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REVIEW

How I treat stage II colon cancer patients

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Stage II colon cancer (CC) is probably one of the best prognosis gastrointestinal tumors seen in our consultations, but often takes a lot of time for physicians to determine appropriate treatment because of the limited benefit of adjuvant chemotherapy (CT) in these patients, together with the limited evidence in this situation. How to choose the best treatment for each individual patient is thus dependent on molecular (microsatellite instability/microsatellite stability status) and clinico-pathological features relevant enough to classify these tumors into low-, intermediate- and high-risk stage II disease and to choose an appropriate attitude for each of these subgroups. In practice, the first step in treatment decision making must be to assess the patient's status and comorbidities to see if the patient is eligible for an adjuvant treatment. Then, as fluoropyrimidines (FPs) are the corner stone of CC adjuvant treatment, screening for dihydropyrimidine dehydrogenase deficiency is mandatory in western countries. Finally, depending on the patient's characteristics and tumor risk stage, the strategy may be surveillance, adjuvant FP alone or oxaliplatin-based adjuvant CT. In the near future, new tools such as Immunoscore® (HalioDx; Luminy Biotech Enterprises, Marseille Cedex, France) and circulating tumor DNA may help to identify more precisely patients with minimal residual disease for more personalized adjuvant treatment approaches.

Key words: colon cancer, stage II disease, early colon cancer

INTRODUCTION

Colon cancer (CC) is the third most common tumor globally and the fourth leading cause of death accounting for >600 000 deaths estimated each year.[1] Currently, patient management and clinical outcome prediction are still entirely defined according to histopathological evaluation. However, the TNM (tumor—node—metastasis) staging provides useful but incomplete prognostic information, with moderate prediction accuracy and limited clinical utility, especially in stage II CC. As compared to other stages, stage II diseases are more heterogeneous comprising low-, intermediate- and high-risk diseases for metastatic dissemination. Although diagnosed at an early stage, they contribute to ∼16% of CC mortality, with 5-year overall survival (OS) rates ranging from 87.5% for T3N0 to 58.4% for T4bN0.[2] Nowadays, adjuvant chemotherapy (CT) based on oxaliplatin and fluoropyrimidine (FP) is currently endorsed for stage III tumors, while there are still unresolved questions surrounding treatment strategies for stage II tumors. Direct evidence from randomized clinical trials to better classify stage II CC and to define which CT and duration of treatment is still insufficient; current recommendations are often based on extrapolating survival benefit from studies' experiences in stage III CC.[3] Appropriate treatment management following curative surgery in stage II CC is the main focus of the present review.

ASSESSMENT OF RECURRENCE RISK AND COMPLICATIONS FOR COLON CANCER THERAPY

The assessment of recurrence risk through major and minor prognostic parameters is crucial to help clinicians in decision making to select the best treatment path for stage II CC: whether to recommend adjuvant treatment, the type and duration of systemic therapy. The most important national societies recognize 'high-risk' stage II CC patients as those having at least one of these factors: stage pT4, bowel perforation or occlusion, lymphatic—vascular—perineural invasion, poorly differentiated histology [excluding microsatellite instability-high (MSI-H) tumors], inadequate lymph node sampling or positive margins after surgery. According the European Society for Medical Oncology (ESMO) statement, lymph node sampling <12 and pT4 are currently recognized as the major prognostic parameters associated

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with worse survival.[3] Swanson et al. noted a significant difference in 5-year OS rate according to number of analyzed nodes: 49.8% with 1-7, 56.2% with 8-12 and 63.4% with >13 inspected nodes.[4] Several data strongly support these results allowing to decrease stage shift and misclassifications.

Indeed, in the recent guidelines published by ESMO for non-metastatic CC patients, <12 lymph nodes examined and T4 tumors are considered high risk whatever their microsatellite status is; in fact the role of MSI in this subgroup is uncertain.[3] About T4 tumors, the American Joint Committee of Cancer (AJCC) eighth edition observed that stage IIB and IIC (T4 disease) show a poorer 5-year OS (72.2%) compared with stage IIIA (T3 tumors; 83.4%), suggesting that deep penetration into the bowel wall can be a poorer prognostic factor than limited node involvement.[5,6]

