Cancer Treatment Reviews 82 (2020) 101930

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Systematic or Meta-analysis Studies

Grey areas and evidence gaps in the management of rectal cancer as revealed by comparing recommendations from clinical guidelines

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ARTICLE INFO

Keywords:
Rectal cancer
Clinical guidelines
ESMO
NCCN
JSCCR
Australia
Ontario

ABSTRACT

Background: While the management of nonmetastatic and oligometastatic rectal cancer has rapidly evolved over the last few decades, many grey areas and highly debated topics remain that foster significant variation in clinical practice. We aimed to identify controversial points and evidence gaps in this disease setting by systematically comparing recommendations from national and international clinical guidelines.

Methods: Twenty-six clinical questions reflecting practical challenges in the routine management of nonmetastatic and oligometastatic rectal cancer patients were selected. Recommendations from the ESMO, NCCN, JSCCR, Australian and Ontario guidelines were extrapolated and compared using a 4-tier classification system (i.e., identical/very similar, similar, slightly different, different). Overall agreement between guidelines (i.e., substantial/complete disagreement, partial disagreement, partial agreement, substantial/complete agreement) was assessed for each clinical question and compared against the highest level of available evidence by using the χ^2 statistic test.

Results: Guidelines were in substantial/complete agreement, partial agreement, partial disagreement, and substantial/complete disagreement for 8 (30.8%), 2 (7.7%), 7 (26.9%), and 9 (34.6%) clinical questions, respectively. High level of evidence supported clinical recommendations in 3/10 cases (30%) where guidelines were in agreement and in 10/16 cases (62.5%) where guidelines were in disagreement ($\chi^2 = 2.6$, $p = 0.106$). Agreement was frequently reached for questions regarding diagnosis, staging, and radiology/pathology proforma reporting, while disagreement characterised most of the treatment-related topics.

Conclusions: Substantial variation exists across clinical guidelines in the recommendations for the management of nonmetastatic and oligometastatic rectal cancer. This variation is only partly explained by the lack of supporting, high-level evidence.

Introduction

Rectal cancers account for 39% of colorectal tumours, and represent the 8th most common malignancy and the 9th leading cause of cancer-related deaths [1]. In 2018, 704,376 new diagnoses and 310,394 deaths for this disease were registered worldwide [1]. The global distribution of rectal cancer is characterised by some geographic variation with incidence rates being higher in Eastern Europe, Australia/New Zealand and Eastern Asia while lower in most African regions and Southern Asia [1]. Rectal cancers are the most common colorectal tumour among people < 50 years, and they affect males in almost two thirds of cases [1,2].

Tumours arising in the rectum have long been considered different from those originating in other segments of the large bowel. While treatment algorithms for metastatic disease are similar across all colorectal cancers, the management of nonmetastatic rectal tumours poses unique challenges [3,4]. Compared to nonmetastatic colon cancer, clinical decision making for nonmetastatic rectal cancer is generally more arduous and regularly requires the expertise of a specialist multidisciplinary team (MDT) [5]. Also, the clinical and social relevance of early and late treatment-related toxicities and the impact that these may have on therapeutic decisions is far more considerable [6,7].

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https://doi.org/10.1016/j.ctrv.2019.101930
Received 27 August 2019; Received in revised form 5 November 2019; Accepted 6 November 2019

Finally, treatment paradigms are continuously challenged with the intent of adopting risk-stratified management strategies [8–10].

By providing a set of practical recommendations, clinical guidelines aim to streamline decisional processes and practices according to the best available evidence, thus providing an invaluable support especially for the management of complex diseases such as nonmetastatic rectal cancer. Adherence to these recommendations represents a guarantee for both physicians and patients that the most appropriate course of action is being pursued, this triggering a virtuous circle that will ultimately ensure delivery of high-quality care and patient safety. Also, from a regulatory perspective, it ensures the implementation of practices that are in line with nationally approved care pathways and standards of cost-effectiveness [11].

