ROLE OF PRE-OPERATIVE CHEMO-RADIOTHERAPY IN LOCALLY ADVANCED RECTAL CANCER

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Abstract

"Colorectal cancer is the third leading cause of cancer and fourth leading cause of cancer deaths worldwide. In India, colon and rectal cancer incidence are 4.4 and 4.1 per 100000 population, making it among the leading cause of cancer related public health burden. Due to various socio-cultural factors, which include lack of awareness, lack of access to specialist care, popularity of alternative systems of medicine and lack of community based screening programs, close to 90% of patients present in locally advanced stage."

"The age standardized rate (ASR) for CRC in India is low at 7.2 per 100,000 population in males and 5.1 per 100,000 population in women. However, in a country with a population of a billion plus people, the absolute number of patients suffering from CRC is large. Five-year survival of CRC in India is one of the lowest in the world at less than 40%. In fact, the CONCORDE-2 study reveals five-year survival of rectal cancer in India is actually falling in some registries. This may be a pointer to inadequacies in the diagnostic and treatment path ways for CRC. An urgent need is to assess reasons for this poor survival."

Introduction

"Prior to the mid-1980s, patients with rectal cancer usually underwent surgery alone, resulting in high rates of pelvic failure with subsequent morbidity and death. Major trials from the 1980s to 1990s showed that postoperative chemo-radiotherapy decreased pelvic failure rates and improved survival, leading to its incorporation into the routine management of patients with resected stage II/III disease."

Therefore, in this study, we have planned to evaluate the response and outcomes of patients with LARC who received neo-adjuvant CRT with Capecitabine.

Aim of Study: To evaluate the response to pre-operative (neo-adjuvant) chemo-radio therapy in patients of locally advanced rectal cancer

Objective of Study:

1. To study the effectiveness of neo-adjuvant chemo-radiotherapy.
2. Study of rate of local recurrence after preoperative chemo-radio therapy followed by surgery.

Review of Literature

Etiology

"Rectal cancer (Cca) could present as sporadic (70%), familial clustering (20%) and inherited syndromes (10%). For sporadic cases average age diagnosis is older than 50 years and mostly linked to environmental factors, different from a minority of patients with a true inherited pattern that carries a higher risk at a younger age (younger than 50 years), and the remaining 20% are familial clustering in the absence of identifiable inherited syndrome. The most common inherited colorectal cancer (CRC) syndromes are familial adenomatous polyposis (FAP) and Lynch syndrome (hereditary non-polyposis colorectal cancer [HNPCC]). [7][8] Approximately 5% of all CRC cancers are attributed to these two inherited syndromes, but as many as 10% to 15% of unselected CRC patients will carry high-risk mutation not related to FAP or HNPCC."

"Personal or family history of CRC, adenomatous polyps and polyps with villousortubulo-villous dysplasia indicate a high risk for synchronous and metachronous CRC primary cancer upto 3% to 5% at 5 years or even longer after resection requiring a closer screening interval. Inflammatory bowel disease (IBD), mainly ulcerative colitis, has a well-known association with CRC, with an estimated incidence 0.5 % peryea between 10 and 20 years after the time of IBD diagnosis and 1% per year after that reaching a 30 % risk probability by the fourth decade of patients with pancolitis. Crohn's disease may increase CRC risk, particularly if present in the ileocolic region."

"Childhood cancer survivors who received abdominal radiation (greater than 30Gy) are at risk of CRC, and screening is recommended 10 years later or at age 35. Other illnesses that increase the risk higher of CRC are diabetes mellitus/insulin resistance, uncontrolled acromegaly disease, and long-term immune suppressed renal transplant."

"Epidemiologic study results indicate strong environmental and lifestyle associations for CRC. Modest weak increased CRC risks are seen with obesity, reid/processed meat, tobacco, alcohol, and rogen deprivation therapy, and cholecystectomy among others. On the other hand, large population studies with variable strength the evidence have found CRC protective

factor such as physical activity, diet (fruits and vegetable, fiber, resistant starch, fish) Vitamin supplements (folate, folic acid, pyridoxine B6, calcium, vitamin D, magnesium) garlic and coffee, and drugs (aspirin, non-sterioidal anti-inflammatory drugs (NSAIDs) hormonal replacement therapy in post menopausal, statins, bisphosphonate and angiotens in inhibitors."

