

SPECIAL ARTICLE

ESMO Clinical Practice Guideline Express Update on the adoption of physical exercise in patients with localised colon cancer

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INTRODUCTION

This Express Update provides new recommendations for the following ESMO Clinical Practice Guideline (CPG): Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.¹

View the original CPG here: <https://www.esmo.org/guidelines/esmo-clinical-practice-guideline-localised-colon-cancer>.

INCIDENCE AND EPIDEMIOLOGY

Colon cancer is the third most common cause of cancer-related death globally.² The reported increase in incidence and shift to early-age carcinogenesis are partly attributed to lifestyles characterised by obesity, reduced physical activity, alcohol consumption, high red meat intake, smoking and imbalances in the microbiota.^{3,4} Pre-clinical and observational studies have correlated higher levels of recreational physical activity after anticancer therapy with a lower risk of malignant recurrence and death, and have suggested metabolic, inflammatory and immune modulating effects as possible protective mechanisms.^{5,6} This epidemiological evidence resulted in recommendations for health-promoting survivorship plans including exercise, cessation of tobacco and alcohol intake and dietary adjustments.⁷ High-level evidence establishing a direct causal relationship between physical activity and improved clinical outcomes for patients with resected colon cancer, as well as data on the volume, intensity and structure of exercise programmes suitable for cancer survivors, were lacking until recently.

TREATMENT OPTIONS

Stage II and stage III disease

The Canadian Cancer Trials Group phase III CHALLENGE trial randomised 962 patients with resected stage III or high-risk stage II colon cancer who had completed standard adjuvant chemotherapy (ChT) to receive either standard-practice health education materials that promote physical activity and healthy nutrition (health education group) or health education materials plus a 3-year structured exercise programme (exercise group).⁸

Eligible patients had completed adjuvant ChT within the past 2-6 months, were fit [Eastern Cooperative Oncology Group performance status (PS) score 0-1] and were able to complete at least two stages of a submaximal treadmill test (walking at a casual pace for 6 minutes) or the 6-minute walk test.⁸

Patients in the exercise group received an exercise guidebook developed for colon cancer survivors and support from a certified physical activity consultant for 3 years.⁸ The support programme included 17 evidence-based techniques for behavioural change delivered over three phases; these included combinations of mandatory and optional behavioural support and exercise sessions delivered in-person and online (Table 1).^{8,9} The goal of the exercise programme was to increase recreational aerobic exercise from baseline by ≥ 10 metabolic equivalent task (MET)-hours per week during the first 6 months and to maintain or further increase MET-hours during the final 30 months. MET values indicate the intensity of the activity, not the duration. The recommended 10 MET-hours equated to ≥ 150 minutes of moderate intensity aerobic activity per week. As an example, brisk walking for an hour equated to 4 MET-hours. Patients could choose the type, frequency, intensity and duration of aerobic exercise.^{8,9}

The primary study endpoint was disease-free survival (DFS) until colon cancer recurrence, a new primary cancer

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Table 1. Structured exercise programme content and duration⁸

Programme phase	Duration	Behaviour support sessions	Supervised exercise sessions	Delivery mode	Exercise intensity	Target MET-h/week
Phase I	1-6 months	12 mandatory face-to-face (biweekly)	• 12 mandatory (biweekly) • 12 optional (alternate weeks)	Onsite (remote allowed during COVID-19)	Moderate-to-vigorous (4-10 METs)	Total increase from baseline by 10 MET-h/week at end of phase I
Phase II	7-12 months	12 mandatory face-to-face or telephone (biweekly)	12 recommended (optional)	Hybrid (in-person or remote)	Moderate-to-vigorous (4-10 METs)	Individualised target of total increase over baseline: • Maintain 10 MET-h/week • Increase to 20 MET-h/week • Adjust to 5 MET-h/week
Phase III	13-36 months	24 mandatory face-to-face or telephone (monthly)	Recommended (optional) monthly	Hybrid (in-person or remote)	Moderate-to-vigorous (4-10 METs)	Individualised target of total increase over baseline: • Maintain or increase to maximum 27 MET-h/week • Adjust downward if needed

MET, metabolic equivalent task; MET-h, metabolic equivalent task-hour.

of any origin or death from any cause.⁸ Secondary end-points were overall survival (OS), quality of life outcomes, physical fitness, safety, programme adherence and economic evaluations. The feasibility of change in exercise behaviour was confirmed previously.⁹

