Adjuvant chemotherapy in stage II–III operated colon cancer patients from a nontrial cohort in a low colon cancer prevalence country with predominant use of modified CAPOX

Anant Ramaswamy, Rushabh Kothari, Ashwin Desouza[1], Tarachand Gupta, Sandeep Bairwa, Akhil Kapoor, Amit Kumar, Pradeep Ventrapati, Mukta Ramadwar[2], Sarika Mandavkar, Nita Chavan, Avanish Saklani[1], Vikas Ostwal

Abstract

Background: Data regarding the practice of adjuvant chemotherapy, specifically with modified CAPOX, and survival outcomes in operated colon cancer patients from a nontrial cohort in a lower-middle income and low prevalence nation like India is scarce. **Materials and Methods:** Patients who underwent upfront curative resection for colon cancer from January 2013 to December 2016 were analyzed for baseline variables and outcomes. **Results:** A total of 491 patients underwent curative resection in the predefined time period. The median age of the patients was 53 years (range: 17–87). Patients with Stage I, Stage II, and Stage III disease comprised 7.9%, 44.8%, and 45.4% of the entire cohort, respectively. Patients with Stage I cancer were observed. Adjuvant chemotherapy was planned for 384 patients (78.2%), with the doublet regimens (capecitabine-oxaliplatin, or 5-fluorouracil-oxaliplatin) being used commonly (77.6%). Common toxicities were Hand-foot syndrome (Grade 2/3 - 21.4%) and peripheral neuropathy (Grade 2/3 - 20.1%). About 85% of patients receiving monotherapy (capecitabine or 5 fluorouracil) and 81.2% of patients receiving doublet chemotherapy (mCAPOX or modified FOLFOX-7) completed their planned adjuvant treatment. With a median follow-up of 22 months, estimated 3 years event-free survival was 86%, and overall survival (OS) was 93.6%. Stage, younger age (<50 years), underlying cardiovascular abnormalities, need for dose reductions and noncompletion of planned chemotherapy predicted for inferior estimated 3-year OS on multivariate analysis. **Conclusions:** Adjuvant chemotherapy especially with modified CAPOX appears well tolerated in the Indian population and early survival outcomes appear to be comparable to published literature.

Key words: Adjuvant chemotherapy, CAPOX, colon cancer, compliance, India

Introduction

Colon cancers, as part of the colorectal cancer (CRC) spectrum, have a low prevalence, low incidence and relatively stable rates in India as compared to the West and even other countries in Asia, where rising incidence rates have been noted.[1-4] It is not among the five most common incident or prevalent cancers across most rural or urban, population-based or hospital-based registries in India.[5] Whether this is a reflection of varying diet patterns, lesser outreach of registries or different socioeconomic factors as compared to other parts of the world remains to be seen.[4,6]

Major improvements in disease-free survival and overall survival (OS) in patients with nonmetastatic colon cancer has been as a result of improving quality of surgery and adjuvant chemotherapy.[7-13] The importance of microsatellite instability (MSI) status in Stage II cancers, the potentially debilitating neuropathy related to oxaliplatin as well as the arguably benefit of oxaliplatin in patients >70 years of age, have all lead to a greater role of personalized adjuvant treatment of colon cancers.[14-17] The results of the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) project have also given options to treating oncologists with regard to the duration of adjuvant chemotherapy.[18,19]

Our institution is a tertiary cancer center in India where approximately 700 CRC patients undergo baseline evaluation and further management.[20] Previous data have suggested certain unique characteristics of patients diagnosed with colon cancer in India, specifically with relation to age (median age of presentation- 4th–5th decades) as well as a higher incidence of signet-ring cancers.[21,22] With these aspects in mind, we retrospectively evaluated patients with Stage I–III colon cancers for outcomes, with a specific emphasis on the practice of adjuvant chemotherapy.

Materials and Methods

Patient selection

The study is a retrospective analysis of operated patients who underwent upfront curative intent resection for nonrectal colon cancers from January 2013 to December 2016 at the Department of GI Oncology, Tata Memorial Hospital (TMH), in Mumbai. These patients were extracted from a prospectively maintained colon cancer database at TMH. Patients included in the study satisfied the following criteria-

1. Adenocarcinoma of the colon, either by presurgical colonoscopic biopsy or postsurgical histopathological report
2. No evidence of metastatic disease, either radiologically or intraoperatively.

