

Comparison of the guidelines for colorectal cancer in Japan, the USA and Europe

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Abstract

Colorectal cancer (CRC) is one of the most common cancers globally as well as in Japan and has shown a pattern of increasing incidence and mortality rates. Therefore, guidelines for CRC are considered to be crucial for establishing standard medical treatment not only in Japan but also around the world. In this article, we explain the features of the representative guidelines in Japan (Japanese Society for Cancer of the Colon and Rectum [JSCCR]), the USA (National Comprehensive Cancer Network [NCCN]) and Europe (European Society for Medical Oncology [ESMO]) and review the differences among these guidelines for CRC. We focus, in particular, on the descriptions of local treatments, including endoscopic treatment for CRC and transanal excision for lower rectal cancer; surgical treatments with lymph node dissection, including management of lower rectal cancer with lateral lymph node metastasis and laparoscopic surgery; and chemotherapy. Although the guidelines share basic principles, some details are different. Consulting the guidelines of various regions from around the world may aid in more precise and effective examination of the details and backgrounds of our own native guidelines.

KEYWORDS

chemotherapy, colorectal cancer, endoscopic treatment, guidelines, surgical treatment

1 | INTRODUCTION

Guidelines are based on the evidence of the published literature and are created by experts in each field in consideration of the actual clinical conditions in each country and region. The guidelines applied to each field are expected to make it possible for general clinicians to carry out medical treatment with consistent quality, thereby leading to a reduction in disparity of outcomes between treatment facilities. Guidelines can also be used as a clear basis when explaining

techniques and procedures to patients, aiding in mutual understanding between medical staff and patients.

Colorectal cancer (CRC) is the third-most common cancer globally, with 1 360 000 cases (9.7% of the total, following lung and breast cancer), and the fourth leading cause of cancer death, with an estimated 694 000 deaths (8.5% of the total, following lung, liver and stomach cancer) in 2012.¹ Furthermore, the number of patients with CRC is expected to increase in the future.² In the Japanese population, CRC is also one of the most common cancers and has shown a pattern of increasing incidence and mortality rates over time.³ Therefore, guidelines for CRC are considered to be crucial for

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establishing standard medical treatment not only in Japan but also around the world.

Guidelines for the medical treatment of CRC in Japan have been published by the Japanese Society for Cancer of the Colon and Rectum (JSCCR).⁴ Similar guidelines applicable to their respective regions have also been published by the National Comprehensive Cancer Network (NCCN) in the USA and the European Society for Medical Oncology (ESMO) in Europe. As with Japan, prevalence of colorectal cancer tends to be higher in Western countries than in other areas.¹ Therefore, in the present article, we will explain the features of these representative guidelines for CRC in Japan, the USA and Europe and review the differences among these guidelines.

2 | GUIDELINES OF EACH COUNTRY

2.1 | Guidelines of the JSCCR

In Japan, the “Japanese Society for Cancer of the Colon and Rectum guidelines for the treatment of colorectal cancer” have been published by the Guideline Committee of the JSCCR. The 2005 edition was published as the first edition, and revisions have been made since the initial publication; the most recent edition available at the time of this writing is the 2016 version.⁴

In the guidelines of the JSCCR, comprehensive contents, such as different treatment policies according to disease staging, treatment policies for recurrent colorectal cancer, therapeutic policies for distant metastasis and chemotherapy guidelines, are shown together with a clear algorithm for each disease condition. In addition, there are items concerning radiation therapy, palliative care and surveillance after surgical procedures for CRC. Explanations of topics for which further analyses are considered necessary are included in comment form. Issues to be further discussed are addressed as “Clinical Questions (CQ)”, and explanations based on clinical trials and evidence are described for each task. Evidence level is classified into four stages: A, B, C and D, and the recommendation degree is specified as two grades of high or low (high: recommendation; low: proposal). These guidelines are based on up-to-date information on clinical treatment in the field concerning endoscopy, surgery and chemotherapy in Japan; therefore, it should be used as the initial basis for the treatment of CRC in Japan. Of note, however, it takes a few years for the latest clinical topics to be described in the guidelines, as the revision interval is several years.