At a median follow-up of 7.9 years, DFS was significantly improved in the exercise group compared with the health education group [hazard ratio (HR) 0.72, 95% confidence interval (CI) 0.55-0.94, $P = 0.02$].⁸ The 5-year DFS rate was 80.3% in the exercise group versus 73.9% in the health education group. OS was also improved in the exercise group versus the health education group (HR 0.63, 95% CI 0.43-0.94).⁸ The exercise intervention achieved the goal of increasing moderate-to-vigorous physical activity from baseline by ~10 MET-hours per week throughout the entire 3-year programme, which is the equivalent of adding ~45-60 minutes of brisk walking three or four times per week or 25-30 minutes of jogging three or four times per week. There were also meaningful improvements in cardiorespiratory fitness and physical functioning.⁸

During the programme, adherence to mandatory behavioural support sessions reduced from 83% to 63%, and adherence to exercise sessions changed from 79% for the mandatory supervised sessions (only applicable for months 1-6) to 44% for the recommended supervised sessions (during months 13-36).⁸ The as-treated safety analysis reported musculoskeletal adverse events (AEs) in 18.5% of patients in the exercise group versus 11.5% in the health education group. These included arthritis as well as joint, back, limb and muscle pain, and were grade ≥ 3 in 0.7% of patients ($n = 3$) in the exercise group and 0.2% of patients ($n = 1$) in the health education group. Grade ≥ 3 AEs were reported in 15.4% of patients in the exercise group versus 9.1% in the health education group.⁸

CHALLENGE provides the first high-level evidence of a clinically meaningful and statistically significant DFS benefit from a structured exercise programme in patients with resected high-risk localised colon cancer after completion of adjuvant ChT. Randomisation, stratification and a large

sample size likely ensured equal distribution of known and unknown potential confounders between study arms. As such, the trial provides key evidence that reinforces the value of survivorship plans that integrate physical exercise and other health-promoting measures. The study also establishes a new standard of care for selected patients in specific clinical and socioeconomic contexts, and advocates for the development of formal structured exercise programmes for patients with resected colon cancer after completion of adjuvant ChT.

CHALLENGE is also associated with limitations related to completeness or generalisability that necessitate clear communication, shared decision making and investigation of feasibility between health care professionals and patients. Limitations include: (i) inclusion of selected relatively fit patients (Eastern Cooperative Oncology Group PS score 0-1, limited comorbidities, young age) completing adjuvant ChT, (ii) insufficient information on distribution and nature of drop-outs and censoring events, (iii) unknown implementability of the exercise programme in the absence of required infrastructures (e.g. supervised sessions, health coaching) or support (e.g. travelling, absence from work, financial toxicity for patients), (iv) unknown impact of potential adaptations of the exercise programme on clinical benefits (e.g. reduced intensity or frequency for patients who are older, less fit or less able to tolerate exercise, optimal initiation time), (v) pending mature follow-up from CHALLENGE and the lack of independent confirmation from other trials or high-quality prospective observational studies, (vi) absence of results from economic analyses on the cost effectiveness of the strategy and on the biology-informed selection of patients who benefit most.

Algorithms for the adjuvant treatment of stage II and stage III colon cancer are provided in [Figures 1 and 2](#).

Recommendations

- Patients with resected stage III or high-risk stage II colon cancer should be informed of the available evidence