Patient data which was not included for analysis were:

1. Operated patients with rectal cancer
2. Patients who received neoadjuvant therapy before surgery of colonic primary.

Details collected and evaluated were preoperative carcinoembryonic antigen levels, site of primary (left, right, etc.), stage (as per AJCC 7th edition), the degree of differentiation, signet-ring morphology, mucinous features, the presence of obstruction and/or perforation, the presence of lymphovascular emboli and/or perineural invasion. These factors

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Departments of Medical Oncology, [1]Surgical Oncology and [2]Pathology, Tata Memorial Hospital, Mumbai, Maharashtra, India
Correspondence to: Dr. Vikas Ostwal, E-mail: dr.vikas.ostwal@gmail.com

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were also were evaluated as prognostic factors with additional factors evaluated being age (<50 years and age >65 years), delay in administration of adjuvant chemotherapy (≤3 weeks vs. >3 weeks; ≤4 weeks vs. >4 weeks; ≤6 weeks vs. >6 weeks) and presence or absence of cardiovascular abnormalities.

Adjuvant chemotherapy

The specifics of regimen administered, chemotherapy compliance, completion rates, and requirement of dose reduction was detailed. Planned therapy for patients receiving 5 – fluorouracil and mFOLFOX-7 was considered as 12, while it was considered as 8 for patients receiving capecitabine or capecitabine-oxaliplatin (CAPOX). The doses for these regimens were as follows:

1. Modified CAPOX – Oxaliplatin (130 mg/m^2 IV on day 1) every 3 weeks plus capecitabine (2000 mg/m^2/day in two divided doses for 14 days on, 7 days off)
2. Modified FOLFOX-7 – Oxaliplatin (85 mg/m^2 IV on day 1), Leukovorin (l-LV) 400 mg IV and 5-FU 2400 mg/m^2 IV over 46 h (days 1–2) continuous intravenous infusion, every 2 weeks
3. Single-agent capecitabine – 2000 mg/m2/day in two divided doses for 14 days on, 7 days off, every 3 weeks
4. Single-agent 5-FU/LV – (l-LV) 400 mg IV and 5-FU 2400 mg/m^2 IV over 46 h (days 1–2) continuous intravenous infusion, every 2 weeks.

As per institution protocols, adverse events were recorded as per NCI– CTCAE National Cancer Institute - Common Terminology Criteria for Adverse Events version 4.03 in this study.

Clinical data collection and statistics

For this study demographic data and baseline clinical and tumor characteristics, chemotherapy regimens, surgical procedures, and outcomes were collected retrospectively from the charts maintained prospectively (GI Medical Oncology Information System and electronic medical record system). All data were entered in SPSS (Statistical Package for the Social Sciences) software Version 21 (IBM) and used for analysis. Descriptive statistics including median, frequency, and percentage for categorical variables is used to describe age, gender distribution, and adjuvant treatment. Survival outcomes in terms of event-free survival (EFS) and OS were analyzed. Median EFS was calculated from the date of diagnosis to the date of clinical or radiological evidence of disease recurrence or the last follow-up date. Median OS was calculated from the date of diagnosis until the last follow-up or death. Survival analysis was performed using Kaplan–Meier estimates and log-rank test for bivariate comparisons. All prognostic factors that approached significance on univariate analysis ($P \leq 0.05$) were considered for multivariate analysis and reported with hazard ratios and 95% confidence intervals. Factors not approaching prespecified $P \leq 0.05$ value are not reported.

Results

Baseline characteristics

A total of 491 patients satisfied the inclusion criteria for entry into the study. The mean duration between surgery and beginning of adjuvant chemotherapy was 25 days (range: 11–94) [Table 1].

