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An expatiate review on adjuvant chemotherapy of colorectal cancer

Shaik Shahireen*[1], Eka Vipplavi[1], Rachamsetty Kavya[1], Duraiswamy Dhachinamoorthi[2], L Rama Chandra Reddy[1]

[1]Department of Pharmacy Practice, QIS College of Pharmacy, Ongole, Prakasam District - 523272, JNTUK University, Andhra Pradesh, India

[2]Department of Pharmaceutics, QIS College of Pharmacy, Ongole, Prakasam District - 523272, JNTUK University, Andhra Pradesh, India

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Abstract

Colorectal cancer is the second leading cause of cancer-related death and the third most common cancer globally. For loco regional colon cancer, surgery is the sole curative option. Adjuvant chemotherapy aims to eliminate micro metastases and increase survival. It has been most convincingly proven in stage III illness, even though there is ongoing debate on the usefulness of adjuvant chemotherapy for stage II illness. For the past fifteen years, six months of adjuvant chemotherapy with an oxaliplatin-based chemotherapy has been the accepted standard of care for stage III colon cancer. It is still advised to use 6 months of adjuvant chemotherapy for individuals with stage II illness and high clinicopathological risk. Chemo radiation therapy (CRT) is frequently used as neoadjuvant or adjuvant therapy in the treatment of stage II and stage III rectal cancers because this cancer type has a higher risk of local recurrence than other cancer types.

*Corresponding Author
Name: Shaik Shahireen
Email: shahireenshaik@gmail.com

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INTRODUCTION

Colon cancer (CC) is the third most common malignancy as well as the second leading cause of cancer-related death globally [1]. The 5-year overall survival (OS) for patients in stages I and II of cancer is 99%, respectively, and for patients in stages III, which makes up around 35% of cases at diagnosis, it is only 45 to 65%. This indicates that lymph node invasion is a significant prognostic factor in localised cancer. The Moertel trial [2] states that during the 1990s, adjuvant fluoropyrimidine-based chemotherapy has been the accepted treatment for patients with stage III CC. As a new standard of therapy for stage III CC, the MOSAIC trial in 2004 established the combination of oxapliplatin and a fluoropyrimidine (FOLFOX regimen) for 6 months (12 cycles), enhancing both long-term overall survival (OS) and disease-free survival (DFS). We are yet unable to determine how many people in reality need this doublet adjuvant treatment. It is generally accepted that, of every 100 stage III CC patients receiving fluoropyrimidine + oxaliplatin, only 30 patients will benefit maximally from this adjuvant treatment, with 20 patients still experiencing disease recurrence despite the adjuvant treatment and 50 patients already cured

by surgical tumour removal [3]. All patients will experience the short- and long-term toxicities caused by these chemotherapeutic medicines, including the cumulative sensitive neuropathy caused by oxaliplatin, even though adjuvant therapy only improves the condition of most patients to a moderate degree. As we awaited the capacity to tailor adjuvant therapy and provide the most effective therapeutic approach to the appropriate patient, strategies to lessen treatment toxicities were tested. It was possible to dramatically lower therapy-induced toxicities by adopting the shorter treatment duration of three months instead of six, as suggested by the multinational Duration Evaluation of Adjuvant (IDEA) multinational effort [4].

Colorectal Cancer

A malignancy that can start as non-cancerous polyps in the colon or rectum. The lower portion of the digestive tract is where colorectal cancer cells proliferate and spread. The majority of these tumors begin life as benign growths known as polyps. For people at high risk or who are over 45, tests are advised since removing polyps can prevent cancer [5].

Epidemiology of Colorectal Cancer in India

Age-standardized rates (ASRs) for colorectal cancer (CRC) are low in India, at 5.2 per 100,000 for men and 5.1 per 100,000 for women. The absolute number of CRC patients is high in a nation with a population of over a billion, nevertheless. India has one of the lowest five-year survival rates for CRC (less than 40%) [6].

