Personalized Adjuvant Treatment of Colon Cancer

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Keywords

Colon cancer · Adjuvant chemotherapy · Personalized · Precision medicine · Mutations

Abstract

Introduction: Colon cancer (CC) is one of the most frequent malignant diseases. Adjuvant chemotherapy is of utmost importance in the management of localized disease. With the emergence of precision medicine, treatment approaches are becoming increasingly personalized and complex. This review contributes to a broader understanding of the role and relevance of personalized adjuvant treatment strategies in colon carcinoma, and summarizes the current status in this disease entity. **Methods:** We searched the websites ClinicalTrials.gov, PubMed, and ASCO (American Society of Medical Oncology) Meeting Library for clinical trials and retrospective analyses in the field of adjuvant treatment of CC with special attention to personalized approaches. **Results:** Various factors, including gender, age, sidedness, stage, dMMR/MSI-H, mutations, molecular profile, CMS, immunoscore, minimal residual disease, type of adjuvant therapy, therapy duration, and the patient's wish play an important role in the adjuvant setting of CC and should be considered in treatment decision making. **Conclusion:** Future molecular profiling ideally assessed and monitored by liquid biopsy might

personalize decision making even more in the adjuvant setting of CC patients. Further research and clinical trials are needed to clarify relevant questions and to highlight important clinical aspects.

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Introduction

Colon cancer (CC) is a leading cause of morbidity and mortality worldwide. CC is the fourth most frequent cancer disease and the third leading cause of cancer death in the world. Nearly 2 million cases were diagnosed in 2018 globally, comprising 11% of all newly diagnosed malignant diseases. Around 1 million patients died from CC in 2018. Nearly 40% of CC patients are diagnosed in a localized disease stage [1].

Surgical resection is the only curative option of patients with localized disease. Nearly half of all patients who undergo surgery alone without adjuvant therapy eventually relapse [2]. To reduce the risk of disease relapse/recurrence by technically undetectable micrometastases, adjuvant systemic chemotherapy is indicated to eradicate occult metastases and to prolong disease-free survival (DFS) and overall survival (OS). The clinical benefit of adjuvant therapy in stage III disease of CC has been

shown and proven by large-scale clinical trials. The first landmark trial by Moertel et al. [3] demonstrated that adjuvant chemotherapy resulted in a reduction of disease recurrence by 41% and in a reduction of the overall death rate by 33%. Thus, surgery and adjuvant therapy are the cornerstones in the management of CC in a curative setting. The landmark MOSAIC phase III trial by André et al. [4] established the combination of fluoropyrimidine and folinic acid with oxaliplatin (FOLFOX) for the duration of 6 months as the gold standard adjuvant chemotherapy regimen in patients with an overall good performance status.

The International Duration Evaluation of Adjuvant (IDEA) was a global collaboration and huge effort that performed a prospective, preplanned, pooled analysis of 6 randomized, phase III trials to assess the adjuvant therapy with either FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPOX (capecitabine and oxaliplatin) administered for 3 versus 6 months in over 12,000 stage III patients. IDEA demonstrated that 3 months of oxaliplatin plus fluoropyrimidine was not non-inferior to 6 months in the overall study population, confirming the role of long-term cytotoxic treatment in stages II and III CC patients. However, in the subgroup of low-risk stage III patients (T1–3 plus N1) the combination of capecitabine (prodrug of fluoropyrimidine) with oxaliplatin (CAPOX) for 3 months was non-inferior to 6 months, thereby reducing the risk of high-grade neuropathy [5].

With the advent of precision medicine, major efforts have been made to characterize various prognostic and predictive factors and biomarkers to define indication, type of regimen, dose, and duration of adjuvant therapy in CC patients. The management of CC in the adjuvant setting is becoming more and more personalized, complex, and intricate, and various factors have to be considered in the process of treatment decision making, including age, sex, fitness, disease stage, sidedness, molecular features, duration, and the wish of the patients. In this review article, we intend to illuminate and elucidate these factors.

