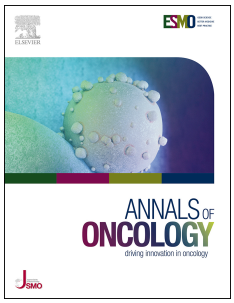

Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis treatment and follow-up of patients with localised colon cancer

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Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis treatment and follow-up of patients with localised colon cancer

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Abstract

The most recent version of the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of localised colon cancer was published in 2020. It was decided by both the ESMO and the Japanese Society of Medical Oncology (JSMO) to convene a special virtual guidelines meeting in March 2021 to adapt the ESMO 2020 guidelines to take into account the ethnic differences associated with the treatment of localised colon cancer in Asian patients. These guidelines represent the consensus opinions reached by experts in the treatment of patients with localised colon cancer representing the oncological societies of Japan (JSMO), China (CSCO), India (ISMPO), Korea (KSMO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS). The voting was based on scientific evidence and was independent of the current treatment practices and drug availability and reimbursement situations in the different Asian countries.

Key words

Localised colon cancer, diagnosis, ESMO, guidelines, Pan-Asian, treatment

Highlights

• This article provides ESMO expert recommendations adapted for the treatment of localised colon cancer in Asian patients.

• The aim was to provide guidance for the optimisation of the management of such patients across Asia.

• The availability and applicability of certain procedures as they relate to certain of the recommendations are discussed.

INTRODUCTION

Of an estimated 18.1 million new cases of cancer diagnosed worldwide in 2018, colorectal cancer (CRC) was the third most common cancer across both genders, representing 10.2% of new cases, and the second highest cause of cancer death (9.2%).[1, 2] Colon cancer alone was estimated to account for 6.1% (1.1 million) of new cancer cases and 5.8% (551,000) of cancer deaths worldwide.[1]

The highest colon cancer incidence rates are found in Europe, in Australia and New Zealand, and in Eastern Asia (China, Japan, South Korea and the female population of Singapore).[1, 3] Upward trends in incidence rates have been reported for Japan,[4] China,[5, 6] Korea,[7, 8] Singapore,[9, 10] Malaysia,[11] Taiwan[12] and India (although in India the overall incidence rate remains low).[13] Indeed, recent estimates show Asia to account for half of the new cases, deaths and 5-year prevalence for CRC,[3] with Asian studies suggesting that individuals of Chinese, Japanese and Korean ethnicity might be more susceptible to CRC.[14-17]

Risk factors for colon cancer include genetic factors, ethnicity, age, gender, family history and lifestyle, with the increasing and higher incidences seen in Asian countries, and in specific regions within these countries, linked to economic development, urbanisation and to a more Western lifestyle.[18, 19] Such Western lifestyle changes include less physical activity, a Westernised diet, obesity, increased alcohol consumption and smoking.[20] In Asia in general,[21, 22] as supported by studies in China,[23, 24] Taiwan,[25] Korea[26] and Japan[27], a westernised diet, containing more red meat and less vegetables and fibre, has been shown to contribute to the development of CRC. A correlation between being obese or overweight and colon cancer has also been demonstrated in Asian populations, with the causality in some studies being reported to be gender specific[28-33] and in others, the same for both genders.[24, 34, 35] Male gender is associated with a higher incidence of CRC in Korea,[7] Japan,[36] China.[37] and Taiwan.[38] Thus, colon cancer/CRC represents a major healthcare challenge across Asia, with the incidence of CRC in developing countries, such as China, predicted to increase sharply over the next decade.[39]

Guidelines for the management of patients with colon cancer/CRC in Asia have been published previously[4, 40-42] and are important for the standardisation of both screening and treatment approaches, with the aim of optimising clinical outcomes. The European Society for Medical Oncology (ESMO) Clinical Practice guidelines for the diagnosis, treatment and follow-up of patients with localised colon cancer have recently been published (ESMO Clinical Practice Guidelines),[43] and a decision was taken by ESMO and the Japanese Society of Medical Oncology (JSMO), that these guidelines should be adapted for patients of Asian ethnicity. Consequently, representatives of JSMO, ESMO, the Chinese Society of Clinical Oncology (CSCO), the Indian Society of Medical and Paediatric Oncology (ISMPO), the Korean Society of Medical Oncology (KSMO), the Malaysian Oncological Society (MOS), the Singapore Society of Oncology (SSO) and the Taiwan Oncology Society (TOS) convened for a virtual, 'face-to-face' working meeting on 13th March 2021 to adapt the recent ESMO Clinical Practice Guidelines[43] for use in the management of Asian patients with localised colon cancer. This manuscript summarises the Pan-Asian adapted guidelines developed at the meeting accompanied by the level of evidence (LoE), grade of recommendation (GoR) and percentage consensus reached for each recommendation.

METHODOLOGY

This Pan-Asian adaptation of the ESMO Clinical Practice Guidelines[43] was prepared in accordance with the principles of ESMO standard operating procedures (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology) and was a JSMO-ESMO initiative endorsed by CSCO, ISMPO, KSMO, MOS, SSO and TOS.

An international panel of experts was selected from the JSMO (n=9), the ESMO (n=9), and two experts from each of the oncological societies of China (CSCO), India (ISMPO), Korea (KSMO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS). Only two of the nine expert members from the JSMO (EO

and HT) were allowed to vote on the recommendations together with the two experts from each of the six other Asian oncology societies (n=14).

A modified Delphi process was used to review, accept or adapt each of the individual recommendations in the latest ESMO Clinical Practice Guidelines.[43] The 14 Asian experts were asked to vote YES or NO (one vote per society) on the *acceptability* (agreement with the scientific content of the recommendation) and *applicability* (availability, reimbursement and practical challenges) of each of the ESMO recommendations in a pre-meeting survey (see supplementary Methodology). For recommendations, where a consensus was not reached, the Asian experts were invited to modify the wording of the recommendation(s) at the 'face-to-face' virtual meeting using rounds of voting in order to determine the definitive acceptance or rejection of an adapted recommendation and discuss the applicability challenges. The 'Infectious Diseases Society of America-United States Public Health Service Grading System' (supplementary Table S 1)[44] was used to define the LoE and strength (grade) of each recommendation. Any modifications to the initial recommendations were highlighted in bold text in a summary Table of the final Asian recommendations and in the main text, if and as applicable. A consensus was considered to have been achieved when ≥ 80% of experts voted that a recommendation was acceptable.