"Interestingly, a randomized controlled clinical trial found that 600 mg of aspirinin Lynch syndrome had a protective effect against colorectal adenomas and cancer with substantially reduced cancer incidence after 55.7 months with an HR of 0.56 [95% confidence interval (CI); 0.32, 0.99; p=0.05]."

Cancer Survival and Prognosis

"Colorectal cancer survival is highly dependent upon stage of disease at diagnosis, and typically ranges from a 90% 5-year survival rate for cancers detected at the localized stage; 70% for regional; to 10 % for people diagnosed for distant metastatic cancer.[11,17] In general, the earlier the stage at diagnosis, the higher the chance of survival."

"Since the 1960s, survival for colorectal cancer at all stages have increasedsubstantially.[11] The relative improvement in 5-year survival over this period and survival has been better in countries with high life-expectancy and good access to modern specialized health care. However, enormous disparities in colorectal cancer survival exist globally and even within regions.[3,5,18]Thisvariation is not easily explained, but most of the marked global and regional disparity in survival is likely due to differences in access to diagnostic and treatment services.[3] In the United States, the 5-year survival for colorectal cancer improved from 1995 to 2000 by more than 10% for both men and women, from 52 to 63% in women and from 50 to 64% in men.[11] The increase in survival during this period was not uniform among racial groups, however, and was reduced among non-whites compared with whites."

Environmental Risk Factors

"Colorectal cancer is widely considered to be an environmental disease, with ―environmental‖ defined broadly to include a wide range of often ill-defined cultural, social, and lifestyle factors. As such, colorectal cancer is one of the major cancers for which modifiable causes may be readily identified, and a large proportion of cases theoretically preventable.[3,10] Some of the evidence of environmental risk comes from studies of migrants

and their off spring. Among migrants from low-risk to high-risk countries, incidence rates of colorectal cancer tend to increase toward those typical of the population of the host country.[8,10] For example, among off spring of southern Europe migrants to Australia and Japanese migrants to Hawaii, the risk of colorectal cancer is increased in comparison with that of populations of the country of origin. In fact, colorectal cancer incidence in the off spring of Japanese migrants to the United States now approaches or surpasses that in the white population, and is three or four times higher than among the Japanese in Japan.[2,3]Apart from migration, there are some other geographic factors in fluencing differences in incidence of colorectal cancer. One of them is urban residence. The incidence is consistently higher among urban residents. Current residence in an urban area is a stronger predictor of risk than is an urban location of birth.[8] This excess incidence in urban areas is more apparent among men than women, and for colon cancer than for rectal cancer".[3]

Nutritional Practices

"Diet strongly influences the risk of colorectal cancer, and changes in food habits might reduce upto 70 % of this cancer burden. Diets high in fat, especially animal fat, are a major risk factor for colorectal cancer.[3,8]The implication of fat, as a possible etiologic factor, is linked to the concept of the typical Western diet, which favors the development of a bacterial flora capable of degrading bile salts to potentially carcinogenic N-nitroso compounds.[2] High meat consumption has also been implicated in the development of colorectal cancer.[2,3] The positive association with meat consumption is stronger for colon cancer than rectal cancer.[3]

Potential underlying mechanisms for a positive association of red meat consumption with colorectal cancer include the presence of heme iron in red meat.[3,4] In addition, some meats are cooked at high temperatures, resulting in the production of hetero cyclicamines and poly-cyclicaromatichydro carbons,[3,5] both of which are believed to have carcinogenic properties. In addition, some studies suggest that people who eat a diet low in fruits and vegetables may have a higher risk of colorectal cancer.[13] Differences in dietary fiber intake might have been responsible for the geographic differences in the colorectal incidence rates.[8] For example, dietary fiber has been proposed as accounting for the differences in the rates of colorectal cancer between Africa and Westernized countries—on the basis that increased intake of dietary fiber may dilute fecal content, increase fecal bulk, and reduce transit time".[2]

