Chapter

Adjuvant Therapies in Colon Cancer

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Abstract

Most of the patients with localized colon cancer undergo curative resection. However, significant number of patients will recur with metastatic disease, especially those with node positive cancer. Adjuvant chemotherapy has shown to improve cure rate and survival by eradicating micrometastases. The benefit of adjuvant therapy is well established in node-positive cancers, while their role in stage II cancer is not well defined. A number of molecular markers have been identified that are prognostic and/or predictive in colon cancer. Such molecular markers, and other clinicopathological features play an important role in selection of appropriate therapy and duration of treatment. Emerging evidence for the utility of genomic profiling or detection of circulating tumor DNA (ctDNA) are promising which may further facilitate decision making in the future. This chapter reviews the evolution of adjuvant therapy for resected colon cancer, the current evidence and the factors influence the choice of therapy.

Keywords: colon cancer, adjuvant therapy, mismatch repair, BRAF, RAS

1. Introduction

Colon cancer is a major cause of morbidity in the world and the second most common cause of cancer death. Most patients undergo curative resection of the primary colon cancer and removal of regional lymph nodes. Colon cancer mortality rates have improved over the years with the advancement of surgical techniques, diagnostic modalities and systemic therapy (**Figure 1**). Most important prognostic determinant is the stage of the cancer. The original pathological staging system used for colon cancer was the Dukes staging system which was based on the extent of penetration of the cancer through the bowel wall and whether there was involvement of regional lymph nodes (**Table 1**). It was originally described for rectal cancer but applied to colon cancer as well [2].

Staging of colon cancer has been further refined in detail and standardized according to the AJCC (American Joint Committee for Cancer)/UICC (Union for International Cancer Control) TNM staging system of which the latest version is the eighth edition which was adopted in 2018 [3]. The tumor and node definitions are shown in **Table 2**. Primary tumor and nodal factors define the stages as shown in **Table 3**.

The risk of recurrence increases with the stage, especially when there are nodal metastases. Postoperative adjuvant chemotherapy is utilized to eradicate the micrometastases which reduce the risk of recurrence and improve the cure rate. The role of adjuvant chemotherapy is well defined I stage III colon cancer; however, it

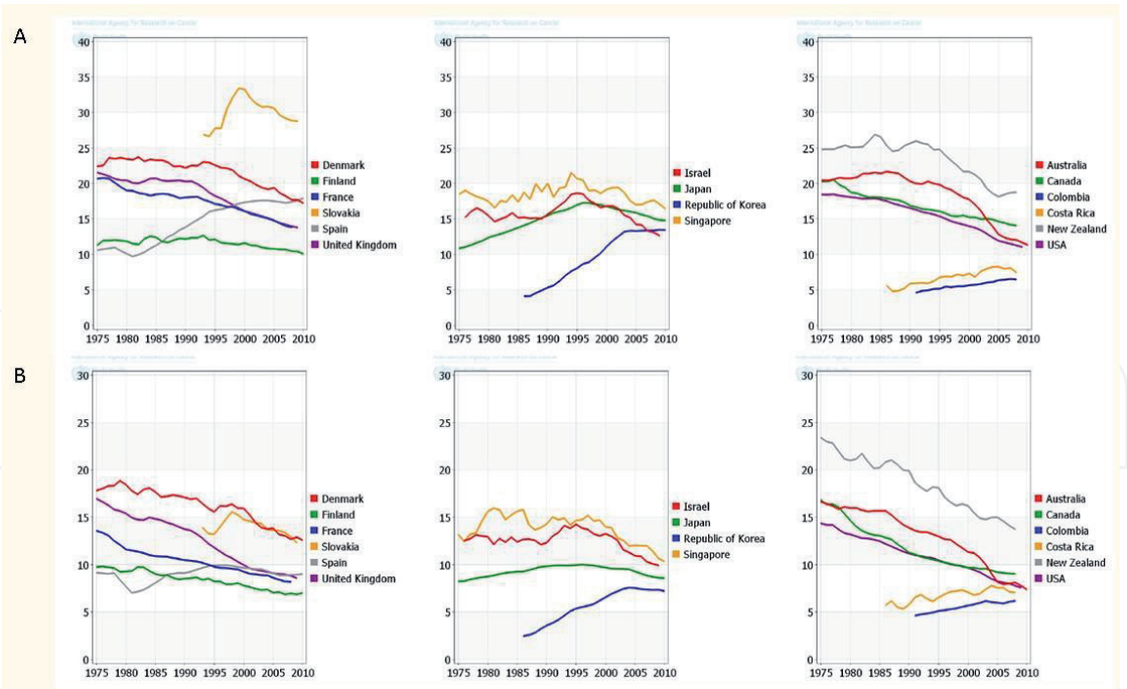

Figure 1.
Colon cancer related mortality from 1975 to 2010, (A) in males and (B) in females. Figures are from International Agency for Research on Cancer, global cancer observatory website [1].

Stage	Description
Dukes A	Tumor confined to within submucosa
Dukes B1	Tumor penetrates muscularis propria but not through bowel wall
Dukes B2	Tumor penetrates through bowel wall
Dukes C1	Tumor not through bowel wall with lymph node metastases
Dukes C2	Tumor through bowel wall with lymph node metastases

Table 1.
Dukes staging system for colorectal cancer.