Table 1: Demographic and baseline characteristics

Characteristic	*n* (percentage where applicable)
Median age (years)	53 (17-87)
Young age (years)	
Age≤50	209 (42.6)
Age>50	282 (57.4)
Elderly age (years)	
Age>65	81 (16.5)
Age≤65	410 (83.5)
Gender	
Male	328 (66.8)
Female	163 (33.2)
Comorbidities	
Hypertension	93 (18.9)
Diabetes mellitus	84 (17.1)
Cardiac dysfunction (including previous history of coronary artery disease, cardiomyopathy, etc.)	11 (2.2)
Site of primary	
Right sided	273 (55.6)
Left sided	172 (35.1)
Transverse colon	30 (6.1)
Epicentre not identifiable	16 (3.3)
Mean nodes retrieved	22 (1-96)
Histopathology	
PDAC	132 (26.9)
MDAC	292 (59.5)
WDAC	15 (3.1)
Adenocarcinoma, NOS	52 (10.6)
Mucinous histology	
Yes	90 (18.3)
No	401 (81.7)
Signet ring histology	
Yes	40 (8.1)
No	451 (91.9)
Presence of perforation	
Yes	17 (3.5)
No	468 (95.3)
Not available	6 (1.2)
Baseline obstruction	
Yes	122 (24.8)
No	369 (75.2)
Presence of lymphovascular emboli	
Yes	113 (23.0)
No	333 (67.8)
Not available	45 (9.2)
Presence of perineural invasion	
Yes	36 (7.3)
No	179 (36.5)
Not available	276 (56.2)

PDAC=Poorly differentiated adenocarcinoma, MDAC=Moderately differentiated adenocarcinoma, WDAC=Well differentiated adenocarcinoma, NOS=Not otherwise specified

Adjuvant chemotherapy in Stage II cancers and in Stage III cancers

Details of chemotherapy administration in Stage II and Stage III are mentioned in Supplementary Tables 1 and 2. Safety analysis and delivery of monotherapy and doublet adjuvant chemotherapy are described in Table 2. Patients with Stage I cancer were observed postresection.

Two hundred and ninety-eight patients received doublet chemotherapy (modified CAPOX – 266 patients; modified FOLFOX-7 – 32 patients), whereas 86 patients received monotherapy (single-agent capecitabine – 80 patients; single-agent 5-fluorouracil – 6 patients).

Survival and prognostic factors

With a median follow-up of 22 months, the median OS was not reached with an estimated 3-year OS of 93.6% for the entire cohort. The estimated 3-year OS of Stage I, Stage II and Stage III cancers was, 100%, 96.1%, and 88.9%, respectively [Figure 1].

Of the prognostic factors evaluated for OS, final stage, the degree of differentiation and younger age approached or attained statistical significance on univariate analysis. On multivariate analysis, Stage (P = 0.02) and younger age (P = 0.028) maintained statistical significance. Factors related to administration of adjuvant chemotherapy and predicting for inferior estimated 3-year OS included the presence of underlying cardiovascular abnormalities (P = 0.023), need for dose reductions (P = 0.038), and noncompletion of planned chemotherapy (<0.001) [Table 3].

A total of 49 events had occurred at median follow-up. The estimated 3 year EFS for Stage I, Stage II, and Stage III was 89.9%, 88.5%, and 75.7%, respectively [Figure 2]. Three years estimated EFS for the entire cohort was 86%.

Of the prognostic factors evaluated for EFS, final stage, signet-ring morphology, and mucinous histology attained statistical significance on univariate analysis. On multivariate analysis, only final stage retained statistical significance for EFS (P = 0.022).

Discussion

The importance of complete mesocolic excision aiming at the separation of the mesocolic from the parietal plane

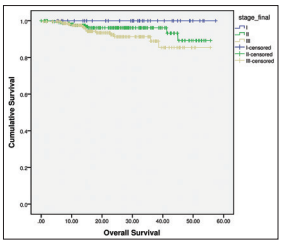

Figure 1: Stage-wise overall survival

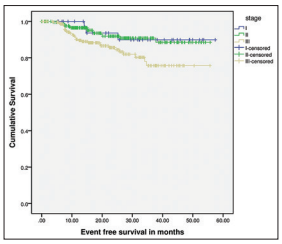

Figure 2: Stage-wise event-free survival stage wise

Table 2: Safety analysis and delivery of monotherapy and doublet adjuvant chemotherapy