Methods

We searched the websites ClinicalTrials.gov, PubMed, and ASCO (American Society of Medical Oncology) Meeting Library for clinical trials and retrospective analyses in the field of adjuvant treatment of CC with special attention to personalized approaches. The following keywords and combinations were used according to the Medical Subject Heading (MeSH) database: “colorectal” OR “colon” AND “cancer” AND “adjuvant” AND “chemotherapy” AND “personalized” OR “individualized” OR “precision.” All reviews, trials, case reports, analyses, and investigations regarding neoadjuvant and palliative treatments of CC, metastatic CC, and pediatric CC were excluded.

TNM Classification and Staging

The tumor node metastasis (TNM) classification developed by the American Joint Committee on Cancer (AJCC) is used worldwide to evaluate patients for adjuvant chemotherapy and potentially curative surgery. Based on large-scale clinical trials, adjuvant chemotherapy is beneficial in stage III disease. Since the MOSAIC trial the application of FOLFOX for the duration of 6 months has been the gold standard adjuvant chemotherapy regimen in CC patients with an overall good performance status [4]. Furthermore, the relevant phase III trial NO16968 by Schmoll et al. [6] proved the efficacy and superiority of capecitabine and oxaliplatin (CAPOX) as compared with fluoropyrimidine and folinic acid in stage III patients.

However, the increased efficacy of FOLFOX/CAPOX versus fluoropyrimidine alone may come at the cost of health-related quality of life. The application of oxaliplatin can cause cumulative and dose-dependent treatment-adverse related events, including oxaliplatin-induced peripheral neuropathy. Neurotoxicity is the most frequent dose-limiting toxicity of oxaliplatin. Thus, attempts have been made to shorten the duration of adjuvant FOLFOX therapy from 6 to 3 months without impairing the efficacy of the therapy. As mentioned above, the subgroup analysis of the IDEA collaboration demonstrated non-inferiority for CAPOX among patients in the lower risk group (T1–3 plus N1) [5].

In contrast to stage III disease, oncologists may face a dilemma in stage II disease since it is unclear and sometimes controversial whether adjuvant chemotherapy is indicated or not. The decision must be made on an individual basis considering the integration of different factors in treatment decision making.

In the FOLFOX arm of MOSAIC, stage II patients benefited from a 20% relative reduction in the risk of recurrence versus those of the fluoropyrimidine + folinic acid arm [7]. In patients with high-risk stage II disease defined as T4, tumor perforation, or fewer than 10 lymph nodes examined, the estimated 10-year OS was 75.4 versus 71.7% ($p = 0.058$). The absolute survival benefit associated with FOLFOX treatment among all patients increased from 2.2% at 6 years to 4.76% at 10 years [8].

Similar findings were reported by Casadaban et al. [9]. The authors collected and analyzed patient data from over 150,000 patients with stage II disease from the National Cancer Database. Adjuvant chemotherapy resulted in a significantly improved OS in all patient subgroups regardless of high-risk features and age. No difference in OS was observed between single and combination adjuvant chemotherapy regimens.

Another study from the Quasar Collaborative Group was conducted in over 3,000 patients with stage II disease.

The relative risk of recurrence with adjuvant fluorouracil and folinic acid versus observation alone was 0.78 (0.67–0.91; $p = 0.001$). Treatment efficacy did not differ by tumor site, stage, sex, or age [10].

The NCCN (National Cancer Care Network) and the ESMO (European Society of Medical Oncology) guidelines generally recommend the indication for adjuvant chemotherapy for stage II CC patients with poor prognostic factors, including grade 3–4, localized perforation or close, uncertain, or positive margins, lymphatic/vascular invasion, bowel obstruction, neural invasion, elevated carcinoembryonic antigen level, need for emergent operation, T4 stage (expansion to neighboring organs), and ≤ 12 lymph nodes examined. However, a randomized phase III trial of adjuvant fluorouracil and folinic acid in stage II patients failed to show any statistical difference between the surveillance group and adjuvant arm in terms of OS and relative risk reduction [11]. Moreover, the subset analysis of stage II patients of the phase III trial NSABP C-07 did not reveal any improvement in DFS or OS for the use/usage of adjuvant therapy. Similarly, an analysis by O'Connor et al. [12] in over 24,000 stage II patients noted no survival benefit for the application of adjuvant treatment regardless of unfavorable features. A study even claimed that stage II patients receiving adjuvant therapy were more likely to have a poor quality of life, higher recurrence rate, and higher all-cause mortality after 24 months compared to those who did not receive chemotherapy [13].

