Chemotherapy use in stage III colon cancer: a National Cancer Database analysis

Smrity Upadhyay, Sumit Dahal, Vijaya Raj Bhatt, Nabin Khanal and Peter T. Silberstein

Ther Adv Med Oncol
2015, Vol. 7(5) 244–251
DOI: 10.1177/1758834015587867

Abstract

Background: Although adjuvant chemotherapy in stage III colon cancer improves overall survival, prior studies have shown that it is underused. We analyzed different factors that may influence its use.

Methods: This is a retrospective study of stage III colon cancer patients ($n = 207,718$) diagnosed between 2000 and 2011 in the National Cancer Data Base (NCDB). The NCDB contains ~70% of new cancer diagnosis from >1500 American College of Surgeons accredited cancer programs in the United States and Puerto Rico. The chi-squared test was used to determine any difference in characteristics of patients who did or did not receive chemotherapy.

Results: A total of 35% of all stage III colon cancer patients, and 38% of stage III cases undergoing surgery, did not receive adjuvant chemotherapy. The use of chemotherapy had increased in recent years (64% in 2007–2011 *versus* 59% in 2000–2002; $p < 0.0001$). Its use was lower in whites (61%), females (60%), patients ⩾60 years (55%), patients with one or more comorbidities (55%), nonacademic centers (62%), those with medicare insurance (52%), lower education (61%) and income levels (59%, all $p < 0.0001$). The nonwhite and uninsured were more likely to be <60 years old.

Conclusion: More than one-third did not receive adjuvant chemotherapy, although its use has increased in more recent years. Age was one of the most important determinants of chemotherapy use, which may explain higher rates in nonwhite and uninsured. In addition to patient characteristics, race, gender and socioeconomic factors influence chemotherapy use. These findings have important implications for healthcare reform.

Keywords: chemotherapy, disparities, stage III colon cancer

Correspondence to:
Smrity Upadhyay, MBBS
Department of Internal Medicine, Creighton University, 601 North 30th Street Suite 5850, Omaha, NE 68131, USA
smrityupadhyay@creighton.edu

Sumit Dahal, MBBS
Department of Medicine, Interfaith Medical Center, Brooklyn, NY, USA

Vijaya Raj Bhatt, MBBS
Department of Internal Medicine, Division of Hematology-Oncology, University of Nebraska Medical Center, Omaha, NE, USA

Nabin Khanal, MBBS
Peter T. Silberstein, MD
Department of Internal Medicine, Creighton University Medical Center, Omaha, NE, USA

Introduction

With an estimated 1.2 million new cases and 600,000 deaths per year, colorectal cancer is an important cause of morbidity and mortality worldwide [Jemal *et al.* 2011]. In the United States, 136,830 new cases of colorectal cancer and 50,310 deaths are estimated to have occurred in 2014 [Siegel *et al.* 2014b]. Although the incidence as well as the mortality of colon cancer has been declining in the United States over the past two decades, with a study reporting an average decrease of 3.4% and 3% per year, respectively, during 2001 to 2010 [Siegel *et al.* 2014a], it remains the third most common malignancy and third leading cause of cancer deaths [Siegel *et al.* 2014a].

Nearly a quarter of all colon cancer cases are stage III at diagnosis [Jullumstro *et al.* 2009; Edge *et al.* 2010]. Surgery is the primary curative modality in 70–80% of colon cancer patients who present with a nonmetastatic disease [Peeters and Haller, 1999; Siegel *et al.* 2014a]. However, recurrence is common and is seen in nearly 30% of stage III cases after 5 years [Tsikitis *et al.* 2014]. Adjuvant chemotherapy can eradicate micrometastases, prevent recurrence and improve overall survival. Several large-scale clinical trials have shown clear survival benefit with adjuvant chemotherapy in stage III colon cancer [Laurie *et al.* 1989; Moertel *et al.* 1990, 1995; Andre *et al.* 2004; Twelves *et al.* 2005; Kuebler *et al.* 2007].

