Abstract

Colorectal cancer is the third most common cancer worldwide and is the third leading cause of cancer mortality. Surgical management remains the mainstay of treatment for early and locally-advanced non-metastatic colon cancers. Systemic therapies have shown to significantly improve outcomes when given in the adjuvant setting in these patients. The addition of adjuvant chemotherapy in patients with Stage III and high risk stage II disease significantly improves recurrence free survival. In this chapter, we summarize important clinical trials that have led to an evidence-based approach to the management of non-metastatic colon cancer.

Introduction

Approximately 75% of all patients with colorectal cancer (CRC) will present at a stage when all gross carcinoma can be surgically resected [1]. Despite of the high resectability rate, nearly half of all patients with stage III colorectal adenocarcinoma die of metastatic disease. These individuals are candidates for adjuvant systemic therapies [2]. The need for adjuvant chemotherapy after resection of the bowel with the adjacent draining lymph nodes depends on disease stage[3].

The natural history and patterns of failure following “curative” resection for colon cancer differ completely from those for rectal carcinomas. Local-regional failure as the only or major site of recurrence is common in rectal cancer, whereas colon cancer tends to recur in the peri-
toneum, liver and other distant sites with a lower rate of local failure [4].

Investigators from Harvard in the early 90th pointed out that certain patients with colon carcinoma, such as those with B3 and C3 lesions, tumors associated with abscess or fistula formation, and residual disease after subtotal resection, may benefit from post-operative radiotherapy in addition to systemic therapy [4].

**Background of systemic adjuvant chemotherapy**

Early in 80th, the administration of either fluorouracil or floxuridine (FUDR) to patients with Dukes’ stage II and III colon tumors following surgical resection has failed to produce a survival advantage over postsurgical observation [5].

Later on, meta-analysis did not show any benefit from adjuvant fluorouracil [6, 7]. Five trials compared the combination of semustine (methyl-CCNU), vincristine (Oncovin), and fluorouracil with no adjuvant treatment, immunotherapy with bacillus Calmette-Guerin (BCG) or its methanol extraction residue (MER), and fluorouracil alone. Four of these trials, with a total of almost 2,500 patients, failed to demonstrate any effect of adjuvant therapy on overall survival [8, 9, 10].

Studies performed in the late 1980s demonstrated that adjuvant fluorouracil (5FU) plus levamisole improved survival in patients with a resected stage III colon cancer. Further studies performed in the mid-1990s established 5FU plus leucovorin (LV) administered for approximately six months as a standard postoperative treatment. The therapeutic potential of systemic treatments for colorectal cancer has expanded rapidly during the past 10 years, with the introduction of oral fluoropyrimidines, oxaliplatin, and irinotecan [11].

Initial analysis of the fifth trial, which included 1,166 patients and was conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), showed an improvement in Disease-Free (DFS) and Overall Survivals (OS) in patients who received combination chemotherapy compared with those in the control arm [12]. Sixty-seven percent of patients treated with adjuvant chemotherapy and 59% of those treated with surgery alone survived for 5 years (P = .05) [12].

A recent update of this trial conclude that a regimen containing methyl-CCNU is effective adjuvant therapy. Despite of the small survival benefit seen in one trial, Methyl-CCNU showed nephrotoxic effect [13].

A Levamisole is an anthelmintic agent with nonspecific immunostimulating properties in patients with cancer. It enhances fluorouracil’s toxicity to human colon cancer cell lines in a dose-dependent manner. This may be caused by levamisole’s inhibition of tyrosine phosphatases in tumor cells. Levamisole may also enhance natural-killer
lymphocyte activity and may induce expression of HLA-1 molecules in cancer cell membranes [14]. Windle and associates first reported the effectiveness of levamisole plus fluorouracil as adjuvant therapy for colorectal cancer [15]. The North Central Cancer Treatment Group (NCCTG) and Mayo Clinic researchers randomly assigned 401 patients with resectable Dukes’ stage II and III colon cancer to receive postoperative observation alone or postsurgical adjuvant therapy with levamisole alone or levamisole plus fluorouracil for 1 year [16,17].