The expression of CDX2 was also described as a biomarker. An absent expression of CDX2 has been found to be positively associated with DFS with a strong predictive value [14].

Mismatch-Repair Deficiency / Microsatellite Instability

Sinicrope et al. [15] investigated the prognostic impact of deficient DNA mismatch repair (dMMR) in patients with stage III treated with FOLFOX-based adjuvant chemotherapy. They described that dMMR was significantly associated with older age, female sex, right-sidedness, high-grade histology, and higher T stage than left-sided CC (LCC). They reported that right-sidedness and higher T or N stages were each significantly associated with worse DFS. The MMR status was not prognostic in the overall cohort. However, the evaluation of MMR status by tumor sidedness showed that dMMR versus proficient MMR (pMMR) was associated with longer DFS in right-sided CC (RCC), whereas the opposite was the case for LCC. pMMR RCC displayed an inferior DFS when compared to pMMR LCC. Furthermore, pMMR tumors harboring mutated BRAF or mutated KRAS were significantly asso-

ciated with worse DFS versus wild-type variants. More clinical studies and trials are warranted to define and determine the role of sidedness and its association with OS and clinical benefit from adjuvant therapy.

Patients with microsatellite instability-high (MSI-H) have a deficiency of the dMMR genes. In several studies it has been shown that the MSI-H status confers a better prognosis regarding OS in stage II [16–18]. At the same time, the role of fluoropyrimidine as an adjuvant treatment in MSI-H stage II CC patients is controversial and has been suspected to be ineffective or even detrimental [19].

Currently, a phase III clinical trial is investigating the efficacy of atezolizumab (NCT02912559) in CC patients with MSI-H status in the adjuvant setting. The DYNAMIC study (Circulating Tumor DNA Analysis Informing Adjuvant Chemotherapy in Stage II Colon Cancer; ACTRN12615000381583) is actively recruiting patients to a randomized controlled trial prospectively evaluating the role of circulating tumor DNA (ctDNA) analysis in guiding adjuvant treatment in patients with stage II CC.

Gender

A growing body of literature suggests gender-specific differences in CC. RCC is observed more often in women than in men [20]. The stratification of tumor TP 53 genotype demonstrated that TP 53 genotype was a significant predictor of DFS and OS. Likely, the germline polymorphisms in the platin genes PLS3 rs6643869 and LCP1 rs4941543 correlate with a shorter time to recurrence (TTR) in female patients [21]. The XPD rs1799793 GA genotype shortened the time to hematologic toxicity grade ≥ 3 in men, whereas in women the ERCC1 rs11615 CC genotype shortened the time to neurological toxicity grade ≥ 2 [22]. Furthermore, a Swedish study reported that stage III CC female patients who harbor the allele variant HLA-A*02 had a better outcome if they were treated with adjuvant chemotherapy instead of surgical resection alone [23].

Shields [24] investigated the effect of age, gender, and performance status on the duration of adjuvant chemotherapy for stage III CC patients. They concluded that overall age, gender, or performance status did not modify the therapy duration.

In their retrospective analysis, Oliver et al. [25] reported that although women were more likely to undergo a surgical resection, they received less often adjuvant chemotherapy and for a shorter duration. Another study suggested that females were less likely to complete adjuvant chemotherapy than male patients [26]. However, several studies have demonstrated a significantly longer OS for female CC patients when compared with their male counterparts [27–30].