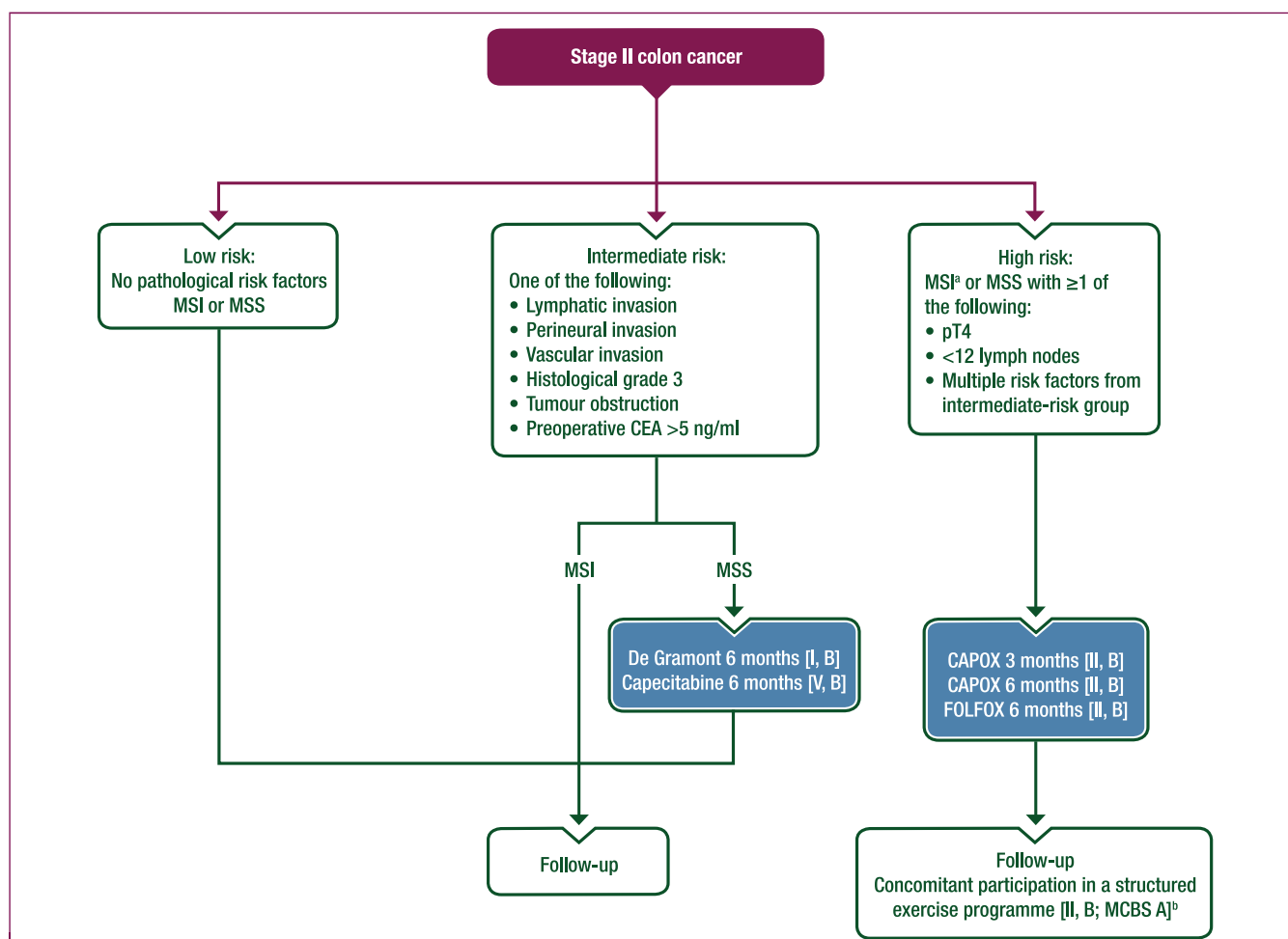


Figure 1. Adjuvant treatment of stage II colon cancer.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.

CAPOX, capecitabine–oxaliplatin; CEA, carcinoembryonic antigen; ChT, chemotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; FOLFOX, leucovorin–5-fluorouracil–oxaliplatin; MCBS, Magnitude of Clinical Benefit Scale; MSI, microsatellite instability; MSS, microsatellite stability.

^aFor pT4 MSI: pT4 is a major risk factor but adjuvant ChT benefit in the presence of MSI is uncertain.

^bESMO-MCBS v2.0¹⁰ was used to calculate scores for new therapies/indications approved by the EMA or FDA, if relevant. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

suggesting survival benefits from a structured exercise programme [I, A].

- Health care professionals should clearly communicate to patients with resected stage III or high-risk stage II colon cancer their eligibility for a structured exercise programme and specify the infrastructure and support needed [I, A]. Health care professionals should also investigate the patient's medical profile, preferences and attitudes, as well as potential challenges for implementation of the exercise programme, including adherence and financial toxicity [I, A].
- After discussion and joint decision making on exercise intensity and implementability, participation of eligible patients in a structured exercise programme can be recommended [II, B; ESMO-Magnitude of Clinical Benefit Scale (MCBS) v2.0 score: A].
- Concerted health system investment can be recommended to build capacity and infrastructures for the implementation of behaviour support and exercise

programmes, along with necessary support and guidance for patients [IV, B].

- Patients with resected localised colon cancer should be encouraged to maintain a healthy lifestyle, including exercise (10 MET-hours per week), smoking cessation, avoidance of excessive alcohol intake and adoption of a healthy diet rich in vegetables, fruit and berries (adapted to gastrointestinal function) [III, A].

METHODOLOGY

This Express Update was developed in accordance with the ESMO standard operating procedures for Express Update development (<https://www.esmo.org/guidelines/esmo-guidelines-methodology>). All recommendations provided are based on current scientific evidence and the authors' collective expert opinion. Where recommendations for multiple different treatment options exist, prioritisation is illustrated by ordering these options according to: level of