RESULTS

In the initial pre-meeting survey, the 14 Asian experts reported on the *acceptability* and *applicability* of the 39 recommendations for the diagnosis treatment and follow-up of patients with localised colon cancer from the 2020 ESMO Clinical Practice Guidelines.[43] These recommendations were made in the seven categories listed below:

1. Screening principles (Recommendations 1a-f)
2. Diagnosis (Recommendations 2a-e)
3. Management of localised tumours (Recommendations 3a-d)
4. Pathological reporting (Recommendation 4)
5. Risk assessment (Recommendations 5a-h)
6. Treatment options (Recommendations 6a-i)
7. Follow-up and long-term implications (Recommendations 7a-f).

A lack of agreement in the pre-meeting survey was established for 'recommendations 5f, 6a, 6d, 6f and 6g' (with no consensus for *acceptability*) and 'recommendations 5g and 5h' only, out of '5b, 5e, 5g and 5h' (initially with no consensus for *applicability),* due to rapidly emerging evidence, including from Asian studies*,* leading to their discussion during the 'face-to-face' meeting.

1. Screening principles – Recommendations 1a–f

Age is the most significant risk factor for the development of colon cancer. The stepwise development of colon cancer from a polyp through to a carcinoma can take up to 10 years. This means that as a consequence of screening programmes, not only are colorectal polyps found and removed before they can develop into carcinomas, but colon cancer itself is more often detected at an early stage, thus offering patients the possibility of a 5-year relative survival rate in the region of 90%.[45]

The Pan-Asian panel of experts agreed with and *accepted* completely (**100% consensus**) the ESMO recommendations on screening, 'recommendations 1a-d' (invasive tests) and 'recommendations 1e and f' (non-invasive tests)', from a scientific point of view (see below and Table 1).

1a. *Colonoscopic techniques, despite being invasive, have the advantage of being both diagnostic and therapeutic.*

1b. A complete colonoscopy is the recommended method for CRC screening in average-risk men and women based on higher sensitivity and specificity when compared with other tests [II, B].[46] The optimal age range for testing is 50–74 years [V, D] with an optimal repetition interval for a negative test of 10 years [III, C].

1c. Flexible sigmoidoscopy performed every 5–10 years may be an alternative for those who refuse colonoscopy [II, B]. The combination of this method with a yearly faecal occult blood test (FOBT) (see below) is recommended to reduce the risk of a right-sided colon tumour [III, B].

1d. Other invasive tests including capsule colonoscopy are not recommended for screening [IV].

1e. Non-colonoscopic tests are recommended in average-risk men and women from the age of 50 who are not already taking part in colonoscopic screening programs. The optimal frequency of testing is every year and no later than every three years [I, B]. A colonoscopy must be performed at the earliest convenience when the test results are positive [I, A].

1f. Among the available tests, faecal immunochemical testing (FIT) appears to be superior to the high-resolution guaiac FOBT with respect to the detection rate and positive predictive value for adenomas and cancer [III]. Other novel methods including DNA-based or other tests using other markers (e.g. M2-pyruvate kinase [M2-PK]) lack formal comparisons of their performance, and integration with other assays needs to be monitored.

However, some reservations were expressed in terms of the *applicability* of some of the recommendations, as colonoscopic screening ('recommendation 1b' above and Table 1) is not routinely conducted in all Asian countries due to resource limitations, although it was agreed that it would be desirable to have it. Similarly, flexible sigmoidoscopy ('recommendation 1c') is not standard practice in all countries, but was considered to be adaptable and doable. Both capsule endoscopy[47] and computed tomography (CT) colonography[48, 49] have been reported to have high sensitivity and specificity for lesions > 10mm (including adenomas) in Japanese studies. However, since it is not possible to perform a pathological evaluation at the same time, these tests are not recommended for screening, except for patients with ileocaecal adhesions/organic anomalies or comorbidities[50, 51] (see the text for 'recommendation 2a' below and Table 1).

Endoscopic techniques for the management of early colon cancer are discussed in detail in the Asian guidelines. The most recent Asia Pacific Consensus Recommendations on CRC screening recommend a risk-stratified scoring system for selecting high-risk patients for colonoscopy[41] and define the age range for CRC screening as 50–75 years. However, consistent with observations in Western countries there is an increase in the incidence of CRC in younger Asian adults[52, 53, 54] thus, it may be prudent to start screening for CRC from 40 years of age in Asia. The morbidity and mortality of CRC increases from the age of 40 years in Japan.[55] The interval for repeat colonoscopy in the absence of polyps should be 10 years.[41, 56, 57]

In some countries, due to resource limitations, screening programmes using the non-invasive invasive FOBT and the FIT are recommended as the first-line approach for screening in average-risk populations and have been shown to reduce mortality from CRC.[58-60] The Asia Pacific Consensus Recommendations on colorectal cancer screening[41] recommend the use of the FIT over the FOBT for screening in average-risk individuals. Colonoscopy and colonoscopy combined with FOBT are considered to provide higher sensitivity than faecal tests alone; however, to the knowledge of the experts, there are currently no randomised controlled trials to support this. The ongoing Japanese population-based Akita pop-colon study aims to compare screening using the FIT combined with colonoscopy with FIT alone and to evaluate the efficacy of colonoscopy screening in reducing CRC mortality in individuals ≥ 40 years of age.[61]

2. Diagnosis – Recommendations 2a–e

A clinical or biological suspicion of CRC should be confirmed by a complete diagnostic work-up,[43] as described in supplementary Table S 2 taken from the ESMO Clinical Practice Guidelines.[43]

The Pan-Asian panel of experts agreed completely (**100% consensus**) with the ESMO recommendations on diagnosis, 'recommendations 2a–e' (see below, Table 1 and supplementary Figure S 1), after the pre-meeting survey, in terms of both a scientific (*acceptability*) and *applicability* point of view.