Tumor Sidedness

It has been shown in many studies and large-scale clinical trials that “side matters” when it comes to prognosis and the therapeutic management of metastatic CC. RCC is significantly more associated with older age, female gender, dMMR/MSI-H status, poor tumor differentiation, high modified Glasgow Prognostic Score (mGPS), higher neutrophil:platelet score, and higher T stages than LCC [20, 31]. Data regarding the efficacy of adjuvant chemotherapy depending on the tumor location/sidedness and stage are inconsistent and sometimes contradictory/conflicting.

In the post hoc analysis of the PETACC8 phase III trial, Blons et al. [32] did not observe any difference regarding the TTR between the RCC and LCC groups with stage III disease (HR 0.86; $p = 0.164$). However, RCC was associated with poorer survival after relapse when RCC became metastatic.

Later, a retrospective analysis by Kennecke et al. [33] in over 5,000 patients with stage I–III CC confirmed these findings in stage III. However, the authors observed a significant difference between RCC and LCC in stage II regarding the relapse-free survival in favor of RCC (HR 0.73, $p = 0.006$). Interestingly, neither the application of adjuvant chemotherapy nor tumor grade influenced relapse-free survival among patients with stage II tumors.

Recently, an Italian study group investigated the prognostic impact of primary tumor location in over 5,000 patients with stages II and III CC receiving adjuvant therapy from 3 randomized Italian trials (SITAC-1; SMAC and TOSCA). In the overall population, tumor sidedness was not significantly associated with DFS. However, unlike the study by Kennecke et al. [33], in CC patients with stage II there was no significant difference concerning DFS and OS between the tumor locations. In contrast, stage III patients with LCC exhibited a highly significantly longer OS than RCC (HR 1.36, 95% CI 1.14–1.62, $p < 0.001$) [34].

A large-scale population-based Surveillance, Epidemiology, and End Results (SEER) analysis by Li et al. [35] conducted in over 200,000 patients showed that stage I–II RCC had significantly longer cause-specific survival than LCC ($p < 0.001$), whereas stage III and IV RCC – with the exception of stage III right-sided poorly differentiated mucinous – displayed a worse OS than LCC. Another large-scale investigation by Warschkow et al. [36] that was also based on the SEER data in over 90,000 stage I–III CC patients revealed that patients with stage II RCC had a superior OS in RCC as compared to LCC.

In contrast, another large population-based SEER analysis in nearly 90,000 patients with stage II CC did not

find any association between sidedness and OS [37]. Similarly, Patel et al. [20] reported that there is no significant relationship between tumor location and adjuvant chemotherapy ($p = 0.632$) or 5-year cancer-specific survival ($p = 0.377$) or 5-year OS ($p = 0.205$).

RAS and BRAF Mutational Status

KRAS or BRAF V600E mutations are described as clinically relevant predictive and prognostic markers. BRAF and KRAS mutations are almost always mutually exclusive [38].

Like MSI-H, the BRAF V600E mutation has a prognostic value and – unlike MSI-H – confers a poorer OS. Two studies demonstrated that patients with MSI-H and BRAF wild-type had a longer OS than patients with MSI-H/BRAF V600E mutations [39, 40].

Hutchins et al. [41] evaluated the value of KRAS and BRAF mutations in predicting recurrence in stage II CC patients from the QUASAR trial. BRAF and dMMR were more frequent in RCC than in LCC. Patients with dMMR or KRAS mutation displayed a significantly lower recurrence rate than MMR-proficient tumors/patients ($p < 0.001$) or KRAS wild-type tumors ($p = 0.002$). BRAF mutant tumors were not linked to the recurrence risk.

Similarly, the post hoc analysis of the PETACC8 phase III showed that patients with stage III LCC harboring KRAS codon 12 mutations (exon 2) and treated with adjuvant chemotherapy had a shorter TTR in LCC ($p < 0.001$). KRAS codon 13 displayed a borderline significance in LCC ($p = 0.051$). However, the KRAS mutation status was not linked to TTR in RCC. KRAS mutations were significantly more frequent in women, in RCC, and were associated with age [32]. Consistent with this analysis, Yoon et al. [42] demonstrated that stage III CC patients with mutations in KRAS codon 12 ($p < 0.0001$) and 13 ($p = 0.0248$) had a significantly shorter DFS compared with patients lacking these genetic aberrations. Mutations in both codons 12 and 13 were associated with RCC.