T—Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intramucosal (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades submucosa (through muscularis mucosae but not into the muscularis propria)
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria into pericolorectalic (subserosal) tissues
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor penetrates to the surface of the visceral peritoneum (including gross perforation of the bowel through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to other organs or structures
N - Regional lymph node	
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph nodes metastases

N1	One to three regional nodes are positive (tumor in lymph nodes measuring >0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the • subserosa • mesentery • or non-peritonised pericolic or perirectal/mesorectal tissues
N2	Four or more regional lymph nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive
M - Distant metastasis	
Mo	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified

Table 2.
The tumor, node, metastasis (TNM) staging system.

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0

Table 3.
Prognostic stage groups.

remains controversial in stage II. This chapter reviews the role of adjuvant therapies in resected colon cancer.

2. Primary treatment of colon cancer

About 70–80% of patients diagnosed with localized non-metastatic colorectal cancer undergo curative resection which is the main modality of treatment for those

with good performance status and acceptable comorbidities. This is achieved by surgical resection of the primary tumor, anastomosis of the bowel and removal of 12 or more regional lymph nodes. The aim of oncological resection is the complete removal of the tumor and potential lymphovascular spread with a clear margin of at least 5 cm proximally and distally for colon cancer, and minimal proximal margin of 5 cm and distal of 2 cm for rectal carcinoma. Circumferential/radial margin clearance of at least 1 mm is considered optimal. Endoscopic resection involves complete tumor resection and adjacent tissue in one block. This may be acceptable for those accept vigorous close surveillance and potential need for further surgical resection or those who are non-surgical candidates.

3. Adjuvant therapies

3.1 Drugs used: 5FU, capecitabine, oxaliplatin

3.1.1 5-Fluorouracil (5-FU)

5FU is an antimetabolite drug that inhibits DNA and RNA synthesis by acting as a false substrate in purine and pyrimidine synthesis thereby interfering in the S phase of the tumor cell cycle. It is metabolized by the rate limiting enzyme dihydropyrimidine dehydrogenase. The main toxicities are related to mucosal inflammation and this presents clinically as mucositis, stomatitis and diarrhea. It can also cause nausea and myelosuppression. Rarely, it can cause cardiotoxicity presumably by inducing coronary artery spasm.

3.1.2 Capecitabine

Capecitabine is an oral fluropyrimidine prodrug which is taken up inside the tumor cells and metabolized to the active 5FU product by thymidine phosphorylase. Repeated oral administration mimicks the pharmacokinetics of protracted infusional 5FU. The side effects are similar to 5FU in term of mucositis and diarrhea but hand-foot syndrome or palmar-plantar erythrodysesthesia with redness, tenderness and swelling of these areas is a common toxicity experienced.

3.1.3 Oxaliplatin

Oxaliplatin is a third-generation platinum drug which acts as an alkylating agent in causing DNA damage by intrastrand crosslinks. The drug is not nephrotoxic or ototoxic but the main side effect is cold related dysesthesia which can lead to cumulative sensory neuropathy. It is moderately emetogenic and myelosuppressive. It exhibits synergy with fluoropyrimidines and so is normally used in combination with this class of cytotoxics.

3.2 Historic data; levamisole, folinic acid

3.2.1 Levamisole

Levamisole is an anti-helminthic drug that is used in veterinary medicine. It was found to have effects on phagocytosis and chemotactic responses of neutrophils as well as on stimulation of lymphocyte proliferation, differentiation and cytotoxicity suggesting an immunomodulatory effect. Preclinical studies suggested an antimetastatic effect in tumor xenograft models.

The initial Leicester trial randomized patients after curative surgery either to observation, 5FU, or 5FU plus levamisole. 5FU was administered intravenously for # days following surgery, and then orally once weekly for 6 months; levamisole was administered for only three postoperative days. After 5 years of follow-up, the survival of patients randomized to 5FU plus levamisole was significantly prolonged compared with 5FU alone ($p = 0.02$) or observation ($p = 0.045$).

Levamisole alone, given intermittently for 1 year, did not produce a survival benefit in an EORTC trial with Dukes C colon cancer patients [4]. In the NCCTG trial levamisole was inferior to the combination with 5FU [5].

Two trials the US Intergroup 0035 and the Netherlands Adjuvant Colorectal Cancer Project (NACCP) study both found a significant benefit of 5FU and levamisole in the adjuvant therapy of resected colon cancer compared to observation [6]. A subsequent meta-analysis of these two studies found that after adjustment for the total planned 5FU dose the effect of levamisole became non-significant. Subsequent trials disproved the benefit of levamisole in adjuvant therapy of colon cancer [7, 8].

3.2.2 Leucovorin (folinic acid)

Leucovorin is an active metabolite of folic acid which works by enhancing enzymatic binding of 5FU onto thymidylate synthetase to prolong the half-life of 5 U and therefore potentiates the 5FU. It is not a cytotoxic agent on its own. Rarely, it can cause rash or itch.

Clinical trials compared 5FU-leucovorin regimens to 5FU-levamisole regimens and disproved the benefit of levamisole. The INT-0089 and QUASAR studies have demonstrated that there is no difference in outcome between the use of high dose or low dose leucovorin [7, 8].