2.2 | Guidelines of the NCCN

These guidelines are released by NCCN, which comprises 25 representative cancer centers in the USA, and is one of the most widely used guidelines in the world. The guidelines for CRC are subdivided into two sections: “colon cancer” and “rectal cancer”. One of the major features of the NCCN guidelines is that revisions are made multiple times a year. Indeed, as of April 2017, version 2 2017 for colon cancer and version 3 2017 for rectal cancer are available (<https://www.nccn.org>). In terms of the diagnosis, surgery and treatment by each disease state,

comprehensive contents are mainly described as a flow chart, followed by about 60 pages of discussion based on the latest clinical trials and evidence. Regarding the recommendation level, these guidelines include four categories established based on available evidence and the consensus: category 1, 2A, 2B and 3 (if not specified, the recommendation level of an item category is 2A). These guidelines are characterized by frequent revision, and the latest clinical evidence is therefore likely to be reflected promptly.

2.3 | Guidelines of the ESMO

These guidelines are prepared by the ESMO, and descriptions concerning CRC are divided into four categories: (i) early colon cancer;⁵ (ii) rectal cancer;^{6,7} (iii) metastatic colorectal cancer;⁸ and (iv) familial risk colorectal cancer.⁹ Revisions are made once every 2-3 years. In contrast to the NCCN guidelines, ESMO guidelines mainly contain a review-style description format, and the contents based on the latest evidence are briefly summarized. As there is no detailed flow chart or algorithm for subdivision, a comparison with other guidelines such as those of the JSCCR or NCCN suggests that practical usefulness (eg selecting a specific chemotherapy regimen) might be inferior.

An adapted version of the “Infectious Disease Society of America-United States Public Health Service Grading system” is used to define the level of evidence (I-V) and strength of each recommendation (A-E) in these guidelines.

3 | COMPARISON OF THE TREATMENT METHODS FOR CRC IN JAPAN, THE USA AND EUROPE

Here, we compare the treatment methods for CRC described in each set of guidelines, particularly with regard to: (i) local treatment, including endoscopic treatment and transanal excision for lower rectal cancer; (ii) surgical treatment with lymph node dissection, including management of lower rectal cancer with lateral lymph node metastasis and laparoscopic surgery; and (iii) chemotherapy.

3.1 | Local treatment

For Tis (M) or some T1 (shallow submucosal invasion) tumors without any findings of lymph node metastasis, local treatment such as endoscopic treatment or transanal excision for lower rectal cancer was feasible under each set of guidelines.

In the JSCCR guidelines, endoscopic treatment through endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) was indicated for Tis or T1 tumors, suggesting that endoscopic en bloc resection is possible. However, even if endoscopic treatment is successful, tumors with unfavorable histological features need to be additionally resected with lymph node dissection. In the NCCN guidelines, unfavorable histological features are defined as grade 3/4 tumors, which are comparable to poorly differentiated or undifferentiated adenocarcinoma, positive lymphovascular invasion and positive

resection margin. In the JSCCR guidelines, in addition to these factors, the pathological finding of deep submucosal invasion (>1000 μm) and budding grade 2/3 are considered to be an indication for additional surgical procedures with lymph node dissection, as the risk of lymph node metastasis is reported to be higher in these lesions than in those without such risk factors.¹⁰ For adequate treatment of T1 CRC, accurate endoscopic evaluation of the invasion depth based on the morphological findings by magnified endoscopy or Kudo's pit pattern classification¹¹ is considered to be important.