Based on the encouraging results from the early trials, the National Institutes of Health (NIH) Consensus Conference in 1990 recommended that patients with stage III colon cancer receive adjuvant chemotherapy [NIH Consensus Conference, 1990]. While 5-fluorouracil (5-FU) based chemotherapy, including combination with leucovorin (LV) and oxaliplatin (FOLFOX) has been the cornerstone of treatment in adjuvant setting, newer drugs such as capecitabine and tegafur with uracil have shown promising results in different clinical trials and offer excellent alternatives for adjuvant chemotherapy [Buyse *et al.* 1988; Moertel *et al.* 1990; Wolmark *et al.* 1993, Marsoni, 1995; Andre *et al.* 2003, 2004; Chau *et al.* 2005; Haller *et al.* 2005; Poplin *et al.* 2005; Twelves *et al.* 2005; Lembersky *et al.* 2006].

Two large trials showed excellent benefits with combining oxaliplatin with 5-FU and LV, the FOLFOX and FLOX regimens, with significant improvement in disease-free and overall survival [Andre *et al.* 2004; Kuebler *et al.* 2007]. The maximum benefit is seen when chemotherapy is started within 8 weeks of surgery [Glimelius *et al.* 2005]. In the background of these results, FOLFOX for 6 months in adjuvant setting within 8 weeks of surgical resection and anastomosis has been adopted as the standard of care in stage III colon cancer patients [Engstrom *et al.* 2009]. Infusional 5-FU/LV or capecitabine alone may be considered in patients who are not fit to tolerate FOLFOX.

The National Comprehensive Cancer Network (NCCN) recommends colectomy with en bloc removal of regional lymph nodes followed by adjuvant chemotherapy for 6 months in stage III colon cancer [Engstrom *et al.* 2009]. While the panel recommends combination of oxaliplatin with infusional 5-FU and leucovorin (FOLFOX) as the standard of care, other options recommended in patients unfit for oxaliplatin therapy include either single agent capecitabine or a combination of 5-FU and LV.

Despite these compelling evidences of benefit and clear recommendations for the use of adjuvant chemotherapy in stage III colon cancer, it is still underused. Literature estimates its use in 62–74% of stage III colon cancer [Jessup *et al.* 2005; Phelip *et al.* 2010; Boland *et al.* 2013]. A study reported an increase in adjuvant chemotherapy use from 39% in 1991 to 64% in 2002 [Jessup *et al.* 2005]. Even more than two decades after being first endorsed by the NIH Consensus Conference, the practice has still not been completely embraced.

Our study is the largest and the most recent study to determine the use of chemotherapy in stage III colon cancer. We also analyzed different treatment related, demographic and socioeconomic factors that may influence its use.

Methods

This is a retrospective study of the NCDB of colon cancer patients diagnosed between 2000 and 2011. The NCDB contains nearly 70% of all new cancer diagnoses from more than 1500 American College of Surgeons accredited cancer programs in the United States and Puerto Rico. Certified tumor registrars at the Commission on Cancer accredited cancer program registries utilize nationally standardized data items and coding definitions to collect oncology data from patient charts and submit data using a specified transmission format. Data integrity and quality monitoring are closely verified [Bilimoria *et al.* 2008; Tsai *et al.* 2010].

We extracted data from the NCDB on 29 January 2014. As our study focused on the use of chemotherapy in stage III colon cancer; all calculations were done on stage III colon cancer cases only. Furthermore, the pattern of chemotherapy use according to different treatment-related, demographic and socioeconomic parameters was calculated as a percentage of the total stage III cases receiving surgery. Cases receiving no first course treatment as well as those receiving only nonsurgical treatment (n = 11,306) were excluded from these pattern calculations.

The treatment facilities in the NCDB are categorized into four categories, depending on the service provided and case volume: community cancer centers (100–649 cancer cases annually, may need referral for a portion of therapy); comprehensive community cancer centers (⩾650 cases annually, may need referral for a portion of therapy); academic comprehensive centers (associated with university medical schools or designated as National Cancer Institute Comprehensive Cancer Care Programs); and others [Conway *et al.* 2009]. The NCDB estimates the educational attainment for the patient's area of residence by matching the zip code of the patient recorded at the time of diagnosis against files derived from US Census 2000 data.