3.3 Stage I colon cancer

Stage 1 colon cancer is often an incidental finding in those patients undergoing polypectomy. Therefore, pedunculated polyps should be resected with excision of the stalk down to the base. When stage 1 colon cancer is found in a polyp that was completely excised with clear margin of more than 2 mm, further surgical excision may not be required, provided there are no high risk features such as lymphovascular invasion, poor cell differentiation, and malignant invasion beyond stalk. Such patients with high risk features should undergo further excision like segmental resection for complete staging. Sessile polyps with invasive cancers also can be managed with segmental colon resection unless they can be removed in one piece [9]. An estimated 5% of resected polyps and 20% of unresectable polyps contain invasive cancer [10]. Five-year survival rate for stage 1 colon cancer is more than 95%, and adjuvant therapy is not indicated [11].

3.4 Stage II colon cancer

The role of adjuvant chemotherapy in stage II is not clearly defined. 5-year disease free survival for these patients is more than 80%. Because of this relatively good prognosis, benefit from adjuvant 5FU-based chemotherapy is small and remains questionable given many of the trials are underpowered. In order to demonstrate a larger benefit or to unravel small differences with statistical significance, a highly efficacious therapy or trials with larger samples are needed. To detect an absolute improvement in survival at 5 years by 4% with more than 90% power, 4700 patients with stage II colon cancer would be required. A retrospective study based on SEER-Medicare linked database explored the outcome of more

than 3000 patients without any adverse features depending whether they received chemotherapy within 3 months after surgery or not. Interestingly, 27% of patients received adjuvant therapy in this group without much evidence to support it [12]. They reported a 5-year survival of 75% for those who did not receive chemotherapy versus 78% in those who received therapy. High grade, younger age, low comorbidities and white race were more likely to receive chemotherapy. After adjusting for known variables there was no difference in survival (HR 0.91, 95% CI 0.77–1.09).

A number of trials have tried to address the role of adjuvant therapy in stage II colon cancer with conflicting results. QUASAR (Quick and Simple and Reliable), a large UK study investigated the role of adjuvant 5FU in this randomized controlled trial [13]. This study enrolled more than 3000 patients with (91%) stage II cancers (node-negative) which also included 30% rectal cancer. After a median follow up of 5.5 years, there was about 20% reduction in the relative risk of death (any cause mortality HR 0.82; 95% CI 0.70–0.95; $p < 0.008$) in those treated with chemotherapy compared to placebo controlled arm which translated into small but significant absolute survival benefit of 3.6% (95% CI 1.0–6.0). Despite significant results, number of pitfalls in this trial has raised questions with regard to the benefit seen. The median number of lymph nodes removed in this study was 6 (in more than 60% of patients <12 lymph nodes were removed) which is well below current standards. In addition, there was a group of patients who received radiation therapy (14%) and another proportion received portal vein infusion therapy (6%), which are not standard practice.

There were a number of meta-analyses which support the use of adjuvant therapy in stage II colon cancer including NSABP, NCCTG and IMPACT. International Multicenter Pooled Analysis of Colon Cancer Trial (IMPACT) was a pooled analysis of randomized trials, showed a 2% improvement in 5-year overall survival. In another analysis of more than 150,000 patients with stage II colon cancer from National Cancer Database reported survival advantage of adjuvant therapy (HR 0.76; $p < 0.001$) [14]. Gill et al. analyzed pooled individual patient data of 3302 patients with stage II and stage III colon cancers. Although there was a statistically significant improvement in disease free survival (by 4%), overall survival difference (absolute benefit of 5%) was not significant [15]. The Adjuvant Colon Cancer End Points (ACCENT) collaboration analyzed individual patient data with regard to long term outcome after adjuvant therapy. Among 6900 patients with stage II cancers, there was 5% improvement survival at 8 years [16].

Given the conflicting data, adjuvant therapy in stage II colon cancer remains controversial. Several clinicopathological features and molecular markers are associated with poor prognosis in stage II colon cancers. These include T4 primary, bowel obstruction of peroration, poorly differentiated phenotype (including signet ring cells and mucinous) high pre-operative carcinoembryonic antigen (CEA), inadequate lymph node sampling (<13 nodes), lymphovascular space invasion and perineural invasion [17, 18]. Although most expert groups consider these factors as high risk features in stage II colon cancer, some discrepancy exist among their definition for high risk stage colon cancer [19–21]. While most expert groups recommend to consider these adverse factors when considering adjuvant therapy, there is limited evidence to suggest that the presence of one or risk factors are more likely to benefit from adjuvant therapy. In the landmark MOSAIQ trial, 434 patients were considered high risk stage II colon cancer. Although there was trend towards better disease-free survival in the FOLFOX arm compared to 5FU arm, overall survival was essentially similar [22]. The decision regarding adjuvant therapy in this setting will need to be individualized and take into account the patient's preferences regarding therapy.