Stages of Colorectal Cancer

Stage 0 Colorectal Cancer: Colorectal cancer at stage 0 only affects the rectum or innermost lining of the colon. It should be removable by surgery. The extent of your treatment will depend on the cancer's size. Your surgeon could take out the tumor and some nearby tissue. This process could be referred to as a polypectomy.To ensure that your bowels continue to function, your surgeon may need to remove the sick portion of your colon and reattach the healthy tissue if you have larger tumors. A term for this is an astomosis.Your doctor may also recommend receiving radiation therapy, either internally (radioactive beads injected into your body) or externally (beams directed at you from the outside) [7].

Stage I Colorectal Cancer: Stage I tumors have reached the colon's or rectum's second and third layers as well as the interior wall. The exterior wall or outside of the bowel are not affected by the malignancy. Most patients at this stage will undergo surgery to remove the cancer and a limited amount of surrounding tissue. Most likely, you won't require any extra treatments. Your doctor might only use radiation if the tumor is small, you are very elderly or ill, or both. To enhance the therapy, they could additionally add chemotherapy.

Stage II Colorectal Cancer: Colorectal cancers in stage II are more severe and invade the bowel's muscular wall. They might have expanded to neighboring structures like the uterus, bladder, or prostate gland. However, there is no cancer in lymph nodes or distant organs, which are small organs that produce and store cells that fight infection and filter out hazardous substances. Surgery will likely be required to remove the cancer, any surrounding tissue, and any locations where it has spread. Before or after surgery, radiation and chemotherapy are options [8].

Stage III Colorectal Cancer: Colorectal tumors in stage III have reached one or more lymph nodes. A, B, or C tumors in stage III which includes:

Stage IIIA. Lymph nodes are affected by tumors that are located within the colon or rectum wall.

Stage IIIB. One to four lymph nodes have been affected by tumors that have penetrated the wall.

Stage IIIC. More than four lymph nodes have been affected by the tumor, and it's possible that other organs in the area have also been affected.

Stage IV Colorectal Cancer: Colorectal cancers in stage IV have migrated to distant organs, frequently the liver or lungs. According to your doctor, the cancer has "metastasized" or is "metastatic" cancer. Your lymph nodes may or may not be involved in the tumor, which can be of any size [9]**.**

TYPES OF TREATMENT

The most typical types of therapy for colorectal cancer are discussed here, followed by a brief summary of the stages of treatment.

- Surgery
- Radiation therapy

- chemotherapy
- Targeted therapy
- Immunotherapy [10].

What is Chemotherapy?

Drugs that can kill cancer cells are known by the term "chemotherapy" in medical circles. Chemotherapy medications may be administered orally or intravenously, or they may be given to you in the form of a pill. Each medicine has particular dosages and schedules and each one fights a particular type of cancer. Doctors use chemotherapy in different ways:

1. **Neoadjuvant chemotherapy** is performed prior to surgery to reduce a tumor's size so that the surgeon can entirely remove it with fewer difficulties. Because it might increase the radiation's effectiveness, it is occasionally administered along with radiation treatments.
2. **Adjuvant chemotherapy** is given after a tumor is surgically removed. Adjuvant chemotherapy eliminates any cancer cells that may remain after surgery, such as those that may have moved to your liver. Surgery may not completely eradicate all cancer cells.
3. **Palliative chemotherapy** is given when colorectal cancer has spread to different parts of your body. If colorectal cancer has spread to other bodily regions, palliative chemotherapy is administered. The cancer in this instance is not completely curable with surgery. Drugs used in chemotherapy may help you live longer and reduce tumor size [11].

Drugs Used in Chemotherapy

The use of drugs called chemotherapy is used to destroy cancer cells. Usually, this is done by stopping the cancer cells from proliferating, growing, or dividing. Known by many as a schedule, a chemotherapy regimen usually consists of a specific number of cycles given over a predefined period of time.