The Institutional Review Board waiver was obtained from the University of Nebraska Medical Center Institutional Review Board.

Statistical analysis

Descriptive statistics were used to calculate the frequency of distribution of cases receiving chemotherapy according treatment-related, demographic and socioeconomic characteristics. The chi-squared test was used to determine any difference in characteristics of patients who did or did not receive chemotherapy.

Results

A total of 912,743 cases of colon cancer were reported to the NCDB by 1661 different hospitals, including 260 academic hospital programs, between 2000 and 2011. Nearly a quarter of these cases (n = 207,718) were in stage III; 95% of these stage III cases (n = 196,412) underwent surgery. However, almost 35% (n = 74,336) of all stage III colon cancer cases, and 38% of stage III colon cancer patients who underwent surgery, did not receive any chemotherapy. Among patients who underwent surgery, the use of chemotherapy had, however, increased in recent years with its use estimated at 59%, 62% and 64% for the time periods between 2000–2002, 2003–2006 and 2007–2011, respectively ($p < 0.0001$).

Patients' demographic characteristics (age, sex, race and comorbidity) were important determinants for chemotherapy use. While its use was 82% in patients below 60 years of age, only 55% of those aged 60 years or above received it ($p < 0.0001$). A total of 65% of males and 60% of females with stage III colon cancer undergoing surgery received chemotherapy ($p < 0.0001$). Its use was 61% in whites, 65% in African Americans and 66% in Hispanics ($p < 0.0001$). Similarly, 67% of those without any significant comorbidity, compared to 55% of those with one or more comorbidity, received chemotherapy ($p < 0.0001$).

The use of adjuvant chemotherapy was also dependent on different socioeconomic factors. Its use stood at 64% for academic healthcare centers and 62% for nonacademic centers ($p < 0.0001$). More patients with private insurance (77%) received chemotherapy than those without insurance (73%) or those with Medicaid (70%) or medicare (52%) ($p < 0.0001$). Similarly, 63% of patients coming from neighborhoods where more than 88% of the population had a high school degree received chemotherapy; in comparison, the usage in neighborhoods that had either 70–88% or less than 70% of their population with a high school degree stood at 62% and 61%, respectively ($p < 0.0001$). Based on annual household income, 63% of those with $49,000 or more, 62% of those with between $28,000 and $48,999, and 59% of those with below $28,000 received chemotherapy ($p < 0.0001$). Of those patients who had to travel 100 miles or more to reach the treatment facility, 59% received chemotherapy compared with 62% of those who had to travel less than 100 miles ($p < 0.0001$) (Table 1).

Discussion

Our analysis of the large NCDB demonstrated that more than one-third of stage III colon cancer cases, diagnosed between 2000 and 2011, did not receive adjuvant chemotherapy. The use of chemotherapy, however, had increased in recent years. These findings are consistent with prior studies, which estimated its use to range from 62% to 74% of the cases, with newer studies showing greater use [Jessup *et al.* 2005; Phelip *et al.* 2010; Boland *et al.* 2013]. The use of adjuvant chemotherapy improves cure rates in stage III colon cancer (Table 2) and is recommended as a standard practice by the NIH and NCCN [IMPACT investigators, 1990; Engstrom *et al.* 2009].

Age at diagnosis was one of the biggest determinants of chemotherapy use, with just 55% of patients $\geq$ 60 years receiving chemotherapy compared with 82% of patients <60 years. This is consistent with prior reports [Schrag *et al.* 2001; Sundararajan *et al.* 2001; Potosky *et al.* 2002; Vaneenwyk *et al.* 2002; Jessup *et al.* 2005; Phelip *et al.* 2010]. A prior NCDB study (1990–2002) demonstrated similar findings with chemotherapy use in 62% of patients $\geq$60 years compared with 82% of patients <60 years [Jessup *et al.* 2005]. Similarly, in another study, 55% of patients aged more than 65 years received adjuvant chemotherapy, with the rate declining steeply with further increase in age [Schrag *et al.* 2001].