Sinicrope et al. [15] investigated over 2,700 patients with stage III CC from the adjuvant chemotherapy phase III trial (NCCTG N0147) and validated their findings with over 700 tumor samples from a separate set of patients with stage III disease. They reported that MMR-proficient patients harboring KRAS mutations ($p < 0.0001$) or BRAF mutations ($p < 0.0065$) had a significantly shorter DFS versus MMR-proficient patients without these genetic alterations. pMMR patients without BRAF and KRAS mutations and dMMR patients did not differ in terms of DFS. These studies show that, apart from tumor sidedness, future clinical trials in the adjuvant setting should also consider KRAS and BRAF mutations as stratification factors.

True Nodal Negativity, Lymph Nodes, and Sidedness

Exact assessment of lymph nodes metastasis is part of the TNM staging system and crucial for therapy decisions regarding the application of adjuvant chemotherapy. According to the current NCCN and ESMO guidelines, the minimum number of lymph nodes for accurate staging of CC is ≥ 12 . For patients with lymph node metastases (LN-positive) and T4 disease regardless of lymph node status, adjuvant chemotherapy is indicated. In cases of <12 lymph nodes evaluated or in patients with T3N0 with high-risk features, NCCN also recommends adjuvant chemotherapy. Dehal et al. [43] investigated the impact of tumor sidedness on nodal staging accuracy in patients with T3 disease. They described true nodal negativity (TNN) as a function of both the number of examined lymph nodes and tumor sidedness. The function revealed that significantly more lymph nodes are needed to accurately predict any given probability of TNN in LCC than RCC. The more lymph nodes that were evaluated, the more TNN was probable and the higher was the survival for both LCC and RCC. Irrespective of how many nodes were examined, LCC had a better prognosis regarding OS than RCC. However, the level of improvement in OS was significantly higher with more nodes evaluated for RCC than LCC. Thus, tumor sidedness influences the number of examined lymph nodes needed to predict TNN in CC. A study by Lee et al. [44] also stated that RCC has worse outcomes than LCC; however, a higher lymph node harvest improved survival for RCC, with ≥ 22 nodes having the highest OS (HR 0.71).

Age

Due to a higher life expectancy, the number of elderly patients diagnosed with CC is growing worldwide. They make up 58% of all CC patients. Currently, the median age at the time of initial diagnosis is 68 years. However, there are no standardized guidelines for the therapeutic management of elderly CC patients due to the exclusion and underrepresentation of this patient group in clinical trials [1, 45]. Different studies showed that chemotherapy application decreases with age, which may partly be explained by the lack of data in this population group. Several studies have demonstrated that adjuvant chemotherapy in elderly patients is positively associated with prolonged OS [45, 46]. In a large retrospective study in over 8,000 octogenarians, Bergquist et al. [46] showed that patients who received adjuvant chemotherapy had a significantly higher OS compared to those who refused the therapy (median OS 42.7 vs. 61.7 months; $p < 0.001$).

In a large-scale retrospective analysis, Sargent et al. [47] pooled data from 7 phase III adjuvant trials and con-

cluded that selected elderly patients aged >70 years treated with adjuvant therapy experienced an improved OS without a significant increase in adverse events. A Danish research group performed a retrospective single center analysis (ACCORE study) of over 500 stage II–III patients who were given adjuvant chemotherapy. The study suggested that age had no influence on DFS and mortality. However, elderly patients more often received single-agent adjuvant therapy and a lower initial dose. Interestingly, dose reduction did not seem to influence DFS or mortality [48].

Similarly, the study of the ACCENT database pooled data of 7 adjuvant chemotherapy trials and did not reveal any significant differences between younger patients and patients older than 70 years in terms of TTR, DFS, and OS. Likewise, Goldberg et al. [49] pooled data of over 3,000 patients from 4 adjuvant trials and did not observe any differences between these 2 age groups regarding TTR, OS, and adverse events.

