ABSTRACT

Background: Locally advanced rectal cancer (LARC) has a high incidence of local and distant relapse even after adequate treatment. The emerging role of neoadjuvant induction chemotherapy may allow initial down staging of the primary tumor, less toxicity profile and early treatment of micrometastatic disease followed by chemoradiation, and optimum local control may be attained, with the hope of increased complete response rates

Objectives: to identify the effect of induction chemotherapy with oxaliplatin and capecitabine (CapeOx) before concurrent chemoradiation in locally advanced rectal cancer in terms of response and toxicity. Primary end point is assessment of complete pathological response rate.

Patient and Methods: patients with MRI based criteria of high-risk LARC (T4 tumors, tumors within 2 mm of mesorectal fascia, T3 tumors at or below levators and T2-4N+ve tumors) were included. Patients received 12 weeks of induction capecitabine/oxaliplatin followed by concomitant capecitabine and conventional three dimensional conformal radiotherapy. Surgery was done at least 6 weeks after CCRTH.

Results: Thirty five patients with LARC were recruited during the period from December 2017 till January 2019. Five patients (20.8%) had a pathological complete response (TRG 0) (ypT0N0). Another three patients (12.5%) had near complete pathological response (TRG 1). While unfortunately 29.2% and 37.5% had partial response and poor response respectively.

Conclusion: Induction chemotherapy could be a promising option for better response rates either clinical or pathological for high risk LARC patients with acceptable toxicity profile. Keywords: Induction chemotherapy, locally advanced rectal cancer, pathological complete response

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy in males and females ***(Howlader et al., 2016).*** More than two-thirds of all cases and about 60% of all deaths occur in highly developed countries ***(Ferlay et al., 2015).***

Globally, it is estimated that approximately 1.57 million patients are diagnosed with colorectal cancer and more than 771,000 are expected to die from it each year, of which 30% are reported to arise in the rectum ***(Fitzmaurice et al., 2015).***

Despite improvements in screening, prevention, and early detection, a large portion of patients with rectal cancer present with more advanced stages of disease. For patients with locally advanced disease, treatment should be carried out in a combined modality therapy given the tendency of rectal cancer to recur both locally and distantly. Internationally, numerous trials were conducted to determine the optimal sequence, duration, and intensity of therapy to maximize outcomes while limiting treatment-related toxicities ***(Wagner, 2014).***

In order to accurately identify locally advanced rectal cancer (LARC) patients amenable to preoperative treatment, initial clinical staging with pelvic MRI and endoscopic rectal ultrasound (ERUS) evaluation is required to determine the

extent of local disease and nodal involvement. Staging provides critical information about the likelihood of achieving a complete resection (R0) as well as the likelihood of sparing the rectal sphincter in lower rectal cancer and thereby maintaining fecal continence ***(Schrag, 2013).***

The precision of MRI in this setting was evaluated in the MERCURY trial in which high-resolution MRI accurately predicted whether the surgical resection margins were clear or affected by tumor ***(Brown, 2006).***

High-risk MRI features (extramural vascular invasion, mesorectal tumor depth >5 mm, T4 stage, involved circumferential resection margin) may correlate with higher risk for distant metastases. In addition to initial staging prognostic features, MRI response to neoadjuvant treatment has been shown to be an indicator of long-term outcomes, including recurrence and survival ***(Hunter et al., 2012).***

Optimal outcomes for LARC patients with high risk features are achieved with a multidisciplinary approach, with the aim of reducing the risk of distant recurrence and to achieving local control with successful sphincter preservation. For many years, the standard of care has been a multimodality approach incorporating neoadjuvant hypofractionated short course radiotherapy (SCRT) or long course chemoradiation (CRT) followed by total mesorectal excision (TME) surgery and adjuvant fluoropyrimidine-based chemotherapy. With this

approach, local recurrence (LR) rates have fallen from 30-45% in historical series to less than 10% ***(Lee et al., 2015).***