Beyond these obvious advantages, clinical guidelines also provide a unique opportunity to assess the overall burden and quality of evidence underlying standards of care as well as to identify evidence gaps limiting the scope and strength of their recommendations. Knowledge of these gaps is key to prioritise research questions and rapidly translate new evidence into clinical guidance. While it is unrealistic to encompass the complexity of routine clinical practice into a set of recommendations, it is of utmost importance to reduce to a minimum the grey areas that may foster substantial variation in clinical practice and potentially cause detriment to patient outcome.

In this study, we aimed to identify grey areas, evidence gaps and unmet needs in the management of nonmetastatic and oligometastatic rectal cancer by systematically analysing and comparing recommendations from national and international clinical guidelines.

Methods

Five clinical guidelines representing major continents/countries were selected. These included the “Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up” [12], the “NCCN Clinical Practice Guidelines in Oncology - Rectal cancer, version 2.2019” [13], the “Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer” [14], the “Cancer Council Australia Colorectal Cancer Guidelines Working Party Clinical practice guidelines for the prevention, early detection and management of colorectal cancer” [15], and the Cancer Care Ontario guidelines [16–18].

Twenty-six clinically relevant questions were selected. These were worded by the senior author (FS) with the intent to cover the most important steps in the management of rectal cancer patients from initial diagnosis to follow-up. Each guideline was interrogated against these questions and specific recommendations were extrapolated. In the first instance these were summarised and reported as a text. Subsequently, consistency across guidelines was assessed. Given the inherent nature and complexity of the questions/recommendations, a qualitative approach for the comparative analysis was used. The clinical guidelines providing the most detailed recommendation (or the ESMO guidelines if all guidelines provided similarly detailed recommendations) were set as a reference and recommendations from the other guidelines were categorised according to the following 4-tier classification system: “identical/very similar”, “similar”, “slightly different”, “different”. When no clear guidance was provided, this was categorised as “no recommendation” if the topic was not even discussed. Otherwise, if the topic was briefly discussed yet without a clear position statement, this was either categorised as “no recommendation” (if none of the other guidelines provided any clear recommendation) or interpreted as a recommendation against the guidance from the reference guidelines and therefore categorised as “different”. Consistency across guidelines was independently assessed by two authors (GB and TAT). If no consensus was reached, the senior author (FS) acted as referee.

Overall agreement between guidelines was assessed according to the following hierarchical criteria: substantial/complete disagreement (if ≥ 1 “different” recommendation), partial disagreement (if ≥ 1 “slightly different” recommendation), partial agreement (if ≥ 1 “similar” recommendation), and substantial/complete agreement (if all recommendations were “identical/very similar”).

The highest level of evidence (LoE) that was used in support of the recommendations for each question was graded according to the Oxford CEBM Levels of Evidence guidelines [19].

Study objectives and statistical considerations

The primary objective of the study was to identify the areas where clinical guidelines were in disagreement. The secondary objective was to evaluate the association between agreement/disagreement and highest level of available evidence. For this analysis the χ^2 test was used and the Oxford CEBM levels of evidence grouped as follows: 1a + 1b + 1c (i.e., high LoE) versus 2a + 2b + 2c + 3a + 3b + 4 + 5 (i.e., moderate/poor LoE). A p value < 0.05 was considered statistically significant.

Results

Question 1. What are the criteria to distinguish rectal cancers from colon cancers?

The ESMO guidelines define rectal cancers as tumours with distal extension ≤ 15 cm from the anal margin as measured by rigid sigmoidoscopy. They recommend, however, that tumours above the peritoneal reflection should be treated as colon cancers. According to the NCCN guidelines rectal tumours arise between a virtual plane stretching from the sacral promontory to the upper edge of the symphysis as determined by MRI and the superior border of the functional anal canal. Similar anatomical landmarks are used by the Ontario guidelines (i.e., between the end of the sigmoid colon, usually corresponding to the sacral promontory, and the dentate line). Of note, these are the only guidelines specifying that cancers need to be adenocarcinomas to be considered rectal tumours. While the Australian guidelines highlight that in clinical trials rectal cancers were largely defined based on their distance from the anal verge (AV), they acknowledge the lack of consensus on the upper limit and recommend that the decision to treat tumours as colon or rectal cancers should be taken by a MDT. No criteria are provided by the JSCCR guidelines. [Substantial/complete disagreement. Highest LoE: 5].

