Benefit of adjuvant chemotherapy in patients with stage II colon cancer: A Retrospective study

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ASUH	**:**	Ain Shams University Hospital
(IGF)	**:**	insulin-like growth factor
5-FU	**:**	fluorouracil
AC	**:**	adjuvant chemotherapy
APC	**:**	adenomatous polyposis coli
ASCO	**:**	the American Society for Clinical Oncology
CIN	**:**	chromosomal instability
CME	**:**	complete mesocolic excision
CRC	**:**	colo-Rectal cancer
DFS	**:**	disease free survival
EGFR	**:**	epidermal growth factor receptor
ER	**:**	estrogen receptor beta
FAP	**:**	Familial adenomatous polyposis
gFOBT	**:**	guaiac-based fecal occult blood test
HNPCC	**:**	hereditary non-polyposis colon cancer
HR	**:**	Hazard ratio
KRAS	**:**	Kirsten rat sarcoma viral oncogene homolog
LV	**:**	Leucovorin
LVI	**:**	lympho-vascular invasion
MMR	**:**	mismatch repair
MSI	**:**	Microsatellite instability
NCCN	**:**	National Comprehensive Cancer Network
NCI	**:**	National Cancer Institute
NOC	**:**	*N*-nitroso compounds
OS	**:**	overall survival
PFS	**:**	progression free survival
PNI	**:**	peri-neural invasion
PS	**:**	performance status
RFS	**:**	Relapse free survival
SEER	**:**	The Surveillance, Epidemiology, and End Results
TNM	**:**	tumor ,node ,metstasis
WHO	**:**	World Health Organization

Abstract

Benefit of adjuvant chemotherapy in patients with stage II colon cancer: A Retrospective study

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States.Colon cancer represents the 7th rank among the 10 most common cancer sites in Egypt , accounts for 4.7% of all incident cancer cases in Egypt .

The Aim of this retrospective stud was to estimate the benefit of adjuvant chemotherapy for patients with stage II colon cancer .

Trial Design : include patients with colon cancer stage II who underwent surgery , in the period from January 2010 to December 2015 in Ain Shams university Hospital. patients received adjuvant Chemotherapy were compared to those who had received no treatment .

Results : The study included sixty-seven patients . The mean age for all patients was 57 years. Thirty-nine patients received adjuvant chemotherapy due to being considered as high risk and twenty-eight low risk patients were followed up without treatment . Median follow up time was 16 months . patients who received adjuvant chemotherapy had median Overall survival 53 months vs 49 months in those who did not (P= 0.921) and median Relapse free survival 37 months vs 26 months (P= 0.145) . In terms of Relapse free survival and overall survival, adjuvant chemotherapy did not provide a statistically significant difference. Within the adjuvant group, the most frequent poor prognostic features included: suboptimal lymph node sampling 64% ,clinical obstruction or perforation 31% , T4 invasion 23% ,lymphovascular invasion 10% and poor differentiation 5% .

When the effects of the significant Variables on death risk were investigated by multivariate analyses , No statistically significant overall survival differrance could be detected among those variables : Age (HR,0.902; 95%CI, 0.204-4.053 [P=0.906]) Lymphovascular invasion (HR,0.271; 95%CI, 0.176-0.237 [P=0.321]) , suboptimal LN resection (HR, 1.866; 95%CI, 1.213-1.637 [P=0.671]) . However, Significant survival difference demonstrated in : clinical obstruction at

diagnosis (HR, 4.630; 95%CI, 2.750-3.712 [P=0.054]) had significant shorter OS , T4 tumors (HR0.181 95%CI 0.118-0.159 [P=0.041]) had significant improvement of OS and Sidedness ,and patients with right sided colon cancer had a small significant improved overall survival (HR 0.85 95% CI 0.75–0.98, p = 0.033) than left sided patients .

No statistically significant RFS differrance could be detected among those variables : age [HR], 1.00; 95%CI, 0.437-2.536 [P=0.805]), suboptimal LN resection (Hazard Ratio [HR], 0.614; 95%CI, 0.399-0.539 [P=0.658]) and Lympho-vascular invasion(HR, 1.336; 95%CI, 0.868-1.172 [P=0.304]) . However, statistical significance did not reach that level of confidence in patients with bowel obstruction at diagnosis (HR, 4.026; 95%CI, 2.617-3.533 [P=0.056]) ; these patients had significantly shorter RFS when compared to the patients who did not have this risk factors and T4 tumors (HR, 0.609; 95%CI, 0.591-0.797 [P=0.021]) , had significantly decreased recurrence rate.

In conclusion, the results of the current study suggest that improved outcomes from the use of Adjuvant chemotherapy in patients with stage II colon cancer are limited toright sided high-risk patients with T4 disease. Other poor prognostic features, such as obstruction, appears to be associated with a significant shorteroverall survival . Right sided colon cancer patients showed a small significant survival benefit than left sided patients.

Introduction

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the united states . In 2015, an estimated 93.090 new cases of colon cancer and approximately 39.610 cases of rectal cancer occur . During the same year , an estimated 49.700 people will die of colon and rectal cancer combined (**Siegel RL ,et al.2015**).