Adverse event	Single agent 5 fluorouracil/ capecitabine (86)	Doublet FOLFOX-7/ CAPOX (298)
Adverse events		
Febrile neutropenia	00	4 (1.3)
Nonneutropenic infections	1 (1.2)	8 (2.7)
Neutropenia	00	4 (1.3)
Thrombocytopenia	00	8 (2.7)
HFS (Grade 2 and grade 3)	22 (25.6)	60 (20.2)
Vomiting	3 (3.5)	10 (3.3)
mucositis	00	4 (1.3)
Diarrhea	8 (9.3)	19 (6.4)
Peripheral sensory neuropathy (Grade 2 and Grade 3)	4 (4.7)	46 (15.4)
Death	00	1 (0.3)
Median number of cycles	8 (1-12)	8 (1-12)
Dose reduction required	8 (9.3)	48 (16.1)
Completed planned adjuvant	73 (85)	242 (81.2)
Total number of doses of chemotherapy planned	712 (100)	2508 (100)
Total number of doses of chemotherapy received	636 (89.3)	2225 (88.7)

FOLFOX=5 Fluorouracil/Leucovorin/Oxaliplatin, CAPOX=Capecitabine-oxaliplatin, HFS=Hand-foot-syndrome

Table 3: Univariate and multivariate analysis of significant prognostic and predictive factors for overall survival

Characteristic	3 years OS	P (univariate analysis)	P (multivariate analysis)	HR (95% CI)
Prognostic factors				
Stage (%)				
I	100	0.050	0.020	2.43 (1.147-5.141)
II	96.1			
III	88.9			
Age (years) (%)				
<50	91.2	0.030	0.028	0.331 (0.123-0.89)
≥50	96.8			
Predictive factors				
Presence of cardiovascular comorbidities (%)				
Yes	88.1	0.016	0.023	2.555 (1.140-5.725)
No	95.6			
Completion of chemotherapy (%)				
Yes	93.3	0.006	<0.001	3.067 (1.675-5.617)
No	82.7			
Dose reduction (%)				
Yes	75.3	0.013	0.038	0.629 (0.406-0.975)
No	95.7			

HR=Hazard ratio, CI=Confidence interval, OS=Overall survival

and true central ligation of the supplying vessels right at their roots has now been routinely adopted across centers and is used as standard in our institution.[9,23] The use of adjuvant chemotherapy, initially with 5-fluorouracil-based bolus regimens, and later with better tolerated infusional 5-fluorouracil – oxaliplatin doublets, has additionally improved outcomes in Stage II and Stage III colon cancers.[10-13,24,25] Such has been the improvement in outcomes that there is a trend toward a reductionist approach regarding duration and regimen of adjuvant therapy. The IDEA project, comprising more than 12,000 patients from six pooled trials has offered patients and treating physicians the options of 3 months of therapy in Stage III cancers.[19]

Data from India regarding incidence, prevalence, and outcomes of CRC is scarce.[2,20] In the current study baseline characteristics which appear different in as compared to published literature include a younger median age of presentation (sixth decade as opposed to seventh in western studies), a relatively smaller proportion of elderly patients (16.2%), and a higher percentage of signet-ring histology (8.1%).[13,26,27]

About 26.4% of patients with Stage II cancers did not receive adjuvant chemotherapy. Of the remaining 73.6% of patients, a majority received a doublet regimen. These patterns are reflective of the unsolved questions of whether MSI status trumps traditional poor prognostic factors, the lack of benefit of 5 FU/capecitabine in MSI-H tumors and the potential for oxaliplatin to overcome lack of benefit of 5-FU in MSI-H tumors.[28-31] Stage II tumors are a heterogeneous cohort, with treatment decisions being individualized. A patient with a T4 disease (25.9% in this subset of Stage II cancers) and poorly differentiated histology, but Stage II is likely to behave closer to a Stage III cohort (with potential benefit from a doublet adjuvant regimen) in terms of outcomes as opposed to a patient with T3 disease, MSI – H status and lack of poor prognostic factors (likely candidate for observation).

Patients with Stage III disease were mostly treated with either CAPOX or mFOLFOX-6 regimens (92.1%), as is currently recommended by guidelines.[29] Despite being a real-world nontrial cohort, completion rates with adjuvant doublet regimens in this study in Stage III cancers were an impressive 83.7%, as opposed to lower rates seen in international seminal studies (André *et al*., FOLFOX – 74.7%; Haller *et al*., CAPOX – 69%).[12,32] 89.8% of doses of all planned chemotherapy was delivered. This is a pointer toward careful patient selection required for administration of adjuvant chemotherapy as well as the use of a lower dose of capecitabine (2000 mg/m^2/day as opposed to 2500 mg/m^2/day).