Question 2. What are the criteria to define low rectal cancers?

In the ESMO, Australian and Ontario guidelines the classification into upper, mid and lower rectal cancers is based on the distance from the AV (i.e., $>$ 10–15 cm, $>$ 5–10 cm, and $\leq$ 5 cm, respectively). While this subdivision is shared by the NCCN guidelines, these provide only the criteria to define lower tumours (i.e., $<$ 5 cm from the AV). In the JSCCR guidelines, a distinction is made between upper and lower cancers but no classification criteria are provided. [Substantial/complete agreement. Highest LoE: 5].

Question 3. What are the optimal investigations for local staging?

Pelvic MRI is considered the gold standard for local staging by the ESMO, NCCN, Australian and Ontario guidelines. In these guidelines, endoscopic ultrasound is considered appropriate to discriminate between T1 and T2 tumours in patients who are candidates for transanal endoscopic microsurgery or transanal excision, or when MRI is contraindicated. It is acknowledged that endoscopic ultrasound is inferior to MRI for staging of locally advanced tumours. The JSCCR guidelines do not provide any recommendation. [Substantial/complete agreement. Highest LoE: 2a] [20,21].

Question 4. What are the minimal requirements of MRI pro-forma reporting at baseline?

The ESMO, NCCN, Australian and Ontario guidelines recommend reporting of at least the following parameters: distance of the tumour from the AV, T stage including depth of extramural invasion, N stage, extramural venous invasion (EMVI), and smallest distance between tumour and mesorectal fascia (MRF). There is no recommendation in

the JSCCR guidelines. [Substantial/complete agreement. Highest LoE: 2a] [21–23].

Question 5. What are the investigations to rule out distant metastases at baseline?

The ESMO and Australian guidelines recommend staging with thoracic/abdominal CT scan. This recommendation is shared by the Ontario guidelines that consider chest X-ray as an alternative to thoracic CT scan (which is still preferred). The NCCN guidelines recommend thoracic CT scan and abdominal CT or MRI scan. As far as the use of PET-CT scan is concerned, this is not included in the routine investigations. Nevertheless, according to the ESMO guidelines it should be considered in certain circumstances such as extensive EMVI on MRI or high levels of CEA, while the NCCN guidelines recommend its use whenever there are equivocal findings or the intravenous contrast cannot be used. No recommendation is provided by the JSCCR guidelines. [Partial agreement. Highest LoE: 2b] [24].

Question 6. Which circulating tumour markers should be tested at baseline?

The ESMO, NCCN and Ontario guidelines recommend testing CEA at baseline. Neither the JSCCR nor Australian guidelines discusses this point. [Substantial/complete agreement. Highest LoE: 5].

Question 7. How should individual patient risk be assessed?

In the ESMO and NCCN guidelines patients are risk-stratified using a combination of TNM parameters and clinico-radiological factors, with 5 and 3 risk categories, respectively, being proposed. The other guidelines rely solely on the TNM classification (Table 1). [Substantial/complete disagreement. Highest LoE: 1b] [9].

Question 8. Which patients should be considered for neoadjuvant treatment?

According to the NCCN, JSCCR, Australian and Ontario guidelines all patients with stage II /III tumours should receive neoadjuvant treatment. In the ESMO guidelines, neoadjuvant treatment is recommended for patients with stage II/III tumours but only if additional clinico-radiological risk factors are present (Table 1). [Partial disagreement. Highest LoE: 1b] [25,26].