In a recently published study, Lee et al. [50] conducted a retrospective analysis in Korean patients older than 70 years who were diagnosed with stage II CC. They maintained that there are no differences between patients with and without receipt of adjuvant chemotherapy in stage II in terms of recurrence-free survival, cancer-specific survival, and OS. Patients were further divided into low- and high-risk subgroups. High-risk was defined as patients with one or more of these criteria: poorly differentiated histology, bowel perforation, bowel obstruction, <12 examined lymph nodes, lymphatic/vascular invasion, and perineural invasion. However, there were no differences between these 2 risk groups in the elderly population.

Some studies highlight the challenges of adjuvant chemotherapy in elderly patients. Neugut et al. [51] analyzed over 1,700 stage III CC patients ≥ 65 years of age in the SEER-Medicare database. They revealed that increasing age was significantly associated with a duration of adjuvant chemotherapy of less than 5 months. More than 30% of elderly patients discontinued treatment early. The mortality among these patients was nearly twice as high as among patients who completed the treatment course. Other studies confirmed this finding that elderly patients are less likely to complete the adjuvant therapy [26, 52].

Although these studies show a clinical benefit for the use of adjuvant chemotherapy also in elderly patients, the benefit of addition of oxaliplatin is still unclear in this age class. The subgroup analysis of the phase III adjuvant trials MOSAIC, XELOXA (NO16968), and NSABP C-07 suggested no survival benefit for oxaliplatin use in patients aged ≥ 65 years [6, 8, 53].

In their work published in the *Journal of Clinical Oncology*, Sanoff et al. [45] indicated that oxaliplatin was associated solely with a trend toward an incremental benefit regarding mortality in patients older than 75 years.

Later, an analysis of the ACCENT database revealed that CC patients aged ≥ 70 years did not benefit from the addition of oxaliplatin to fluoropyrimidines.

However, these retrospective analyses are biased and selected and do not adequately reflect elderly patients. The IDEA collaboration has not yet presented a subgroup analysis of the elderly subpopulation. Thus, prospective phase III trials are needed to investigate the efficacy of adjuvant chemotherapy and particularly that of oxaliplatin in elderly patients. These trials may help to make therapy decisions in the adjuvant setting in light of the individual risk profile of the patients.

At present, the ongoing randomized phase III trial PRODIGE 34 ADAGE is the only trial aiming to assess different adjuvant therapy in elderly patients with stage III CC. The results are still pending [54].

Liquid Biopsy in an Adjuvant Setting

Attempts have been made to assess the amount of post-operative free ctDNA in blood as a form of liquid biopsy for detection of minimal residual disease for identifying patients at high risk of experiencing disease relapse. The detection of minimal residual disease may facilitate adjuvant therapy decisions. Second, serial evaluation of ctDNA may also help to monitor possible dynamic changes in the concentration of ctDNA in the course of postoperative time for evaluating the efficacy of the adjuvant therapy.

In 2016, Tie et al. [55] explored the concentration of ctDNA in a prospective cohort of 230 patients with stage II CC. In total, 34 patients were diagnosed with disease relapse, including 27 (15%) of 178 patients who had not received adjuvant therapy and 7 (13%) of 52 patients given adjuvant therapy. In 14 (7.9%) of 178 patients not treated with adjuvant therapy, ctDNA was detected post-operatively and 11 (78.6%) of those 14 patients relapsed at a median follow-up of 27 months. Thus, detection of ctDNA was significantly associated with shorter recurrence-free survival.

Later, Tie et al. [56] repeated this study concept in 95 stage III CC patients who were treated with adjuvant chemotherapy. Nineteen (20%) of 95 patients had measurable ctDNA after surgical resection and relapsed at a median follow-up time of 21.1 months. Thus, postsurgical ctDNA positivity was associated with poorer recurrence-free survival (HR 3.52; $p = 0.004$).