In the NCCN guidelines, transanal excision is described as appropriate only for select T1, N0 cancers (<3 cm in diameter), well to moderately differentiated tumors located within 8 cm of the anal verge and limited to less than 30% of the rectal circumference. In the JSCCR guidelines, the adapted tumor location for transanal excision is described as rectal lesions of the second Houston valve, and the need for additional resection with lymph node dissection is determined by a histopathological assessment of the surgical specimens (excisional biopsy). Indication for additional resection is the same as with endoscopic treatment, as mentioned earlier.

3.2 | Surgical treatment

Basic treatment strategy for localized CRC without distant metastasis is surgery with lymph node dissection, especially for lesions with invasion deeper than the submucosal layer. Management of lateral lymph node metastasis with lateral lymph node dissection (LLND) or preoperative chemoradiation therapy (CRT) is a major topic in each set of guidelines. In addition, laparoscopic surgery is an important newly developed treatment strategy for CRC.

3.2.1 | Management of lateral lymph node metastasis

In the JSCCR guidelines, tumor staging is defined by the Japanese classification of CRC. Under this classification system, lymph node metastasis around iliac and obturator artery is defined as lateral lymph node metastasis. Such metastases are considered to be regional lymph node metastasis rather than distant metastasis (Table 1), although the survival rate with lateral lymph node metastasis is reported to be poor.¹² Therefore, in the JSCCR guidelines, total mesorectal excision (TME) (or tumor-specific mesorectal excision [TSME]) with LLND for T3-4 lower rectal cancers is recommended, and effective reduction of local recurrence and improved survival rate are shown.¹³

Although the revised American Joint Committee on Cancer (AJCC) staging system also defines internal iliac lymph nodes as regional lymph nodes of rectal cancer,¹⁴ preoperative CRT followed by TME without LLND is recommended for advanced rectal cancer in the NCCN and ESMO guidelines. Preoperative CRT is reported to reduce the risk of local recurrence but not to improve the survival rate.¹⁵ Although the effectiveness of preoperative CRT is described as "not established" in the JSCCR guidelines, a randomized control trial (RCT) from Japan showed no difference in either the overall or disease-free survival between the groups of surgery with and without LLND after

TABLE 1 Comparison of the TNM classification and Japanese classification of colorectal carcinoma

| TNM classification ^a | Japanese classification of colorectal carcinoma | | |
|---------------------------------|--|-----|---|
| Primary tumors (T) | | | |
| Tis | Carcinoma in situ: intraepithelial or invasion of lamina propria | Tis | Within lamina propria |
| T1 | Submucosa | T1a | Submucosa <1000 μm |
| | | T1b | Submucosa \geq 1000 μm |
| T2 | Muscularis propria | T2 | Muscularis propria |
| T3 | Subserosa/perirectal tissue | T3 | Subserosa or within adventitia |
| T4a | Perforation into visceral peritoneum | T4a | Exposed to the serosal surface |
| T4b | Invasion to other organs | T4b | Invasion to other organs |
| Regional lymph nodes (N) | | | |
| N1 | 1-3 regional nodes involved | N1 | 1-3 paracolic or intermediate lymph node metastases |
| N1a | 1 lymph node | | |
| N1b | 2-3 lymph nodes | | |
| N1c | Small deposits in the fat | | |
| N2 | 4 or more regional nodes involved | N2 | 4 or more paracolic or intermediate lymph node metastases |
| N2a | 4-6 lymph nodes | | |
| N2b | 7 or more lymph nodes | | |
| | | N3 | Main or lateral lymph node metastasis |
| Distant metastasis (M) | | | |
| M1 | Distant metastases | M1 | Distant metastases |
| M1a | One distant organ or set of lymph nodes | M1a | One distant organ metastasis |
| M1b | More than one organ or to the peritoneum | M1b | More than one organ metastases |

^aTNM classification is referred from 8th Edition of the UICC TNM classification of Malignant Tumors.³⁹

CRT; however, urinary and sexual function were significantly better in the group without LLND than in the group with it.¹⁶ Efficacy and safety of preoperative CRT warrant future further assessment.