Several factors may contribute to this low usage in the elderly patients. With increasing age, the burden of comorbidities becomes higher, which may complicate or even preclude the use of adjuvant chemotherapy. In our study, only half of the patients with significant comorbidities (*versus* 67% in patients without any comorbidity)

Table 1. Chemotherapy use in stage III colon cancer patients.

	Cases receiving chemotherapy	Cases not receiving chemotherapy	% of cases receiving chemotherapy	*p* value
Age				<0.0001
<60 years	41,954	9103	82	
⩾60 years	80,122	65,233	55	
Gender				<0.0001
Male	61,040	33,513	65	
Female	61,036	40,823	60	
Race/ethnicity				<0.0001
White	95,741	60,128	61	
Black	15,273	8384	65	
Hispanic	5972	3141	66	
Treatment facilities				<0.0001
Academic hospitals	29,775	16,896	64	
Other hospitals	92,301	57,440	62	
Year of treatment				<0.0001
2000–2002	28,282	19,979	59	
2003–2006	40,036	24,473	62	
2007–2011	53,758	29,884	64	
Insurance status				<0.0001
Private	50,733	14,731	77	
Not Insured	,214	1551	73	
Medicaid	4935	2102	70	
Medicare	56,796	52,983	52	
Education (% with high school degree)				<0.0001
⩽69%	15,934	10,333	61	
70–88%	69,112	42,201	62	
>88%	29,899	17,737	63	
Household income				<0.0001
<$28,000	11,467	7,815	59	
$28,000–48,999	65,082	39,943	62	
⩾$49,000	38,405	22,515	63	
Charlson Comorbidity score				<0.0001
None	69,289	34,487	67	
⩾1	24,505	19,870	55	
Distance traveled to treatment facility				<0.0001
<100 miles	111,198	67,639	62	
⩾100 miles	3985	2750	59	

received chemotherapy. In addition, nonmedical barriers such as poor financial status and family support may also contribute to limited access of older patients to chemotherapy. Although chemotherapy use was lower in patients with Medicare insurance, this likely reflects the older age group of these patients rather than their financial status. Many studies show survival benefit with adjuvant chemotherapy in the elderly population, without any significant increase in toxicity profile [Sargent *et al.* 2001; Hanna *et al.* 2012; Sanoff *et al.* 2012]. However, FOLFOX may not necessarily be the optimal adjuvant chemotherapy as a few studies suggest that adding oxaliplatin to 5FU/LV may not improve survival in patients above 70 years [Yothers *et al.* 2011; Sanoff *et al.* 2012; Tournigand *et al.* 2012; McCleary *et al.* 2013].

Table 2. Adjuvant chemotherapy in stage III colon cancer.