MSI status or deficiency in DNA mismatch repair (dMMR) system, to date, represents the most reliable prognostic molecular marker in deciding the treatment management for stage II CC. Approximately 20% of stage II CCs have an MSI/dMMR status and usually they are associated with younger age, higher T stage, lower N stage, right-sided tumors and high-grade lesions. Interestingly, untreated stage II CC patients with MSI-H/dMMR have an excellent prognosis (90%) compared with those with microsatellite stability (MSS) or proficient mismatch repair (pMMR) (66%) and a potential resistance to 5-fluorouracil (5-7FU).[7] In the MOSAIC trial, translational analysis on microsatellite status showed a significant OS improvement in stage II and III CC by adding oxaliplatin, with trends in favor of FOLFOX4 in patients with dMMR, despite the small number of these tumors. In the NSAPC-07, oxaliplatin did not show activity in dMMR tumors, possibly due to the determination of only MLH1 and MSH2. A pooled analysis of MOSAIC and NSABP C-07 is currently ongoing to demonstrate the statistically significant impact of MMR.[8]

In addition to these high-risk histopathological features, lymphatic, vascular and perineural invasion are associated with high risk of recurrence, demonstrated in a prospective analysis conducted on 448 patients with stage II CC (HR 2.1; 95% CI 1-4.4; P=0.04).[9] Moreover, 54.8% of patients with lymphovascular invasion developed distant metastasis compared to 24.9% of patients without microinvasion (P=0.01).[10] In 255 patients with stage II CC, perineural invasion was independently associated with 5-year disease-free survival (DFS) and OS (HR 3.11; P=0.046 and HR 9.39; P=0.019, respectively).[11]

It is noteworthy that age, patient's comorbidities and potential risk of complications must be considered, especially in this setting of patients where balance between risk and benefit is so difficult to determine.[3] In particular, FP administration could be associated with toxicities including mucositis, diarrhea, vomiting, neutropenia, thrombocytopenia, cardiac symptoms and hand and foot syndrome. Approximately 20% of patients experience grade 3-4 adverse events and 0.5%-1% experience fatal toxicity.[12] The combination of oxaliplatin and FPs can worsen adverse events, disabling patients. Genetic testing for *DPYD* polymorphisms and uracilemia assay [uracilemia <16 ng/ml or ratio of dihydrouracil to uracil to assess dihydropyrimidine dehydrogenase (DPD) activity] represent an important tool for physicians in determining which patients could develop life-threatening adverse events secondary to FP-based CT administration.[13] Thereby, *DPYD* and uracilemia assessment allow to manage dose modification without compromising the treatment's efficacy or to avoid treatment administration in patients with complete *DPYD* deficiency or a high uracilemia level ≥150 ng/ml[13] (Figure 1). However, the doses recommended by current guidelines could be increase though titration if treatment is well tolerated after two cycles of chemotherapy.[14]

TREATMENT ALGORITHM IN STAGE II COLON CANCER

As already discussed, most guidelines endorse a risk stratification approach to aid physicians in better determining the appropriate treatment strategy algorithm for stage II CC. In particular, adjuvant CT, type and duration, in stage II tumors should be considered by incorporating tumor-related prognostic features and should be balanced against patient's age and comorbidities. Current guidelines recommend follow-up in case of comorbidities, reduced life expectancy and DPD deficiency (or high uracilemia level ≥150 ng/ml), while adjuvant CT should be offered for intermediate- and high-risk patients.[3] In the intermediate-risk population (MSS tumors with no or low competing risks), fluoropyrimidines could be pursued according age, comorbidities and patient's wish. Of note, available evidence in the literature demonstrates only data about de Gramont administration; however, capecitabine could be considered.[3] In those patients with a low level of evidence for a benefit of adjuvant therapy, treatment must be stopped permanently in case of any grade ≥2 side effects (Figure 1).

Conversely, in patients with high-risk tumors (pT4 and/or inadequate lymph-nodes sampling, or accumulation of minor risk factors) in which incidence of recurrence is >20%, adjuvant treatment should be prescribed. Furthermore, these patients should add oxaliplatin to the fluoropyrimidines-based treatment considering the trend to an increased benefit, despite the subgroup analysis of the 10-year update of the MOSAIC study, which demonstrated a non-significant improvement in terms of survival outcomes in patients receiving FOLFOX compared with 5-FU/LV alone. Though non-significant, there was late split of OS curves favoring FOLFOX4 in high-risk patients with a delta of 3.7%.[15,16] At 10 years, the DFS difference was 1.6% in the overall stage II population and 5.7% in high-risk individuals.[15,16] Patients with poor prognostic features stand to gain greater absolute benefit (albeit the same relative benefit) from CT compared to low-risk patients, remembering that analysis for stage II disease should be framed in absolute rather than relative terms (Table 1).