Levamisole plus fluorouracil significantly reduced the recurrence rate compared with no adjuvant therapy (P = .003), and a benefit from levamisole alone was also suggested (P = .05). In addition, survival advantages were observed in stage III patients treated with levamisole plus fluorouracil (P = .03) [16,17].

Moertel CG and his colleague lead a confirmatory national intergroup trial using essentially the same methodology, except that patients with stage II tumors were randomly assigned to one of two arms (postoperative observation or levamisole plus fluorouracil) and patients with stage III disease were randomly assigned to one of three arms (observation, levamisole alone, or fluorouracil plus levamisole) [18].

A total of 1,269 patients with resected colon cancer were included in the trial. Among the 929 evaluable patients with stage III tumors, therapy with levamisole plus fluorouracil reduced the risk of cancer recurrence by 41% and the overall death rate by 33%. The 3-year OS rate for the levamisole plus fluorouracil arm was estimated at 71% vs 55% for the observation arm (P = .0064). Levamisole alone did not produce a DFS advantage over observation alone. Follow-up of patients with stage II tumors is insufficient to allow analysis at this time[18].

The intergroup trial updated its data on patients with stage III colon carcinoma in 1992 [19]. With all 929 stage III colon cancer patients receiving follow-up for 5 years or more (median, 6.5 years), levamisole plus fluorouracil was found to reduce the risk of cancer recurrence by 40% (P < .0001) and the death rate by 33% (P < .0007). Levamisole alone produced no benefit in patients with stage III colon carcinoma. The reported toxicity was mild with no late side effects noted [19].

Levamisole plus fluorouracil is not universally accepted by other investigators for several reasons: levamisole’s claimed immunomodulatory effects have been difficult to substantiate, this effect appears more significant at higher doses than those used, single-agent levamisole appears to have no antitumor activity, and the possibility exists of long-term adverse effects such as multifocal leukoencephalopathy. Also, European study findings have raised suspicions about an increase (in a small number of patients) in cancer- and non-cancer-related deaths. Fi-
nally, the NCCTG-Intergroup trials lacked a single-agent fluorouracil study arm. In fact, these trials compared the efficacy of fluorouracil plus levamisole with results in historical controls using different doses, schedules, and patient compliance [20].

Since then, investigators reported their results using the combination of fluorouracil and leucovorin in the adjuvant setting. Results of a NSABP C-03 adjuvant colon cancer trial comparing fluorouracil plus leucovorin to MOF (semustine, vincristine, and fluorouracil) suggest that postoperative fluorouracil plus leucovorin results in a 30% reduction in the risk of developing treatment failure and a 32% reduction in mortality compared with patients treated with MOF [21]. This combination also significantly prolongs DFS and OS [21] based on results 3 years follow up after surgery.

Preliminary results from other studies have also suggested benefits of fluorouracil plus leucovorin in the adjuvant treatment of colon carcinomas [22, 23].

In 95th, The International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators analyzed the role of adjuvant fluorouracil plus leucovorin for stage II and stage III colon cancer compared with surgery only [23]. These investigators independently undertook three randomized trials done in Italy, Canada, and France and pooled the data for analysis. The dosage was 370 to 400 mg/m² fluorouracil plus 200 mg/m² folinic acid intravenously for 5 days every 28 days for a total of 6 cycles. A total of 1,493 patients were eligible for analysis. The treatment arm showed significant reductions in mortality (by 22%; 95% CI, 3–38; P = .029) and relapse (by 35%; 95% CI, 22–46; P = .0001). The 3-year relapse-free survival and overall survival rates increased from 62% to 71% and from 78% to 83%, respectively. Toxicity was mild, with less than 3% of the patients experiencing grade III toxicity [23].