- Capecitabine (Xeloda)
- Fluorouracil (5-FU)
- Irinotecan (Camptosar)
- Oxaliplatin (Eloxatin)
- Trifluridine/tipiracil (Lonsurf)

Some popular treatment regimens involving these drugs are:

5FU alone

5-FU combined with leucovorin (folinic acid), a vitamin that enhances the efficiency of 5-FU

Capecitabine is an oral version of 5-FU

FOLFOX: 5-FU plus leucovorin and oxaliplatin.

FOLFIRI: 5-FU plus leucovorin and irinotecan.

Irinotecan alone

FOLFOXIRI: 5-FU with leucovorin, oxaliplatin, and irinotecan.

XELOX/CAPEOX: Capecitabine plus oxaliplatin.

Combining targeted therapy with chemotherapy may be recommended: bevacizumab (avastin), cetuximab (erbitux), or panitumumab (vectibix)[12]

Timing of Adjuvant Chemotherapy

A meta-analysis in stage III CC revealed that delaying adjuvant chemotherapy past 8 weeks following curative surgery resulted in a decreased OS (RR: 1.20; 95% Confidence Interval (CI) 1.15-1.26), possibly due to complications following surgery and an overall unfavourable state [13]. Even after a protracted delay of up to 4-6 months, individuals may still benefit from adjuvant chemotherapy, the efficacy of the treatment declines after 8 weeks. Chemotherapy should therefore be started 6 to 8 weeks after curative surgery for the maximum benefit, and it is completely ineffective 6 months following surgery.

Adjuvant Chemotherapy in Stage III Colon Cancer

For clinical trials examining the efficacy of adjuvant therapy in stage III colon cancer, disease-free survival (DFS) endpoints of 2 and 3 years are accepted. The Adjuvant Colon Cancer End Points (ACCENT) joint group investigation provided data supporting this claim. Specifically, the data showed that the 2- and 3-year disease-free survival (DFS) and 5- and 6-year overall survival (OS) of colon cancer patients who received adjuvant chemotherapy based on the drug 5-fluorouracil (5-FU) corresponded positively [14]. The majority of relapses, or those that happen

within two years of surgery, are revealed in an update to this data, which also reveals that, after five years, recurrence rates are fewer than 1.5% each year. When it comes to adjuvant chemotherapy scheduling, patients with resected colorectal cancer had lower survival rates when adjuvant chemotherapy was delayed more frequently. According to meta-analyses, adjuvant chemotherapy delays of more than 8 weeks after surgery and delays of adjuvant chemotherapy of more than 4 weeks have been linked to lower OS [15]. As a result, it is advised to start adjuvant chemotherapy as soon as the patient is medically able, ideally within 12 weeks.

Benefit of Specific Regimens

5-fluourouracil (5-FU)-based chemotherapy

First to demonstrate the benefits of adjuvant chemotherapy was a landmark trial by Moertel et al. in 1990. Giving adjuvant treatment with 5-FU and levamisole for a full year following surgery resulted in higher survival and a decreased rate of recurrence as compared to surgery alone [16]. Later trials have demonstrated that the combination of 5-FU and leucovorin (LV) was superior, and that 6 months of therapy was adequate to provide comparable improvements in overall survival (OS) when compared with 12 months. In a 28-day cycle spanning six months, both the Mayo Clinic regimen as well as the daily 5-FU bolus and the Roswell Park regimen (weekly 5-FU bolus for six weeks in an eight-week cycle, for six months) have shown advantages in terms of survival. However, the toxicity profiles varied, with diarrhea present in the latter and greater stomatitis and neutropenia in the former. Additionally examined and discovered to be equally effective as bolus 5-FU regimens with less effects is the use of intravenous 5-FU. When compared the Mayo Clinic treatment for stage III colon cancer, oral capecitabine was found to be a convenient, safe, and comparably effective substitute [17]. In tumor tissue, the oral fluoropyrimidine capecitabine preferentially manufactures 5-FU via a three-step enzymatic cascade. Thymidine phosphorylase, which is more active in tumours than in healthy tissue, catalyses the final conversion of 5-FU.