Physical Activity and Obesity

"Several lifestyle-related factors have been linked to colorectal cancer. Two modifiable and

interrelated risk factors, physical inactivity and excess bodyweight, are reported to account for about a fourth to a third of colorectal cancers. There is abundant evidence that higher overall levels of physical activity are associated with a lower risk of colorectal cancer, including evidence of a dose–response effect, with frequency and intensity of physical activity inversely associated with risk.[3,16] Regular physical activity and a healthy diet can help decrease the risk of colorectal cancer, although the evidence is stronger for colonic than for rectal disease.[2,17] The biologic mechanisms potentially responsible for the association between reduced physical activity and colorectal cancer are beginning to be elucidated. Sustained moderate physical activity raises the metabolic rate and increases maximal oxygen uptake.[16] In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity, as well as reducing blood pressure and insulin resistance. In addition, physical activity increases gut motility.[2] The lack of physical activity in daily routines also can be attributed to the increased incidence of obesity in men and women, another factor associated with colorectal cancer.[16,8] Several biologic correlates of being overweight or obese, notably increased circulating estrogens and decreased insulin sensitivity, are believed to influence cancer risk, and are particularly associated with excess abdominal adiposity independent of overall body adiposity.[16] However, the increased risk associated with overweight and obesity does not seem to result merely from increased energy intake; it may reflect differences in metabolic efficiency.[16] Studies suggest that individuals who use energy more efficiently may be at a lower risk of colorectal cancer."

Path physiology

"The transformation of the normal rectal epithelium to a precancerous lesion(adenoma) and ultimately to invasive carcinoma requires an accumulation of genetic mutations either somatic (acquired) and/or germ line (inherited). The theory of colonic carcinogenesis features a clonal mutation evolution that gives a cell survival-immortality advantage and allows to develop more mutations providing other cancer hallmarks as proliferation, invasion, metastasis, and others.[12][13]Clinical evidence has shown that CRCs frequently arise from adenomatous polyps that typically acquiredys plastic changes in a 10 to 15-year period before developing invasive carcinoma, and the early detection-removal of polyps will reduce the incidence of CRC. New evidence has exposed that hamartomatous and serrated polyps could lead to CRC. There are three major molecular pathways linked to CRC, chromosomal instability, mismatch repair, and hypermethylation."

"The chromosomal in stability pathway is again of mutations unbalancing oncogene and tumor suppressors equilibrium as seen with mutations in the adenomatous polyposis coli (APC), a hallmark of FAP. Cells with deficiency of DNA mismatch repair (dMMR), commonly MLH1 or MSH2, accumulate errors within the genome that further will be repeated a using high levels of microsatellite instability (MSI-H), ahallmark of Lynch syndrome. Cp G hyper-methylation of DNA could activate or silence the expression of certain genes, BRAF and MLH1 respectively. Sporadic Oncogenes Somatic Mutations (RAS, SRC, MYC) have been implicated in CRC, being RAS the most clinical relevance. RAS mutations variants (HRAS, KRAS, NRAS) are found in 50% of CRC sporadic cases and currently being exploited on CRC screening by stool-DNA testing along with the absence of epidermal growth fact or receptors (EGFR) targeted therapy response and potential direct targeted agents. On the other hand, tumor suppressors genes require bi-allelicloss (―two-hitmodel‖) and are described in loss of APC 5q21 gene (80 %s poradic), TP5317 pgene (50-70 % sporadic), and DCC/SMAD2-418q gene (73 % sporadic). Specific MMR gene mutations could occur in MSH2, hMLH1, hPMS1 andh PMS2, hMSH6, and hMLH3; each one of them that interact with MLH1 and approximately found in 15 % of all sporadic CRC causing aLynch-like syndrome with MSI-H calling for universal testing."