**Treatment by Stage**

Colon cancer divided into 4 stages based on the TNM staging system [24]. Stage 0 and I patients do not require adjuvant therapy, stage IIA, B and C (node-negative) is controversial. Stages I and II are categorized as early-stage colon cancer, Stage III as locally-advanced cancer, and Stage IV as metastatic disease [25]. Adjuvant therapy refers to treatment given in addition to, or following surgical treatment. It is aimed at elimination of residual microscopic disease, with the intention of cure and to lower the risk of cancer recurrence. Adjuvant chemotherapy plays no role in Stage I colon cancer given a 93.1% five-year survival with surgery alone [26].

The standard chemotherapy for patients with stage III and some patients with stage II colon cancer for the last two decades consisted of 5-fluorouracil in combination with adjuncts such as levamisole and leucovorin [27,28,29] which shown to reduce individual 5-year risk
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of cancer recurrence and death by about 30%.

Adjuvant therapy in stage II colon cancer

The role of adjuvant chemotherapy for stage II colon cancer is controversial, with survival rates of 82.5% with surgery alone. Different prognostic factors and tools have been investigated to assist with risk stratification and identification of that stage II patients who would benefit from adjuvant chemotherapy [26].

The American Society of Clinical Oncology does not recommend the routine use of adjuvant chemotherapy for patients with stage II colon cancer, and instead recommends encouraging these patients to participate in clinical trials [30].

When determining the benefit of adjuvant therapy for this group, several factors should be taken into consideration, including the number of lymph nodes analyzed after surgery, the prognostic features (T4 lesion, perforation, peritumoral lymphovascular invasion, poorly differentiated histology, and MSI status), life expectancy, and comorbid conditions. A multigene assay (Oncotype DX colon cancer assay, Genomic Health, Inc) is now available to help define the risk of recurrence for patients with stage II colon cancer.

A large European trial (QUASAR) demonstrated small but significant benefit (3.6%) in terms of absolute 5-year survival rate for those patients who received fluorouracil/leucovorin versus those in the control group [31]. In contrast, a study by O’Connor et al found that in Medicare patients with stage II colon cancer, with or without poor prognostic features, overall survival was not substantially improved by adjuvant chemotherapy [32].

Our experience between January 2006 to January 2011, 162 patients with pathologically documented stage II colon cancer presented to Clinical Oncology Department, Tanta University Hospital, were randomly distributed into two groups to received adjuvant chemotherapy regimens after curative resection. The first group (80 patients) received Capetiabine 1250 mg / m2 twice daily for 14 days every 21 days for 6 cycles & the second group (82 patients) received FOLFOX4 (Oxaliplatin 85mg/m2 D1 and D15 plus de Gramont regimen) for 6 cycles. This study have demonstrated patients with microscopic disease do behave more like stage III colon cancer patients, therefore these data, suggest that we must analyze out tumors to this level if at all possible and those patients with < 12 lymph nodes resection should receive adjuvant chemotherapy in favor FOLFOX4 regimen with significant improvement in DFS which can be translated into an OS benefit [33].

Ongoing adjuvant trials are investigating additional risk stratification of stage II colon cancer based on clinicopathological and molecular markers. The ECOG 5202 trial
is comparing two forms of adjuvant therapy (oxaliplatin, leucovorin, and fluorouracil with or without bevacizumab) in high-risk patients, with low-risk patients undergoing observation only.

In this trial, high-risk patients are defined as those with microsatellite stability (MSS) or low-frequency microsatellite instability (MSI-L) and loss of heterozygosity at 18q. Low-risk patients are those with MSS or MSI-L and retention of 18q, or high-frequency MSI with or without loss of heterozygosity at 18q (https://clinicaltrials.gov/ct2/show/NCT00217737).

**Adjuvant therapy in stage III colon cancer**

Analysis of a data set assembled by the Adjuvant Colon Cancer Endpoints group showed that adjuvant chemotherapy provides a significant disease-free survival benefit because it reduces the recurrence rate. The benefit was particularly evident within the first 2 years of adjuvant therapy but some benefit extended to years 3-4[34].

