

## Adjuvant chemotherapy for colon cancer: a consensus statement of the Hellenic and Cypriot Colorectal Cancer Study Group

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### Abstract

Colorectal cancer remains a major cause of cancer mortality in the Western world both in men and women. In this manuscript a concise overview and recommendations on adjuvant chemotherapy in colon cancer are presented. An executive team from the Hellenic Society of Medical Oncology was assigned to develop a consensus statement and guidelines on the adjuvant treatment of colon cancer. Fourteen statements on adjuvant treatment were subjected to the Delphi methodology. Voting experts were 68. All statements achieved a rate of consensus above than 80% (>87%) and none revised and entered to a second round of voting. Three and 8 of them achieved a 100 and an over than 90% consensus, respectively. These statements describe evaluations of therapies in clinical practice. They could be considered as general guidelines based on best available evidence for assistance in treatment decision-making. Furthermore, they serve to identify questions and targets for further research and the settings in which investigational therapy could be considered.

**Keywords** Colon cancer, adjuvant chemotherapy, guidelines, Hellas, Cyprus

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## Introduction

Colorectal cancer (CC) remains a major cause of cancer mortality in Europe both in men and women. Notably, it is the second most common malignancy and cause of cancer death [1]. Despite the fact that its incidence and mortality still remain high, they both declined the last 40 years in the developed world [2]. Cancer prevention through screening tests and better treatment modalities are thought to be the major factors of this improvement. Furthermore, it was shown that patients with high-risk stage II and stage III CC who received treatment adhering to National Comprehensive Cancer Network guidelines had a survival benefit [3].

Focusing on better management and improved outcomes, the Hellenic Society of Medical Oncology (HeSMO) chose an executive team with proven experience in CC, assigned to develop a consensus statement and guidelines on the main topics, based on the review of literature and the principles of the evidence-based medicine: image staging, pathology, surgical treatment, chemotherapy in the adjuvant and metastatic setting and follow up. In the present study, the guidelines on the adjuvant chemotherapy for CC are presented. Consensus documents on: a) surgical treatment of rectal cancer; b) surgical treatment of CC; and c) management of metastatic colorectal disease are presented elsewhere.

HeSMO considers adherence to these guidelines to be voluntary. The ultimate determination regarding their application is to be made by the physician in light of each patient's individual circumstances. In view of the consulting, these guidelines cannot form the basis for legal action or litigation for compliance or absence of compliance in the clinical practice setting. They could only be considered as general guidelines based on best available evidence for assistance in decision-making. Any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. HeSMO disclaims any responsibility for their application or use in any way. In addition, these guidelines describe evaluations and administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative management strategies in a disease for which better treatment is sorely needed. However, by reviewing and synthesizing the latest literature, this practice guideline serves to identify questions for further research and the settings in which investigational therapy should be considered.

## Methodology

Through online communication of the executive team members drafting, statements, recommendations and amendments were processed from February 2011 to August 2013. Furthermore, a Hellenic-Cypriot task force meeting convened on May 5-6, 2011 in Heraklion, Crete. During the

initial meeting an overview of main aspects in CC management was presented by one of the task force experts and comments were invited from the other group members. Levels of evidence (LOE) and grades of recommendation presented according to their strength, based on the version adopted by the ESMO Consensus Guidelines for CC (Table 1) [4]. Thereafter, consensus on statements was developed by using Delphi methodology [5].

Initially, one round of anonymous online voting and feedback by experts were conducted. Experts were identified from a systematic search of published literature and recommendations of other experts. The round of the online voting process started on November 10<sup>th</sup>, 2014 and ended on April 30<sup>th</sup>, 2015. At voting, options were: agree (AG), disagree (D), or abstain (A). Abstaining votes were intended for non-experts and did not count towards the overall percentage agreement (rate of voting consensus, ROVC). Statements achieving an agreement of 80% or more were considered as having reached consensus. Those statements achieving an agreement of less than 80% were considered as having achieved a low consensus and were planned to be a subject of a major revision and amendments by the members of the executive team. Thereafter, they would enter a second round of online voting process.