Question 9. Which neoadjuvant treatments should be used?

The NCCN guidelines endorse up to 4 different types of neoadjuvant treatment: long-course chemo-radiotherapy (LCRT), short-course radiotherapy (SCRT), chemotherapy (preferably CAPOX/FOLFOX) followed by either LCRT or SCRT, and SCRT followed by chemotherapy (preferably CAPOX/FOLFOX). Also, they suggest that intraoperative radiotherapy (IORT), an additional boost with external radiation, or brachytherapy may be considered for T4 tumours or tumours with a positive/close to positive surgical margin. The ESMO and Australian guidelines recommend using either LCRT or SCRT with the former being preferred in the presence of certain risk factors. Also, the ESMO guidelines consider SCRT followed by chemotherapy (FOLFOX) as an alternative option for patients with high-risk tumours (Table 1). In the JSCCR guidelines only LCRT is recommended due to concerns regarding lack of enough data on late toxicity of SCRT. Also, similarly to the NCCN guidelines, they recommend IORT for tumours with a positive or unclear surgical dissection plane. The Ontario guidelines recommended LCRT with SCRT being an option for patients who present relative contraindications to chemotherapy (Table 1). [Substantial/complete disagreement. Highest LoE: 1a] [27].

Question 10. What is the timing of surgery following neoadjuvant LCRT?

The Australian guidelines recommend carrying out surgery 6–12 weeks after completion of LCRT, with longer intervals being preferred if maximal downstaging is needed. According to the NCCN guidelines, surgery should be performed 5–12 weeks after LCRT. The JSCCR guidelines suggest performing surgery 6–8 weeks after completion of LCRT. The Ontario guidelines recommend that surgery should be carried out 7–11 weeks after completion of LCRT. The ESMO guidelines acknowledge the controversy around this topic highlighting that in routine practice surgery is generally performed 4–12 weeks after LCRT. [Partial disagreement. Highest LoE: 1b] [28,29].

Question 11. What is the timing of surgery following neoadjuvant SCRT?

According to the NCCN guidelines, surgery can be carried out either 1 week or 6–8 weeks after SCRT completion. The ESMO guidelines recommend carrying out surgery within 7 days after the end of SCRT (or within 3 days in patients ≥75 years old). While they acknowledge that delaying surgery may increase the rate of pathological complete response, they also warn about potential risks. Similar recommendations are provided by the Ontario Guidelines (i.e., at least in relatively healthy patients, surgery should take place within 10 days after the start of SCRT). No recommendation is provided by the JSCCR and Australian

Table 1
Patient risk categories and recommended, risk-adapted, neoadjuvant treatments.

Guideline	Risk category	Recommended neoadjuvant treatments			
		LCRT	SCRT	SCRT + CT	LCRT + CT
ESMO	Very early (cT1 sm1 N0)				
	Early (Good) (cT1-cT2; cT3a/b if middle or high, N0 [or also cN1 if high], MRF clear, no EMVI)				
	Intermediate (cT3a/b very low, levators clear, MRF clear, or cT3a/b in mid- or high rectum, cN1-2 [not extranodal], no EMVI)	x (only if TME quality not assured)	x (only if TME quality not assured)		
	Bad (cT3c/d or very low localization, levators threatened, MRF clear cT3c/d mid-rectum, cN1–N2 [extranodal], EMVI +, limited cT4aN0)	x	x		
	Advanced (Ugly) (cT3 with any MRF involved, any cT4a/b, lateral node)	x		x	
NCCN	cT1-2N0				
	T3, N any with clear CRM (by MRI); T1-2, N1-2	x	x	x	x
	T3, N any with involved CRM (by MRI); T4, N any	x		x	x
JSCCR	TNM stage II	x			
	TNM stage III	x			
Australian	TNM stage II	x (preferred if T4 or MRF involved)	x		
	TNM stage III	x (preferred)	x		
Ontario	TNM stage II	x			
	TNM stage III	x			

Abbreviations: CRM: circumferential resection margin; CT: chemotherapy; EMVI: extramural venous invasion; LCRT: long-course chemoradiotherapy; MRF: mesorectal fascia; MRI: magnetic resonance imaging; SCRT: short-course radiotherapy; sm: submucosal; TME: total mesorectal excision.

guidelines. [Partial disagreement. Highest LoE: 1b] [30,31].