Compliance and completion rates with adjuvant chemotherapy in this study were high and this is heartening to note. Eighty-five percent and 81.2% of patients receiving monotherapy and doublet chemotherapy, respectively, were able to complete their planned 6 months of adjuvant treatment. Toxicities seen with monotherapy were mainly hand-foot-syndrome (HFS: Grade 2 and Grade 3%–25.6%) and diarrhea (9.5%), while with oxaliplatin-based doublet, sensory peripheral neuropathy was the most common dose-limiting toxicity (Grade 2 and Grade 3%–14.5%), though incidence of HFS was also high (20.2%). The incidence of neuropathy is similar to published literature, but also is a cautionary note with regard to the need for constant surveillance while on oxaliplatin. The short follow-up duration of this study means we are unable to comment on the incidence of long-term residual neuropathy, which may be irreversible and range anywhere between 10% and 79%.[11,13,33] The incidence of myelosuppression-related side-effects was low in this study. While the incidence of myelosuppression across studies has been low with FOLFOX/CAPOX across regimens in published literature, an additional reason for this low incidence in this study is the use of modified FOLFOX-7 regimen (no bolus 5-FU) as adjuvant chemotherapy in our institution.

Due to the lower age incidence of CRC in India, there is a surfeit of data regarding the survival and use of adjuvant chemotherapy in elderly patients (>65 years).[34-36] 16.5% of patients in this study were elderly, and they had a stage-wise distribution that mirrored the entire cohort. We also noted a lower incidence of signet and mucinous CRC in the elderly population as compared to the entire cohort and this difference was statistically significant for both characteristics (not shown). Completion rates of adjuvant chemotherapy were 76.3% for the elderly population, and this was nearly 10% less than completion rates for the entire cohort. This highlights the need for careful patient selection as well as the potentially similar benefit elderly patients derive from fully-dosed adjuvant chemotherapy as compared to a younger population.

There have been increasing data evaluating the correlation of outcomes with completion rates of adjuvant chemotherapy, lower completion rates of chemotherapy in an elderly population as well as the presence of comorbidities like diabetes mellitus being associated with poorer survival in CRC.[36-39] The high burden of cardiovascular comorbidities in the Indian population is reflected in our study and enabled us to evaluate whether such comorbidities affect outcomes (diabetes mellitus – 17.1%, hypertension – 18.9%).[40] Despite the short follow in this study, patients who had comorbidities required dose reduction and were unable to complete planned chemotherapy clearly had an inferior survival. The recently published ACCORE study also had identified a cohort of elderly patients receiving <50% of planned cycles of chemotherapy as having an inferior survival.[36] The conundrum of whether patients with comorbidities receive lesser dose intensity to avoid toxicities as opposed to uncontrolled comorbidities affecting the delivery of maintained intensity of chemotherapy is a common problem to tackle for treating physicians.

The short follow-up and lack of events in this study preclude a detailed analysis of outcomes and prognostic factors. Early outcomes in all stages of colon cancer in this cohort appear satisfactory with very low recurrence rates. A longer follow-up will enable a more accurate picture of actual survival and outcomes. Besides stage, the only factor associated with inferior OS was a younger age group (<50 years). Such a correlation between age and inferior outcomes in CRC has been seen in previous Indian and Chinese studies, though at various age cut-offs.[2,41,42] While overall initial outcomes for all cohorts in this study appear high, the inferior survival in a younger age group merits further evaluation.[43]

The current study is the first of its kind from India and gives a snapshot of the practice of adjuvant chemotherapy and compliance with the same in a purely nonmetastatic colon cancer cohort. We have also identified certain practice-related factors like the need for dose reduction and the presence of comorbidities influencing outcomes adversely. However, multiple caveats exist, considering this is a retrospective study. MSI status is not reported in all stages and we have concentrated only on Grade 3 and Grade 4 side effects in reporting toxicities. We have also not reported as to why patients were treated with 5-fluorouracil versus capecitabine-based regimens despite treatment in a single center. Most importantly, the short median follow-up of 22 months precludes any firm judgment on the survival outcomes of Indian patients as compared to those from other countries where colon cancers are more common.