3.4.1 Role of oxaliplatin

Two large phase III trials explored the role of oxaliplatin in stage II colon cancer; MOSAIC and NSABP C-07 which have virtually shown the lack of benefit of oxaliplatin in stage II colon cancer [22, 23]. Forty percent and 27% of patients were stage II in MOSAIC and NSABP C07 trials, respectively. An updated 10-year follow up report of MOSAIC confirmed the lack of benefit from oxaliplatin in stage II colon cancer. In fact there was a trend towards adverse outcome in low-risk stage II in MOSAIC, while there is a non-significant trend of improvement in disease free survival (7%) and overall survival (2%) [22]. No disease-free survival or overall survival benefit was seen in NSABP C-07 trial in patients with stage II colon cancer [23]. Therefore oxaliplatin is unlikely to benefit most patients with stage II colon cancer; however, it may be appropriate to discuss oxaliplatin in those with extremely high risk features, given the findings from MOSAIC.

3.5 Stage III colon cancer

Patients with node positive colon cancer are at higher risk of recurrence with a 5-year overall survival estimate of 40–60%. Adjuvant therapy is indicated for most patients with stage III disease to eliminate micro metastases and to improve disease free survival and overall survival. Combination 5FU/leucovorin and oxaliplatin regimen is the standard of care unless they are medically unfit to receive intensive chemotherapy where single agent 5FU/Leucovorin may be appropriate.

A landmark study in the 1990s established the benefit of adjuvant therapy in resected stage III colon cancer where 5FU/levamisole for 12 months decreased recurrence and improved survival [5]. Results remained significant at 5 years with a 41% reduction in recurrence and 33% reduction in death [24]. However subsequently leucovorin has emerged as an effective potentiator of anti-tumor activity of 5FU, whereas levamisole lacked significant biological activity. 5-FU is metabolized in cancer cells to 5-fluorouridine 5′-monophosphate (FUMP), by uridine monophosphate synthetase, with a resultant active form, 5-fluoro-2′-deoxyuridine 5′-monophosphate (FdUMP). FdUMP then forms a ternary complex with thymidylate synthase in the presence of reduced tetrahydro folate (5,10-CH_2-THF) which eventually inhibit DNA replication. Leucovorin is metabolized into 5,10-CH_2-THF and enhance formation of thymidylate synthase/5FU ternary complex and anti-tumor activity. Subsequent studies confirmed the lack of utility of levamisole and efficacy of leucovorin in combination with 5FU in adjuvant therapy of colon cancer [25].

Two large randomized studies established the role of oxaliplatin in the adjuvant treatment of stage III colon cancer. Multicentre International Study of Oxaliplatin/5FU/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIQ) utilized a 2 hour bolus infusional 5FU followed by 22 hours 5FU infusion along with oxaliplatin in a 2 weekly cycle (FOLFOX4) for 6 months in resected colon cancer patients (60% stage III and 40% stage II). A total of 2246 patients were randomized to receive either FOLFOX4 or 5FU/leucovorin. In the intention to treat population FOLFOX4 significantly improved 5-year disease free survival (73.3% 67.4%) compared to 5FU/leucovorin (HR 0.80, 95% CI 0.68–0.93; p = 0.003). Overall survival at 6 years was 78.5% versus 76.0% (HR 0.84; 95% CI, 0.71–1.00; p = 0.04). In a subgroup analysis, there was 4.2% improvement by the addition of oxaliplatin in 6-year overall survival in stage III disease (72.9% versus 68.7%, HR =0.80; 95% CI =0.65–0.97; p = 0.023), however, no overall survival benefit was evident by the addition of oxaliplatin in stage II cancer (85% versus 83.3%, p = 0.65). In a 10-year updated analysis, results essentially remained consistent. Oxaliplatin was approved for adjuvant treatment of colon cancer and is the standard of care for most patients

with stage III colon cancer. The FOLFOX4 regimen is associated with more toxicity compared to 5FU/leucovorin, notably grade 3/4 neutropenia was 41% in FOLFOX4 compared to 5% in 5FU/leucovorin and grade 3/4 diarrhea was 11% versus 7%. Oxaliplatin was associated with cold related dysesthesia and mostly reversible peripheral sensory neuropathy. Grade 3 neuropathy was reported in 12% of patients who received FOLFOX4. Although considered reversible, minority of patients may suffer long term or permanent sensory loss. About 30% of patients still had residual numbness at 12 months (5.9% grade 2/3) with another 24% experiencing some degree of neuropathy at 18 months from the end of treatment (3.9% grade 2/3).

A large second study confirmed the efficacy of oxaliplatin in adjuvant therapy for stage III colon cancer. NSABP C-07 enrolled 2409 patients with stage III (71%) and stage II (29%) colon cancer. They were randomized to receive either combination 5FU/leucovorin/oxaliplatin (FLOX) or 5FU/leucovorin. A weekly bolus 5FU Roswell Park regimen was used here instead of infusional 5FU. FLOX regimen improved disease-free survival compared to control arm (69.4% versus 64.2%; HR 0.82; 95% CI 0.72–0.93; p = 0.002), however overall survival differences were not statistically different. (HR 0.88; 95% CI 0.72–1.02; P = 0.08) No interaction was seen between treatment on the stage, however treatment effect did vary by age overall survival significantly improved in patients younger than 70 (HR 0.80; 95% CI 0.68–0.95; p = 0.01) with no effect seen in older patients [23]. However, FLOX regimen was associated with high incidence of grade 3/4 diarrhea (38% versus 32%) and hospitalization (5.5% versus 3%). Given the lack of survival benefit and toxicity with bolus 5FU regimen, infusional 5FU regimens like FOLFOX have become standard of care.