Oxaliplatin-based therapies

Based on a 3-year DFS objective, oxaliplatin was approved as an adjuvant therapy in 2004 for stage III colon cancer. A 20% relative risk reduction for DFS is associated with the addition of oxaliplatin to 5-FU or capecitabine, and this benefits overall survival in a similar manner [18]. A 5.9% and a 2.5% improvement in the 5-year DFS rates and 6-year OS rates, respectively, was attained in the historic MOSAIC study as a result of the inclusion of oxaliplatin to chemotherapy based on 5-FU. Adjuvant capecitabine as well as oxaliplatin combination (XELOX) and bolus 5-FU/LV were assessed in patients with stage III colon cancer included in the XELOXA research. Similar DFS benefits were observed [19].

Application in clinical practice

Colon cancer in stage III should receive adjuvant treatment. If possible medically, it should begin sooner than 12 weeks after surgery. After discussing the pros and cons of adjuvant chemotherapy with the patient and deciding on the appropriate period, adjuvant chemotherapy for low-risk stage III illness (T1-3, N1) can last for three or six months (especially when XELOX is administered). When a patient has stage III cancer and high risk (T4 and/or N2) tumours, six months of adjuvant chemotherapy with an oxaliplatin-based doublet treatment is still recommended.

Adjuvant Chemotherapy in Stage II Colon Cancer

The choice of adjuvant chemotherapy for patients with stage II cancer is still difficult, in contrast to stage III disease, where it is almost always advised. It is challenging to defend the use of adjuvant chemotherapy for all patients given the modest benefit it provides in unselected individuals when weighed against toxicities, inconvenience, along with cost [20]. Surgery alone delivers great outcomes.

Benefit of Specific Regimens

5-FU-based chemotherapy for colon cancer at stage II

Many trials have been conducted to evaluate the benefits of adjuvant chemotherapy for stage II colon cancer. adjuvant treatment for diseases in stage II has not been found to be beneficial in meta-analyses of five studies from the IMPACT B2 investigators with 1,016 patients, an examination

of the Surveillance, Epidemiology and End Results (SEER) database containing 3,151 stage II patients and a pooled analysis of seven studies totaling 3,302 participants [21]. The Quick, Simple, as well as Reliable (QUASAR) study found a 20% relative reduction in the risk of recurrence and mortality, but only a moderate (4%) absolute benefit. These results show that the findings differ from each other. Patients with stage II colon cancer were randomly assigned to either 5-FU treatment or postoperative observation in this study. More than 60% of patients had fewer than 12 lymph nodes removed, which is a major criticism of the study. Previous research has shown that if a colon cancer is to be staged as node negative, at least 13 lymph nodes must be sampled [22]; this is in contrast to the study's findings.

Oxaliplatin-based chemotherapy

Oxaliplatin-based chemotherapy was proven to be useful in stage II sickness based on a subgroup analysis from the MOSAIC investigation. FOLFOX provided a nearly 3.5% improvement in DFS over 5-FU/LV alone in patients with stage II disease. Patients with clinically high-risk features (undifferentiated tumours, T4, perforation, blockage, fewer than 10 lymph nodes found, as well as lymph vascular invasion) in addition to stage II malignancies also experienced this effect in greater than 5% of cases [23]. Trial updates revealed that patients with stage III cancer, but not those with stage II disease, benefited significantly from an adjuvant oxaliplatin-based treatment in terms of 6-year overall survival.

Application in clinical practice

If the tumor displays high-risk clinicopathological features, 5-FU-based treatment is advised for 6 months in patients with stage II colon cancer. With the addition of oxaliplatin, there is little benefit. All stage II cancers should be evaluated for MSI or MMR status to identify patients (with high MSI or dMMR status) who might not benefit from adjuvant chemotherapy. To assess if adjuvant therapy is necessary, the current state of research does not support the widespread use of Immunoscore, ctDNA, or multigene tests for colon cancer. Regarding individuals with stage II colorectal cancer, a shared decision-making process should be employed to consider the risks and advantages of treatment for each patient.