Question 12. How should response to neoadjuvant treatment be assessed?

The ESMO guidelines recommend restaging with digital rectal examination, proctoscopy and pelvic MRI scan. Repeat thoracic/abdominal CT scan is recommended for high-risk patients (i.e., T4, EMVI, or MRF threatening/involvement) to rule out metastases prior to surgery. Similar guidance is provided by the NCCN guidelines that recommend digital rectal examination +/- rigid or flexible endoscopy, thoracic CT scan, abdominal CT or MRI scan and pelvic MRI scan. According to the Ontario guidelines, restaging MRI scan is optional. Nevertheless, they recognise that this could be useful for patients with tumours involving the MRF or for those who could benefit from a change in management if complete response was observed (i.e., high-risk surgical patients or patients requiring abdominoperineal resection). The Australian guidelines highlight the limited use of MRI scan after neoadjuvant treatment in Australia possibly due to the lack of routine funding. If this is performed, however, they recommend that the report should include the same information taken at baseline. This question is not addressed in the JSCCR guidelines. [Substantial/complete disagreement. Highest LoE: 1a-] [32].

Question 13. Should further treatment be considered before surgery if response to standard neoadjuvant treatment is suboptimal?

Administration of 12 to 16 weeks of systemic chemotherapy before surgery is recommended by the NCCN guidelines for patients with involved MRF or bulky residual disease. The ESMO guidelines recommend that if there is persistent MRF involvement, patients should be referred to an MDT with experience in multivisceral resection for consideration of *en bloc* tumour removal. They add that, while unproven, further chemotherapy may be beneficial. The Ontario guidelines highlight the lack of studies to demonstrate the impact of MRI findings after neoadjuvant treatment on change in treatment strategy or patient outcomes. No guidance is provided by the JSCCR and Australian guidelines. [Substantial/complete disagreement. Highest LoE: 4] [33].

Question 14. Should "watch and wait" be proposed to patients who achieve clinical complete response after neoadjuvant treatment?

According to the NCCN guidelines, a "watch-and-wait" approach may be offered in centres with experienced MDTs as long as the potential risk of a suboptimal oncological outcome is carefully discussed with the patient. The Australian guidelines consider this an option whenever standard surgical resection is either not possible or declined by the patient and an intensive surveillance program with salvage surgery can be implemented. Again, they stress the importance of discussing risks and benefits with the patient. Neither the ESMO nor the Ontario guidelines considers "watch and wait" a validated treatment approach and they recommend that it should only be considered within the context of clinical trials. The JSCCR guidelines do not issue any recommendation. [Partial disagreement. Highest LoE: 2a] [34].

Question 15. What is the standard surgical technique?

All guidelines agree that total mesorectal excision (TME) or partial/tumor-specific mesorectal excision should be the gold standard. [Substantial/complete agreement. Highest LoE: 2b] [35].

Question 16. How should the quality of surgery be assessed?

The ESMO, NCCN, Australian, and Ontario guidelines recommend that pathologists evaluate the plane of surgical resection and the completeness of the mesorectal excision according to a three-tier classification system (i.e., good/complete mesorectal excision or mesorectal surgical plane versus intermediate/nearly complete excision or intramesorectal surgical plane versus poor/incomplete excision or muscolaris propria surgical plane). The ESMO guidelines also recommend a photographic record of the surgical specimens. No criteria for the evaluation of the quality of surgery are proposed in the JSCCR guidelines. [Substantial/complete agreement. Highest level of evidence: 1b] [36,37].