At the present document all statements are presented as recommendations of care. At the end of each recommendation the LOE and the strength of recommendation (SOR) are mentioned, followed by the ROVC. In this manuscript an overview and recommendations on the adjuvant chemotherapy in CC are presented.

**Table 1** Evidence levels and recommendation grades

Level of evidence	
I	Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity
II	Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions
Strength of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages, optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

*RCTs, randomized controlled trials*

Finally, fourteen statements entered the Delphi methodology and 68 experts participated in the online voting procedure. All statements achieved a rate of consensus above 80% (>87%) and none was revised or entered a second round of voting. Three and 8 statements achieved a 100% and an over 90% consensus, respectively. The median abstain rate was 8.2% (1.5-13.2).

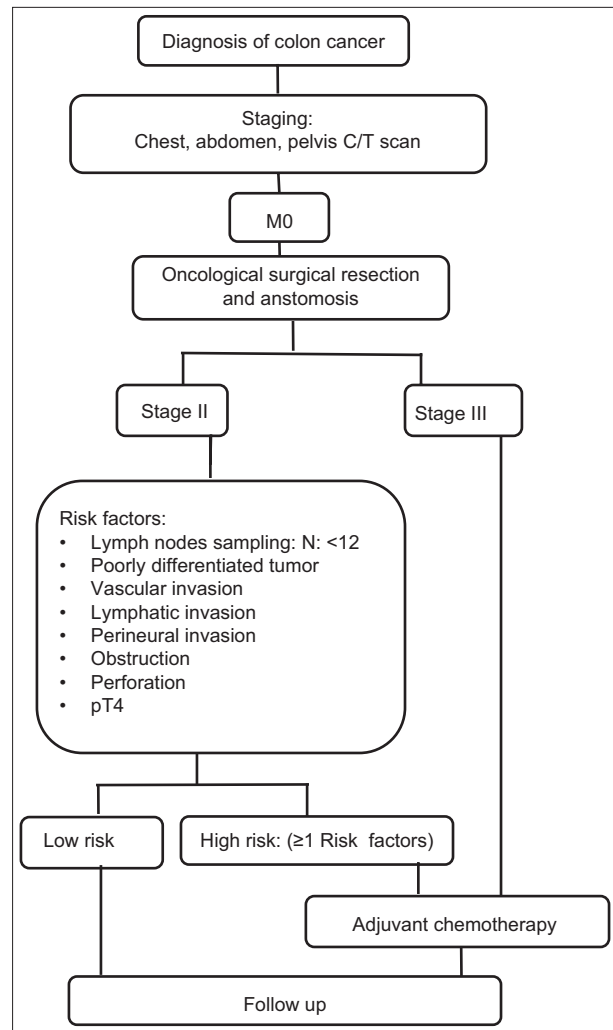
Adjuvant therapy after primary tumor resection aims at reducing the risk of relapse and death by eliminating residual micro-metastatic disease[6]. It has to be started as soon as it is practically feasible and ideally not later than 8 weeks from surgery [7]. Treatment administration based on current evidence should last for 6 months. Shorter treatment duration (3 months) is currently under prospective evaluation by the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) trial [8].

1. Adjuvant chemotherapy has to be started within 3-8 weeks after surgery. It is questionable whether adjuvant chemotherapy commencing beyond 12 weeks is of any benefit (LOE II, SOR B), (ROVC: 95% - AG: 62, D: 3, A: 3)
2. IDEA, a large international collaboration, will give a definitive answer regarding the duration of therapy in stage III patients (LOE I), (ROVC: 98% - AG: 60, D: 1, A: 7)

Currently, the majority of patients with stage I or II CC are treated and cured by surgery. The Pathology staging system used is based on American Joint Committee on Cancer, AJCC, 7th edition [9]. Chemotherapy should be considered for all patients with high-risk stage II disease (defined by the presence of at least one of the following risk factors: lymph nodes sampling <12, poorly differentiated tumor, vascular, lymphatic or perineural invasion, obstruction or perforation and pT4 stage) and stage III (Fig. 1). Moreover, the various therapeutic options need to be discussed with the patient on an individual basis taking into account the performance status, age, comorbidities and preferences, as well as tumor characteristics (pathological stage, grading, and overall risk of relapse).