Adjuvant Chemotherapy in the Elderly

Given that the median age of colon cancer patients at diagnosis is 70, it is important to thoroughly assess elderly patients in order to determine their unique risk/benefit ratios for adjuvant therapy. The results of treating elderly individuals are inferred from subgroup analyses, which depend on the inclusion of younger patients in many clinical trials. Selection bias, as seen by the enrollment of older adults who were likely more physically fit in the individual clinical trials, as well as the fact that less than 1% of trial participants were in their 80s, are limitations of the pooled data.

Stage III colon cancer in elderly

Adjuvant therapy is advantageous for elderly individuals, according to numerous population studies. More than 7,000 patients over 65 with stage 3 colon cancer were included in the SEER-Medicare Databases, and researchers discovered a survival benefit for using 5-FU/LV (HR 0.70; P 0.001). Adjuvant chemotherapy improved survival even in individuals 75 years of age and beyond, according to the SEER-Medicare and NCCN Outcomes Databases (HR 0.60; 95% CI, 0.53-0.68) [24].

Oxaliplatin was added to 5-FU in the adjuvant setting, according to the ACCENT database, with a lower benefit in patients under the age of 70. Using the National Cancer Database, which contains information on over 100,000 patients with stage III colon cancer, Margalit and colleagues found that doublet chemotherapy was not beneficial for low-risk patients (T3 and N1, as defined by IDEA collaborators) or high-risk patients (T4 or N2 disease) older than 85 years. This finding suggests that oxaliplatin omission in IDEA low-risk patients older than 72 years old can be taken into consideration. There was no survival benefit with the addition of oxaliplatin to 5-FU/LV treatment, according to subset analyses of patients in the NSABP C-07 and MOSAIC trials who were under 70 years old. However, data from stage III colon cancer patients in the NSABP-C08, XELOXA, X-ACT, and AVANT studies that were pooled from individual patient data showed a benefit for DFS when adding oxaliplatin in older patients who would match the entrance requirements for adjuvant clinical studies (HR 0.77, P0.014) in combination with 5-FU-based chemotherapy [25].

Stage II colon cancer in elderly

According to the QUASAR research, adjuvant chemotherapy did not benefit patients over the age of 70 with stage II disease at average risk [26]. In this older patient group, the little absolute benefit in the general population makes skipping adjuvant treatment tolerable. Examining 24,847 patients 65 years of age and above who had a colectomy for stage II colon cancer using the associated SEER/Medicare database, even in those with high-risk characteristics, a survival benefit for fluoropyrimidine-based adjuvant chemotherapy was not seen [27]. Older dMMR patients are thought to have a low risk of recurrence, similar to the general population, and do not benefit from adjuvant therapy.

Application in clinical practice

Since older persons' physical function varies greatly from one to the next, choosing a course of treatment cannot be based solely on chronological age. Overall, all stage III illness patients, regardless of age, seem to benefit from 5-FU/LV as adjuvant therapy. Oxaliplatin should not always be added to treatment plans for individuals over the age of 70 because the evidence for its benefits is substantially less strong in this group. It has been demonstrated that patient age has no influence on toxicities such as nausea, diarrhoea, or stomatitis. However, elderly patients do have a higher risk of haematological toxicities [28].