2a. *In the absence of indications for urgent tumour resection, a total colonoscopy is recommended for diagnostic confirmation of colon cancer and to rule out synchronous tumours. Combining limited left-sided colonoscopy with CT colonoscopy is an alternative if full colonoscopy is not possible [I, A].*[62]

2b. When not carried out before or during the surgical procedure, a complete colonoscopy should be carried out within 3–6 months following tumour resection [IV, B].[63]

2c. A comprehensive physical examination and laboratory tests including full blood counts, biochemistry, and serum carcinoembryonic antigen (CEA)[64] *must be carried out prior to decisions on the definitive treatment approach [III, A].*

2d. CT of the thoracic, abdominal and pelvic cavities with intravenous contrast administration is the preferred radiological method for the evaluation of the extent of CRC [II, B].

2e. Contrast-enhanced magnetic resonance imaging (MRI) constitutes the reference test for evaluation of the relationship of locally advanced tumours with surrounding structures or in defining ambiguous liver lesions [II, A].

3. Management of localised colonic tumours – Recommendations 3a–d

The Pan-Asian panel of experts agreed completely (**100% consensus**) with the ESMO recommendations on the management of localised tumours, 'recommendations 3a–d' (see below, Table 1, and supplementary Figure S 1), after the pre-meeting survey, from both a scientific (*acceptability)* and *applicability* point of view.

3a. *En bloc endoscopic resection of the polyp is sufficient for non-invasive (pTis, i.e. intraepithelial or intramucosal) adenocarcinomas [IV, B].*[43, 65]

3b. The presence of invasive carcinoma (pT1) in a polyp requires a thorough review with the pathologist and surgeon.[66, 67] *High-risk features mandating surgical resection with lymphadenectomy include lymphatic or venous invasion,*[68] *grade 3 differentiation,*[68] *and significant (grade > 1) tumour budding*[69] *[IV, B].*

3c. Laparoscopic colectomy can be safely carried out for colon cancer when technical expertise is available in the absence of contraindications, in view of reduced morbidity, improved tolerance and similar oncological outcomes [I, C].

3d. Obstructive CRCs can be treated using one- or two-stage procedures, as indicated [III, B].

In the case of infiltrative colon cancers, surgery is mandated with the aim being to achieve wide resection of the target lesion and associated lymphatic drainage [III, A].[70] *En bloc* colonic and mesentery resection is required to define stage II versus stage III disease and to facilitate the identification of potential lymph node metastases. Ideally at least 12 lymph nodes should be analysed [IV, B].[71] Asian guidelines advocate extended (D3) lymphadenectomy on a routine basis in T3/T4 and in selected T2 patients.[72] Laparoscopic colectomy is an option when technical expertise is available in the absence of contraindications [I, C].[73, 74] Patients with obstructive colon cancers can be treated using one-or two-stage procedures, as the situation requires [III, B].[43]

4. Pathological reporting – Recommendation 4

The pathological stage must be recorded according to the Union for International Cancer Control guidelines tumour node metastasis (TNM) classification[75] and the Japanese Classification of Colorectal, Appendiceal and Anal Carcinoma.[76] The Pan-Asian panel of experts agreed completely (**100% consensus**) with the ESMO Clinical Practice Guidelines 'recommendation 4' (Table 1), after the pre-meeting survey, from both a scientific (*acceptability)* and *applicability* point of view, with the caveat that in Malaysia, DNA mismatch repair (MMR)/microsatellite instability (MSI) testing is only conducted at selected centres and even then, it is currently not fully routine.

4a. *A standard surgical/pathological report should include[77]: specimen description, and surgical procedure, tumour site and size, macroscopic tumour perforation, histological type and grade, extension into the bowel wall and adjacent organs, distance of cancer from resected margins (proximal, distal and radial), presence or absence of tumour deposits, lymphovascular and/or perineural invasion, tumour budding,[69] site and number of removed and involved regional lymph nodes, MMR/MSI status and involvement of other organs [IV, A].*

5. Risk assessment – Recommendations 5 a–f

All the Asian experts accepted completely (**100% consensus**) the ESMO 'recommendations 5a–e' (below and Table 1) without change.

5a. Adjuvant therapy options should be fully discussed with the patient, taking into consideration the risk of tumour recurrence, expected benefit from chemotherapy and risk of complications [V].

5b. The risk of relapse after a colon cancer resection should be assessed by integrating the TNM staging, MMR/MSI status and number of lymph nodes sampled (+/- 12) [III, A].

5c. Other additional clinicopathological features such as the histological subtype and grading, lymphatic or venous or perineural invasion, lymphoid inflammatory response, involvement of resection margins and serum CEA should be taken into consideration for 'fine-tuning' the risk assessment on stage II tumours [III, A].

5d. Patient age alone has no predictive value for or against the use of adjuvant treatment and must be considered in the context of (potential) benefit, underlying risk for relapse, life expectancy in relation to (biological) age and comorbidities. However, it can be generalised that benefits of treatment with fluoropyrimidines plus/minus oxaliplatin, seem to be more limited, with a higher likelihood of toxicity in older patients [II, B].

5e. MSI/MMR status is the only validated molecular marker used in adjuvant decision making and should be determined in stage II CRC. In stage III, the use of MMR status is limited to the detection and identification of Lynch syndrome [IV, A].

TNM staging remains the most important tool for risk assessment following surgical resection for colon cancer.[75] The other major clinical prognostic factors for stage II risk assessment are lymph node sampling and pT4 stage, including perforation. Age alone has no predictive value for or against the use of adjuvant treatment. A comparison of the efficacy and safety of adjuvant fluoropyrimidine-oxaliplatin combination therapy versus leucovorin (LV)/5-fluorouracil (5-FU) using pooled data from four randomised, controlled trials, in patients with stage III CRC, showed disease-free survival (DFS) benefits for fluoropyrimidine-oxaliplatin combination therapy over LV/5-FU therapy regardless of age or medical comorbidity.[78] Overall survival was also significantly improved in those patients aged ≥ 70 years receiving oxaliplatin-containing therapy, although grade 3/4 serious adverse events rates were higher in patients aged ≥ 70.[78] In another study, of data from three adjuvant therapy trials, patients aged ≥ 70 years seemed to experience a reduced benefit from the addition of oxaliplatin to fluoropyrimidines compared with those patients aged < 70 years[79]. Thus, the addition of oxaliplatin to any fluoropyrimidine should be assessed on an individual basis for the treatment of older patients, coupled with careful monitoring.