3. Adjuvant chemotherapy should not be recommended for stage I disease (LOE I, SOR E), (ROVC: 100% - AG: 67, D: 0, A: 1)
4. Adjuvant chemotherapy should be recommended to all patients with high-risk stage II and stage III disease (LOE I, SOR A), (ROVC: 88% - AG: 56, D: 8, A: 4)

There is no consensus about the survival benefit of postoperative chemotherapy in stage II CC [10]. Due to this uncertainty and its relative toxicity, cost, and inconvenience there is no clear justification for the administration of chemotherapy. For that reason it should not be routinely offered to unselected cases. Although direct evidence from randomized controlled trials does not exist for a survival benefit of adjuvant chemotherapy in high-risk stage II disease, oncologists who recommend therapy



**Figure 1** Colon cancer treatment algorithm

in this setting accept the results from stage III disease as indirect evidence of improvement. Moreover, because of a possible small absolute benefit with single agent 5-fluorouracil (5-FU), chemotherapy could be considered for medically fit high-risk stage II patients [11]. Combination chemotherapy with oxaliplatin could also be discussed for selected cases with high-risk features. However, it should be noted that the current definition of high-risk stage II CC is inadequate, given the fact that many patients deemed to be of average risk may have a recurrence and patients with high-risk features may not.

5. For low-risk stage II disease, single agent fluoropyrimidine could be considered, but the absolute risk reduction for recurrence is limited (LOE II, SOR B), (ROVC: 87% - AG: 55, D: 8, A: 5)
6. High-risk stage II patients should be considered for adjuvant chemotherapy with single agent fluoropyrimidine or FOLFOX for a duration of 6 months (LOE II, SOR B), (ROVC: 87%-AG: 54, D: 8, A: 6)

For stage III disease, combination chemotherapy with a backbone of fluoropyrimidine and oxaliplatin (FLOX, FOLFOX, XELOX) is superior when compared to single agent 5-FU, in terms of disease-free survival (DFS) and overall survival (OS), and is the current standard of care [12,13]. It is well established that adjuvant therapy in CC reduces the risk of death by 10-15% in stage III with fluoropyrimidines alone plus a further 4-5% with oxaliplatin-containing combinations [14,15]. Furthermore, with a 10-year follow up in the Multicenter International Study of oxaliplatin/5-FU/leucovorin (LV) in the Adjuvant Treatment of Colon Cancer (MOSAIC), benefit of oxaliplatin as adjuvant therapy for stage III disease is preserved for DFS and OS [16]. The results for OS and DFS for stage II patients are eagerly awaited.

7. Stage III patients should receive fluoropyrimidine- and oxaliplatin-based adjuvant chemotherapy for a duration of 6 months (LOE I, SOR A), (ROVC= 97% - AG: 58, D: 2, A: 8)
8. Whenever fluoropyrimidine- and oxaliplatin-based combination is contraindicated, single agent fluoropyrimidine could be considered (LOE II, SOR B), (ROVC: 98% - AG: 60, D: 1, A: 7)

Certainly, there are several reports giving conflicting evidence on the degree of oxaliplatin benefits in the elderly patients. Efficacy and safety of adjuvant XELOX/FOLFOX versus LV/5-FU or capecitabine were compared with respect to age in several trials and pooled analysis. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial, patients  $\geq 70$  years of age failed to derive a statistically significant benefit from the addition of oxaliplatin [17]. Furthermore, in the MOSAIC trial, the DFS and OS benefits in the same group of patients were similar to those of younger patients after a 3-year follow up, but were lost later due to deaths from other causes and different management or outcome of relapses [18]. In addition, ACCENT database analysis suggests that patients  $\geq 70$  years of age may not receive additional benefit from combination chemotherapy as opposed to single agent fluoropyrimidine [19]. On the other hand, in the XELOXA trial benefits were maintained although to a lesser degree with a hazard ratio for survival of 0.94 [20]. Analysis of the X-ACT trial showed improved outcomes of capecitabine when compared with bolus 5-FU/LV in patients  $\geq 70$  years and at least equivalency in stage III disease [21]. A recently published pooled analysis of NSABP C-08, XELOXA, X-ACT, and AVANT support the administration of combined oxaliplatin/5-FU in stage III patients irrespective of their age and comorbidity [22]. However, even in this highly selected clinical trial patient population, the benefit was modestly attenuated in patients  $\geq 70$  years of age. In addition, there are potential concerns about the methodology used, as it involves the indirect comparison of treatments not randomized against each other.