Neo-Adjuvant Chemotherapy for Locally Advanced Colon Cancer

The beneficial results of pre-operative therapies in gastric, esophageal, as well as rectal malignancies have led to research into neoadjuvant chemotherapy for patients with colon cancer. First shown to be well tolerated, with no increase in surgical morbidity and interesting downstaging rates, FOLFOX neo-adjuvant chemotherapy (4 cycles) for patients with locally advanced cancer (T3/T4 and/or N2 on the initial CT scan evaluation) was not significantly associated with a major histological response (TRG1) when compared to patients who did not receive neo-adjuvant treatment, according to the PRODIGE 22 phase 2 trial [29]. Under these conditions, the larger phase 3 FOxTROT trial (n = 1050 patients) showed similar outcomes with three cycles of neo-adjuvant FOLFOX, with no statistically significant differences but a strong tendency to reduce the study's primary endpoint, the 2-year recurrence rate (13.6% versus 17.2%, respectively, HR: 0.75, p = 0.08). Still, in these two trials, low-risk CC patients were selected for the baseline pre-therapeutic CT scan in 25 to 30% of instances, possibly avoiding the need for chemotherapy, highlighting the need for better pre-treatment illness evaluation in this situation. Both studies [30] found no benefit from combining neo-adjuvant FOLFOX with anti-EGFR medication for individuals with RAS wild-type tumours.

CONCLUSION

Rectal cancer patients are more likely to experience a pelvic recurrence than colon cancer patients due to the rectum's close proximity to pelvic organs, the lack of a serosa encircling the rectum, and the technical challenges of obtaining broad surgical margins during resection. As a result, neoadjuvant or adjuvant locoregional therapy, such as CRT, is frequently used in the treatment of rectal cancer in stages II and III. Contrary to colon cancer, rectal cancer is diagnosed through clinical staging, which uses imaging and endoscopic results to guide recommendations for pre- or post-operative therapy. This process is challenging since there is a chance that the tumor could be under- or over-staged. Therefore, it is important to carefully choose the patients who will receive particular treatments, and to use sequenced multi-modal therapy that combines chemotherapy, radiation, and surgery. Total mesorectal excision (TME), which has been demonstrated to reduce local seeding and eventual recurrences in conditions other than T1 stage rectal cancer, is frequently carried out [44].

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REFERENCES

[1] D Sargent, Q Shi, G Yothers, E Van Cutsem, J Cassidy, L Saltz, N Wolmark, B Bot, A Grothey, M Buyse, and A de Gramont. Two or three year disease-free survival (DFS) as a primary end-point in stage III adjuvant colon cancer trials with fluoropyrimidines with or without oxaliplatin or irinotecan:data from 12,676 patients from MOSAIC, X-ACT, PETACC-3, C-06, C-07 and C89803. European Journal of Cancer, 47(7):990-996, 2011.

[2] James J Biagi, Michael J Raphael, William J Mackillop, Weidong Kong, Will D King, and Christopher M Booth. Association Between Time to Initiation of Adjuvant Chemotherapy and Survival in Colorectal Cancer. JAMA, 305(22):2335, 2011.

[3] C G Moertel, T R Fleming, J S Macdonald, D G Haller, J A Laurie, P J Goodman, J S Ungerleider, W A Emerson, D C Tormey, and J H Glick. Levamisole and Fluorouracil for Adjuvant Therapy of Resected Colon Carcinoma. New England Journal of Medicine, 322(6):352-358, 1999.

[4] N Wolmark, H Rockette, B Fisher, D L Wickerham, C Redmond, E R Fisher, J Jones, E P Mamounas, and L Ore, N J Petrelli. 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. Journal of Clinical Oncology, 11(10):1879-1887, 1993.

[5] Daniel G Haller, Paul J Catalano, John S Macdonald, Mark A O'Rourke, Michael S Frontiera, Don V Jackson, and Robert J Mayer. Phase III Study of Fluorouracil, Leucovorin, and Levamisole in High-Risk Stage II and III Colon Cancer: Final Report of Intergroup 0089. Journal of Clinical Oncology, 23(34):8671-8678, 2005.

[6] A Saini, A R Norman, D Cunningham, I Chau, M Hill, D Tait, T Hickish, T Iveson, F Lofts, D Jodrell, P J Ross, and J Oates. Twelve weeks of protracted venous infusion of fluorouracil (5-FU) is as effective as 6 months of bolus 5-FU and folinic acid as adjuvant treatment in colorectal cancer. British Journal of Cancer, 88:1859-1865, 2003.