Year	Study	Study type	Intervention	Findings
1988	Buyse *et al.* [1988]	Meta-analysis	5-FU based regimen *versus* surgery alone	The odds of death was about 17% lower in 5-FU group 5 year OS improved by 3.4%
1989	NCCTG/ Laurie *et al.* [1989]	Randomized trial	5-FU/LEV *versus* surgery alone	Cancer recurrence reduced by 31% Mortality rate reduced by 13%
1990	INT-0035 Trial/ Moertel *et al.* [1990]	Randomized trial	5-FU/LEV *versus* surgery alone	Cancer recurrence reduced by 41% Mortality rate reduced by 33%
1993	NSABP C-03/ Wolmark *et al.* [1993]	Randomized trial	5-FU/LV *versus* 5-FU plus semustine or vincristine	5 year DFS and OS improved by 12% and 9% respectively in the 5-FU/LV group
1995	IMPACT [IMPACT investigators, 1995]	Retrospective analysis	5-FU/LV *versus* surgery alone	Cancer recurrence reduced by 35% Mortality rate reduced by 22% 3 year OS improved by 5%
2004	MOSAIC/ Andre *et al.* [2004]	Randomized trial	FOLFOX-4* *versus* infusional 5-FU/LV	3 year DFS and OS improved by 6.9% and 1.1% respectively Cancer recurrence reduced by 24%
2005	INT-0089 Trial/ Haller *et al.* [2005]	Randomized trial	Low dose LV plus 5-FU *versus* high dose LV plus 5-FU *versus* low dose LV plus 5-FU plus Lev *versus* control (5-FU plus LEV)	No statistically significant differences among the four groups, with 5 year DFS of 60% for each of the three treatment arms and 56% for the control arm. Similarly, 5 year OS was around 66% for each of the three treatment arms and 63% for the control arm. No additional benefit by adding Lev to 5-FU/LV regimen High and low dose LV are equally effective 6–8 months of therapy is as effective as 12 months
2005	X-ACT Trial/ Twelves *et al.* [2005]	Randomized trial	Oral capecitabine *versus* bolus 5-FU/LV	Capecitabine showed a trend towards superior DFS and OS than 5-FU/LV after a follow-up period of 3.8 years Capecitabine improved relapse free survival and was associated with fewer adverse events.
2006	NSABP C-06/ Lembersky *et al.* [2006]	Randomized trial	UFT (tegafur and uracil) plus LV *versus* bolus 5-FU/LV	Similar DFS and OS between the treatment groups
2007	NSABP C-07/ Kuebler *et al.* [2007]	Randomized trial	FLOX$ *versus* bolus 5-FU/LV	3 year DFS improved by 4.3% Cancer recurrence reduced by 20%
2007	CALGB 89803/ Saltz *et al.* [2007]	Randomized trial	Irinotecan plus 5-FU plus LV *versus* bolus 5-FU/LV	Addition of irinotecan did not improve DFS or OS, but increased both lethal and nonlethal toxicity
2010	XELOXA Trial/ Haller *et al.* [2010]	Randomized trial	XELOX‡ *versus* bolus 5-FU/LV	5 year DFS improved by 6.3%

*Oxaliplatin in combination with bi-weekly infusional 5-FU/FV
$Oxaliplatin in combination with weekly bolus 5-FU/FV
‡Capecitabine plus oxaliplatin
5-FU, 5-fluorouracil; DFS, disease free survival; IMPACT, International Multicenter Pooled Analysis of Colon Cancer Trials; LEV, levimasole; LV, leucovorin; MOSAIC, Multicenter International Study of OHP/5FU/LV in Adjuvant Treatment of Colon Cancer; NCCTG, North Central Cancer Treatment Group; NSABP C-03, National Surgical Adjuvant Breast and Bowel Project Protocol C-03; OS, overall survival.

Academic hospitals were more likely to administer chemotherapy than nonacademic hospitals. Though women were as likely as men to benefit from adjuvant chemotherapy, males were slightly more likely to receive chemotherapy than females, consistent with prior studies [Mahoney *et al.* 2000; Jessup *et al.* 2005]. Chemotherapy use was slightly higher among Hispanics and African-Americans than Caucasians. This finding differs from the results of many other studies [Baldwin *et al.* 2005; Jessup *et al.* 2005]. This may be explained, at least partly, by a higher prevalence of older patients among Caucasians; 77% of Caucasians were ⩾60 years, compared with 62% of African-Americans and 61% of Hispanics. Patients from areas with higher educational or income status and those who required a shorter commute to the hospital were slightly more likely to receive chemotherapy. Several studies corroborated our findings of significant influence of different socioeconomic factors in the utilization of adjuvant chemotherapy in stage III colon cancer [Roetzheim *et al.* 2000; Vaneenwyk *et al.* 2002; Boland *et al.* 2013].

The retrospective study design and lack of patient level data for multivariate analysis are the major limitations of our study. In addition, the NCDB contains only the total number of cases in which systemic chemotherapy was used, without specifying whether such chemotherapy was used in adjuvant or neo-adjuvant setting; however, neo-adjuvant chemotherapy is not the standard of care in stage III colon cancer. Even though some of the differences between different subgroups in receipt of chemotherapy are statistically significant, the actual clinical difference may be small. This may be seen with inclusion of a large sample size, as in this study. Large databases, as in this study, may have a risk of coding error; however, the data in NCDB undergo extensive quality monitoring and evaluation for integrity. Despite these limitations, our study utilizes a very large national cancer database and is able to evaluate the impact of several treatment-related, demographic and socioeconomic on the receipt of chemotherapy in stage III colon cancer.