The XELOXA trial supported the benefit of oxaliplatin in combination with capecitabine. In this randomized trial, 1866 patients with stage III colon cancer were either treated with capecitabine/oxaliplatin or bolus 5FU/leucovorin regimen (Mayo clinic or Roswell Park) for 6 months. After a median follow up of 7 years disease free survival (63% versus 56%, HR 0.80; 95% CI; 0.69–0.93; p = 0.004) and overall survival (73% versus 67%, HR 0.83; 95% CI 0.70–0.93; p = 0.04) improved significantly compared to 5FU/leucovorin.

In all three trials oxaliplatin was associated with significant neurotoxicity which can be acute or chronic. Acute cold related neurotoxicity present as paresthesia or dysesthesia of hands and feet or muscular cramps including laryngospasm. This is often reversible but tends to recur with each treatment. On the other hand chronic neuropathy causes primarily a sensory neuropathy in limbs is thought to be due to accumulation of platinum products in dorsal root ganglia in a dose -dependent manner. About 10–15% of patients experience severe neuropathy after cumulative dose of 780–850 mg/m^2. Other clinical factors are implicated in the onset of neuropathy, but none shows strong association. Patents with existing other comorbidities such as diabetes, hypertension and smoking may be associated with higher incidence of neuropathy from oxaliplatin, these results were not statistically significant. But patients with diabetes seem to develop neuropathy at lower cumulative dose [26]. Another report suggests that incidence neuropathy may be less XELOX 3-wekely (130 mg/m^2) regimen than FOLFOX 2-weekly (85 mg/m^2) regimen [27]. Therefore, choice of oxaliplatin in the adjuvant treatment of colon cancer should be based on individual assessment of risk of recurrence and other clinical factors.

3.5.1 Role of radiation

Adjuvant and neoadjuvant radiotherapy is routinely used in the treatment of rectal cancer and has an impact on reducing the local recurrence rate and

therefore improving local control. However, the use of this modality in non-rectal colon cancer is controversial and not supported by randomized controlled trials. It is however considered in the situation of T4 tumor which invades surrounding structures such as the bladder or the abdominal wall where there is a perceived high risk of local recurrence of the tumor. A retrospective analysis of 21,789 patients with T4 colon cancer using the US SEER (Surveillance, Epidemiology and End Results) database found 1001 patient who received radiotherapy [28]. After adjustment for sex, age, N stage and tumor grade the relative risk of death from cancer at 5-years was 0.88 (95CI 0.8008–0.9779, p = 0.0165) in patients who received radiotherapy.

3.6 Role of adjuvant therapy for resected colorectal cancer metastases

Liver is the commonest site of metastases in colon cancer. Unlike many other solid organ cancers, metastasectomy improves survival in colorectal cancer, where 5-year overall survival may reach 50%. The best postoperative management strategy is not well defined, however, often perioperative chemotherapy is utilized in the form of FOLFOX or CAPOX with agents like irinotecan, anti-EGFR, or anti-VEFG therapy often added for eligible patients in the neoadjuvant setting if downstaging was necessary. In the EORTC 40983 trial, perioperative chemotherapy was associated with 7.3% absolute increase in 3-year progression-free survival, however there was no difference in overall survival [29, 30]. Another Japanese study also did not show overall survival benefit with adjuvant chemotherapy [31]. Given the established role of adjuvant therapy in stage III colon cancer, despite lack of strong evidence many expert groups support perioperative or postoperative chemotherapy for resectable colorectal cancer metastases.

4. Molecular markers

4.1 Mismatch repair enzyme deficiency

Colon cancers that lack mismatch repair enzyme (dMMR) exhibit high microsatellite instability (MSI-High) and are associated with better prognosis compared to those with proficient mismatch repair enzymes (pMMR). Consistently, frequency of dMMR is higher in stage II colon cancer (20%) compared stage III (12%) and stage IV (4%) [32]. In a seminal study by Ribic et al., reported the prognostic differences between dMMR and pMMR in 570 patients from 5 different trials of 5FU based adjuvant chemotherapy (stage II and III) [33]. Five-year overall survival was significantly better in dMMR compared to pMMR(HR 0.31; 95% CI, 0.14–0.72;p = 0.004). Furthermore, there was no survival difference between dMMR and pMMR among those who received adjuvant chemotherapy (HR 1.07; 95% CI, 0.62–1.86; p = 0.80). The benefit of adjuvant chemotherapy was restricted to those with pMMR only. Although not all studies are consistent, a systemic review of 32 trials supported the above finding [34]. The key enzyme involved 5FU metabolism in cancer cells, thymidylate synthase, is found to be overexpressed in dMMR colon cancers which confer resistance to 5FU based therapy. Therefore, most patients with stage II colon cancer would not benefit from 5FU (only) based adjuvant therapy. Nevertheless, the role of dMMR in adjuvant therapy for stage III colon cancer is less clear. Despite lack of prospective data, retrospective studies support the use of oxaliplatin based adjuvant therapy, although Sinicrope et al. reported reduced distant recurrence in stage III cancers after treatment with 5FU [35, 36].