[7] M J O'Connell, J A Mailliard, M J Kahn, J S Macdonald, D G Haller, R J Mayer, and H S Wieand. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer, Journal of Clinical Oncology, 15(1):246-250, 1997.

[8] J Philip Kuebler, H Samuel Wieand, Michael J O'Connell, Roy E Smith, Linda H Colangelo, Greg Yothers, Nicholas J Petrelli, Michael P Findlay, Thomas E Seay, James N Atkins. Oxaliplatin Combined With Weekly Bolus Fluorouracil and Leucovorin As Surgical Adjuvant Chemotherapy for Stage II and III Colon Cancer: Results From NSABP C-07. Journal of Clinical Oncology, 25(16):2198-2204, 2007.

[9] Thierry André, Corrado Boni, Matilde Navarro, Josep Tabernero, Tamas Hickish, Clare Topham, Andrea Bonetti, Philip Clingan, John Bridgewater, Fernando Rivera, and Aimery de Gramont. Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial. Journal of Clinical Oncology, 27:3109-3116, 2009.

[10] Quasar Collaborative Group, Richard Gray, Jennifer Barnwell, Christopher McConkey, Robert K Hills, Norman S Williams, and David J Kerr. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet, 370(9604):2020-2029, 2007.

[11] David Cunningham, and Naureen Starling. Adjuvant chemotherapy of colorectal cancer. Lancet, 370(9604):1980-1981, 2007.

[12] Ronald L Koretz. Adjuvant chemotherapy increased survival in colorectal cancer patients with low recurrence risk. ACP Journal Club, 148(3):6, 2008.

[13] Neil H Segal, and Leonard B Saltz. Is adjuvant therapy for stage II colon cancer worthwhile, and for whom?. Nature Clinical Practice. Gastroenterology and Hepatology, 5(8):422-423, 2008.

[14] Sharlene Gill, Charles L Loprinzi, Daniel J Sargent, Stephan D Thomé, Steven R Alberts, Daniel G Haller, Jacqueline

Benedetti, Guido Francini, and Lois E Shepherd. Pooled Analysis of Fluorouracil-Based Adjuvant Therapy for Stage II and III Colon Cancer: Who Benefits and by How Much?. Journal of Clinical Oncology, 22:1797-806, 2004.

[15] Richard S Swanson, Carolyn C Compton, Andrew K Stewart, and Kirby I Bland. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Annals of Surgical Oncology, 10(1):65-71, 2003.

[16] Katerina O Wells, Alexander T Hawkins, Devi M Krishnamurthy, Sekhar Dharmarajan, Sean C Glasgow, Steven R Hunt, Matthew G Mutch, Paul Wise, and Matthew L Silviera. Omission of Adjuvant Chemotherapy Is Associated With Increased Mortality in Patients With T3N0 Colon Cancer With Inadequate Lymph Node Harvest. Diseases of the Colon and Rectum, 60(1):15-21, 2017.

[17] George J Chang, Miguel A Rodriguez-Bigas, John M Skibber, and Virginia A Moyer. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. Journal of the National Cancer Institute, 99(6):433-441, 2007.

[18] Anand Govindarajan, and Nancy N Baxter. Lymph node evaluation in early-stage colon cancer. Clinical Colorectal Cancer, 7(4):240-246, 2008.

[19] Radovanovic Dragan, Mitrovic Nebojsa, Stevanovic Dejan, Pavlovic Ivan, Stojanovic Dragos, Jasarovic Damir, Stevanovic Predrag, and Zivaljevic Vladan. Clinical application of sentinel lymph node biopsy for staging, treatment and prognosis of colon and gastric cancer. Hepatogastroenterology, 56(96):1606-1611, 2009.

[20] Frances C Wright, Calvin H L Law, Scott Berry, and Andrew J Smith. Clinically important aspects of lymph node assessment in colon cancer. Journal of Surgical Oncology, 99(4):248-255, 2009.