Question 17. Should extended lymph node dissection be carried out?

The JSCCR guidelines recommend that lateral lymph node dissection should be routinely performed (regardless of the use of neoadjuvant radiotherapy) in patients with clinically suspected lateral lymph nodes and in those with ≥T3 tumours with the inferior border lying below the peritoneal reflection. According to the NCCN guidelines extended lymph node dissection is not indicated, but suspected lymph nodes should be either biopsied or removed. While the ESMO guidelines do not provide a clear statement, they acknowledge that this procedure is rarely carried out in Europe in the absence of persistently enlarged lateral lymph nodes after LCRT. According to the Ontario guidelines there is insufficient evidence to make any recommendation while the Australian guidelines do not address this question. [Substantial/complete disagreement. Highest LoE: 1b] [38].

Question 18. Is laparoscopic surgery an option?

The ESMO, NCCN, JSCCR and Australian guidelines generally consider laparoscopic surgery as a valid option. Nevertheless, they recommend this should be carried out by expert surgeons, in hospital with adequate infrastructure, and for patients with low-risk tumours. As noted by the JSCCR and Australian guidelines, this technique has not yet been demonstrated to be safe and effective for all patients. The Ontario guidelines do not provide any recommendation. [Substantial/complete agreement. Highest LoE: 1b] [39,40].

Question 19. Are minimally invasive surgical techniques an option for patients with low-risk tumours?

According to the ESMO guidelines, local excision (preferably in the form of transanal endoscopic microsurgery) is recommended only for patients with early tumours (T1sm1, N0) with no risk factors (such as poor differentiation, lymphatic or vascular invasion). For tumours with one of these risk factors, standard TME should be the gold standard while local excision followed by LCRT should be considered only in peri-operative high-risk patients bearing in mind the lack of supportive data. Local excision following complete or almost complete response to LCRT should be considered only within the context of clinical trials. Similar recommendations are provided by the NCCN guidelines that include size ≥3 cm, extension ≥30% of the bowel circumference, fixed tumour and perineural invasion among the risk factors that would contraindicate local excision. The JSCCR guidelines endorse local excision for Tis and T1aN0 tumours, recommending standard surgical resection if either tumour invasion of the submucosal ≥1000 μm, lymphovascular invasion, poor grading, signet-ring cell/mucinous histology, tumour budding (grade BD2/3) or positive deep margin is found. The Australian guidelines consider local excision as a suitable option for patients with T1 tumours as long as clear margins can be achieved and patients are made aware of the risk of recurrence and the need of salvage surgery should tumour recur. The Ontario guidelines do not issue any recommendation. [Substantial/complete agreement. Highest LoE: 1a-] [41,42].

Question 20. Which information should be included in the pathology report from surgical resection in addition to the TNM stage?

The ESMO and NCCN guidelines recommend regular evaluation and reporting of the quality of the TME, status of surgical margins, EMVI, perineural invasion, tumour budding and degree of tumour regression after neoadjuvant treatment. Also, they recommend reporting of extranodal extension of lymph node metastases and tumour grade, respectively. The Australian guidelines recommend regular evaluation and reporting of histological tumour type, tumour grade, status of surgical margins, lymphovascular invasion, and presence of fibrosis, necrosis or acellular mucin pools. Neither the JSCCR nor the Ontario guidelines provides any recommendation. [Partial agreement. Highest LoE: 2a] [43].

Question 21. Is adjuvant chemotherapy indicated after pre-operative (chemo)radiotherapy?