Despite these high numbers , the incidence of colon and rectal cancers per 100.000 people decreased from 60.5 in 1976 to 46.4 in 2005 **(Cheng L ,et al. 2011**). In fact , the incidence of colorectal cancer decreased at a rate of 4 % per year or greater between 2008 and 2011 (**Siegel RL ,et al.2015**). The incidence rate for colorectal cancer reported by the CDC for 2011 is 40.0 per 100.000 persons (**Henley SJ ,et al.2015**) . In addition , mortality from colorectal cancer decreased by almost 35 % from 1990 to 2007 , **(Siegel R ,et al.2011)** and in 2011 was down by 47 % from peak mortality rates (**Siegel RL ,et al.2015**).

These improvement in incidence of and mortality from colorectal cancer are thought to be a result of cancer prevention and earlier diagnosis through screening and better treatment modalities . Despite the observed improvement in the overall colorectal cancer incidence rate , a retrospective cohort study of the SEER colorectal cancer registry found that the incidence of

colorectal cancer in patients younger than 50 has been increasing **(Baily CE ,et al.2014).**

The risk of developing colon cancer depends on factors which can be classified into lifestyle or behavioral factors (such as smoking, high red meat consumption, obesity, physical inactivity) and genetically determinant factors. According to international guidelines **(Schmoll HJ,et al. 2012)** , screening tests are stratified according to the personal risk of disease. Age is considered the major unchangeable risk factor for sporadic colon cancer: nearly 70% of patients with colon cancer are over 65 years of age, and this disease is rare before 40 years even if data from SEER and Western registries show an increased incidence in the 40–44 years group and a decrease in the oldest groups **(Davis DM, et al. 2011).**

Individuals with a personal history of adenoma, colon cancer, inflammatory bowel disease (Crohn's disease and ulcerative colitis), significant family history of CRC or polyps, an inherited syndrome (5–10% of all colon cancers) such as Familial Adenomatous Polyposis coli and its variants (1%), Lynch-associated syndromes [hereditary nonpolyposis colon cancer (3–5%)], Turcot-, Peutz-Jeghersand MUTYH-associated polyposis syndromes, are considered at high risk of colon cancer and must be actively screened and, in cases of inherited

syndromes, also referred for genetic counseling **(Schmoll HJ,et al. 2012 & Balmaña J, et al. 2013)**.

The prognosis of colon cancer is clearly related to the staging features of the TNM classification, including the degree of penetration of the tumour through the bowel wall and the presence, or absence, of nodal involvement. However, many additional parameters such as grading, lymphatic or venous or perineural invasion, lymphoid inflammatory response and involvement of resection margins, which are reflected by the Dukes and TNM classifications, have been shown to have strong prognostic impact.

Furthermore, factors such as p53, k-ras and bcl-2 expression, TGF-alpha, EGFR, proliferation index and aneuploidy are under evaluation for their single or combined value under high-risk conditions.

Risk assessment is particularly important in order to decide when to propose an adjuvant treatment to an individual patient. It is well established that in colon cancer, adjuvant therapy decreases the risk of death by absolute 3%–5% in stage II with single-agent 5-FU and by 10%–15% in stage III with fluoropyrimidines alone plus a further 4%–5% with oxaliplatin-containing combinations .

The benefit of oxaliplatin in adjuvant therapy for patients with stage 2 colon cancer has also been addressed .Results from a

recent post-hoc exploratory analysis of the MOSAIC trial did not show a significant DFS benefit of FOLFOX over 5-FU/LV for patients with stage 2 disease at a follow up of 6 years (HR,0.84;95%Cl,0.62-1.14;P=.258) **(Tournigand C, et al.2012)** . After a longer follow up , no difference in 10 year OS was observed in the stage 2 subpopulations (79.5% vs 78.4%; HR,1.00;P = .98).**(Andre T, et al.2015).**

Each treatment option, including observation alone, should be thoroughly discussed with the patient, taking into consideration prognostic aspects of the tumor disease, non-disease-related characteristics (such as performance status, age, co morbidities, etc.) and the individual's preferences.

Notably, there is no evidence for a predictive marker regarding the benefit of adjuvant chemotherapy for early CRC, and therefore the use of any predictive marker information for decision making is not indicated.

Generally, adjuvant treatment is recommended for stage III and 'high-risk' stage II patients. The first issue is therefore how to define the risk. The 5-year survival after surgical resection alone is 85%–95% for stage 1 , 60%–80% for stage 2, and 30%–60% for stage 3 . Several newer predictors have been recently examined, including microsatellite instability (MSI)/mismatch repair (MMR), 18q deletion, k-ras mutations, TP53, TGFBR2, DCC and thymidilate synthase gene expression.

The general consensus suggests that patients with stage II areconsidered at high risk if they present at least one of thefollowing clinical characteristics: lymph nodes sampling <12; poorly differentiated tumor; vascular or lymphatic or perineural invasion; tumor presentation with obstruction or tumor perforation and pT4 stage [II].

Despite optimal primary treatment, with adequate surgery with or without adjuvant chemotherapy, 30%–50% of patients with colon cancer will relapse, and most of those patients will die from their disease.

Aim of the study

In stage II colon cancer , Is there subgroup that may benefit of adjuvant chemotherapy ?