For the high-risk group, the IDEA trial explored the optimal duration of adjuvant treatment, reporting similar results to those observed for stage III patients. In particular, because of low numbers of patients

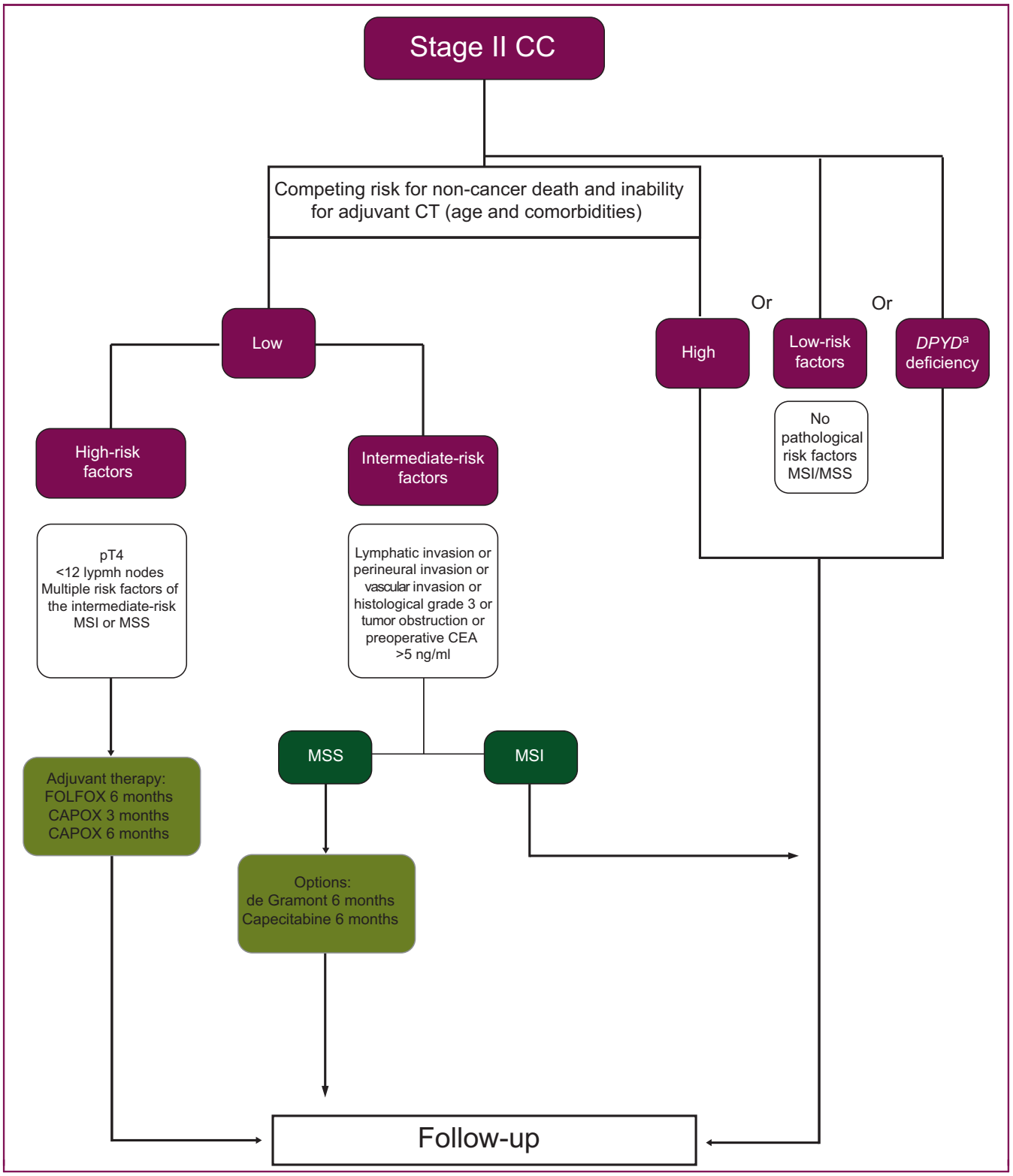

Figure 1. Treatment algorithm in stage II colon cancer (CC).
CAPOX, capecitabine and oxaliplatin; CEA, carcinoembryonic antigen; CT, chemotherapy; MSI, microsatellite instability; MSS, microsatellite stability.
[a] If partial but not complete *DPYD* deficiency, with uracilemia >16 ng/ml, discuss each patient case individually depending on the benefit/risk balance for adjuvant fluoropyrimidine.