Conclusions

The current study identifies a lower age of presentation of non– metastatic colon cancers in India, with high compliance and completion rates of planned adjuvant chemotherapy. Early survival outcomes appear comparable to published literature, but longer follow-up is required. Stage and younger ages (<50 years) were prognostic, while the presence of cardiovascular comorbidities, and inability to administer planned chemotherapy due to dose reduction and premature cessation, appear to affect survival adversely.

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Conflicts of interest

There are no conflicts of interest.

References

1. Mohandas KM. Colorectal cancer in India: Controversies, enigmas and primary prevention. Indian J Gastroenterol 2011;30:3-6.
2. Gupta S, Bhattacharya D, Acharya AN, Majumdar S, Ranjan P, Das S. Colorectal carcinoma in young adults: A retrospective study on Indian patients: 2000-2008. Colorectal Dis J Assoc Coloproctol G B Irel 2010;12:e182-9.
3. Kokki I, Papana A, Campbell H, Theodoratou E. Estimating the incidence of colorectal cancer in South East Asia. Croat Med J 2013;54:532-40.
4. Mallath MK, Taylor DG, Badwe RA, Rath GK, Shanta V, Pramesh CS, *et al.* The growing burden of cancer in India: Epidemiology and social context. Lancet Oncol 2014;15:e205-12.
5. NCRP Anual Reports. Available from: http://www.ncrpindia.org/Annual_Reports.aspx. [Last accessed 2017 October 30].
6. Sinha R, Anderson DE, McDonald SS, Greenwald P. Cancer risk and diet in India. J Postgrad Med 2003;49:222-8.
7. Påhlman LA, Hohenberger WM, Matzel K, Sugihara K, Quirke P, Glimelius B. Should the benefit of adjuvant chemotherapy in colon cancer be re-evaluated? J Clin Oncol 2016;34:1297-9.
8. Govaert JA, van Dijk WA, Fiocco M, Scheffer AC, Gietelink L, Wouters MW, *et al.* Nationwide outcomes measurement in colorectal cancer surgery: Improving quality and reducing costs. J Am Coll Surg 2016;222:19-29.e2.
9. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: Complete mesocolic excision and central ligation – Technical notes and outcome. Colorectal Dis 2009;11:354-64.
10. Böckelman C, Engelmann BE, Kaprio T, Hansen TF, Glimelius B. Risk of recurrence in patients with colon cancer stage II and III: A systematic review and meta-analysis of recent literature. Acta Oncol 2015;54:5-16.
11. Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, *et al.* Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: Results from NSABP C-07. J Clin Oncol 2007;25:2198-204.
12. André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, *et al.* Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109-16.
13. André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, *et al.* Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: Updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. J Clin Oncol 2015;33:4176-87.
14. Dotan E, Cohen SJ. Challenges in the management of stage II colon cancer. Semin Oncol 2011;38:511-20.
15. Saridaki Z, Souglakos J, Georgoulias V. Prognostic and predictive significance of MSI in stages II/III colon cancer. World J Gastroenterol 2014;20:6809-14.
16. Mols F, Beijers T, Lemmens V, van den Hurk CJ, Vreugdenhil G, van de Poll-Franse LV, *et al.* Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: Results from the population-based PROFILES registry. J Clin Oncol 2013;31:2699-707.
17. Ishikawa T, Ishiguro M, Nakatani E, Uetake H, Ueno H, Murotani K, *et al*. Prognostic impact of MSI in stage II colon cancers: An additional translational study of the SACURA trial. J Clin Oncol 2017;35 Suppl 15:e15155.
18. André T, Iveson T, Labianca R, Meyerhardt JA, Souglakos I, Yoshino T, *et al.* The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) collaboration: Prospective combined analysis of phase III trials investigating duration of adjuvant therapy with the FOLFOX (FOLFOX4 or modified FOLFOX6) or XELOX (3 versus 6 months) regimen for patients with stage III colon cancer: Trial design and current status. Curr Colorectal Cancer Rep 2013;9:261-9.
19. ASCO 2017: The IDEA Collaboration: Global Study Sets New Risk-Based Standard to Personalize Chemotherapy for Colon Cancer After Surgery – The ASCO Post. Available from: http://www.ascopost.com/News/55708. [Last accessed on 2017 Oct 04].
20. Pokharkar AB, Bhandare M, Patil P, Mehta S, Engineer R, Saklani AP, *et al.* Young vs. old colorectal cancer in Indian subcontinent: A tertiary care center experience. Indian J Surg Oncol 2017;8:491-8.
21. Tamhankar AS, Ingle P, Saklani A. PWE-284 Signet ring colorectal carcinoma (SRCC): Do we need to improve the treatment algorithm? Gut 2015; 64 Suppl 1:A336-7.
22. Patil PS, Saklani A, Gambhire P, Mehta S, Engineer R, De'Souza A, *et al.* Colorectal cancer in India: An audit from a tertiary center in a low prevalence area. Indian J Surg Oncol 2017;8:484-90.
23. Dimitriou N, Griniatsos J. Complete mesocolic excision: Techniques and outcomes. World J Gastrointest Oncol 2015;7:383-8.
24. O'Connell MJ, Mailliard JA, Kahn MJ, Macdonald JS, Haller DG, Mayer RJ, *et al.* Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. J Clin Oncol 1997;15:246-50.
25. Andre T, Colin P, Louvet C, Gamelin E, Bouche O, Achille E, *et al.* Semimonthly versus monthly regimen of fluorouracil and leucovorin administered for 24 or 36 weeks as adjuvant therapy in stage II and III colon cancer: Results of a randomized trial. J Clin Oncol 2003;21:2896-903.
26. Tan Y, Fu J, Li X, Yang J, Jiang M, Ding K, *et al.* A minor (<50%) signet-ring cell component associated with poor prognosis in colorectal cancer patients: A 26-year retrospective study in China. PLoS One 2015;10:e0121944.
27. Hyngstrom JR, Hu CY, Xing Y, You YN, Feig BW, Skibber JM, *et al.* Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: Analysis from the national cancer data base. Ann Surg Oncol 2012;19:2814-21.
28. Varghese A. Chemotherapy for stage II colon cancer. Clin Colon Rectal Surg 2015;28:256-61.
29. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Cervantes A, *et al.* Early colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi64-72.
30. Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, *et al.* Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med 2003;349:247-57.
31. Kim ST, Lee J, Park SH, Park JO, Lim HY, Kang WK, *et al.* Clinical impact of microsatellite instability in colon cancer following adjuvant FOLFOX therapy. Cancer Chemother Pharmacol 2010;66:659-67.
32. Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, *et al.* Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol 2011;29:1465-71.