This standard of care was defined since the German Rectal Cancer Trial. This landmark study randomized patients with LARC to either preoperative or postoperative CRT and demonstrated that the rate of local recurrence was lower in the preoperative CRT group than in the postoperative CRT group (6% vs 13%; p value= 0.006). Furthermore, toxicity was lower, and quality of life was better in the group that received preoperative therapy ***(Sauer et al., 2012).***

While local control rates in rectal cancer are now excellent, studies are finding that distant failure remains a persistent issue. One reason to explain this, that after aggressive neoadjuvant chemoradiation and surgery, many patients never get their full course of adjuvant systemic therapy ***(Wagner, 2014).***

In this context, the emerging role of neoadjuvant chemotherapy have been reviewed and how this change in treatment sequence may improve outcomes, particularly in terms of reducing rates of distant metastatic disease ***(Boland and Fakih, 2014).***

This was emphasized in a study conducted using the National Comprehensive Cancer Network (NCCN) Colorectal Cancer Database, patients with rectal cancer were evaluated on the frequency of receiving neoadjuvant and postoperative

systemic chemotherapy. Results of that study indicated that the number of patients who completed postoperative treatment was significantly lower than anticipated. From these observations, a shift is emerging towards administering full-dose systemic treatment in the neoadjuvant setting to minimize micro-metastatic disease ***(Kalyan et al., 2016).***

Such a rationale makes the strategy of induction chemotherapy followed by CRT, sometimes called the "total neoadjuvant approach", appear very attractive. Several trials with various designs have been conducted to examine this strategy: the CONTRE study; the EXPERT trial; the Danish study, by Schou et al; and the Swiss study, by Koeberle et al. All four trials treated patients with LARC with induction chemotherapy (consisting of CAPOX or FOLFOX), followed by neoadjuvant CRT, followed by surgery. The pathological complete response (pCR) rates being the primary end point ranged from 20% to 33% ***(Salem et al., 2016).***

On the other hand, while not all studies have clearly demonstrated improved outcomes in the induction group as compared to adjuvant chemotherapy, yet it clearly demonstrated less toxicity profile and better adherence to completion of systemic treatment. This was shown in the Spanish GCR-3 study in which acute grade 3/4 toxicity was observed in 19% of patients who received pre-operative

chemotherapy versus 54% of post-operatively treated patients ***(Fernández-Martos et al., 2010).***

In sum, induction chemotherapy may allow for initial down staging of the primary tumor, less toxicity profile and early treatment of micro metastatic disease. In turn, by following this immediately with chemoradiation, optimal local control may be attained, with the hope of increased complete response rates ***(Boland and Fakih, 2014).***

AIM OF THE STUDY

The study aims at identifying the effect of induction chemotherapy with oxaliplatin and capecitabine (CapeOx) before concurrent chemoradiation in locally advanced rectal cancer in terms of response and toxicity.

Primary end points include; assessment of radiological and pathological responses for this regimen.

Secondary end points include assessment of toxicity profile and the rate of achieving an R0 resection surgery and pathologic downstaging.

Chapter 1

EPIDEMIOLOGY

Colorectal cancer (CRC) is the third most common malignancy in males and females ***(Howlader et al., 2016).*** More than two-thirds of all cases and about 60% of all deaths occur in highly developed countries ***(Ferlay et al., 2015).***

Globally, it is estimated that approximately 1.57 million patients are diagnosed with, and more than 771,000 are expected to die from, CRC each year, of which 30% are reported to arise in the rectum ***(Fitzmaurice et al., 2015).***

The American Cancer Society had estimated that there will be about 145,600 new cases of CRC diagnosed in the United States in 2019 of which 44,180 cases are in the rectum. While the estimated deaths are expected to be 51,020 cases for both colon and rectum ***(Siegel et al., 2019).***

Certain demographic features associated with the disease differ between world regions such as distribution by sex, age, and race. For example, CRC is more commonly diagnosed in older individuals and in men in most of the developed countries, its incidence is higher in African Americans, and higher CRC mortality is often associated with lower socioeconomic status ***(Bohorquez et al., 2016).***