4.2 Other molecular markers

Lack of CDX2 was associated with lower 5-year survival rate compared to CDX2-positive tumors, especially in stage II tumors (49% versus 87%, p = 0.003). CDX2 was also predictive of treatment benefit with higher disease-free survival in CDX2-negative tumors in both stage II and III tumors. This need to be further validated in prospective studies. The presence of BRAF V600E mutation confers a poor prognosis in colon cancer; however, concomitant loss of one or more MMR enzymes (dMMR) seems to improve the survival. In an analysis of three adjuvant chemotherapy trials of stage II and III colon cancer, BRAF mutation was not prognostic, however overall survival was poor among those with pMMR [32]. While another study of 2299 patients from two NSABP trials showed similar results, where BRAF mutation was not predictive of oxaliplatin benefit [37]. The presence of RAS (KRAS and NRAS) mutation is associated with resistance to EGFR targeted therapy in metastatic colon cancer. Although the presence of KRAS mutation seems to confer poor prognosis, not all studies are consistent [32, 37–39]. Number of other molecular markers such as DCC, TP53, thymidylate synthase and POL-E are also found to have prognostic significance [40–43]. Despite emerging evidence of these molecular markers, their predictive value is still not validated in clinical practice and they are not routinely considered in decision making regarding adjuvant therapy, except for MMR status.

Gene expression profiling has been utilized to characterize colon cancers and to identify gene signatures that could be predictive and prognostic. A number of commercial assays are developed in the recent past (OncoDefender-CRC, ColonPRS, ColoPrint colon cancer recurrence assay, GeneFx colon) but none have been approved for routine use in clinical practice. The Oncotype-DX colon cancer assay is perhaps the most validated tool which is a 12-gene assay developed to predict the recurrence score in stage II colon cancer. It was validated using prospective data from large studies including QUASAR, CALGB9581 and SUNRISE [44–46]. Despite the ability in predicting the risk of recurrence with confidence, it is unclear whether patients in higher risk category will benefit from adjuvant chemotherapy. A treatment score was developed using the data from QUASAR, but it was not predictive of the treatment effect. At this stage the data are insufficient to recommend routine use of multi-gene assays when deciding adjuvant therapy for stage II colon cancer.

4.3 Circulating tumor DNA (ctDNA)

Gene sequencing of colorectal cancer have identified number of common somatic mutations and these tumor-specific mutations can be utilized to detect the tumor DNA (ctDNA) in the cell free component of peripheral blood. Detectable ctDNA after surgical resection or after completion of adjuvant chemotherapy seem to be associated with high risk of recurrence. In a study of 230 patients with resected stage II colon cancer, 14 patients out of 178 who did not receive adjuvant chemotherapy had detectable ctDNA. Eleven of the 14 (79%) developed recurrence at a median follow up of 27 months. Among those who received chemotherapy 3/44 had detectable ctDNA and all of them have relapsed within 11 months [47]. In metastatic setting, changes in ctDNA correlate with radiological responses [48]. Consistently in the early stage colon cancer, patients who clear ctDNA after adjuvant therapy have favorable prognosis [49]. Currently available data suggest that ctDNA is robust marker of minimal residual disease after surgery or after adjuvant chemotherapy with good prognostic and predictive value. Although current assays used to detect ctDNA have high specificity and positive predictive value, the sensitivity of these assays need optimization. In addition, a consensus on the methodology and larger number of prospective trials are needed before their routine use in clinical practice.

5. Timing of chemotherapy

Adjuvant therapy should be initiated as soon as patient has recovered from surgery with complete healing of surgical wounds which usually takes about 2–4 weeks. A meta-analysis in 2019 which included 34 comparative studies of resected colon cancer reported that delay in treatment beyond 6–8 weeks was associated with inferior survival (HR 1.27,95% CI 1.21–1.33; $p < 0.001$) [50]. Another review which included more than 15,000 patients concluded that a 4-week increase in time to initiate adjuvant chemotherapy was associated with a 14% relative decrease in disease free survival and overall survival [51]. A number of other studies have consistent findings suggesting inferior outcomes when chemotherapy was initiated more than 6–8 weeks. However, most of these studies are retrospective in nature and potentially biased by confounding factors such as comorbidities, post-operative complications, and emergency resections which are all likely to delay the recovery.