with stage II compared with stage III disease, a wider non-inferiority margin was set with the upper limit of confidence interval (CI) <1.20. Though the global analysis was unable to significantly prove non-inferiority, results of the pooled analysis of the four IDEA studies including stage II CC demonstrated that 3 months of capecitabine and oxaliplatin (CAPOX) was comparable to 6 months (5-year DFS of 81.7% versus 82%,

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Table 1. Relevant studies in stage II colon cancer

Study	Population	Patients (*N*)	Control arm	Experimental arm	Results and conclusions
Intergroup (INT) 0035	Stage II and III	1296	Observation	5-FU bolus plus LV for 1 year	No survival benefit with experimental arm for stage II CC.
IMPACT B2	Stage II	1016	Observation	5-FU bolus plus LV for 6 months	No significant benefit in survival with adjuvant CT. The 5-year EFS was 73% for controls versus 76% for 5-FU/LV (HR, 0.83; 90% CI 0.72-1.07). The 5-year OS was 80% for controls versus 82% for 5-FU/LV (HR, 0.86; 90% CI 0.68-1.07).
QUASAR	High-risk stage II and stage III	3239 (2963 stage II)	Observation	5-FU monthly bolus plus LV for 6 months	3.6% (95% CI 1.0% to 6.0%) absolute improvement in 5-year OS with adjuvant CT in stage II CC patients.
NSABP C01	Stage II and III	1166	Observation	MOF (semustine, vincristine and 5-FU) or BCG	No significant benefit was achieved with adjuvant CT. The 5-year OS rate was 75% versus 72%, respectively; $P = 0.73$.
NSABP C02	Stage II and III	1158	Observation	5-FU	The 5-year OS was 88% for adjuvant 5-FU versus 76% for observation only; $P = 0.005$.
NSABP C07	Stage II and III	2407	5-FU bolus plus LV for 6 months	FLOX	No significant benefit in DFS (HR 0.94; $P = 0.67$) or OS (HR 1.04; $P = 0.84$) in stage II CC receiving oxaliplatin-based therapy, even in patients with high-risk features.
MOSAIC	High-risk stage II and stage III	2246 (899 stage II)	de Gramont regimen for 6 months	FOLFOX4 for 6 months	The 10-year DFS difference was 1.6% in the overall stage II (75.2% versus 73.6%) and 5.7% in high-risk individuals (72.7% versus 67.0%). No OS differences in stage II CC (78.4% versus 79.5%). Delta of 3.7% in high-risk patients (75.4% versus 71.7%) with non-significant late split of OS curves favoring FOLFOX4 in high-risk patients.
The IDEA pooled analysis	High-risk stage II and stage III	12834 stage II)	FOLFOX or CAPOX 6 months	FOLFOX or CAPOX 3 months	3 months of CAPOX was comparable to 6 months (5-year DFS of 81.7% at 3 months versus 82% at 6 months). Differences in treatment duration for FOLFOX were pronounced (5-year DFS of 79.2% at 3 months versus 86.5% at 6 months).

5-FU, 5-fluorouracil; CAPOX, capecitabine and oxaliplatin; CC, colon cancer; CI, confidence interval; CT, chemotherapy; DFS, disease-free survival; EFS, event-free survival; FLOX, 5-flourouracil, leucovorin and oxaliplatin; HR, hazard ratio; LV, leucovorin; OS, overall survival.

respectively), and was associated with reduced toxicity and improved quality of life.[17] However, the different benefit of treatment duration in patients receiving FOLFOX was pronounced (5-year DFS of 79.2% versus 86.5%; Table 1).[18] Therefore, duration of oxaliplatin-based adjuvant treatment of stage II CC based on the IDEA data may be tailored to 3 or 6 months for CAPOX or 6 months for FOLFOX, with particular caution for T4b tumors that have the highest risk of recurrence, ranging from 30% to 40%, in which 6 months of treatment should be the first option to pursue evaluation of patient's comorbidities and wishes (Figure 1).

