer has spread to one to three nearby lymph nodes or cancer cells have formed in tissue near the lymph nodes; or to the muscle layer or to the serosa (outermost layer) of the rectal wall. Cancer has spread to four to six nearby lymph nodes; or"
- "through the mucosa (inner most layer) of the rectal wall to the submucosa (layer of tissue next to the mucosa) or to the muscle layer of the rectal wall. Cancer has spread to seven or more nearby lymph nodes."

Instage III C, cancer has spread:

- "through the serosa (outermost layer) of the rectal wall to the tissue that lines the organs in the abdomen (visceral peritoneum). Cancer has spread to four to six nearby lymph nodes; or"
- "through the muscle layer of the rectal wall to the serosa (outermost layer)of the rectal wall or has spread through the serosa to the tissue that lines the organs in the abdomen (visceral peritoneum). Cancer has spread to seven or more nearby lymph nodes; or"

- "through the serosa (outermost layer) of the rectal wall to nearby organs. Cancer has spread to one or more nearby lymph nodes or cancer cells have formed in tissue near the lymph nodes"

Stage IV colon cancer is divided into stages IV A, IV B, and IV C.

- Stage IVA : "Cancer has spread to one area or organ that is not near the rectum, such as the liver, lung, ovary, or a distant lymph node."
- Stage IV B: "Cancer has spread to more than one area or organ that is not near the rectum, such as the liver, lung, ovary, or a distant lymph node."
- Stage IVC: " Cancer has spread to the tissue that lines the wall of the abdomen and may have spread to other areas or organs."

Computed tomography

"The accuracy of computed tomography is also stage dependent. In the review by Kwok patients were pre operatively staged, with CT using the TNM classification. In staging T1-2 tumors 25 of the 40 patients with a pT1-2 tumor were correctly staged, sensitivity of 63 % (specificity 93 %, accuracy 84 %).For T3-4 tumors 83 patients out of 95 were staged correctly (sensitivity 87 %,specificity 50 %, accuracy 76 %). The poor sensitivity of CT in the staging ofT1-2 tumors in patients with rectal cancer is mainly related to the inability to demonstrate the single layers of the rectal wall."

"New developments in computed tomography show promising results in diagnostic accuracy. Matsuoka compared multi-slice spiral computed tomography to conventional CT. They found in a group of 20 patients, a prediction of T3-4 tumor stage (n=15) with a sensitivity of 100 % compared to80 % in conventional CT. Conventional CT did not detect three T3 tumors. Spiral CT scan has the advantages of fast volume scanning, absence of artifacts related to motion, absence of missed slices, and availability of reformations in multiple planes and three-dimensional reconstruction. Also the assessment of distant metastases with one spiral CT scan of lungs, liver and retro peritoneum is possible. This is the so-called one stop shop'. Previously not detected metastatic disease is no wearly visible."

Magnetic Resonance Imaging

"MRI studies on staging of rectal cancer can be divided into two groups; one using external surface coils, the other using endo rectal coils. The use of an endo rectal coil results in an increased signal-to-noise ratio compared with use of a surface coil; higher-resolution images can be obtained because the field of view is decreased. Kwok found an overall sensitivity of

86 % (specificity 77 %, accuracy 82 %) in a group of 521 patients from 18 different studies on the detection of rectal wall penetration in MRI studies with surface coils. In endo rectal coil studies a median sensitivity of 89 % (specificity 79 %, accuracy84 %) was reported in 169 patients from 6 studies. Surface coil MRI studies reporting on the assessment of T4 tumor stage (8studies, including 246 patients) found a sensitivity of 78 % (specificity 99 %, accuracy 98 %). In a recent MRI study by Beets-Tan, using an external (phased array) coil, with 2 different observers a sensitivity of 75 % and 100 % was found on predicting T4 tumors. Kwok reported from 4 studies, including 124 patients, a sensitivity of 83 % (specificity 100 %, accuracy 99 %) using an endo rectal coil. Studies comparing endo rectal ultra sonography with endo rectal coil MRI showed a difference in overall tumor stage accuracy between the 0 and 10 % favoring MRI (15-19). One study by Meyenberger (n=32) found an 84 % accuracy in assessment of trans mural tumor infiltration compared to 80 % with endo rectal coil MRI."