In an observational study of 1291 patients with stage III colon cancer, adjuvant chemotherapy reduced the risk of distant recurrence after surgery by about half. Elderly patients benefited to a similar degree as younger patients [35]. Overall, 56% of the study participants received adjuvant chemotherapy, 31% developed distant metastases, and 37% were 75 years of age or older. In the total population, the use of adjuvant chemotherapy was associated with a significantly reduced risk of distant recurrence. In separate analyses of patients ≤75 years of age and those ≥75 years of age, the effect of adjuvant chemotherapy on recurrence risk was similar in both age groups, with hazard ratios of 0.50 and 0.57, respectively [35].

**Chemotherapy agents and trials:**

*5-Fluorouracil* (5FU) is an antimetabolite and pyrimidine analogue, which acts by irreversible inhibition of the enzyme thymidylate synthase involved in DNA replication, and forms the chemotherapy backbone in CRC [21]. Mainly in the past, 5-FU was administered as a bolus injection either weekly or daily for 5 days, every 4 to 5 weeks. With these regimens, response rates have been approximately 10% to 15%. 5-FU has predominantly gastrointestinal side effects, such as nausea, vomiting, diarrhea and stomatitis. The pattern of 5-FU toxicity differs depending on whether it is administered as a bolus or a prolonged infusion or by other methods. Bolus administration has pronounced myelotoxic effects, whereas the dose-limiting toxic effects of prolonged-infusion 5-FU are mucositis and diarrhea. Palmar-plantar erythrodysthesia (hand-foot syndrome) has been reported with prolonged infusions [18].

*Leucovorin* (LV) is a reduced form of folic acid that acts synergistically with 5-FU, trapping thymidylate synthetase in its inactive form [36], and thus enhancing 5-FU’s antimetabolite effect [37]. Studies have demon-
strated the benefits of 5-FU plus leucovorin in the adjuvant treatment of colon carcinomas. Acceptable adjuvant regimens of 5-FU plus leucovorin for colon cancer include both low-dose leucovorin and high-dose leucovorin regimens. Since the late 80th, 5-FU and LV therapy have become the standard first-line adjuvant chemotherapeutic options in advanced CRC. The addition of LV to 5FU produces a two-fold increase in response rate compared to 5-FU monotherapy (21% v 11%; odds ratio (OR), 0.53; 95% CI, 0.44 to 0.63; p, <0.0001) [38].

The IMPACT investigators conducted a pooled analysis of three large randomized trials comparing adjuvant 5FU/LV to surgery alone in patients with colon cancer where the tumor has penetrated the bowel wall, with or without lymph node involvement [23]. Patients who received adjuvant 5FU/LV had a higher 3-year event free survival (EFS) (71% v 62%), a greater OS (83% v 78%), a 22% reduction in mortality (p, 0.029), and a 35 percent reduction in events (p, < 0.0001) when compared to those who had surgery alone [23].

Toxicities of 5FU are largely dependent on the mode of administration, with better tolerability when given as a continuous infusion via a portable pump when compared to bolus administration. In addition, infusion 5FU is associated with significantly higher response rates (30% for infusion 5FU v 7% for bolus 5FU; p, <0.001) [39]. However, an infusion pump requires central venous access which has potential thrombotic and infectious complications. This led to the development of capecitabine (xeloda), an oral pro-dug of 5FU.

**Capecitabine**

Capecitabine is an oral fluorinated pyrimidine approved by the FDA for adjuvant therapy for patients with stage III colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred. The Xeloda colorectal cancer group conducted a large phase III multicenter randomized clinical trial (RCT) that compared infusion 5-FU to capecitabine. Capecitabine was non-inferior to 5FU, with fewer cases of stomatitis, alopecia and neutropenia, but with a higher incidence of hand-foot syndrome and hyperbilirubinemia [40]. The X-ACT trial showed that adjuvant capecitabine had comparable disease-free survival (DFS), better relapse-free survival (HR 0.86; p, 0.04)(95% CI, 0.75–1), similar OS and significantly fewer adverse events when compared to the adjuvant 5-FU/LV group of patients with Stage III colon cancer [41]. Capecitabine is an alternative for patients who are unlikely to tolerate 5-FU, leucovorin, and oxaliplatin.