In the past years incidence rates have been declining in the United States by nearly three percent per year in males and more or less stable in females as shown in (figure 1) ***(Siegel et***

al., 2019). These reductions could be attributed both to changes in risk factors as well as increased use of colonoscopy for screening allowing for early detection and treatment of premalignant lesions ***(Siegel et al., 2012).***

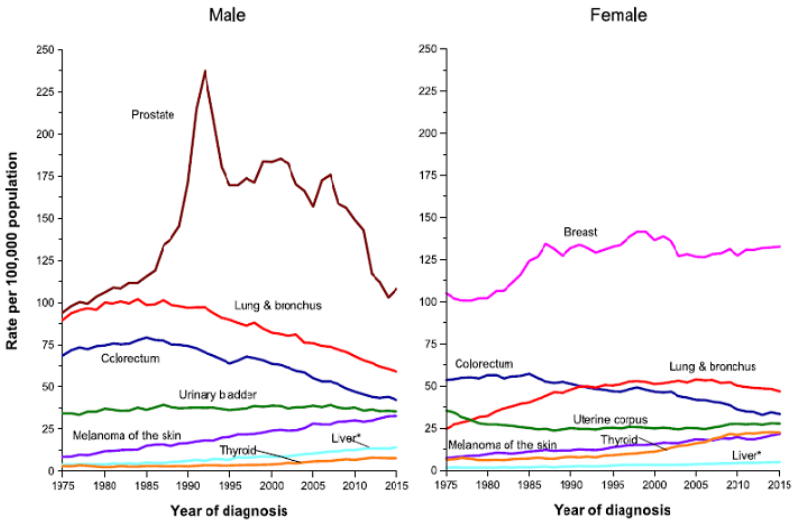

Figure (1): Trends in Incidence Rates for Selected Cancers by Sex, United States from 1975 to 2015 ***(Siegel et al., 2019).***

While in Egypt the early database from ElGharbeya cancer registry through the years 2003-2007 rectal cancer crude incidence rate was 1.7 and 1.5 per 100,000 population among males and females respectively ***(Curado et al., 2013).***

While according to data based on the National Cancer Registry Program, estimated number of cases of CRC in 2015 was 3977 in both males and females with a slightly higher incidence in males and this number is estimated to increase by the year 2020 to reach 4673 new cases ***(Ibrahim et al., 2014).***

Throughout the past 5 years (2014-2018), 567 new cases of colorectal cancer presented to the Clinical Oncology department at Ain Shams University from which 47% of the patients had their tumor located in the rectum or rectosigmoid junction. This makes CRC represent 5% of the incident new cases presented to the department.

The risk of CRC increases with age; the median age at diagnosis for rectal cancer is 63 years in both males and females ***(Howlader et al., 2016).***

Regarding trends in age distribution, CRC incidence and mortality rates are decreasing among age groups above 50 while increasing in younger populations (as demonstrated in figure 2) who are usually not incorporated in screening programs. Young onset CRC mostly present in the rectum and distal colon as well as being less differentiated, with mucinous and signet ring types and more advanced stages ***(Ahnen et al., 2014)***.

In a report done on CRC patients presented to Ain Shams University Clinical Oncology department through the years 2010-2014, among 348 patients 30.7% were younger than 40 years while only 15% were ≥65 years ***(Kamal et al., 2018).***