Available data from numerous retrospective studies strongly support the assessment of microsatellite instability

(MSI) testing to become routine clinical practice [23]. Twenty five percent of tumors proximal to the splenic flexure will be deficient mismatch repair, and, knowing that such tumors have a 50% lower risk for primary tumor recurrence, will help guide the use of chemotherapy in this subset of patients [24]. These patients should not be excluded from receiving chemotherapy if this is otherwise indicated (e.g. for high-risk pathology such as T4 stage, lympho-vascular invasion, neural invasion). Regarding the value of MSI status there are still grey zones and questions to be answered. In addition, routine testing would aid identification of insidious hereditary non-polyposis CC in individuals showing loss of staining of hMSH2 or hMLH1, in the absence of *BRAF* mutations.

9. Patients older than 70 years of age with high risk for recurrence could be considered for adjuvant chemotherapy with single agent fluoropyrimidine for 6 months. Although combination treatment with oxaliplatin is an option for stage III disease, it should be noted that the additional benefit conferred is questionable for this age group (LOE I, SOR B), (ROVC: 97% - AG: 62, D: 2, A: 4)
10. For stage II patients MSI testing should be strongly considered as it can have a significant impact on prognosis and outcome (LOE II, SOR B), (ROVC: 98% - AG: 59, D: 1, A: 8)
11. Infusional 5-FU should be preferred over bolus 5-FU (LOE II, SOR B), (ROVC: 93% - AG: 55, D: 4, A: 9)
12. Oral capecitabine is an effective alternative to intravenous fluorouracil plus LV in the adjuvant treatment of colon cancer (LOE II, SOR B), (ROVC: 100% - AG: 62, D: 0, A: 6)

Infusional 5-FU should be preferred compared to bolus 5-FU due to better tolerability, although the need for a port device and its potential associated complications (thrombosis, lung embolism, infection) should be also considered.

There is no evidence suggesting that infusional 5-FU is superior regarding efficacy to bolus 5-FU in the adjuvant setting [25]. The use of capecitabine in combination with oxaliplatin, which does not require central venous access, is another option.

Irinotecan administration in combination with 5-FU was also studied in several trials (CALGB 89803, PETACC3, ACCORD02/FFCD9802, N0147) [26-29]. The addition of irinotecan did not translate into improved outcomes.

13. Irinotecan combinations cannot be recommended for use in the adjuvant setting (LOE I, SOR E), (ROVC: 98% - AG: 58, D: 1, A: 9)

In the era of targeted therapy, NSABP C-08 and AVANT trials evaluated the addition of Bevacizumab to FOLFOX/XELOX combinations for stage II/III disease, but no benefit



was demonstrated [30,31]. Also, addition of cetuximab to FOLFOX combination in the adjuvant setting did not improve the outcomes [32].

14. Monoclonal antibodies [anti-vascular endothelial growth factor (bevacizumab) or anti-epidermal growth factor receptor (cetuximab/panitumumab)] cannot be recommended for use in the adjuvant setting (LOE I, SOR E), (ROVC: 100% - AG: 60, D: 0, A: 8)

### Concluding remarks

Adjuvant chemotherapy should be recommended for all patients with high-risk stage II and stage III disease. For stage III patients the benefit is clear with the administration of fluoropyrimidine- and oxaliplatin-based adjuvant chemotherapy. Patients older than 70 years of age with high risk for recurrence could be considered for adjuvant chemotherapy with single agent fluoropyrimidine, although combination treatment with oxaliplatin is an option for stage III disease. Irinotecan, bevacizumab or cetuximab combinations should not be recommended for use in the adjuvant setting.

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