Treatment / Management Surgery:

"Surgical resection is the main treatment modality for localized non-metastatic stage rectal cancer at any age with acceptable performance status and optimized co morbidities. Endoscopic resection (ER) is reserved for selected favorable-risk and early-stage colon carcinomas found in a polyp (cT0-1). Neo-adjuvant therapy is the current standard of care for colorectal cancer and not only reserved for advanced disease surgical conversion. Adjuvant therapy is recommended for all Cca stage III (node-positive) and individualized by stage II with high-risk features. Surgery in conjunction with peri-chemotherapy may provide a curative option on oligo-metastatic lung and liver disease. [17][6]Palliative systemic chemotherapy is offered to non-surgical candidates with unrespectable locally advanced disease or high metastatic burden to improved quality of life and prolongs life expectancy. Individualized local-recurrent disease patients may achieve cure with further multi-modality therapy."

Surgical Resection

"The main goal for invasive rectal cancer is the complete resection of the tumor and potential lymph ovascular spread by a goal of a minimal negative proximal and distal margin of 5 cm for colon cancer, and minimal proximal margin of 5cm and distal of 2cm for rectal carcinoma. Circumferential/radial margin should be greater than 1 mm. The essentials of oncologic resection involve central vascular ligation of the feeding main artery and complete

mesocolic resection of the involved colonic section. On cologic resection requires removal of 12 or more lymph nodes. The initial step for colectomy is accessing the retro peritoneum and elevating the mesentery of the colon contained within the fascia of Toltd. In laparoscopic procedures, this dissection is started medial to lateral fashion, but in open procedures, this dissection is done lateral to medial way. A secondary aim is the restoration of the bowel continuity, either by one-stage primary anastomosis or two-stage approach with temporary diversion. Conventional open colectomy or laparoscopic colectomy is the preferred surgical modality. High-volume, experienced surgeons should perform the laparoscopic approach. Experience with robotic surgery is under further investigation. Potential palliative surgical procedures for unresectable Cca tumors include resection with primary anastomosis, diverting colostomy, and internal bypass procedures."

"Meta-analysis of randomized clinical trials (including COLOR trial, CLASSIC trial, and COST trial) indicates that laparoscopic-assisted colecto my surgery for Cca provides the same outcomes for 5-year overall survival (OS) (69 % versus 68 %) and disease-free survival (DFS) (76% versus 75 %) as open laparotomy. Reported conversion rates from laparoscopic to open remains at 20 % as described in the United States Inter group Clinical Outcomes of Surgical Therapy (COST) trial. Positive margins have been retrospectively found in 5.3% of Cca resection with a worse OS (hazard ratio [HR] 3.39, 95%CI 2.41 to 4.77). Sentinel lymph node biopsy is not considered a standard of care and consensus guidelines recommend 12 lymph nodes or more with improved 5-year OS at 90% regardless of open or laparoscopic approach. Loco-regional recurrence can occur up to 12 % of C care section and is classified into four categories: anastomotic; mesenteric/nodal; retroperitoneal; and peritoneal. Poor prognostic factors include more than one site of recurrence and involvement of the mesentery/nodal basin whereas the ability to obtain an R0 resection was the strongest predictor of outcome, and these patient shada median survival of 66 months".[9]

"Surgery alone can be curative for patients with stage I disease. For stage III disease (node-positive), the 5-year survival rate is 20 % to 50 % with surgical resectional one thus adjuvant therapy is recommended. For patients with stage II disease, the 5-year survival fluctuates between 50 % and 65 %. Factors other than the stage adversely affect the outcome. These include old age, malegender, performances status, pMMR/ MSI-Sstatus, LVI, PNI, pre-operative CEA level greater than 5, poor histological grade, mucinous or signetring features, the extent of local invasion T4, bowel perforation/obstruction, and insufficient node sampling

less than 12. Mutationsin KRAS and BRAF have not shown to be a negative prognostic impact in the adjuvant setting. Adjuvant therapy for stage II with high-risk features should be individualized".[2][3]

Materials and Methods

The present hospital base descriptive study was conducted in Department of Surgery from November 2017 to June 2019. A Total of 40 patients diagnosed with rectal cancer were included in the study population. All the patients of both the sexes were included in the study who were diagnosed as having stage II or III rectal Cancer. Patients with stage I and IV were excluded. The study was conducted after taking ethical clearance from the institute and informed consent from the patients. The data was collected and analysis done by SPSS version 22.