As previously reported, MSI/MMR represents the most reliable prognostic and predictive molecular marker in stage II CC. It confers a better prognosis and less benefit from adjuvant FPs; therefore, adjuvant CT should be indicated only in high-risk patients (T4 tumors) in addition to oxaliplatin.[3,19] A recent study revealed a trend towards better DFS in patients receiving FOLFOX (HR = 0.13, 95% CI 0.02-1.05, P=0.06) and not for 5FU administration compared with surgery alone.[20]

Notably, clinical trials are conducted in well selected populations with strict inclusion criteria that could exclude elderly patients. The median age of patients with CC diagnosis is 70 years; thereby, many patients are elderly and it is important to balance individual risk/benefit for adjuvant chemotherapy. However, conclusions drawn from treating elderly patients are based on subgroup analyses and often less than 1% of the trial participants are 80 years old. In particular, no survival efficacy for adjuvant therapy was observed in older individuals in many clinical trials. with limited benefit from adjuvant FOLFOX in patients aged >65 with stage II and III CC.[16,21] In contrast, a pooled analysis including 3000 stage II and III CC reported similar benefit in elderly patients compared with whole population without significant differences in adverse events.[22] Therefore, treatment decision-making for elderly individuals with stage II CC should be carefully considered, evaluating patient comorbidities, performance status and life expectancy.

EMERGING BIOMARKERS

In the last few years, additional tumor and biological biomarkers have been identified to better refine risk categories and to improve patient outcomes in stage II CC.

Mutations in the *BRAF* gene are associated with short OS, and survival after recurrence in the pMMR population.[23] Conversely, no associations have been demonstrated for *KRAS* mutations with relapse-free survival (RFS) and OS in the adjuvant setting.[24]

Notably, Oncotype Dx Colon consisting of 12 cancer-related genes provide a recurrence score, grouping patients in high and low risk of recurrence.[25] However, this assays is much too expensive and its clinical performance has precluded the use in clinical practice. Other gene-expression-based tests include ColoPrint, an 18-gene-expression profile, and ColDX, a 634-probe signature

gene-expression panel, with potential clinical utility in this setting in distinguishing good and poor outcomes.[26,27]

Several studies have shown that circulating tumor DNA (ctDNA) likely holds the greatest promise for revolutionizing the current paradigm for risk stratification in stage II and III disease, with the distinct advantage that it can be determined by a blood test.[28] Tie et al. detected post-operative ctDNA in 7.9% of stage II disease patients reporting an increased risk of recurrence (79% versus 9.8%, respectively).[28] Whether adjuvant CT can clear ctDNA in stage II CC is currently under evaluation in several ongoing clinical trials including the DYNAMIC study (NCT03737539), COBRA trial (NCT04068103) and PRODIGE70-CIRCULATE (NCT04120701).

Interestingly, recent studies have increasingly recognized the growing role of the immune system in cancer progression. The Immunoscore Colon test from HalioDx quantifies the infiltration of CD3+ and CD8+ T cells in tumor biopsy providing a score based on immune-cell infiltration and thus assess the risk of recurrence and benefit of adjuvant chemotherapy. Stage II patients with low immunoscore identify high-risk category (HR 3.03, 95% CI 1.92-4.76, $P<0.001$) who are likely to benefit from adjuvant treatment. These interesting results involving colon Immunoscore may be combined in the future with ctDNA for a better risk estimation.[29]

CONCLUSIONS

The benefit of adjuvant CT in stage II CC is still under debate. All results were derived from subgroup analyses of phase III trials, and no specific studies have been dedicated to those patients. According to these premises and the 2%-5% improvement in survival outcomes with anticancer drugs, treatment decision making in this setting should be carefully considered evaluating patient's comorbidities, performance status, *DPYD* status, risk assessment and life expectancy. Post-operative management may go from surveillance only to 6 months of FOLFOX depending on the estimated risk of recurrence. The only molecular marker involved in treatment decision to date is the MSI/MMR status of the tumor. In the near future, rather than launching a new large phase III trial testing doublet CT versus observation, most cooperative groups around the world have decided to track minimal residual disease through ctDNA assessment and to test the interest of adjuvant therapy in positive patients or guide therapy depending on ctDNA results.

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DISCLOSURE

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