**Oxaliplatin** is another chemotherapeutic agent used in the adjuvant setting in colon cancer. It is a third generation antineoplastic platinum agent that inhibits DNA cross-linking. It has enhanced antitumor activity when used in combination with 5-FU/LV. Oxaliplatin’s toxicity
profile includes nausea, vomiting and cumulative, reversible peripheral neuropathy. Patients may also develop a reversible, cold-induced, acute pharyngolaryngeal neuropathy. Peripheral neuropathy is a common and dose-limiting toxicity of oxaliplatin [42, 43].

Other common side effects include nausea, vomiting, diarrhea, liver sinusoidal injury, elevation in transaminases and alkaline phosphatase, thrombocytopenia, and hypersensitivity reactions [44, 45].

In a phase III trial for resected stages II and III colon cancer from Europe (MOSAIC), stage II and III colon cancer patients were randomized following resection with curative intent, to receive either 5-FU/LV or 5-FU/LV plus oxaliplatin (FOLFOX4) [46]. The use of FOLFOX4 compared with the same infusional regimen without oxaliplatin led to a higher 3-year disease-free survival rate (78% vs 73%) in those receiving FOLFOX [46]. Patients in the oxaliplatin-containing group had a 23% reduction in the risk of recurrence at 3-year median follow-up [46].

In a subgroup analysis, a significant disease-free survival benefit was seen for patients with stage III colon cancer and for patients with high-risk stage II colon cancer. A significant overall survival advantage was also seen for patients with stage III disease [41]. More recently, FOLFOX6 or a modified version of it has been used in clinical trials as well as in clinical practice.

In a separate randomized phase III trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) for patients with resected stage II or III colon cancer, FLOX was compared with a weekly bolus of 5-FU and leucovorin. There was a significant improvement in DFS with the addition of oxaliplatin to 5-FU/LV (FLOX) regimen (4-year DFS: 73.2% for FLOX v 67% for 5-FU/LV) [43].

Adjuvant chemotherapy protocols for resectable colon cancer

Stage 0 and I:
Patients do not require adjuvant therapy

Stage IIA, B and C (node-negative):
The value of adjuvant therapy in stage II disease is at best controversial; however, the following regimens may be used [44, 47, 48]:

Capecitabine: 1250 mg/m² PO BID on days 1-14; repeat cycle every 21 d for eight cycles or

Leucovorin 500 mg/m² given as a 2-h infusion and repeated weekly for 6 wk plus 5-fluorouracil (5-FU) 500 mg/m² given as a bolus 1 h after the start of leucovorin and repeated six times weekly; every 8 wk for four cycles or

Leucovorin 400 mg/m² IV over 2 h on day 1 plus 5-FU bolus 400 mg/m² 2, then 1200 mg/m² 2/day for 2 d
Stage II in high-risk or intermediate-risk patients:

Adjuvant therapy for high-risk patients with stage II is an option. Common regimens include 5-FU and leucovorin with or without oxaliplatin or capecitabine, as follows [44]:

mFOLFOX6: Oxaliplatin 85 mg/m² 2 IV over 2 h on day 1 plus leucovorin 400 mg/m² 2 IV over 2 h on day 1 plus 5-FU 400 mg/m² 2 IV bolus on day 1, then 1200 mg/m² 2/day for 2 d continuous infusion; repeat every 2 wk or

FLOX: 5-FU 500 mg/m² 2 IV weekly plus leucovorin 500 mg/m² 2 IV weekly for 6 wk (days 1, 8, 15, 22, 29, and 36) of each 8-wk cycle plus oxaliplatin 85 mg/m² 2 IV administered on days 1, 15, and 29 of each 8-wk cycle for three cycles or

Capecitabine 1250 mg/m² 2 PO BID on days 1-14; repeat cycle every 21 d for eight cycles or

CapeOx: Oxaliplatin 130 mg/m² over 2 h on day 1 plus capecitabine 1000 mg/m² 2 PO BID on days 1-14 every 3 wk for eight cycles or

Leucovorin 500 mg/m² 2 given as a 2-h infusion and repeated weekly for 6 wk plus 5-FU 500 mg/m² 2 given as a bolus 1 h after the start of leucovorin and repeated six times weekly; every 8 wk for four cycles or

Leucovorin 400 mg/m² 2 IV over 2 h on day 1 plus 5-FU bolus 400 mg/m² 2, then 1200 mg/m² 2/day for 2 d (total 2400 mg/m² 2 over 46-48 h) continuous infusion; repeat every 2 wk.