MSI/MMR is the most validated prognostic molecular marker and should be integrated into the assessment.[80] MSI/MMR status may be useful for the identification of a subgroup of patients with localised colon cancer with a better prognosis and less expected benefit from chemotherapy.[81-84] Other genetic markers, such as *RAS* or *BRAF* mutations, are not recommended in the adjuvant decision making process for patients with localised colon cancer.[85]

Deficiencies in the functioning of dihydropyrimidine dehydrogenase (DPD), due to genetic polymorphisms, occur in 3%–5% of Western/European patients and can lead to lethal fluoropyrimidine toxicity,[86] and, testing for DPD insufficiency, before initiating fluoropyrimidine-based chemotherapy, and is strongly recommended in the ESMO Clinical Practice Guidelines prior to initiating fluoropyrimidine therapy.[43]

However, the representatives of the JSMO and the SSO did not consider this recommendation ('recommendation 5f') acceptable in the pre-meeting survey (supplementary Table S 3) on the basis that the incidence of DPD deficiency is estimated to be very low in Asian populations compared with non-Asian populations. A Japanese study investigated the incidence of DPD deficiency in 1,362 Asian colon cancer patients, who were enrolled in the JOIN[87] and ACHIEVE[88] adjuvant chemotherapy trials, and suggested that the incidence of DPD deficiency for these patients was in the region of 0.6%, with no clear association observed between DPD deficiency and safety.[89] In addition, DPD deficiency was not detected by analysing DPD full-length RNA polymorphisms in peripheral blood mononuclear cells in 67 Taiwanese patients using multiplex nested reverse-transcription-polymerase chain reaction (RT-PCR) and non-isotopic RNase cleavage assays (NIRCA).[90] DPD deficiency is also reported not to be common in Korea.[91] Thus, due to the low incidence of DPD deficiency in Asian patients, DPD genotyping and phenotyping is not carried out in routine daily practice in Asia, but is recommended for patients, who experience severe 5-FUtoxicity during and after their first cycle of chemotherapy. As a consequence, the original 'recommendation 5f' was amended, with a 100% consensus, and the changes highlighted in bold text, to read as follows:

5f. ***Depending on the anticipated genetic profile of a specific Asian patient population****, DPD genotyping or phenotyping* ***may be considered*** *before initiating fluoropyrimidine-based adjuvant therapy [III, A].* ***DPD genotyping or phenotyping should be implemented in patients who experience severe fluoropyrimidine toxicity [V; consensus = 100%]*** (Table 1).In terms of *applicability*, there was also considerable discussion about the application of 'recommendations 5g and h' in relation to the use of gene expression signatures and Immunoscore® (Immunoscore), (supplementary Tables S 4 and S 5 that subsequently lead to the revision of 'recommendations 5g and h'.

The 12-gene Recurrence Score (Oncotype DX Colon Recurrence Score assay)[92] and Gene Fx Colon[93] assays, both using reverse transcription–polymerase chain reaction techniques and formalin-fixed, paraffin-embedded colon tumour samples, have been used to evaluate the risk of recurrence in patients with colon cancer independently of the standard prognostic factors.[92-94] A Japanese study has confirmed the prognostic utility of the 12-gene Recurrence Score assay in both stage II and stage III colon cancer patients treated with surgery alone and established its clinical validity in Asian patients.[95] In addition, this was the first study to establish the clinical validity of the assay for prognostication by assessing the risk of recurrence in patients with stage III colon cancer, who had not received any adjuvant chemotherapy subsequent to surgical resection and adequate lymph node assessment.[95] By providing prognostic information, gene expression signatures may aid health-care professionals in their decision-making regarding the administration of adjuvant chemotherapy to patients with resected stage II colon cancer. However, these tests were not shown to reliably predict the benefit of adjuvant chemotherapy. Thus, the text of the original 'recommendation 5g' was reworded to read as follows:

> 5g. *Gene expression signatures* ***may provide prognostication in stage II disease but are not recommended for use in routine practice due to a lack of predictive value for*** *chemotherapy benefit* ***[IIC; consensus = 100%]*** (Table1).

Immunoscore involves the quantification of lymphocyte populations, in particular CD3- and CD8-positive T-cells, both at the tumour centre and at the invasive margin using digital pathology, and is both prognostic and predictive.[96]

A retrospective study from an international consortium of 14 centres in 13 countries, led by the Society for Immunotherapy of Cancer, evaluated the standardised Immunoscore assay in primary tumours from patients with stage I–III colon cancer and showed it to provide a reliable estimate of the risk of recurrence in patients with colon cancer.[97] Analysis of the data for the Asian population from the same dataset confirmed that the Immunoscore was also strongly prognostic for the risk of recurrence in Asian patients with stage I-III colon cancer.[98] A subsequent, study from the same consortium, evaluated selected retrospective North American, European and Asian cohorts of patients with stage III colon cancer managed with observation versus fluoropyrimidine monotherapy versus combination chemotherapy, from the same patient dataset and showed the consensus Immunoscore to be prognostic for survival in all patients and predictive for benefit from adjuvant chemotherapy.[99] Specifically, an outcome comparison between patients on adjuvant chemotherapy versus on

observation disclosed a survival benefit only in patients with Immunoscore-high colon cancer.[99] In addition, retrospective analysis of data from the IDEA FRANCE adjuvant study showed an intermediate and high Immunoscore to significantly predict the benefit of 6 months as opposed to 3 months of FOLFOX adjuvant therapy, including for patients with clinically low- and high-risk stage III colon cancer.[100] A study in the United Stated has also shown Immunoscore to enhance the accuracy of survival prediction in patients with stage III colon cancer.[101] Thus, these results may support (low-level evidence)the use of Immunoscore as an adjunct to classical TNM staging, for the provision of prognostic information for patients with stage II and III colon cancer, and may facilitate the identification of those patients (with Immunoscore-high colonic tumours) who might derive a marked benefit from adjuvant chemotherapy. The original 'recommendation 5h' was thus modified to read as follows:

5h. *Immunoscore® could be considered in order to refine the prognosis of **localised** colon cancer patients **when** used in conjunction with TNM scoring in stage II and stage III **disease** [III, C], although its role in predicting **an adjuvant** chemotherapy **effect** is uncertain* **[IV,C; consensus = 100%]** (Table 1)*.*

6. Treatment options – Recommendations 6a–i

Stage III disease

All the Asian experts accepted completely (**100% consensus**) 'recommendations 6b and c' (Table 1) without change, but did not accept 'recommendations 6a and d' (supplementary Table S 3), after the pre-meeting survey. Following discussion at the 'face-to-face' virtual meeting it was decided that 'recommendation 6a' (Table 1) could also be accepted and the wording remain unchanged.

6a. *Combinations of fluoropyrimidines, either 5-FU or capecitabine, and oxaliplatin constitute the basis of stage III colon cancer adjuvant treatment [I, A; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: B; **consensus = 100%**].*

6b. The length of oxaliplatin-based adjuvant treatment for stage III colon cancer based on the IDEA data may be tailored to 3 or 6 months for CAPOX [I, A] or 6 months for FOLFOX [I, A], also taking into consideration pathological risk characteristics, patient comorbidity and risk assessment.

6c. Further adaptation of the treatment according to risk subgroups: 3 months for CAPOX (T1–3 N1 disease), 6 months for CAPOX (T4 or N2 disease) or 6 months for FOLFOX (T1–3 N1 or T4 or N2 disease) based on IDEA collaboration should be made with caution, since this was based on a post hoc analysis, which was non-significant for interaction [V].

Regardless of MSI/microsatellite stability status, the current standard adjuvant therapy for patients with stage III localised colon cancer is fluoropyrimidine-oxaliplatin combination chemotherapy (FOLFOX or CAPOX) based on data from the pivotal MOSAIC,[102] NSABP C-07 [94, 103] and XELOXA[104] trials. However, the major cumulative and debilitating toxicity associated with fluoropyrimidine-oxaliplatin therapy is peripheral sensory neuropathy (PSN).

Recently, a prospective pooled analysis of 12834 stage III colon cancer patients enrolled in six adjuvant trials conducted in different geographical regions, including Asia, and randomised to receive either 3 months or 6 months of FOLFOX or CAPOX adjuvant therapy (the IDEA study),[105] showed PSN grade ≥ 2 to be significantly reduced in patients receiving 3 months of fluoropyrimidine-oxaliplatin treatment compared with those receiving 6 months of treatment (11% versus 34%).[105] Also, in terms of disease-free survival (DFS), 3 months of CAPOX therapy was non-inferior to 6 months of CAPOX therapy (Hazard Ratio [HR]: 0.95; 95% confidence interval [CI]: 0.85-1.06), but 3 months of FOLFOX therapy was not non-inferior to 6 months of FOLFOX therapy (HR: 1.16: 95% CI: 1.06-1.26).[105] Thus, the data support the use of either 3 months of CAPOX or 6 months of FOLFOX therapy as adjuvant treatment options for patients with stage III colon cancer.

In the Asian ACHIEVE study the HRs for DFS in the 3-month treatment arm compared with the 6-month treatment arm were 1.07 (95% CI: 0.71-1.60) for FOLFOX and 0.90 (95% CI: 0.68-1.20) for CAPOX.[88] Also, consistent with the results of the IDEA analysis the incidence of long-lasting PSN was significantly

lower for patients receiving 3 months of therapy than for those receiving 6 months of therapy, and significantly lower for patients receiving CAPOX than for those receiving FOLFOX. As a consequence, the authors concluded that for Asian patients, a 3-month course of CAPOX may be the most appropriate treatment option, particularly for patients with low-risk (T1-3 and N1) disease.

However, the experts from the JSMO did not accept the original ESMO 'recommendation 6d' for the treatment of those stage III patients who are unable to receive an oxaliplatin-containing adjuvant therapy regimen. This was due to the fact that LV5FU2 is not widely used for adjuvant treatment in Japan and other Asian countries and the preference is for the use of oral fluoropyrimidines, such as capecitabine, UFT/LV and S-1. Moreover, bolus 5-FU/LV regimens are used in some Asian countries. Furthermore, phase III adjuvant studies in Japanese patients with stage III colon cancer have shown UFT/LV to be non-inferior to 5-FU/LV in terms of DFS,[106] S-1 to be non-inferior to UFT/LV,[107] but S-1 not to be non-inferior to capecitabine.[108] Furthermore, two randomised studies, comparing 6 months of UFT/LV with 18 months of UFT/LV,[109] and 6 months of capecitabine with 12 months of capecitabine therapy,[110] both failed to prove the superiority of > 6 months of chemotherapy in Japanese patients.

As a consequence, the wording of the original ESMO 'recommendation 6d' was amended, with a **100% consensus***, and an* ESMO-MCBS v1.1 score: B to read as follows:

> 6d. *For patients not fit* ***or unable to tolerate*** *oxaliplatin, capecitabine or* ***any 5-FU infusional or bolus regimens or UFT/LV are acceptable 6-month adjuvant regimens in various Asian populations [I, A; ESMO-MCBS v1.1 score: B; consensus = 100%]*** (Table 1 and see also Figure 1).

There was also a **100% consensus** on the *applicability* of all the 'recommendations 6a–d' (Supplementary Table S 4), for the adjuvant treatment of Asian patients with stage III colon cancer after a brief discussion about the evidence for 3 months of CAPOX therapy ('recommendation 6b' above).

Stage II disease

All the Asian experts accepted completely 'recommendation 6e' below (Table 1) without change.