3.2.2 | Laparoscopic surgery

Nowadays, laparoscopic surgery for CRC is carried out at many institutions around the world, and the efficacy and safety of the

methods have been validated by many studies. The reported advantages of laparoscopic surgery over conventional surgery are reduced pain, reduced length of hospital stay and reduced duration prior to first bowel motion.¹⁷ Recently, the JCOG0404 study from Japan reported that laparoscopic surgery was an acceptable treatment option.¹⁸ In the NCCN and ESMO guidelines, indication for laparoscopic surgery is divided into colon cancer and rectal cancer. As for colon cancer, laparoscopic surgery is still recommended in limited cases only, such as cancer without locally advanced disease, without acute bowel obstruction or perforation. In addition, the techniques are to be carried out by well-experienced surgeons. For rectal cancer, NCCN guidelines commented on the similar short- and long-term outcomes of open and laparoscopic surgery from some studies.^{19,20} However, other studies showed that laparoscopy was associated with higher rates of circumferential margin positivity and incomplete TME.^{21,22} Therefore, minimally invasive resection by laparoscopic surgery may be considered for limited cases, as with colon cancer. In the ESMO guidelines, it is commented that “the surgeon should take into account his/her experience with the technique, the stage and location of the cancer and patient factors such as obesity and previous open abdominal surgery”.⁷ JSCCR guidelines also recommended that indication for laparoscopic surgery be decided after sufficient consideration of the laparoscopic skills of the operation team. Further evaluations and standardization of laparoscopic surgery techniques are expected.

3.3 | Chemotherapy

Chemotherapy for CRC consists of adjuvant chemotherapy to prevent postoperative recurrence and systemic chemotherapy to treat unresectable progressive CRC. Approved anticancer drugs for CRC in Japan are shown in Table 2.

3.3.1 | Adjuvant chemotherapy

Postoperative adjuvant chemotherapy is systemic chemotherapy given after surgery to prevent recurrence of CRC and to improve the prognosis of patients who have undergone R0 resection. In all three guidelines (JSCCR, NCCN and ESMO), the indications for adjuvant chemotherapy are stage III (T1-4, N1-2, M0 in the TNM classification and T1-4, N1-3, M0 in the Japanese classification) CRC for which R0 resection has been carried out. For patients with stage II CRC, adjuvant chemotherapy is not recommended for all patients, but is considered for high-risk patients. In the ESMO guidelines, high-risk patients with stage II CRC are defined as those with one of the following clinical characteristics: <12 lymph nodes sampled; poorly differentiated tumor; vascular, lymphatic or perineural invasion; tumor presentation with obstruction or tumor perforation and pT4 stage.⁵ These risk factors are also considered in the JSCCR guidelines when judging the indication for adjuvant chemotherapy.

Regarding the regimen of adjuvant chemotherapy, adjuvant fluorouracil (5-FU) and oxaliplatin (OX) combination (FLOX, FOLFOX or CapeOX) chemotherapy has shown superiority to single-agent 5-FU in

TABLE 2 Anticancer drugs approved in Japan

| Oral drugs | |
|------------------|--|
| 5-FU | (fluorouracil) |
| Tegafur | |
| UFT | (tegafur-uracil) |
| 5'-DFUR | (doxifluridine) |
| HCFU | (carmofur) |
| S-1 | (tegafur-gimeracil-oteracil potassium) |
| UFT+LV | (tegafur-uracil+leucovorin) |
| Cape | (capecitabine) |
| regorafenib | |
| TAS-102 | (trifludine-tipiracil hydrochloride) |
| Injectable drugs | |
| 5-FU | (fluorouracil) |
| mitomycin C | |
| IRI | (irinotecan) |
| 5-FU+/-LV | (fluorouracil+/-leucovorin) |
| OX | (oxaliplatin) |
| Bmab | (bevacizumab) |
| Rmab | (ramucirumab) |
| Cmab | (cetuximab) |
| Pmab | (panitumumab) |