Based on these important results, Taieb et al. [57] measured ctDNA from CC patients included in the IDEA-France phase III trial to assess its prognostic and predictive value in the course of adjuvant therapy. The 2 methylated markers WIF1 and NPY were used for the identification of ctDNA. Postoperative ctDNA detection was linked to T4, poor tumor differentiation, tu-

Table 1. Adjuvant treatment of CC according to the ESMO and NCCN guidelines

Stage of CC	Adjuvant treatment
Stage I	No need for adjuvant treatment
Stage II	Not recommended in MSI-H CC Recommended in cases of poor prognostic factors including grades 3–4, localized perforation or close, uncertain, or positive margins, lymphatic/vascular invasion, bowel obstruction, neural invasion, elevated carcinoembryonic antigen level, need for emergent operation, T4 stage (expansion to neighboring organs), and ≤ 12 lymph nodes examined
Stage III	Adjuvant treatment for all patients 6 months of FOLFOX is not non-inferior to 3 months of FOLFOX 3 months of CAPOX is non-inferior to 6 months in low-risk CC (T1–3, N1)

mor perforation, and shorter 2-year DFS. In this analysis, ctDNA was shown to be an independent prognostic marker. Two-year DFS was 64 vs. 82% in ctDNA-positive and negative patients, respectively ($p = 0.001$). Interestingly, ctDNA-positive patients treated with 6 months adjuvant therapy had a similar prognosis to ctDNA-negative patients given only 3 months of therapy.

Consensus Molecular Subtypes (CMS1–4)

Based on distinct molecular and clinical features, the Colorectal Cancer Subtyping Consortium defined and described 4 different CC consensus molecular subtypes, CMS1 (immune: microsatellite instability immune, hypermutated, microsatellite unstable, and strong immune activation), CMS2 (canonical: epithelial, marked WNT and MYC signaling activation), CMS3 (metabolic: epithelial and evident metabolic dysregulation), and CMS4 (mesenchymal: prominent transforming growth factor- β activation, stromal invasion and angiogenesis) [58].

Song et al. [59] performed a retrospective analysis of the NSABP C-07/NRG Oncology Randomized Clinical Trial and found that stage III CC patients with CMS2 benefited from adjuvant chemotherapy containing oxaliplatin. In contrast, CMS4 was identified as the worst prognostic subtype in both stage II and III. Later, Marisa et al. [60] confirmed this finding by showing that the CMS4 subtype was significantly associated with a poorer OS (HR 1.7, $p = 0.021$). In another multicentric study by Allen et

Table 2. Factors influencing the adjuvant setting of CC

Factors	Relevance
MSI-H	Associated with better prognosis in stage II [16–18], Controversial effects of fluoropyrimidine demonstrated [19] More frequently in RCC [20]
BRAF mutation	Associated with poorer survival [15] More often in RCC than in LCC [20]
KRAS mutation	Associated with shorter time to recurrence [15, 32] Associated with shorter DFS [42] Mutations in both codons 12 and 13 were associated with RCC [42]
CDX2	Absence of CDX2 associated with DFS [14]
RCC	Associated with poorer DFS [15] More often in women than in men [20] More lymph nodes are needed to achieve the same probability of TNN in patients with LCC than RCC [43]
Female gender	Associated with longer OS [27–30]
Age	Elderly patients have a clinical benefit from adjuvant chemotherapy [46, 47] Oxaliplatin less effective [6, 8, 53]
ctDNA	Postsurgical ctDNA is positivity associated with poorer recurrence-free survival and DFS [56, 57]
Consensus molecular subtypes (CMS1–4)	CMS4 subtype is associated with poorer OS [60]
IS	A low IS is associated with higher risk of relapse or death [62] Adjuvant chemotherapy is not effective in low IS [62]
IS, immunoscore.	

al. [61] both stages II and III CC patients with CMS2 subtype experienced a clinical benefit from adjuvant chemotherapy, whereas CMS3 patients benefitted in stage III only.