33. Park SB, Lin CS, Krishnan AV, Goldstein D, Friedlander ML, Kiernan MC, *et al.* Long-term neuropathy after oxaliplatin treatment: Challenging the dictum of reversibility. Oncologist 2011;16:708-16.
34. McCleary NJ, Meyerhardt JA, Green E, Yothers G, de Gramont A, Van Cutsem E, *et al.* Impact of age on the efficacy of newer adjuvant therapies in patients with stage II/III colon cancer: Findings from the ACCENT database. J Clin Oncol 2013;31:2600-6.
35. Swaminathan V, Audisio R. Cancer in older patients: An analysis of elderly oncology. Ecancermedicalscience 2012;6:243.
36. Lund CM, Nielsen D, Dehlendorff C, Christiansen AB, Rønholt F, Johansen JS, *et al.* Efficacy and toxicity of adjuvant chemotherapy in elderly patients with colorectal cancer: The ACCORE study. ESMO Open 2016;1:e000087.
37. Kleeff J, Costello E, Jackson R, Halloran C, Greenhalf W, Ghaneh P, *et al.* The impact of diabetes mellitus on survival following resection and adjuvant chemotherapy for pancreatic cancer. Br J Cancer 2016;115:887-94.
38. Lin HS, Turner DJ, Srivastava A, Jameson MB. The benefit and tolerability of adjuvant chemotherapy in elderly stage III colon cancer patients: A 3 year retrospective audit. Gerontol Geriatr Res 2016;5:318. doi: 10.4172/2167-7182.1000318. Available from: https://www.omicsonline.org/open-access/the-benefit-and-tolerability-of-adjuvant-chemotherapy-in-elderly-stage-iii-colon-cancer-patients-a-3-year-retrospective-audit-2167-7182-1000318.php?aid=77055. [Last accessed on 2017 Oct 04].
39. Gajra A, Klepin HD, Feng T, Tew WP, Mohile SG, Owusu C, *et al.* Predictors of chemotherapy dose reduction at first cycle in patients age 65 years and older with solid tumors. J Geriatr Oncol 2015;6:133-40.
40. Gupta S, Gudapati R, Gaurav K, Bhise M. Emerging risk factors for cardiovascular diseases: Indian context. Indian J Endocrinol Metab 2013;17:806-14.
41. Fu J, Yang J, Tan Y, Jiang M, Wen F, Huang Y, *et al.* Young patients (≤35 years old) with colorectal cancer have worse outcomes due to more advanced disease: A 30-year retrospective review. Medicine (Baltimore) 2014;93:e135.
42. Yeole BB, Sunny L, Swaminathan R, Sankaranarayanan R, Parkin DM. Population-based survival from colorectal cancer in Mumbai, (Bombay) India. Eur J Cancer 2001;37:1402-8.
43. Population Pyramids of the World from 1950 to 2100. Available from: https://www.populationpyramid.net/India/2017/. [Last accessed on 2017 Oct 31].