terms of disease-free survival (DFS) and overall survival (OS).^{23–25} Therefore, in the NCCN and ESMO guidelines, patients with stage III CRC are recommended to receive adjuvant chemotherapy with 5-FU and OX (FLOX, FOLFOX or CapeOX) as well as capecitabine (Cape) or fluorouracil+/-leucovorin (5-FU+/-LV). However, given that side-effects such as diarrhea or peripheral neurotoxicity are often reported with OX, these combination regimens should not be applied to all patients with stage III CRC. Furthermore, for elderly patients (>70 years of age) or patients with high-risk stage II CRC, additional benefits of OX on the DFS or OS have not been reported.^{26,27} However, non-inferiority of oral anticancer drugs (tegafur-uracil+leucovorin [UFT+LV] and Cape) as adjuvant chemotherapy for patients with postoperative CRC (excluding lower rectal cancer) has been reported by RCT.^{28–30} An RCT from Japan also showed that tegafur-gimeracil-oteracil potassium (S-1) as adjuvant chemotherapy for patients with stage III colon cancer is not inferior to UFT+LV.³¹ Given these results, in the JSCCR guidelines, oral UFT+LV, Cape and S-1 are recommended as adjuvant chemotherapy in addition to OX combined regimens, such as FOLFOX and CapeOX, for patients with stage III or high-risk CRC (Table 3).

Regarding timing and duration, in the JSCCR guidelines, it is recommended to start adjuvant chemotherapy within 4–8 weeks after surgery and continue for 6 months. In the ESMO guidelines, induction timing of adjuvant chemotherapy is described as “as early as possible”, starting from the third week up to a maximum of 8 to 12 weeks after surgery. Although the recommended total duration of treatment is also 6 months, a shorter adjuvant treatment duration (3 months) is currently under prospective evaluation (International

TABLE 3 Adjuvant chemotherapy regimens by region

| JSCCR | NCCN | ESMO |
|-----------|-----------|-----------|
| UFT+LV | FOLFOX | FOLFOX |
| Cape | CapeOX | CapeOX |
| S-1 | FLOX | Cape |
| 5-FU+/-LV | Cape | 5-FU+/-LV |
| FOLFOX | 5-FU+/-LV | |
| CapeOX | | |

Cape, capecitabine; CapeOX, capecitabine+oxaliplatin; ESMO, European Society for Medical Oncology; FLOX, infusional fluorouracil+/-leucovorin (weekly)+oxaliplatin (biweekly); FOLFOX, infusional fluorouracil+/-leucovorin+oxaliplatin; 5-FU+/-LV, fluorouracil+/-leucovorin; JSCCR, Japanese Society for Cancer of the Colon and Rectum; NCCN, National Comprehensive Cancer Network; S-1, tegafur-gimeracil-oteracil potassium; UFT+LV, tegafur-uracil+leucovorin.

Duration Evaluation of Adjuvant chemotherapy meta-analysis project).

3.3.2 | Chemotherapy for unresectable progressive CRC

The purpose of systemic chemotherapy for unresectable progressive CRC is to prolong survival and control symptoms by delaying tumor enlargement. Choice of treatment strategy depends on the treatment aim (eg tumor shrinkage, control of progression), the clinical presentation pattern and characteristics of the tumor (eg metastasis limited or not limited to the liver and/or lung, whether or not there is progressive disease, and RAS [derived from "Rat sarcoma", important components of signaling pathways of cell surface receptors] status) and patient factors (eg symptomatic or asymptomatic, presence of comorbidity and available capacity for conversion treatment). In this section, we focus on first-line chemotherapy regimens for unresectable progressive CRC and compare those described in each guideline. Most of the recommended regimens are common (eg FOLFOX, FOLFIRI and CapeOX), whereas some details differ depending on classification of the patients (eg IRIS in the ESMO guidelines, nivolumab and pembrolizumab in the NCCN guidelines). In the JSCCR and NCCN guidelines, patients with unresectable progressive CRC are divided into two groups: "patients appropriate for intensive therapy" and "patients NOT appropriate for intensive therapy", according to the presence of comorbidity and the potential to tolerate chemotherapy. In contrast, in the ESMO guidelines, patients are individually divided into three groups: "Group 1", intensive treatment for liver or lung metastasis, not R0 (R1) resectable; "Group 2", intermediate intensive treatment; and "Group 3", not intensive/sequential treatment. The recommended regimens of chemotherapy are different in each guideline and in each patient group. Details of regimens are summarized in Table 4.