6. Duration of therapy

The recommendations for duration of adjuvant therapy for colon cancer are evolving. Early adjuvant trials treated patients for 12 months with 5FU/levamisole which was the standard of care in 1990s. Subsequent studies revealed 6 months of therapy was at least comparable to 12 months which became the standard of care in late 1990s [25, 52]. MOSAIQ an NSABP C-07 trials utilized 6 months of oxaliplatin and 5FU based regimen which remained as standard practice until recently the IDEA (International Duration Evaluation of Adjuvant Chemotherapy) collaboration study explored non-inferiority of 3 months of adjuvant therapy versus 6 months. IDEA collaboration study was a prespecified exploratory combined analysis of six separate international randomized trials of 6 versus 3 months of oxaliplatin based adjuvant therapy. Although non-inferiority of 3-months was not proven in the intention to treat population, sub-group analysis revealed patients those who received capecitabine and oxaliplatin (CAPOX) for 3 months, 5-year disease free survival was non-inferior to 6 months, however 3 months of 5FU and oxaliplatin FOLFOX did not meet the non-inferiority margin [53, 54]. Among low risk patients (T1–3,N1) the 5-year overall survival benefit between 3 versus 6 months therapy was 89.6% versus 88.9% (absolute difference of 0.7%) whereas the absolute difference was 2.7 among higher risk patients (T4N2 and above). Therefore, in lower risk patients, 3 months of therapy is acceptable if CAPOX regimen was chosen, while 6 months of therapy should be offered with FOLFOX regimen for others with stage III disease with clear discussion with patients regarding the small added benefit and risk of long-term neuropathy. 5FU/Leucovorin without oxaliplatin is offered as adjuvant therapy in stage III colon cancer sometimes, when patients are medically unfit or elderly. Six months adjuvant therapy is the standard recommendation in this situation, given absence of prospective data comparing 3 months versus 6 months. Similarly, 6 months of 5FU based adjuvant therapy is standard in stage II colon cancer. However, patients with high risk stage II disease are sometimes treated with oxaliplatin based regimen. TOSCA trial investigated 3 months versus 6 months of adjuvant therapy in stage II and III colon cancer where one-third of them were stage II [55]. In the overall population, 6 months was superior to 3 months, however, 3 months of CAPOX regimen was non-inferior to 6 months. There were 1254 patients with high risk stage II disease in the IDEA collaborative study (including TOSCA study) which investigated the optimal duration of adjuvant therapy [56]. Investigators concluded that 3 months of CAPOX may be non-inferior to 6 months

in high risk stage II cancers, reflecting the finding in stage III disease. Consistently 3 months of FOLFOX was not non-inferior to 6 months.

7. Adjuvant therapy in elderly

Systemic chemotherapy in older adults may possess unique challenges due to comorbidities, and age-related organ dysfunction which may limit their life expectancy. In addition the impact on quality of life from chemotherapy may be more prominent in older adults. Benefit of adjuvant chemotherapy in older adults is well established. A pooled analysis of seven randomized trials of adjuvant chemotherapy (5FU/levamisole or 5FU/leucovorin) in stage II and III found comparable overall survival and disease free survival benefit in patients of over 70 compared to those less than 70 [57]. Similar outcomes were seen in another analysis of prospective data from 85,934 patients [58]. Although it is not clearly determined whether older patients experience more toxicities from chemotherapy, an analysis of 37,568 patients from ACCENT database (Clinical Trials From the Adjuvant Colon Cancer Endpoints Database) reported early mortality was significantly higher among those who are >70 compared to younger patients [59]. A pooled analysis suggested no difference in toxicity from 5FU based therapy in older adults; however, it is important to consider that toxicity from 5FU may vary depending on the schedule, specially gastrointestinal side effects in older adults may be more frequent with bolus regimens compared to short term infusional regimens [60]. In addition capecitabine may be associated with more severe toxicities in older adults, especially in those with diminished renal function. In a phase 3 trial of stage III colon cancer, particular toxicities like diarrhea were higher among patients over 65 with capecitabine [61]. Similarly, in X-ACT trial which examined capecitabine versus bolus 5FU (Mayo clinic), treatment-related toxicity was higher in patients above 70 (51%) compared to those less than 70 (39%) [62].

Although oxaliplatin based adjuvant chemotherapy improves survival in stage III colon cancer, its role in older adults above 70 is debatable. Subset analysis of three large randomized trials failed to demonstrate survival advantage in older patients. In an updated analysis of the MOSAIQ study, addition of oxaliplatin did not improve survival in 315 patients above 70 years (HR 1.16; 95% CI, 0.83–1.7) [22]. NSABP C-07 study enrolled 396 patients over 70 years, and no added benefit was seen with oxaliplatin in either in disease free survival (HR 1.03; 95% CI 0.77–1.36) or overall survival (HR 1.18; 95% CI 0.68–1.62) [23]. Consistently XELOXA study failed to demonstrate benefit of oxaliplatin over capecitabine alone in patients above 70 years (Disease free survival: HR 0.86; 95% CI, 0.64–1.16 and overall survival: HR 0.98; 95% CI, 0.62–1.56) [63]. A pooled analysis of seven randomized trials from ACCENT database with more than 14,500 patients (including 2575 patients over 70 years) suggested no survival advantage of oxaliplatin in those above 70 years (Disease free survival: HR 0.94; 95% CI, 0.78–1.13; Overall Survival: HR, 1.04; 95% CI, 0.85–1.27) [64]. However, it is unclear as to why addition of oxaliplatin was beneficial in metastatic setting and not in early cancer setting. Therefore, with currently available data, oxaliplatin is not recommended for routine use in patients above 70 who need adjuvant therapy, however, in those with high risk cancer and medical fit with good life expectancy, the benefit and risk of oxaliplatin should be discussed.