Conclusion

Mitigation of risk factors along with better screening and treatment modalities, including adjuvant chemotherapy, have resulted in a decline of the incidence and mortality of colon cancers. Despite compelling evidences of the benefit and clear recommendations for the use of adjuvant chemotherapy in stage III colon cancer, it is still underused. Different demographic, socioeconomic and treatment related factors continue to influence its use. Careful discussion about the risks and benefits of chemotherapy in older patients, use of geriatric assessment tools to anticipate the risk of associated toxicities in older patients [Extermann and Hurria, 2007; Ramjaun *et al.* 2013], greater involvement of patients >70 years old in future trials, improving physician awareness regarding healthcare disparities, provision of improved supportive care to avoid toxicities as well as utilizing multidisciplinary care to improve overall health can help in addressing some of these disparities. At institutional level, development of multidisciplinary assessment and care models, an institutional protocol, and measures to improve physician awareness can be beneficial. Further studies focusing on these disparities are necessary to improve our understanding of these issues.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Peter T. Silberstein reports receiving payment for lectures from Bristol Myers and Celgene in the past. There are no conflicts of interest for any other authors.

Acknowledgement

This paper was presented as an abstract at the 50th Annual Meeting of the American Society of Clinical Oncology on 31 May 2014.

References

Andre, T., Boni, C., Mounedji-Boudiaf, L., Navarro, M., Tabernero, J., Hickish, T. *et al.* (2004) Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 350: 2343–2351.

Andre, T., Colin, P., Louvet, C., Gamelin, E., Bouche, O., Achille, E. *et al.* (2003) 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* 21: 2896–2903.

Baldwin, L., Dobie, S., Billingsley, K., Cai, Y., Wright, G., Dominitz, J. *et al.* (2005) Explaining

black-white differences in receipt of recommended colon cancer treatment. *J Natl Cancer Inst* 97: 1211–1220.

Bilimoria, K., Stewart, A., Winchester, D. and Ko, C. (2008) The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol* 15: 683–690.

Boland, G., Chang, G., Haynes, A., Chiang, Y., Chagpar, R., Xing, Y. *et al.* (2013) Association between Adherence to national comprehensive cancer network treatment guidelines and improved survival in patients with colon cancer. *Cancer* 119: 1593–1601.

Buyse, M., Zeleniuch-Jacquotte, A. and Chalmers, T. (1988) Adjuvant Therapy of colorectal cancer. Why we still don't know. *JAMA* 259: 3571–3578.

Chau, I., Norman, A., Cunningham, D., Tait, D., Ross, P., Iveson, T. *et al.* (2005) A Randomised comparison between 6 months of bolus fluorouracil/ leucovorin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer. *Ann Oncol* 16: 549–557.

Conway, W., Faries, M., Nicholl, M., Terando, A., Glass, E., Sim, M. *et al.* (2009) Age-related lymphatic dysfunction in melanoma patients. *Ann Surg Oncol* 16: 1548–1552.

Edge, S., Byrd, D., Compton, C., Fritz, A., Greene, F. and Trotti, A. (2010) Colon and rectum. In: Edge, S., Byrd, D., Compton, C. *et al.*, *AJCC Cancer Staging Manual*, 7th edn. New York: Springer-Verlag, pp. 143–164.

Engstrom, P., Arnoletti, J., Benson, A., 3rd, Chen, Y., Choti, M., Cooper, H. *et al.* (2009) NCCN clinical practice guidelines in oncology: colon cancer. *J Natl Compr Canc Netw* 7: 778–831.

Extermann, M. and Hurria, A. (2007) Comprehensive Geriatric assessment for older patients with cancer. *J Clin Oncol* 25: 1824–1831.