The NCCN and Ontario guidelines recommend use of adjuvant chemotherapy in all patients with clinical stage II or III tumours. Similar recommendations are provided by the JSCCR guidelines stating that high-risk stage II and stage III rectal cancer patients should generally receive adjuvant chemotherapy. They do not specify, however, if

patient selection should be based on the clinical or pathological stage. According to the ESMO guidelines it is reasonable to consider adjuvant chemotherapy in patients with pathological high-risk stage II and stage III tumours. They suggest, however, sharing this decision with the patient taking into account potential risks and benefits. The Australian guidelines acknowledge the lack of strong data to support regular use of adjuvant chemotherapy and suggest that any or most benefit from this treatment is possibly limited to patients with clinical or pathological stage III upper rectal tumours. [Substantial/complete disagreement. Highest LoE: 1a] [44].

Question 22. Which adjuvant chemotherapy regimen should be used after pre-operative (chemo)radiotherapy?

According to the NCCN and the Ontario guidelines oxaliplatin-based treatment should be preferred over fluoropyrimidine alone (especially for patients with high-risk tumours at baseline and/or poor response to pre-operative chemotherapy with fluoropyrimidine alone as specified in the NCCN guidelines). The ESMO and the JSCCR guidelines list fluoropyrimidine monotherapy or oxaliplatin-based treatments as possible options. The Australian guidelines just highlight the controversy around the benefits of oxaliplatin in this setting as well as the increased risk of toxicities with such treatment. [Partial disagreement. Highest LoE: 1a] [45].

Question 23. When should adjuvant (chemo)radiotherapy be indicated?

All guidelines recommend that post-operative chemoradiotherapy should be offered to all patients who did not receive neoadjuvant treatment but were found to have high-risk tumours after pathology review of the resection specimens. High-risk features includes upstaging from clinical stage I to pathological stage II or III (NCCN, Ontario and Australian guidelines), pathological stage II or III tumours with a positive/unclear resection margin (JSCCR guidelines), incomplete mesorectal excision, positive circumferential resection margin (CRM), tumour perforation, extranodal deposits or nodal deposits with extracapsular spread in proximity to the MRF or other high-risk factors for local recurrence (ESMO guidelines). [Partial disagreement. Highest LoE: 1b] [46,47].

Question 24. How and for how long should patients be followed up after curative surgery?

In order to detect recurrence as early as possible, the ESMO, NCCN, JSCCR and Australian guidelines recommend different, risk-adapted, follow-up programs with a number of investigations including CEA, CT scans and colonoscopy to be carried out at regular intervals for up to 3–5 years. Table 2 compares the recommendations from each guideline (except the Ontario guidelines that do not provide any guidance). [Substantial/complete disagreement. Highest LoE: 2a-] [48].

Question 25. How should patients with isolated, potentially resectable, local recurrence be managed?

The ESMO guidelines recommend that radiotherapy-naïve patients should be managed with standard LCRT (or SCRT followed by oxaliplatin-based chemotherapy) and surgery. In previously irradiated patients, low-dose radiotherapy with chemotherapy can be considered before surgery. Of note, resections should be carried out by specialist teams. The NCCN guidelines recommended LCRT followed by surgery +/− IORT/brachytherapy (preferred option for radiotherapy-naïve patients), or upfront surgery followed by post-operative CRT. According to the JSCCR guidelines, resection is the treatment of choice if clear margins can be achieved otherwise pre-operative CRT should be considered. The Australian guidelines recommend surgery alone or CRT followed by surgery (if no previous radiotherapy). Of note, they highlight that surgery should be attempted only when a curative R0 resection is deemed possible and carried out by teams with expertise in pelvic exenteration. Furthermore, it should follow a detailed discussion with the patient regarding the impact of resection in terms of morbidity, quality of life and survival outcome. No recommendation is provided by the Ontario guidelines. [Partial disagreement. Highest LoE: 2b] [49].

Question 26. How should patients with synchronous resectable liver or lung metastases be managed?