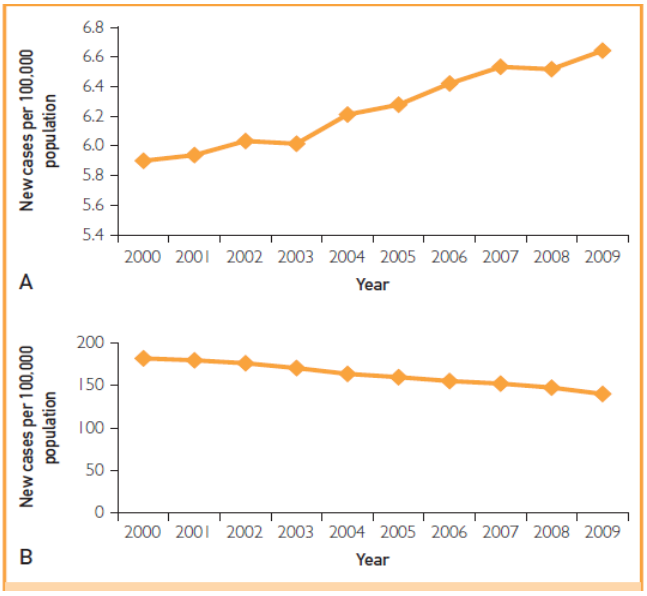

Figure (2): Surveillance, Epidemiology, and End Results (SEER) age-adjusted colorectal cancer incidence per 100,000 individuals in those younger than 50 years (A) and those 50 years or older (B) ***(Ahnen et al., 2014).***

Survival rates vary differently between races, being higher among white race, and stage at diagnosis, rates in the united states are shown in (figure 3) ***(Siegel et al., 2019).***

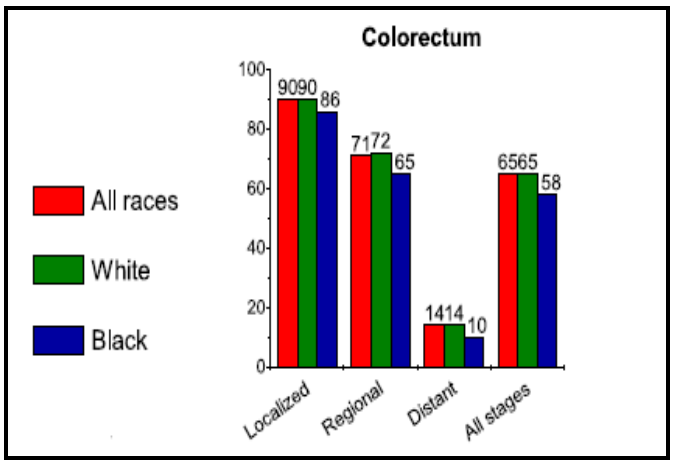

Figure (3): Five Year Survival Rates for colorectal cancer by race and stage at diagnosis, United States, 2008-2014 ***(Siegel et al., 2019).***

There is marked variations in mortality rates in CRC among different socioeconomic classes, this has shown a marked trend shift from the late 1970s where rates were twenty percent lower for poor countries than for wealthy ones and now being higher by 35%. This could be as an influence of change in dietary and smoking patters as well as less adoption of screening programs among low socioeconomic class countries ***(Wang et al., 2012).***

Risk factors:

Environmental exposures and personal or family history of colorectal polyps are both known risk factors for CRC development. CRC outcomes depend primarily on the distribution and spread of the disease, and also early diagnosis and intervention ***(Bohorquez et al., 2016).***

Development of rectal cancer is a multistep heterogeneous process resulting from an alteration in cell division and replication. The major molecular pathways for the development of rectal cancer have been described as chromosomal instability, microsatellite instability (MSI), and hypermethylation of DNA ***(Niederhuber et al., 2019).***

Colorectal cancer may be sporadic related to mutation errors in DNA, transcriptional silencing of suppressor tumor genes, genes involved in the control of the cellular cycle, repair, and apoptosis. Or it may be genetic in origin related to

mutations in suppressor gene tumors such as APC, DCC, BRAF, PIK3CA, AKT, and TP53 or the presence oncogenes as K-RAS and CTNNB1. Epigenetic changes involving proliferation, differentiation, apoptosis and angiogenesis are also causes ***(Granados-Romero et al., 2017).***

Up to 30% of CRC patients have a family history of the disease, about 5% of which are due to an inherited genetic abnormality. People with a first-degree relative who has been diagnosed with CRC have 2 to 4 times the risk of developing the disease ***(Samadder et al., 2014).***