Glimelius, B., Dahl, O., Cedermark, B., Jakobsen, A., Bentzen, S., Starkhammar, H. *et al.* (2005) Adjuvant Chemotherapy in colorectal cancer: a joint analysis of randomised trials by the Nordic Gastrointestinal Tumour Adjuvant Therapy Group. *Acta Oncol* 44: 904–912.

Haller, D., Cassidy, J., Tabernero, J., Maroun, J., De Braud, F., Price, T. *et al.* (2010) Efficacy findings from a randomized phase III trial of capecitabine plus oxaliplatin versus bolus 5-FU/LV for stage III colon cancer (NO16968): impact of age on disease-free survival (DFS). *J Clin Oncol* 28: 3521.

Haller, D., Catalano, P., Macdonald, J., O'Rourke, M., Frontiera, M., Jackson, D. *et al.* (2005) Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. *J Clin Oncol* 23: 8671–8678.

Hanna, N., Onukwugha, E., Choti, M., Davidoff, A., Zuckerman, I., Hsu, V. *et al.* (2012) Comparative Analysis of various prognostic nodal factors, adjuvant chemotherapy and survival among stage III colon cancer patients over 65 years: an analysis using surveillance, epidemiology and end results (SEER)-Medicare Data. *Colorectal Dis* 14: 48–55.

Marsoni, S. (1995) Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet* 345: 939–944.

Jemal, A., Bray, F., Center, M., Ferlay, J., Ward, E. and Forman, D. (2011) Global cancer statistics. *CA Cancer J Clin* 61: 69–90.

Jessup, J., Stewart, A., Greene, F. and Minsky, B. (2005) Adjuvant chemotherapy for stage III colon cancer: implications of race/ethnicity, age, and differentiation. *JAMA* 294: 2703–2711.

Jullumstro, E., Lydersen, S., Moller, B., Dahl, O. and Edna, T. (2009) Duration of symptoms, stage at diagnosis and relative survival in colon and rectal cancer. *Eur J Cancer* 45: 2383–2390.

Kuebler, J., Wieand, H., O'Connell, M., Smith, R., Colangelo, L., Yothers, G. *et al.* (2007) 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* 25: 2198–2204.

Laurie, J., Moertel, C., Fleming, T., Wieand, H., Leigh, J., Rubin, J. *et al.* (1989) Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil. The North Central Cancer Treatment Group and the Mayo Clinic. *J Clin Oncol* 7: 1447–1456.

Lembersky, B., Wieand, H., Petrelli, N., O'Connell, M., Colangelo, L., Smith, R. *et al.* (2006) Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. *J Clin Oncol* 24: 2059–2064.

Mahoney, T., Kuo, Y., Topilow, A. and Davis, J. (2000) Stage III colon cancers: why adjuvant chemotherapy is not offered to elderly patients. *Arch Surg* 135: 182–185.

McCleary, N., Meyerhardt, J., Green, E., Yothers, G., De Gramont, A., Van Cutsem, E. *et al.* (2013) 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* 31: 2600–2606.

Moertel, C., Fleming, T., Macdonald, J., Haller, D., Laurie, J., Goodman, P. *et al.* (1990) Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 322: 352–358.

NIH Consensus Conference (1990) Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 264: 1444–1450.

Moertel, C., Fleming, T., Macdonald, J., Haller, D., Laurie, J., Tangen, C. *et al.* (1995). Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. *Ann Intern Med* 122(5): 321–326.

Peeters, M. and Haller, D. (1999) Therapy for early-stage colorectal cancer. *Oncology* 13: 307–315; discussion 315–307: 320–301.

Phelip, J., Molinie, F., Delafosse, P., Launoy, G., Tretarre, B., Bara, S. *et al.* (2010) A Population-Based study of adjuvant chemotherapy for stage-II and -III colon cancers. *Gastroenterol Clin Biol* 34: 144–149.