Differentiation between resectable and irresistible rectal cancer

"The accuracy of any diagnostic technique has to be validated against a gold standard. In resectable rectal cancer the pathological specimen can serve this purpose. Therefore information on sensitivity and specificity of various staging techniques originate from observations in the resected tumors that usually have a low tumor (T) stage. The diagnosis of irresectability for a rectal tumor requires especially information on the endopelvic fascia with its relation to the primary tumor and less of the regional nodes. In choosing an optimal staging technique it may be appropriate to concentrate on the accuracy to detect extensive T3 and T4 tumors. Most studies of imaging techniques report only on the accuracy of T and N stage. As a result of this the differentiation between a limited and extensive T3 tumor is not possible (figure 1). The importance of this lies in the relation between the distance of the primary tumor to the endopelvic fascia and the rate of local recurrence. A distance less than 5 mmis considered in adequate. In this section were port on historical studies investigating preoperative T stage (irresectable) rectal tumors realizing that more recent studies focus on prediction of the circumferential resection margin."

"Although surgery is still the main stay of treatment but the compliance is poor duet of ear of living with permanent colostomy associated with APR (abdominoperineal resection). Although preoperative chemo-radiation followed by surgery is well established for over a decade, data from India is lacking. In 2006, we implemented neo-adjuvant CT-RT as a uniform treatment for all the locally advanced rectal cancers that were not amenable to surgery and retrospectively evaluated this protocol with regard to feasibility, tolerance and their impact on disease-free survival (DFS) and overall survival."

Digital rectal examination (DRE)

"Originally digital rectal examination was the most important and often only technique available. Patient history and physical examination can be of value in determining the local extension of the tumor. The involvement of surrounding structures may provoke symptoms such ashematuria, pneumaturia, vaginal bleeding and radicular pain. The presence of lower extremity edema is an ominous sign of venous or lymphatic out flow obstruction due to spread of tumor."

"DRE can assess local tumor spread with an accuracy ranging from 44 % to 83 %, as shown in a study by Nicholls. In this study a panel of 10 clinicians investigated the limitations and reproducibility of DRE in 70 patients with palpable rectal tumors. Under staging was a particular problem in this study. Tumors penetrating through the rectal wall were assessed as confined in 2-16 % of the cases. This broad range of ―accuracy‖ was mainly due to the difference in experience of the clinicians. Another limitation of digital rectal examination is that in 30 % of rectal cancers, the tumor is too proximal (≥ 10cm). Non-reproducible terms like 'tethered' or 'fixed' where used to indicate irresistibility."

Laparotomy and Laparoscopy

"In the past a 'staging' laparotomy was performed on patients with a clinical suspicion of an irresectable rectal tumor. The concept of this laparotomy comprises the possibility to assess the extent of a rectal tumor bimanually, to perform an inspection of the abdominal cavity and to construct an end colostomy to ensure bowel passage. The results of this staging laparotomy could be embedded in the diagnostic workup. More recently the role of laparoscopy as a staging modality in locally advanced disease was studied. This procedureal lows the inspection of the abdominal cavity to identify patients with unsuspected peritoneal disease and also the construction of a colostomy. The distal recto sigmoid can be left in the

pelvic cavity to act as a biological spacer, facilitating radiotherapy without damaging the small bowel. Since it is important not to open the peritoneum of the pelvic cavity, accurate assessment of the endopelvic fascia or ingrowths in other organs below the pelvic reflect ionin abdominal staging is restricted to the liver, peritoneal surface and retroperitoneal lymph nodes. The introduction of endorectal ultra-sonography, CT and MRI made a less invasive and reasonable accurate tagging possible."

Endorectal ultra sonography (EUS)

"Endorectal ultrasonography is very accurate in determining the infiltration of the tumor in the rectal wall, mainly for stages T1and T3 with a sensitivity of 82 % and 92 %, a specificity of 99 % and 84 % and an accuracy of 92 % and 85 % respectively. The sensitivity of 82 % is high compared to other staging techniques like CT, MRI and MRI with an endorectal coil. These data are from a review by Kwok et al. who reviewed 83 studies including 4897 patients determining the wall penetration of rectal tumors. Investigated staging techniques were CT, endorectal ultrasound, MRI and MRI with endorectal coil."