Characterized hereditary syndromes account for about 5% of all CRCs. The most common hereditary CRC syndrome is Lynch syndrome (Hereditary Non Polyposis Colorectal Cancer), which accounts for approximately 2% to 4% of all cases. An estimated 18% of men and 19% of women with Lynch syndrome will develop CRC by age 50, rising to 45% and 54%, respectively, by age 70 ***(Dowty et al., 2013).***

Familial adenomatous polyposis (FAP) is the second most common predisposing genetic syndrome, accounting for less than 1% of all CRCs. It is characterized by the development of hundreds to thousands of colorectal polyps beginning at 10-12 years of age. Without intervention, the lifetime risk of CRC approaches 100% by age 40 ***(Ricciardiello et al., 2016).***

Colorectal hamartomatous polyposis syndromes including Peutz–Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and Cowden disease are very rare with incidences below 1 per 100,000. The life time risk of developing CRC in different inherited syndromes is illustrated in table (1) ***(Mishra and Hall, 2012).***

Table (1): Colorectal cancer predisposition syndromes ***(Mishra and Hall, 2012)***

syndrome	colorectal presentation	CRC lifetime risk
FAP	Over 100 adenomatous colorectal polyps (average age of polyposis onset is 16 years)	Nearly 100%
Lynch syndrome	Colon cancer (often early onset, average age of onset 44–61 years)	50–80%
AFAP	10–100 adenomatous colorectal polyps with a tendency toward polyps in the right side of the colon (average age of polyposis onset is 26)	80%
MAP	10 to over 100 colorectal polyps	Undefined, but increased over the general population
HMPS	Colorectal polyposis with polyps of different histologies (adenomas–classic, serrated, tubular; hyperplastic; juvenile; mixed juvenile-adenomatous or hyperplastic adenomatous)	Undefined
HPS	Colorectal polyposis featuring large, hyperplastic polyps and some adenomas/serrated adenomas	Undefined
Peutz-Jeghers	Colorectal polyposis involving characteristic hamartomatous polyps	39%
JPS	Colorectal polyposis involving juvenile polyps	17–22% by age 35, ~ 68% by age 60
Cowden syndrome	Colorectal hamartomas	Unclear, around 9%

FAP, familial adenomatous polyposis; AFAP, attenuated familial adenomatous polyposis; MAP, MYH-associated polyposis; HMPS, hereditary mixed polyposis syndrome; HPS, hereditary polyposis syndrome; JPS, juvenile polyposis

Patients with chronic inflammatory bowel disease, have almost double the risk of developing CRC compared to people in the general population. Cancer risk increases with the extent, duration, and severity of disease ***(Beaugerie and Itzkowitz, 2015).***

Type 2 diabetes has been shown to have a positive association with CRC risk. This could be attributed to insulin resistance in the setting of hyperinsulinemia which affects insulin-like growth factor 1 (IGF-1), which influences colonic carcinogenesis by prolonging cell survival and promoting proliferation ***(Vigneri et al., 2017).***

In a study conducted on a total of 3000 CRC cases from multiple cohorts during up to 32 years of follow-up. Type 2 diabetes was associated with increased risk of CRC (HR: 1.42; 95% CI: 1.12-1.81). This was more statistically significant for men than for women ***(Ma et al., 2018).***

Metabolic syndrome is a combination of three or more components (abdominal obesity, hypertension and dyslipidemia). A meta-analysis of 17 studies revealed that the risk of colorectal cancer is 33% to 41% higher in individuals with metabolic syndrome ***(Esposito et al., 2013).***

Some other known behavioral and dietary risk factors include physical inactivity and sedentary life style, obesity, low fiber diet, high intake of red and processed meat, low calcium and vitamin D, smoking and alcohol consumption are known to increase risk of CRC. Their relative risks are summarized in table (2) ***(American Cancer Society, 2017).***