Regarding the common points of the three guidelines, FOLFOX, FOLFIRI and CapeOX are listed as common standard first-line regimens, and all of them are recommended to be started with molecular-targeting drugs, such as bevacizumab (Bmab), cetuximab (Cmab) or panitumumab (Pmab). If the RAS status is wild type, anti-

TABLE 4 Comparison of the first-line chemotherapy regimens for unresectable progressive CRC

| JSCCR | NCCN | ESMO |
|---|---|--|
| Patients appropriate for intensive therapy | Patients appropriate for intensive therapy | Group 1 (intensive) Group2 (intermediate intensive) |
| FOLFOX+Bmab *1 | FOLFOX±Bmab | FOLFOX±Bmab |
| CapeOX+Bmab *1 | CapeOX±Bmab | CapeOX±Bmab |
| FOLFIRI+Bmab *1 | FOLFIRI±Bmab | FOLFIRI±Bmab |
| SOX+Bmab *1 | | |
| FOLFOX+Cmab/Pmab *1,2 | FOLFOX+Cmab/Pmab *2 | FOLFOX+Cmab/Pmab *2 |
| FOLFIRI+Cmab/Pmab *1,2 | FOLFIRI+Cmab/Pmab *2 | FOLFIRI+Cmab *2 |
| FOLFOXIRI±Bmab | FOLFOXIRI±Bmab | FOLFOXIRI |
| FL/Cape/UFT+LV/S-1+Bmab *1 | FL/Cape±Bmab | IRIS |
| Cmab/Pmab *2 | | |
| Patients NOT appropriate for intensive therapy | Patients NOT appropriate for intensive therapy | Group3 (NOT intensive) |
| FL/Cape/UFT+LV/S-1+Bmab *1 | FL/Cape±Bmab | FUFOL/Cape±Bmab |
| Cmab/Pmab *2 | Cmab/Pmab *2 | FOLFOX |
| | Nivolumab/Pembrolizumab *3 | CapeOX |
| | | FOLFIRI |
| | | IRIS |

Bmab, bevacizumab; CapeOX, Cape+OX; Cmab, cetuximab; CRC, colorectal cancer; ESMO, European Society for Medical Oncology; FL, infusional 5-FU+/-LV; FOLFIRI, infusional 5-FU+/-LV+IRI; FOLFOX, infusional 5-FU+/-LV+OX; FOLFOXIRI, infusional 5-FU+/-LV+OX+IRI; FUFOL, 5-FU+folinic acid; IRIS, IRI+S1; JSCCR, Japanese Society for Cancer of the Colon and Rectum; NCCN, National Comprehensive Cancer Network; SOX, S-1 + OX; Pmab, panitumumab.

*1, combination with molecular-targeting drugs, such as Bmab, Rmab and anti-epidermal growth factor receptor (EGFR) antibodies, is recommended, but for patients who are not candidates, chemotherapy alone can be carried out.

*2, RAS wild type.