[21] N N Hanna, E Onukwugha, M A Choti, A J Davidoff, I H Zuckerman, V D Hsu, and C D Mullins. 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 Disease, 14(1):48-55, 2012.

[22] Ilene H Zuckerman, Thomas Rapp, Ebere Onukwugha, Amy Davidoff, Michael A Choti, James Gardner, Brian Seal, and C Daniel Mullins. Effect of age on survival benefit of adjuvant chemotherapy in elderly patients with Stage III colon cancer. The Journal of the American Geriatrics Society, 57(8):1403-1410, 2009.

[23] Hanna K Sanoff, William R Carpenter, Til Stürmer, Richard M Goldberg, Christopher F Martin, Jason P Fine, Nadine Jackson McCleary, Jeffrey A Meyerhardt, Joyce Niland, Katherine L Kahn, Maria J Schymura, and Deborah Schrag. Effect of Adjuvant Chemotherapy on Survival of Patients With Stage III Colon Cancer Diagnosed After Age 75 Years. Journal of Clinical Oncology, 30(21):2624-2634, 2012.

[24] Hanna K Sanoff, William R Carpenter, Christopher F Martin, Daniel J Sargent, Jeffrey A Meyerhardt, Til Stürmer, Jason P Fine, Jane Weeks, Joyce Niland, Katherine L Kahn, Maria J Schymura, and Deborah Schrag. Comparative effectiveness of oxaliplatin vs non-oxaliplatin-containing adjuvant chemotherapy for stage III colon cancer. The Journal of the National Cancer Institute, 104(3):211-227, 2012.

[25] Ilene H Zuckerman, Thomas Rapp, Ebere Onukwugha, Amy Davidoff, Michael A Choti, James Gardner, Brian Seal, C Daniel Mullins. Effect of age on survival benefit of adjuvant chemotherapy in elderly patients with Stage III colon cancer. Jornal of the American Geriatrics Society, 57(8):1403-1410, 2009.

[26] Ofer Margalit, Ronac Mamtani, Yu-Xiao Yang, Kim A Reiss, Talia Golan, Naama Halpern, Dan Aderka, Bruce Giantonio, Einat Shacham-Shmueli, and Ben Boursi. A new look at the International Duration Evaluation of Adjuvant therapy (IDEA) classification—Defining novel predictive and prognostic markers in stage III colon cancer. European Journal of Cancer, 96:105-110, 2018.

[27] Daniel Brungs, Morteza Aghmesheh, Paul de Souza, Martin Carolan, Philip Clingan,

June Rose, and Marie Ranson. Safety and Efficacy of Oxaliplatin Doublet Adjuvant Chemotherapy in Elderly Patients with Stage III Colon Cancer. Clinical Colorectal Cancer, 17(3): e549-e555, 2018.

[28] Erin S O'Connor, David Yu Greenblatt, Noelle K LoConte, Ronald E Gangnon, Jinn-Ing Liou, Charles P Heise, and Maureen A Smith. O'Connor ES, Greenblatt DY, LoConte NK, et al. Adjuvant chemotherapy for stage II colon cancer with poor prognostic features. Journal of Clinical Oncology, 29(25):3381-3388, 2011.

[29] Cheng E Chee, and Neal J Meropol. Current Status of Gene Expression Profiling to Assist Decision Making in Stage II Colon Cancer. Oncologist, 19(7):704-711, 2014.

[30] Greg Yothers, Michael J O'Connell, Mark Lee, Margarita Lopatin, Kim M Clark-Langone, Carl Millward, Soonmyung Paik, Saima Sharif, Steven Shak, and Norman Wolmark. Validation of the 12-Gene Colon Cancer Recurrence Score in NSABP C-07 As a Predictor of Recurrence in Patients with Stage II and III Colon Cancer Treated With Fluorouracil and Leucovorin (FU/LV) and FU/LV Plus Oxaliplatin. Journal of Clinical Oncology, 31(36):4512-4519, 2013.