Prognostic and predictive markers for response to chemotherapy

High-risk clinic-pathologic features in colon cancer patients include T4 tumors, poorly differentiated tumors, presence of lympho-vascular invasion, perineural
invasion, or bowel obstruction, pre-operative elevation in CEA levels, close, indeterminate, or positive margins, and inadequately sampled lymph nodes [30].

Microsatellite Instability as a Biomarker in Colorectal Cancer

Biomarkers can be classified as being prognostic or predictive. Prognostic biomarkers can give us information on the likely outcome of a cancer in an untreated individual. Presently, this term is also used to predict outcomes in patients treated with chemotherapy, which has the potential to impact the natural history of the disease. Predictive biomarkers give information on a subpopulation of patients that can respond to a given therapy.

Genetic alterations have been used as predictive markers for response to chemotherapy. Mismatch repair genes “MMR” genes, primarily MLH1 and MSH2 are responsible for the production of MMR proteins involved in repair of microsatellite instability (MSI) occurring during DNA replication. MSI can serve as a prognostic and predictive biomarker in colon cancer [49].

Mutations in MMR genes are seen in Lynch syndrome—previously called hereditary nonpolyposis CRC “HNPCC” [49, 50], and may occur in about 15% of patients with sporadic colon cancer [51]. This leads to MSI that can be categorized based on degree of instability into MSI-high (MSI-H), MSI-low (MSI-L), or microsatellite stable (MSS) [51].

Microsatellite Instability and Outcomes in Colorectal Cancer

CRCs with MSI have a statistically significantly better prognosis compared with those with intact mismatch repair [52]. MMR status is a prognostic and predictive factor in colon cancer. The presence of an MMR gene mutation correlates with a better prognosis. Patients who express MMR gene proteins as MMR proficient (pMMR) patients have been shown to have an increased rate of death from recurrent disease compared to their MMR deficient (dMMR) counterparts (32.8% v 8.8%; p, <0.0001). Similar outcomes were noted in MSI-L/MSS v MSI-H patients (35.1% v 10.7%, p, 0.0002) [53].

Tumor specimens were collected by Ribic et al from patients with colon cancer who were enrolled in five randomized trials of fluorouracil- (FU-) based adjuvant chemotherapy. Among 287 patients who did not receive adjuvant therapy, those with tumors displaying high-frequency MSI had a better 5-year survival rate than patients with tumors exhibiting microsatellite stability or low-frequency instability (hazard ratio for death [HR], 0.31; 95% confidence interval [CI], 0.14–0.72; P = 0.004) [53].

Popat et al reviewed 32 eligible studies of 7642 patients, including 1277 with MSI. The combined HR for overall survival (OS) associated with MSI was 0.65 (95%
CI, 0.59–0.71; P = 0.16). This benefit was maintained when restricting analyses to clinical trial patients (HR, 0.69; 95% CI, 0.56–0.85) and patients with locally advanced CRC (HR, 0.67; 95% CI, 0.58–0.78) [52].

An analysis of MSI from archival tissues from four National Surgical Adjuvant Breast and Bowel Project (NSABP) adjuvant chemotherapy trials was conducted by Kim et al. [54]. In an analysis using the entire cohort of patients (treated and untreated), there was a suggestion of an increased relapse-free survival (RFS) for the MSI-H versus the MSS/MSI-L patients. The estimated relative risk (RR) of relapse for MSI-H patients versus MSS/MSI-L patients was 0.68 (95% CI, 0.42–1.09, P = 0.10). In this cohort, there was little evidence of an association with OS. RR of death for MSI-H patients versus MSS/MSI-L patients was 0.91 (95% CI, 0.59–1.4; P = 0.67) [54].