Poplin, E., Benedetti, J., Estes, N., Haller, D., Mayer, R., Goldberg, R. *et al.* (2005) Phase III Southwest Oncology Group 9415/Intergroup 0153 Randomized trial of fluorouracil, leucovorin, and levamisole *versus* fluorouracil continuous infusion and levamisole for adjuvant treatment of stage III and high-risk stage II colon cancer. *J Clin Oncol* 23: 1819–1825.

Potosky, A., Harlan, L., Kaplan, R., Johnson, K. and Lynch, C. (2002) Age, sex, and racial differences in the use of standard adjuvant therapy for colorectal cancer. *J Clin Oncol* 20: 1192–1202.

Ramjaun, A., Nassif, M., Krotneva, S., Huang, A. and Meguerditchian, A. (2013) Improved Targeting of cancer care for older patients: a systematic review of the utility of comprehensive geriatric assessment. *J Geriatr Oncol* 4: 271–281.

Roetzheim, R., Pal, N., Gonzalez, E., Ferrante, J., Van Durme, D. and Krischer, J. (2000) Effects of health insurance and race on colorectal cancer treatments and outcomes. *Am J Public Health* 90: 1746–1754.

Saltz, L., Niedzwiecki, D., Hollis, D., Goldberg, R., Hantel, A., Thomas, J. *et al.* (2007) Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. *J Clin Oncol* 25: 3456–3461.

Sanoff, H., Carpenter, W., Sturmer, T., Goldberg, R., Martin, C., Fine, J. *et al.* (2012) Effect of adjuvant chemotherapy on survival of patients with stage iii colon cancer diagnosed after age 75 years. *J Clin Oncol* 30: 2624–2634.

Sargent, D., Goldberg, R., Jacobson, S., Macdonald, J., Labianca, R., Haller, D. *et al.* (2001) A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med* 345: 1091–1097.

Schrag, D., Cramer, L., Bach, P. and Begg, C. (2001) Age and adjuvant chemotherapy use after surgery for stage III Colon cancer. *J Natl Cancer Instit* 93: 850–857.

Siegel, R., Desantis, C. and Jemal, A. (2014a) Colorectal cancer statistics, 2014. *CA Cancer J Clin* 64: 104–117.

Siegel, R., Ma, J., Zou, Z. and Jemal, A. (2014b) Cancer statistics, 2014. *CA Cancer J Clin* 64: 9–29.

Sundararajan, V., Grann, V., Jacobson, J., Ahsan, H. and Neugut, A. (2001) Variations in the use of adjuvant chemotherapy for node-positive colon cancer in the elderly: a population-based study. *Cancer J* 7: 213–218.

Tournigand, C., Andre, T., Bonnetain, F., Chibaudel, B., Lledo, G., Hickish, T. *et al.* (2012) Adjuvant therapy with fluorouracil and oxaliplatin in stage II and Elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the multicenter international study of oxaliplatin, fluorouracil, and leucovorin in the Adjuvant Treatment of Colon Cancer Trial. *J Clin Oncol* 30: 3353–3360.

Tsai, S., Balch, C. and Lange, J. (2010) Epidemiology and treatment of melanoma in elderly patients. *Nat Rev Clin Oncol* 7: 148–152.

Tsikitis, V., Larson, D., Huebner, M., Lohse, C. and Thompson, P. (2014) Predictors of recurrence free survival for patients with stage II and III colon cancer. *BMC Cancer* 14: 336.

Twelves, C., Wong, A., Nowacki, M., Abt, M., Burris, H., 3rd, Carrato, A. *et al.* (2005) Capecitabine as Adjuvant treatment for stage III colon cancer. *N Engl J Med* 352: 2696–2704.

Vaneenwyk, J., Campo, J. and Ossiander, E. (2002) Socioeconomic and demographic disparities in treatment for carcinomas of the colon and rectum. *Cancer* 95: 39–46.

Wolmark, N., Rockette, H., Fisher, B., Wickerham, D., Redmond, C., Fisher, E. *et al.* (1993) The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-03. *J Clin Oncol* 11: 1879–1887.

Yothers, G., O'Connell, M., Allegra, C., Kuebler, J., Colangelo, L., Petrelli, N. *et al.* (2011) Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 29: 3768–3774.