*3, deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) only.

epidermal growth factor receptor (EGFR) antibody drugs (Cmab or Pmab) are recommended in combination with FOLFOX or FOLFIRI. If the RAS status is a mutant, Bmab is selected instead with FOLFOX, FOLFIRI and CapeOX. In the ESMO guidelines, these regimens are also recommended for patients in Group 2 (intermediate intensive treatment group). In the JSCCR guidelines, which were revised in 2016, new regimens including SOX+Bmab, FOLFOXIRI+Bmab, UFT+LV+Bmab, S-1+Bmab and Cmab/Pmab were added to the list of recommended first-line chemotherapy regimens. Among these regimens, FOLFOXIRI (±Bmab) is also commonly listed in the other two guidelines. In the ESMO guidelines, FOLFOXIRI is mentioned as an alternative to FOLFIRI/FOLFOX combined with anti-EGFR

antibodies and is the preferred option for KRAS mutant tumors.³² The NCCN guidelines referenced the “Gono trial” and “HORG trial” in the discussion section; the former showed that FOLFOXIRI was associated with a better progression-free survival (PFS) (9.8 months vs 6.9 months; HR 0.63; $P = .0006$) and OS (22.6 months vs 16.7 months; HR 0.70; $P = .032$) than FOLFIRI,³³ whereas the latter reported no significant difference in the OS between the two regimens (21.5 months vs 19.5 months; $P = .337$), and although the toxicity tended to be higher in the FOLFOXIRI group, there was no significant difference in the rate of toxicity death.³⁴ In addition, the NCCN guidelines also referenced the “TRIBE trial”, which reported the superiority of FOLFOXIRI+Bmab to FOLFIRI+Bmab in the PFS and response rate,³⁵ and the “OLIVIA trial”, which showed that FOLFOXIRI+Bmab improved the R0 resection rate of CRC with unresectable liver metastasis compared with FOLFOX+Bmab.³⁶

With regard to the different points, in the ESMO guidelines only, IRIS (irinotecan+S-1) is listed as one of the first-line regimens for patients in all groups. For the patients in “NOT intensive therapy group” in the NCCN guidelines, nivolumab and pembrolizumab, which are both newly developed anti-programmed death 1 (PD-1) immune checkpoint inhibitors, are added to the recommendation especially for disease with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) characteristics. Recent phase II studies evaluated the efficacy of nivolumab and pembrolizumab for patients with metastatic dMMR CRC.^{37,38} One of the defining characteristics of the NCCN guidelines is early reflection of the findings from very recent clinical trials with substantial influence.

3.3.3 | Other topics

The NCCN and ESMO guidelines also include an analysis of the NRAS/BRAF mutation, neoadjuvant chemotherapy for advanced cancer and guidelines on maintenance of chemotherapy. These new topics are not yet described in the JSCCR guidelines, further underscoring the importance of obtaining updated information by guidelines from various regions.

4 | CONCLUSION

We reviewed and compared the representative guidelines for the treatment of CRC from Japan (JSCCR), the USA (NCCN) and Europe (ESMO). Although the basic principles of the contents are common, some details differ among regions. In the process of preparing the guidelines, not only the medical situation of the region but also the social background, such as the insurance system and culture, is taken into consideration; therefore, the guidelines from one country cannot simply be applied to other regions. It is also important to account for differences in the revision frequency. However, consulting the guidelines of various regions from around the world may aid in more precise and effective examination of the details and backgrounds of our own native guidelines.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359–86.
2. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66:683–91.
3. Katanoda K, Matsuda T, Matsuda A, et al. An updated report of the trends in cancer incidence and mortality in Japan. *Jpn J Clin Oncol*. 2013;43:492–507.
4. Watanabe T, Muro K, Ajioka Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. *Int J Clin Oncol*. 2017. <https://doi.org/10.1007/s10147-017-1101-6>. [Epub ahead of print].
5. Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(Suppl 6):vi64–72.
6. Glimelius B, Tiret E, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(Suppl 6):vi81–8.
7. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2017;28:iv22–40.
8. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27:1386–422.
9. Balmana J, Balaguer F, Cervantes A, et al. Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2013;24(Suppl 6):vi73–80.
10. Kitajima K, Fujimori T, Fujii S, et al. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. *J Gastroenterol*. 2004;39:534–43.
11. Kudo S, Rubio CA, Teixeira CR, et al. Pit pattern in colorectal neoplasia: endoscopic magnifying view. *Endoscopy*. 2001;33:367–73.
12. Akiyoshi T, Watanabe T, Miyata S, et al. Results of a Japanese nationwide multi-institutional study on lateral pelvic lymph node