8. Drugs that are not routinely indicated as adjuvant therapy

Irinotecan, via its active metabolite SN-38 inhibits topoisomerase 1 enzyme, causing inhibition of DNA replication and cell death. Irinotecan has well

established activity in metastatic colorectal cancer in combination with 5FU/leucovorin and as single agent. However, three phase III randomized controlled trials have failed to show any benefit of irinotecan based regimens [65–67]. Bevacizumab and cetuximab have shown survival advantage in metastatic colon cancer when added to irinotecan or oxaliplatin based regimens. Bevacizumab is a vascular endothelial growth factor inhibitor, failed to show benefit when added to FOLFOX or capecitabine [68–70]. The NCCTG-N0147 trial examined the utility of cetuximab which is a mouse/human chimeric monoclonal antibody that targets the epidermal growth factor receptor, with FOLFOX compared to FOLFOX alone in resected colon cancer [71]. The trial was closed prematurely after the interim analysis showed no benefit of cetuximab. This was confirmed in another European PETACC8 trial which enrolled RAS wild-type patients [72]. Edrecolomab is a murine monoclonal antibody against EpCam antigen. Addition of edrecolomab to standard 5FU based adjuvant therapy did not improve disease-free survival or overall survival in stage III colon cancer [73]. Raltitrexed is a quinazoline folate analogue that acts as a direct and specific thymidylate synthase inhibitor which is often utilized in patients who experience cardiac toxicity with 5FU based therapy. PETACC1 trial examined the role of adjuvant raltitrexed in stage III colon cancer compared to 5FU/leucovorin. This trial was closed prematurely due to high rate of treatment related toxicity and death. However, an independent review found multiple incidences of protocol violations in relation to dose adjustment for renal function. Therefore, it may be appropriate to consider raltitrexed as an alternative to 5FU in patients with high risk stage III colon cancer who experience significant cardiac toxicity. Appropriate discussion about the evidence and potential toxicity is key in such instances [74, 75].

Non-steroidal anti-inflammatory (NSAID) drugs like aspirin or celecoxib have been examined as adjunctive therapies, however large randomized trial data are lacking. Most of the evidence supporting the use of aspirin in secondary prevention of colon cancer recurrence are from observational studies, though not all studies are consistent. Subset analysis of number of such studies have identified potential link to PIK3CA status, prostaglandin-endoperoxidase synthase 2 expression, and BRAF mutations. Although these data are interesting, they need to be confirmed in prospective trials. A large randomized controlled study examined the benefit of celecoxib in more than 2500 patients and there was no disease-free survival or overall survival benefit from the addition of celecoxib. Therefore updated 2013 American Society for Clinical Oncology (ASCO) guidelines did not endorse routine use of aspirin in this setting [76, 77]. Therefore, routine use of NSAIDs is not recommended currently until further studies are available. An association between serum vitamin D levels and resected colon cancer has been postulated; however, there is no high-quality evidence to support the routine use of vitamin D for this indication. Given the adverse of effect of vitamin D deficiency in skeletal system, it is not unreasonable to replace vitamin D in those who are deficient.

9. Surveillance

Aim of surveillance after curative resection of primary colorectal cancer is to identify asymptomatic recurrences who may be a potential candidate for curative resection. Although most randomized trials suggest modest survival benefit, not all trials are consistent. The benefit Intensive versus less intensive follow up strategies is still debated. Accordingly, surveillance strategies vary among different expert groups. Multiple meta-analyses have been conducted in an attempt to rationalize the surveillance plan, the latest being Cochrane analysis 2019, which examined the data from 13,216 patients from 19 randomized trials and found there was no

overall survival benefit from intensive surveillance. Intensive follow up resulted in higher rates of salvage surgeries with curative intent; however, this did not result in improved survival. Furthermore, these results were confounded by heterogeneity of the trials included in the meta-analyses. For example, definition of intensive versus less intensive follow up varied among the trials in terms of frequency of follow up [78]. In addition some trials included patents with stage I disease who have low rates of recurrence. Despite inconsistencies in the data, and the fact that curative metastasectomy improves survival in colorectal cancer patients, intensity of follow up should be tailored according to patient and cancer characteristics. Surveillance modalities include physical examination, carcino-embryonic antigen (CEA) and computerized tomography (CT) for surveillance. Follow up guidelines varies between the expert groups [79, 80]. A relatively intense follow up is reasonable for the first 3 years after the curative surgery, with 3–6 monthly physical examination and measurement of CEA. A 12 monthly CT scan is appropriate for the first 3 years and CT scans should be performed on any clinical suspicion thereafter. A colonoscopy is indicated after adjuvant therapy, if a complete colonoscopy was not performed at the time of surgery. Otherwise a routine colonoscopy should be performed at 12 months and then 5-yearly unless an adenomatous polyp is found which should prompt an earlier follow up colonoscopy.

10. Conclusion

Colon cancer is one of the leading cause or morbidity and mortality in the world with incidence increasing, especially in younger population. Advances in systemic chemotherapeutic options have improved the survival. Adjuvant chemotherapy has been shown to reduce the risk of recurrence after resection of primary colon cancer; however, it is associated with chemotherapy related morbidity and mortality. Clinicopathological features and molecular characteristics of the tumor need to be carefully assessed and adjuvant therapy should be tailored accordingly in order to avoid futile treatment and serious toxicities. Advances in genomic profiling and evolution of detection of circulating tumor DNA are promising and may guide the choice and intensity of treatment in the future.

Conflict of interest

The authors declare no conflicts of interests.

DOI: http://dx.doi.org/10.5772/intechopen.93874

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