> 6e. *For patients with low-risk stage II colon cancer, follow-up is recommended [I, A; consensus = 100%].*

However, the Asian experts did not accept 'recommendations 6f and g' (supplementary Table S 3). This was due to the fact that the criteria for intermediate risk were disputed by the Japanese experts due to data from the Japanese Phase III SACURA trial, which showed tumour budding and pathological grade to be strong independent prognostic factors for patients with stage II colon cancer.[111] The budding grade significantly correlated with recurrence in the liver, lungs, lymph nodes and peritoneum, and resulted in the recommendation that tumour budding should be routinely evaluated in pathology practice.[111] Furthermore, in the same study, fluoropyrimidine monotherapy was seen to improve relapse-free survival in stage II patients with high tumour budding.[111] There was also concern over the distinction between high- and intermediate-risk patients in 'recommendations 6f and g' of the original ESMO recommendations. As a consequence, 'recommendations 6f and g' were reworded, and the levels of evidence adjusted (see bold text below), to read as follows:

> 6f. *For patients with intermediate-risk* ***stage II*** *(non-MMR/MSI + any risk factor except pT4****/perforation*** *or < 12 lymph* ***nodes*** *assessed) 6 months of fluoropyrimidine therapy is recommended [****II, B****].* ***Three months of CAPOX is an acceptable alternative in fit patients, after being informed of the risk/benefit profile [V; consensus = 100%]*** (Table 1 and Figure 2).

> 6g. ***For*** *patients with high-risk stage II disease (pT4****/perforation*** *or < 12 lymph nodes* ***assessed*** *or multiple intermediate risk factors, regardless of MSI status) the addition of oxaliplatin* ***should be considered, in view of a higher risk of relapse and anticipated benefit [II, C; consensus = 100%]*** (Table 1 and Figure 2).

The original ESMO 'recommendations 6h and i' below were accepted completely.

6h. Patients with high-risk stage II colon cancer may be considered for 3 months of CAPOX, as the IDEA-pooled analysis showed non-inferiority of 3 months of CAPOX and inferiority of 3 months of FOLFOX when compared with 6 months of FOLFOX, with all the limitations of post-hoc analyses [II, B, consensus = 100%].]

6i. *It is important to start adjuvant chemotherapy as soon as possible after surgery and ideally not later than 8 weeks[112] [I, A, consensus = 100%].*

There was a **100% consensus** on the *applicability* of all the 'recommendations 6e–i' (Supplementary Table S 4), for the adjuvant treatment of Asian patients with stage II colon cancer.

7. Follow-up and long-term implications – Recommendations 7a–f

All the Asian experts accepted completely (**100% consensus**) 'recommendations 7a-f' (Table 1), without change, in terms of *acceptability* and *applicability.*

7a. *Intensive follow-up allows earlier detection of relapses in patients at risk [II, B].*

7b. History and physical examination and CEA determination are advised every 3–6 months for 3 years and every 6–12 months at years 4 and 5 after surgery [II, B].

7c. Colonoscopy must be carried out at year 1 and every 3–5 years thereafter, looking for metachronous adenomas and cancers [III, B].

7d. CT scan of chest and abdomen every 6-12 months for the first 3 years can be considered in patients who are at higher risk of recurrence according to the TNM classification [II, B].

7e. Other laboratory and radiological examinations are of unproven benefit and must be restricted to patients with suspicious symptoms [V, C].

7f. Long-term follow-up, rehabilitation and survivorship care programs should be implemented, aiming at detection of recurrent or new cancers, assessment and management of late and psychosocial effects and implementation of health promotion measures [III, A].

There was a query over the availability of practitioners for long-term follow-up from one country in terms of *applicability* (supplementary Table S 4), but this did not require discussion. Availability of oncology-trained health professionals for the long-term follow-up of patients with resected localised colon cancer is variable in Asian countries, with a lack of workforce resources often a problem. In such instances, follow-up should be adapted to the characteristics of each healthcare system, with provisions in place for the appropriate training of family doctors, general practitioners, and internal medicine and surgery experts in follow-up procedures.

Drug and testing availability

The drug and testing availability for each of the seven Asian countries is summarised in Table 2 and the ESMO-MCBSs for the different systemic therapy options for the treatment of localised colon cancer are presented in supplementary Table S 6. Resource limitations are the most important barrier to offering optimal diagnosis and treatment to patients with localised colon cancer across the different Asian countries.

CONCLUSIONS

The results of the voting by the Asian experts both before and after the 'face-to-face' meeting showed high concordance (supplementary Tables S3 and S4) with the ESMO recommendations for the treatment of patients with localised colon cancer.[43] Following the 'face-to-face' discussions, and the

450 revisions made to the wording of ‘recommendations 5f-h’ and ‘recommendations 6d, f and g’ (above
451 and Table 1), a **100% consensus** was reached with regard to all recommendations.

452 Thus, the guidelines listed in Table 1 can be considered to be consensus clinical practice guidelines for
453 the treatment of patients with localised colon cancer in Asia. As mentioned previously, the acceptance
454 of each recommendation by each of the Asian experts was based on the available scientific evidence,
455 and was independent of the approval and reimbursement status of certain drugs in their individual
456 countries. A summary of the availability of recommended tests and recommended drugs, as of March
457 2021, is presented for each participating Asian country in Table 2, and will obviously impact on some of
458 the disease and patient management strategies that can be adopted by certain countries.

459
460

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Legends

Table 1. Summary of Asian recommendations

CAPOX, capecitabine plus oxaliplatin; CEA, carcinoembryonic antigen; CRC, colorectal cancer; CT, computed tomography; DPD, dihydropyrimidine dehydrogenase; ESMO, European Society for Medical Oncology; FIT, faecal immunochemical testing; FOBT, faecal occult blood test; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; 5-FU, 5-fluorouracil; LV5FU2, 5-fluorouracil leucovorin; M2-PK, M2-pyruvate kinase; MCBS, Magnitude of Clinical Benefit Scale; MMR, mismatch repair; MRI, magnetic resonance imaging; MSI, microsatellite instability; TNM, tumour node metastases; UFT/LV, uracil tegafur plus leucovorin.