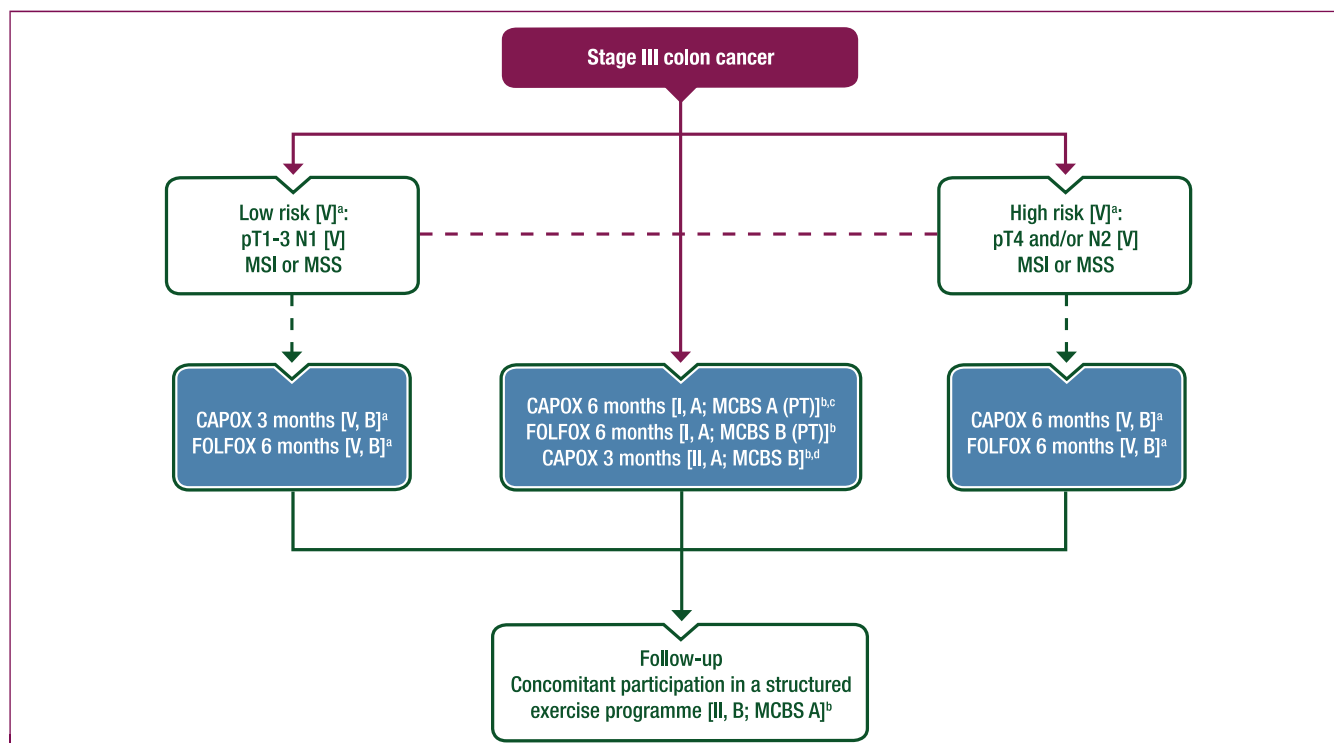


Figure 2. Adjuvant treatment of stage III colon cancer.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects; dashed lines: optional branches, colour used as described in the categories above.

5-FU, 5-fluorouracil; CAPOX, capecitabine–oxaliplatin; ChT, chemotherapy; CPG, Clinical Practice Guideline; EMA, European Medicines Agency; FDA, Food and Drug Administration; FOLFOX, leucovorin–5-fluorouracil–oxaliplatin; LV, leucovorin; MCBS, Magnitude of Clinical Benefit Scale; MSI, microsatellite instability; MSS, microsatellite stability; PT, persistent toxicity.

^aStage III risk subgroups are based on a *post hoc* analysis from the IDEA collaboration and should be applied with caution. Levels of evidence and grades of recommendation for ChT regimens are lower for low-risk and high-risk subgroups compared with the overall population due to the exploratory nature of the analyses. A full explanation is included in the original CPG.¹

^bESMO-MCBS v2.0¹⁰ was used to calculate scores for new therapies/indications approved by the EMA or FDA, if relevant. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

^cMCBS A (PT) versus 5-FU–LV; NO16986 trial.

^dMCBS B versus CAPOX 6 months; IDEA trial.

evidence (LoE) and grade of recommendation (GoR); where equal, by ESMO-MCBS score; where equal, by alphabetical order. The relevant literature has been selected by the expert authors. ESMO-MCBS v2.0¹⁰ was used to calculate scores for new therapies/indications approved by the European Medicines Agency or Food and Drug Administration, if relevant (<https://www.esmo.org/guidelines/esmo-mcbs>). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. LoEs and GoRs have been applied using the system shown in [Supplementary Table S1](#), available at <https://doi.org/10.1016/j.esmoop.2025.106019>.¹¹ Statements without grading were considered justified standard clinical practice by the authors. For future updates to the localised colon cancer CPG, including Express Updates and Living Guidelines, please see the ESMO Guidelines website: <https://www.esmo.org/guidelines/esmo-clinical-practice-guideline-localised-colon-cancer>.

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