Immunoscore

Recently, the prognostic and predictive value of an immunoscore (IS) as assessed in the FOLFOX subgroup of the IDEA-France cohort study (PRODIGE-GERCOR, NCT03422601) in stage III CC patients was published. Densities of CD3+ and cytotoxic CD8+ T cells in the tumor and invasive margin as determined by immunohistochemistry were factored in the development of the IS. A low IS was associated with higher risk of relapse or death ($p < 0.0001$). The 3-year DFS was 66 and 77% for a low and intermediate/high IS, respectively. The 3-year DFS of patients with an intermediate/high IS in patients treated with 3 months of FOLFOX was 71.5 versus 83.8% in the 6-month arm ($p = 0.0004$). Adjuvant treatment with 6 months of FOLFOX showed no significant benefit for patients with a low IS ($p = 0.269$). Thus, the prognos-

tic value of the IS was shown in the IDEA-France cohort study. However, the predictive value still needs to be confirmed in an external validation cohort [62].

Discussion

In the past few years, more and more factors and biomarkers have been identified and studied that may play a role in the personalized management of CC in the adjuvant setting. However, the examination of these factors has led to new challenging questions, and some of them have not been conclusively answered.

There is an ongoing discussion about the proper adjuvant therapeutic management of stage II CC, particularly in borderline cases such as stage II with MSI-H status and concurrent high-risk features like T4 or perforation. Apart from MSI-H, it would also be important to identify and introduce new biomarkers to predict the efficacy and antitumoral activity of the applied chemotherapy regimen. MSI-H status may signify that the administration of fluoropyrimidine-based adjuvant therapy may even lead to reduced OS in CC patients.

Another important issue is the indication, type of chemotherapy, and therapy duration for elderly patients. Because of strict age exclusion criteria, elderly patients are underrepresented in many clinical trials. Thus, due to the paucity of solid and sound data, there is no standardized management for these patients. Compounding the problem is the fact that there is no agreed upon clear definition of the phrase “elderly patients.” According to the WHO, patients older than 65 years are defined as elderly. However, the majority of studies have set the cutoff point for elderly patients at 70 or 75 years. Therefore, it is difficult to compare the trials with one another to draw correct conclusions. Another reason is that there has been no prospective trial randomized for different age classes to evaluate the impact of age on the efficacy of adjuvant chemotherapy. Besides age, it would also be important to take functional status and biologic factors – such as cognitive abilities, bone marrow reserves, liver resources, and kidney function – into consideration in clinical trials. The development and application of scores for the prediction of the tolerability of adjuvant chemotherapy in elderly patients may help to identify patients who would benefit from the therapy.

To overcome clinical dilemmas, liquid biopsy and the IS may be one possible way to define and determine subsets of patients who would most likely derive a clinical benefit from adjuvant chemotherapy by assessing the amount of minimal residual disease. Liquid biopsy may also help to identify and explore novel biomarkers for clinical application.

The clinical significance, relevance, and impact of the prognostic and predictive value of laterality, minimal residual disease, molecular subtypes, gender, and biomarkers such as the genetic aberrations in BRAF, KRAS, and p53 have yet to be fully elucidated in further randomized clinical trials. Tables 1 and 2 provide a clear overview of different factors influencing the adjuvant setting of CC.

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Conclusion

For adequate decision making in the adjuvant management of CC patients, various factors and variables, including age, stage, gender, sidedness, molecular profile, minimal residual disease, type of adjuvant therapy, therapy duration, and the patient’s wish, have to be considered and integrated into the clinical routine. This stratification of factors might spare unnecessary toxicity to patients in the adjuvant setting by optimizing the prognosis. Future molecular profiling ideally assessed and monitored by liquid biopsy might personalize decision making even more in the adjuvant setting of CC patients. Further research and clinical trials are needed to clarify relevant questions and to illuminate important clinical aspects.

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Statement of Ethics

The study was conducted in accordance with the International Conference on Harmonization E6 requirements for Good Clinical Practice and with the ethical principles outlined in the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.T. and G.W.P.: conception, design, collection and assembly of data, interpretation of data, and manuscript writing. Both authors reviewed and approved the manuscript.

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