Inclusion criteria

1. All age group patients of both sexes.
2. Cases will be included according to the definition of locally advanced (stages II and III) rectal cancer.

Exclusion criteria

1. Patients with stages I or IV of rectal cancer will not be included in the study.
2. Patients undergoing surgery as the primary treatment modality will not be included in the study.

METHOD:

The patients were enrolled in the study followed up for outcome till November 2019.

Facilities in equipment, etc. available in the department concerned and/or in the institution of the proposed investigations:

The project by its very nature involved the use of biochemistry, pathology, radiology for investigations and expert medical/surgical management which were available in our institute.

STATISTICALANALYSIS

- Normally distributed variables were analyzed using parametric tests of significance (students' test).
- Association between categorical / nominal variables was tested using non-parametric tests (Chi-square test).

The outcome of interest was calculated within 95% confidence limits. The difference between two observations was considered significant if the calculated P value was<0.05

Budget: No extra costs were incurred in this study as only the investigations or procedures already performed or planned to be performed for management of the patient were be referred and noted.

Observation and Results

Gender wise Distribution

In the present study, we observed that majority of the cases were females (52.5%), and 47.5 % were males. The male: female ratio was 1:1.10.

Age wise Distribution

In the current study, we assessed the age distribution of the study subjects. We observed that majority of the them belonged to the age group of 56-65 years (27.5%) followed by 46-55 years (25%), 66-76 years (17.5%). The detailed age wise distribution of the cases is mentioned in the subsequent table and chart. The mean age of the study subjects was 59.87 ±14.56 years

Distance from Dentate Line

In the present study, we compared the pre-radiation and post-radiation distance from the dentate line among the study subjects. We observed that inpre-therapy group majority of the cases had distance of the lesion between 2-5 cm from dentate line (30%), followed by5-10 cm among 27.5 % cases.

After neo-adjuvant chemotherapy, the distance was increased significantly. Majority of the cases had the distance of 5-10 cm followed by 25% cases had distance more than 10 cm. (Chi-square statistic is 6.48. The p-value is 0.039).

Discussion

In the present study we studied the gender distribution of the study subjects. We observed that majority of them were females (52.5%), and 47.5% were males. The male: female ratiowas1:1.10.In the current study, we assessed the age distribution of the study subjects. We observed that majority of the them belonged to the age group of 56-65 years (27.5 %) followed by 46-55 years (25%), 66-76 years (17.5%). The detailed age wise distribution of the cases is mentioned in the subsequent table and chart. The mean age of the study subjects was 59.87 ±14.56 years

Summary and Conclusion

In this study, we found that all the cases presented with adenocarcinoma among which 17 % cases were of Signet cell adenocarcinoma.

Majority of the cases it is situated at mid-rectum (45%), followed by lower rectum (35%) cases and it was situated at recto-sigmoid junction among 20 % cases.

In the present study, we observed that post neo-adjuvant therapy majority of the cases were managed using anterior resection (52.5%), followed by LAR among 37.5 % cases and APR was done among 10% cases only. Among 17.5 % cases reported development to fradiationeneter it is after neo-adjuvant chemotherapy.

1. 17.5 % cases reported development to fradiation eneteritis after neo-adjuvant therapy.
2. Post neo-adjuvant therapy (52.5%) cases were managed using anterior resection, 37.5% by LAR among and APR was done among 10% cases only.
3. However, more experience is needed with better expertise and larger number of patients to establish neo-adjuvant approach as standard of care.

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