Neo-adjuvant radio chemo therapy

"Three randomized trials investigated the benefit of a combined modality therapy in the preoperative treatment of primary irresectable rectal cancer. They found no significant survival benefit and only Frykholm found a difference in local recurrence free survival (38% vs 66%, p=0.03). The main toxicities were diarrhea, mucositis, leucopenia and skin problems, which were significantly increased in the group of patients who received the combination treatment."

"In these 6 studies the drug used to synergize the effect of radiotherapy has been 5FU. This drug can be given either as bolus or as continuous infusion. Arandomized study by O'Connell demonstrated the superiority of 5FU continuous in fusion to 5FU bolusin terms of time to relapse and overall survival in a post operative radio-chemotherapy regimen."

Materials and Methods

Study duration: The study was conducted for the approximate time period of 2 years, that is from November 2017 to November 2019.

Study design: The study design was Hospital based Descriptive Study

Sample size: Sample size was calculated considering the prevalence of the disease in the general population and keeping in mind the attrition factor. The sample size came to be 40.

Source of data

The source of data for our study was 40 consecutive patients having locally advanced rectal cancer i.e. stage II and III rectal cancer admitted or attended the on cosurgery OPD in Krishna hospital during the study period. The source of data was collected in a specially designed case recording preform a from the patients and the informant and by doing detailed clinical examination and relevant investigations.

Method of collection of data

The patients were studied from OPD attendance up to June 2019. The data analysis included-age distribution in rectal cancer, sex distribution, etiology, delay in hospitalization, mortality, line of management, cause of death, post-operative complications, and hospital stay. The data was collected with the help of standard, pre-validated, semi-structured case record proforma.

Investigations required-Complete blood count, biochemical analysis of blood, Microbiology for serology, X-ray erect abdomen, CT scan (abdomen/ Pelvis)/ Ultrasonography (abdomen/ pelvis/ transrectal). After staging, the patients were subjected to neo-adjuvant therapy which involved concurrent chemotherapy (625 mg/m^2 Capecitabine orally in 4 doses) and radiotherapy (50.4Gy given in 28 fractions) and then examined again after 4 weeks for plan of surgery.

Statistical Analysis

- The collected data was entered with the help of Microsoft Excel spread sheets version 2016. The data was presented in the form of tables and graphs for frequency analysis, to know the measures of central tendency and to study the distribution of the data.
- Statistical analysis is done using IBM SPSS version 22.0 software

The outcome of interest was calculated within 95% confidence limits. The difference between two observations was considered significant if the calculated Pvalue was <0.0.5

Discussion

“Colorectal cancer is a common cancer worldwide with majority of cases occurring in the

developed countries. India has a low prevalence of CRC—estimated five-year prevalence is 87 per 100,000 population.

Differences in dietary patterns and lifestyles are thought to be responsible for the low incidence of CRC in the developing world. Also, prevalence of obesity which is a risk factor for CRC differs in the developed and the developing world. Another possible reason for low incidence can be a younger population—CRC is more common in the elderly. It should be noted that the population registries in India cover only 7.45 % of the population, while worldwide can cerregistries cover 21% of the population; so, some amount of under reporting may be possible in India"[5].

However, "studies on Indian immigrants from countries with a high prevalence of CRC like the USA and Singapore show that CRC incidence is lower in Indians than in the native population but higher than that observed from the Indian registries [6,7]. This shows although there are likely to be some genetic factors involved in the lower incidence of CRC, environmental factors also have a role to play."

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. From the current study, it is concluded that:

1. The male: female ratio was 1:1.10.
2. The mean age of the study subjects was 59.87±14.56 years
3. After neo-adjuvant therapy, the mean distance of the lesion from the anal verge was increased significantly from 4.8±3.13cm to 6.13±2.11cm
4. Aden carcinoma was the commonest form of rectal cancer observed among the cases, middle and lower rectum being the commonest site of lesions.

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