Table 2. Summary of applicability (availability) of drugs, equipment and testing according to Asian country

[a]ESMO-MCBS version 1.1.[113] The scores have been calculated by members of the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee

CEA, carcinoembryonic antigen; dMMR, mismatch repair deficient; DPD/DYPD, dihydropyrimidine dehydrogenase; ESMO, European Society for Medical Oncology; FIT, faecal immunochemical testing; FOBT, faecal occult blood test; IHC, immunohistochemistry; MCBS, Magnitude of Clinical Benefit Scale; MSI, microsatellite instability; NEB, no evaluable benefit; PCR, polymerase chain reaction; S-1, tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxanate; UFT/LV, uracil tegafur plus leucovorin.

*****PCR-MSI only approved and reimbursed

**Available but not routinely performed

*******Available at specialist centres

†Available as sent to overseas lab

‡Available but not used for early stage colon cancer

‡‡Not reimbursed by National Health Insurance system

Figure 1. Recommendations for the adjuvant treatment of stage III Asian colon cancer patients[43a]

CAPOX, capecitabine plus oxaliplatin; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MSI, microsatellite instability; MSS, microsatellite stability.

[a] By kind permission of Elsevier

Figure 2. Recommendations for the adjuvant treatment of stage II Asian colon cancer patients

CAPOX, capecitabine plus oxaliplatin; CEA, carcinoembryonic antigen; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; MSI, microsatellite instability; MSS, microsatellite stability.

[a]For pT4 MSI: pT4 is a major risk factor, but adjuvant chemotherapy benefit in the presence of MSI is uncertain

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Table 1. Summary of Asian recommendations

Recommendation 1: Screening principles		***Acceptability consensus***
Invasive tests	1a. Colonoscopic techniques, despite being invasive, have the advantage of being both diagnostic and therapeutic.	100%
	1b. A complete colonoscopy is the recommended method for CRC screening in average-risk men and women based on higher sensitivity and specificity when compared with other tests [II, B]. The optimal age range for testing is 50–74 years [V, D] with an optimal repetition interval for a negative test of 10 years [III, C].	100%
	1c. Flexible sigmoidoscopy performed every 5–10 years may be an alternative for those who refuse colonoscopy [II, B]. The combination of this method with a yearly FOBT (see below) is recommended to reduce the risk of a right-sided colon tumour [III, B].	100%
	1d. Other invasive tests including capsule colonoscopy are not recommended for screening [IV].	100%
Non-invasive tests	1e. Non-colonoscopic tests are recommended in average-risk men and women from the age of 50 who are not already taking part in colonoscopic screening programs. The optimal frequency of testing is every year and no later than every three years [I, B]. A colonoscopy must be performed at the earliest convenience when the test results are positive [I, A].	100%
	1f. Among the available tests, FIT appears to be superior to the high-resolution guaiac FOBT with respect to the detection rate and positive predictive value for adenomas and cancer [III]. Other novel methods including DNA-based or other tests using other markers (e.g. M2-PK) lack formal comparisons of their performance, and integration with other assays needs to be monitored.	100%
Recommendation 2: Diagnosis		
	2a. In the absence of indications for urgent tumour resection, a total colonoscopy is recommended for diagnostic confirmation of colon cancer and to rule out synchronous tumours. Combining limited left-sided colonoscopy with CT colonoscopy is an alternative if full colonoscopy is not possible [I, A].	100%
	2b. When not carried out before or during the surgical procedure, a complete colonoscopy should be carried out within 3–6 months following tumour resection [IV, B].	100%

	2c. A comprehensive physical examination and laboratory tests including full blood counts, biochemistry, and serum CEA must be carried out prior to decisions on the definitive treatment approach [III, A].	100%
	2d. CT of the thoracic, abdominal and pelvic cavities with intravenous contrast administration is the preferred radiological method for the evaluation of the extent of CRC [II, B].	100%
	2e. Contrast-enhanced MRI constitutes the reference test for evaluation of the relationship of locally advanced tumours with surrounding structures or in defining ambiguous liver lesions [II, A].	100%
Recommendation 3: Management of localised colon tumours		
	3a. *En bloc* endoscopic resection of the polyp is sufficient for non-invasive (pTis, i.e. intraepithelial or intramucosal) adenocarcinomas [IV, B].	100%
	3b. The presence of invasive carcinoma (pT1) in a polyp requires a thorough review with the pathologist and surgeon. High-risk features mandating surgical resection with lymphadenectomy include lymphatic or venous invasion, grade 3 differentiation, and significant (grade > 1) tumour budding [IV, B].	100%
	3c. Laparoscopic colectomy can be safely carried out for colon cancer when technical expertise is available in the absence of contraindications, in view of reduced morbidity, improved tolerance and similar oncological outcomes [I, C].	100%
	3d. Obstructive CRCs can be treated using one- or two-stage procedures, as indicated [III, B].	100%
Recommendation 4: Pathological reporting		
	4a. A standard surgical/pathological report should include specimen description, and surgical procedure, tumour site and size, macroscopic tumour perforation, histological type and grade, extension into the bowel wall and adjacent organs, distance of cancer from resected margins (proximal, distal and radial), presence or absence of tumour deposits, lymphovascular and/or perineural invasion, tumour budding, site and number of removed and involved regional lymph nodes, MMR/MSI status and involvement of other organs [IV, A].	100%
Recommendation 5: Risk assessment		
	5a. Adjuvant therapy options should be fully discussed with the patient, taking into consideration the risk of tumour recurrence, expected benefit from chemotherapy and risk of complications [V].	100%