- metastasis in low rectal cancer: is it regional or distant disease? *Ann Surg.* 2012;255:1129–34.
13. Sugihara K, Kobayashi H, Kato T, et al. Indication and benefit of pelvic sidewall dissection for rectal cancer. *Dis Colon Rectum.* 2006;49:1663–72.
 14. Amin MB, Edge S, Greene F, et al. *AJCC Cancer Staging Manual.* Cham, Switzerland: Springer International Publishing; 2017.
 15. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg.* 2007;246:693–701.
 16. Nagawa H, Muto T, Sunouchi K, et al. Randomized, controlled trial of lateral node dissection vs. nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy. *Dis Colon Rectum.* 2001;44:1274–80.
 17. Hewett PJ, Allardyce RA, Bagshaw PF, et al. Short-term outcomes of the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer: the ALCCaS trial. *Ann Surg.* 2008;248:728–38.
 18. Kitano S, Inomata M, Mizusawa J, et al. Survival outcomes following laparoscopic versus open D3 dissection for stage II or III colon cancer (JCOG0404): a phase 3, randomised controlled trial. *Lancet Gastroenterol Hepatol.* 2017;2:261–8.
 19. Jeong SY, Park JW, Nam BH, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. *Lancet Oncol.* 2014;15:767–74.
 20. Bonjer HJ, Deijen CL, Abis GA, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med.* 2015;372:1324–32.
 21. Stevenson AR, Solomon MJ, Lumley JW, et al. Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial. *JAMA.* 2015;314:1356–63.
 22. Fleshman J, Branda M, Sargent DJ, et al. Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes: the ACOSOG Z6051 randomized clinical trial. *JAMA.* 2015;314:1346–55.
 23. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol.* 2007;25:2198–204.
 24. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med.* 2004;350:2343–51.
 25. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol.* 2009;27:3109–16.
 26. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol.* 2011;29:3768–74.
 27. Tournigand C, Andre T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. *J Clin Oncol.* 2012;30:3353–60.
 28. Lembersky BC, Wieand HS, Petrelli NJ, et al. Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. *J Clin Oncol.* 2006;24:2059–64.
 29. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med.* 2005;352:2696–704.
 30. Shimada Y, Hamaguchi T, Mizusawa J, et al. Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levofolinate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205. *Eur J Cancer.* 2014;50:2231–40.
 31. Yoshida M, Ishiguro M, Ikejiri K, et al. S-1 as adjuvant chemotherapy for stage III colon cancer: a randomized phase III study (ACTS-CC trial). *Ann Oncol.* 2014;25:1743–9.
 32. Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO Consensus Guidelines: Management of patients with colon and rectal cancer. A personalized approach to clinical decision making. *Ann Oncol.* 2012;23:2479–516.
 33. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol.* 2007;25:1670–6.
 34. Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer.* 2006;94:798–805.
 35. Loupakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOX-IRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med.* 2014;371:1609–18.
 36. Gruenberger T, Bridgewater J, Chau I, et al. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. *Ann Oncol.* 2015;26:702–8.
 37. Overman MJ, Kopetz S, McDermott RS, et al. Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results. *J Clin Oncol.* 2016;34:3501–3501.
 38. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med.* 2015;372:2509–20.
 39. Brierley JD, Gospodarowicz MK, Wittekind C. *TNM classification of malignant tumours.* 8th ed. Chichester, West Sussex, UK: Wiley-Blackwell; 2016.

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