In a pooled analysis of 1027 patients by Sargent et al, dMMR status was associated with improved disease-free survival (DFS; HR, 0.51; 95% CI, 0.29–0.89; P = 0.009) and OS (HR, 0.47; 95% CI, 0.26–0.83; P = 0.004) in patients who were not treated with 5FU-based adjuvant therapy. No association was observed between MMR status and outcome in FU-treated patients (DFS: HR, 0.79; 95% CI, 0.49–1.25; P = 0.30; OS: HR, 0.78; 95% CI, 0.49–1.24; P = 0.28).

Sargent et al. [55] demonstrated that when compared to surgery alone, adjuvant 5FU improved DFS in pMMR patients (HR, 0.67; p, 0.02), while this benefit was not seen in dMMR patients receiving adjuvant chemotherapy (HR, 1.10; p, 0.85). Moreover, adjuvant chemotherapy in stage II dMMR patients led to a lower OS in comparison to surgery alone (HR, 2.95; p, 0.04). Multiple gene assays have been developed for stage II and III colon cancer patients to identify those who would benefit from chemotherapy [56]. Oncotype DX colon cancer assay measures the expression of seven recurrence risk genes and five reference genes, and has been shown to adequately estimate recurrence risk [57], with higher scores corresponding to an increased absolute benefit with oxaliplatin therapy [58].

**Adjuvant systemic chemotherapy in elderly patients**

Elderly patients (65 years and older) have the highest incidence of colon cancer [59] and are often underrepresented in large clinical trials. The decision on chemotherapy in this group can be challenging given their multiple comorbidities and medical unfitness for chemotherapy. A pooled analysis of seven phase 3 RCTs evaluating the role of 5FU-based chemotherapy in patients with resected stage II or III colon cancer, showed a higher 5-year OS in patients who received adjuvant chemotherapy (71% v 64%; (HR, 0.76; 95% CI, 0.68 - 0.85). There was no significant interaction between age and efficacy of treatment. The incidence of toxicities was not increased among patients older than age 70, except for an increased risk of
leukopenia in one study [60]. To further support these findings, a recent subgroup analysis of the MOSAIC trial established no statistically significant interaction between DFS, time to recurrence, or OS among 315 stage II and stage III patients aged between 70 and 75 who received chemotherapy with 5-FU/LV and oxaliplatin (FOLFOX) versus 5-FU/LV alone [60].

**Conclusion**

The use of systemic chemotherapy has markedly improved outcomes in patients with colon cancer. Understanding the pharmacology of each chemotherapeutic agent has helped clinicians and researchers combine therapies leading to a synergistic effect. Scientific research has helped develop treatments tailored to patient and tumor characteristics. The relative resistance of certain tumors to conventional therapies is now better understood with the use of biomarkers in predicting response. While stage I and favorable risk Stage II CRC can be cured with surgery alone, patients with high-risk Stage II and Stage III disease benefit from adjuvant chemotherapy.

**Acknowledgement**

Thanks for my colleagues from Tanta University Hospital, Clinical Oncology Department who provided insight and expertise that greatly assisted me.

Great thanks for my colleague who share in our project from Competitive Excellence Project of Egyptian Higher Education Institutions since 2014. I serve as President of the executive teams of the outputs of the training in (Genetic Signature center for fostering next generation translational cancer research) which a clear mission to facilitate research and training in miRNA in cancer.

I would like to thank all staff members in “Klinikum Augsburg Medicine II Clinic– Academic Teaching Hospital Ludwig Maximilian- Munich University- Germany” for assistance with [particular technique, methodology in research] which greatly improved my experience in this field. This was during working on my MD thesis titled” Study the value of chemotherapy with or without radiotherapy in colorectal cancer”. Specially thanks for both Dr. med. Daniel OruzioE-Mail: daniel.oruzio@klinikum-augsburg.de and Professor Dr. med. Günter SchlimokE-Mail: schlomok@klinikum-augsburg.de.

I would also like to thank my patients for sharing their pearls of wisdom with me during the scientific research life.
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