	5b. The risk of relapse after a colon cancer resection should be assessed by integrating the TNM staging, MMR/MSI status and number of lymph nodes sampled (+/- 12) [III, A].	100%
	5c. Other additional clinicopathological features such as the histological subtype and grading, lymphatic or venous or perineural invasion, lymphoid inflammatory response, involvement of resection margins and serum CEA should be taken into consideration for 'fine-tuning' the risk assessment on stage II tumours [III, A].	100%
	5d. Patient age alone has no predictive value for or against the use of adjuvant treatment and must be considered in the context of (potential) benefit, underlying risk for relapse, life expectancy in relation to (biological) age and comorbidities. However, it can be generalised that benefits of treatment with fluoropyrimidines plus/minus oxaliplatin, seem to be more limited, with a higher likelihood of toxicity in older patients [II, B].	100%
	5e. MSI/MMR status is the only validated molecular marker used in adjuvant decision making and should be determined in stage II CRC. In stage III, the use of MMR status is limited to the detection and identification of Lynch syndrome [IV, A].	100%
	5f. **Depending on the anticipated genetic profile of a specific Asian patient population**, DPD genotyping or phenotyping **may be considered** before initiating fluoropyrimidine-based adjuvant therapy [III, A]. **DPD genotyping or phenotyping should be implemented in patients who experience severe fluoropyrimidine toxicity *[V].***	100%
	5g. Gene expression signatures **may provide prognostication in stage II disease but are not recommended for use in routine practice due to a lack of predictive value for** chemotherapy benefit **[IIC].**	100%
	5h. Immunoscore® could be considered to refine the prognosis of **localised** colon cancer patients **when** used in conjunction with TNM scoring in stage II stage III disease [III, C], although its role in predicting **an adjuvant** chemotherapy **effect** is uncertain.	100%
Recommendation 6: Treatment options		
Stage III disease	6a. Combinations of fluoropyrimidines, either 5-FU or capecitabine, and oxaliplatin constitute the basis of stage III colon cancer adjuvant treatment [I, A; ESMO-MCBS v1.1 score: B].	100%
	6b. The length of oxaliplatin-based adjuvant treatment for stage III colon cancer based on the IDEA data may be tailored to 3 or 6 months for CAPOX [I, A] or 6 months for FOLFOX [I, A], also taking into consideration pathological risk characteristics, patient comorbidity and risk assessment.	100%

	6c. Further adaptation of the treatment according to risk subgroups: 3 months for CAPOX (T1–3 N1 disease), 6 months for CAPOX (T4 or N2 disease) or 6 months for FOLFOX (T1–3 N1 or T4 or N2 disease) based on IDEA collaboration should be made with caution, since this was based on a *post hoc* analysis, which was non-significant for interaction [V].	100%
	6d. *For patients not fit* ***or unable to tolerate*** *oxaliplatin, capecitabine or* ***any 5-FU infusional or bolus regimens or UFT/LV are acceptable 6-month adjuvant regimens in various Asian populations [I, A; ESMO-MCBS v1.1 score: B].***	100%
Stage II disease	6e. For patients with low-risk stage II colon cancer, follow-up is recommended [I, A].	100%
	6f. For patients with intermediate-risk **stage II** (non-MMR/MSI + any risk factor except pT4/**perforation** or < 12 lymph **nodes** assessed) 6 months of fluoropyrimidine therapy is recommended [**II, B**]. **Three months of CAPOX is an acceptable alternative in fit patients, after being informed of the risk/benefit profile [V].**	100%
	6g. For patients with high-risk stage II disease (pT4/**perforation** or < 12 lymph nodes **assessed** or multiple intermediate risk factors, regardless of MSI status) the addition of oxaliplatin **should** be **considered, in view of a higher risk of relapse and anticipated benefit [II, C].**	100%
	6h. Patients with high-risk stage II colon cancer may be considered for 3 months of CAPOX, as the IDEA-pooled analysis showed non-inferiority of 3 months of CAPOX and inferiority of 3 months of FOLFOX when compared with 6 months of FOLFOX, with all the limitations of *post-hoc* analyses [II, B].	100%
Timing of adjuvant chemotherapy	6i. It is important to start adjuvant chemotherapy as soon as possible after surgery and ideally not later than 8 weeks [I, A].	100%
Recommendation 7: Follow-up and long-term implications		
Follow-up	7a. Intensive follow-up allows earlier detection of relapses in patients at risk [II, B].	100%
	7b. History and physical examination and CEA determination are advised every 3–6 months for 3 years and every 6–12 months at years 4 and 5 after surgery [II, B].	100%
	7c. Colonoscopy must be carried out at year 1 and every 3–5 years thereafter, looking for metachronous adenomas and cancers [III, B].	100%
	7d. CT scan of chest and abdomen every 6-12 months for the first 3 years can be considered in patients who are at higher risk of recurrence according to the TNM classification [II, B].	100%

	7e. Other laboratory and radiological examinations are of unproven benefit and must be restricted to patients with suspicious symptoms [V, C].	100%
Long-term implications/survivorship care plans	7f. Long-term follow-up, rehabilitation and survivorship care programs should be implemented, aiming at detection of recurrent or new cancers, assessment and management of late and psychosocial effects and implementation of health promotion measures [III, A].	100%

Table 2.

Drugs/Equipment	CSCO	ISMPO	JSMO	KSMO	MOS	SSO	TOS	ESMO-MCBS SCORE[a]
	Available Y/N	Available Y/N	Available Y/N	Available Y/N	Available Y/N	Available Y/N	Available Y/N	
FOBT	Y	Y	Y	Y	Y	Y	Y	
FIT	Y	N	Y	Y	Y	Y	Y	
dMMR IHC or MSI genotyping	Y	Y	Y*	Y	Y	Y	Y	
Laparoscopic colectomy	Y	Y	Y	Y	Y	Y	Y	
CEA	Y	Y	Y	Y	Y	Y	Y	
DPYD genotyping	Y	Y	N	Y/N**	Y	N†	N**,***	
DPD phenotyping	Y	Y	N	Y/N**	N***	N†	N**, ***	
Gene expression signatures	Y	Y	N	Y/N**	N***	N†	N**, ***	
Immunoscore®	Y	N	N	Y/N**	N***	Y	N**, ***	
5-fluorouracil	Y	Y	Y	Y	Y	Y	Y	
CAPOX 3 months vs CAPOX 6 months CAPOX vs 5-FU/LV	Y	Y	Y	Y	Y	Y	Y	Stage III: B Stage III: B
FOLFOX vs 5-FU/LV meta-analysis	Y	Y	Y	Y	Y	Y	Y	ITT: C Stage III: B
UFT/LV	Y**	Y	Y	Y	Y	Y‡	Y	NEB
S-1	Y**	N	Y	N	Y	Y‡	Y‡‡	NEB