Supplementary Table 1: Administration of adjuvant chemotherapy in stage II cancers (*n*=220)

Characteristic	*n* (%)
Adjuvant chemotherapy planned	
Yes	162 (3.6)
No	58 (26.4)
Reasons for lack of adjuvant chemotherapy (*n*=58)	
Age (years) >70	4 (6.9)
MSI –H status with no clinicopathological poor prognostic factors	42 (72.4)
Absence of clinicopathological poor prognostic factors with MSI – S status	4 (6.9)
Multiple uncontrolled comorbidities	1 (1.7)
Patient choice	4 (6.9)
>1 of factors 1–5	3 (5.2)
Regimens administered (*n*=162)	
Monotherapy	68 (42.0)
Capecitabine	65 (40.1)
5 fluorouracil	3 (1.9)
Doublet chemotherapy	94 (58.0)
Capecitabine-oxaliplatin	82 (50.6)
5 fluorouracil – oxaliplatin (FOLFOX-7)	12 (7.4)
Completion of adjuvant chemotherapy (*n*=162)	
Yes	138 (5.2)
No	24 (14.8)
Dose reduction during chemotherapy	
Yes	27 (16.7)
No	135 (83.3)
Median no cycles of chemotherapy received	8 (1-12)
Total number of doses of chemotherapy planned	1356 (100)
Total number of doses of chemotherapy received	1177 (86.8)
Reasons for premature cessation of planned adjuvant chemotherapy (*n*=24)	
Grade 3 and Grade 4 toxicities	18 (75)
Death during adjuvant chemotherapy	1 (4.2)
Recurrence	1 (4.2)
Lost to follow-up	4 (16.6)

MSI=Microsatellite instability

Supplementary Table 2: Administration of adjuvant chemotherapy in stage III cancers (*n*=223)

Characteristic	*n* (%)
Adjuvant chemotherapy administered (*n*=218)	
Yes	215 (96.8)
No	8 (3.2)
Regimen planned (*n*=215)	
Monotherapy	17 (7.9)
Capecitabine	14 (6.5)
5 fluorouracil	3 (1.4)
Doublet chemotherapy	198 (92.1)
Capecitabine-oxaliplatin	179 (83.3)
5 fluorouracil – oxaliplatin (FOLFOX-7)	19 (8.8)
Completion of planned chemotherapy (*n*=215)	
Yes	180 (83.7)
No	35 (16.3)
Dose reduction during chemotherapy (*n*=215)	
Yes	29 (13.5)
No	186 (86.5)
Median number	8 (1-12)
Total number of doses of chemotherapy planned	1808 (100)
Total number of doses of chemotherapy received	1624 (89.8)
Reasons for premature cessation of planned adjuvant chemotherapy (*n*=35)	
Grade 3 and Grade 4 toxicities	25 (71.4)
Recurrence on adjuvant chemotherapy	4 (11.4)
Patient death due to chemotherapy related complications	1 (2.9)
Lost to follow-up	5 (14.3)

FOLFOX=5 Fluorouracil/Leucovorin/Oxaliplatin