A total neoadjuvant approach followed by synchronous or staged resection/local therapy is recommended by the NCCN guidelines. If a clear CRM is expected, treatment with chemotherapy (oxaliplatin-based doublet preferred) followed by SCRT (preferred) or LCRT is recommended. If the CRM is at risk of involvement, chemotherapy (oxaliplatin-based doublet preferred) followed by LCRT or SCRT/LCRT followed by chemotherapy should be considered. The ESMO guidelines recommend chemotherapy followed by metastasectomy +/- SCRT to the primary tumour. Nevertheless, in view of the evidence gap, they recommend that any treatment strategy in this setting should be decided by MDTs. Neither the JSCCR nor the Australian guidelines makes a distinction between colon and rectal cancers or provide recommendation regarding use of pre-operative (chemo)radiotherapy. The JSCCR guidelines recommend that liver or lung metastasectomy should be carried out after confirmation of radical resection of the primary tumour and followed by single agent fluoropyrimidine-based chemotherapy. The Australian guidelines state that chemotherapy should be offered to patients who have undergone liver metastasectomy for high-risk tumours and may also be beneficial after lung resection. Also, pre-operative chemotherapy could be considered before surgery in patients with synchronous liver and lung metastases. No recommendation is provided by the Ontario guidelines. [Substantial/complete disagreement. Highest LoE: 2b] [50].

Overall agreement and level of evidence

Substantial/complete agreement, partial agreement, partial disagreement, and substantial/complete disagreement were found for 8 (30.8%), 2 (7.7%), 7 (26.9%), and 9 (34.6%) questions, respectively. High LoE was available to support recommendations for 13/26 (50.0%) questions overall, including 3/10 (30%) questions where guidelines were in agreement and 10/16 (62.5%) questions where guidelines were in disagreement ($\chi^2 = 2.6$, $p = 0.106$) (Fig. 1).

Discussion

In this study we showed that recommendations for the management of nonmetastatic and oligometastatic rectal cancer differ substantially between guidelines. In up to 62% of cases, two or more guidelines provided recommendations that were at least partially dissimilar. Interestingly, the high rate of disagreement did not appear to be driven by the lack of high-quality evidence.

Despite the routine adoption of an evidence-based decision-making approach and wide implementation of MDT-centered, integrated care pathways, variation in oncology clinical practice remains a well-established phenomenon for several tumours including rectal cancer [51–54]. This can be influenced by many factors such as availability of health care facilities and professional expertise for service provision, local reimbursement policies, institutional/network pathways, social pressure and cultural prejudices, physician attitude and patient preferences. When variation occurs, this is often perceived by patients and physicians themselves as a deviation from universally accepted standards of care. It should be noted, however, that scientifically-validated general principles cannot fully encompass the complexity of routine practice, with inference and extrapolation being necessary when good-quality data are not available to inform the management of individual patients. Furthermore, as demonstrated by the results of our analysis, variation may actually be the result of thoughtful adoption of practical recommendations from different national or international guidelines.

When we designed this study, we aimed not only to systematically compare recommendations from clinical guidelines but also to provide physicians dealing with rectal cancer with a brief overview of the global guidance for this disease. For this purpose, we selected 26 topics that reflect key steps in the management of rectal cancer from diagnosis to staging, treatment and follow-up, and represent actual challenges that are to be faced in everyday clinical practice. We interrogated five guidelines that cover a population of more than 1,200,000,000

Table 2
Minimum investigations and time points recommended for the follow-up after curative intent resection.

			Year 1				Year 2				Year 3				Year 4				Year 5			
			3	6	9	12	3	6	9	12	3	6	9	12	3	6	9	12	3	6	9	12
ESMO	CRM-	CEA		•		•		•		•		•		•								
		Chest-abdomen-pelvis CT scan				•				•												
		Colonoscopy[a]																				•
NCCN	Stage I	Colonoscopy[b]				•												•				
	Stage II-III	CEA		•		•		•		•		•		•		•		•		•		•
		Chest-abdomen-pelvis CT scan				•				•				•				•				•
		Colonoscopy				•												•				
JSCCR	Stage I-II	DRE		•		•		•		•		•		•								
		Chest-abdomen-pelvis CT scan		•		•		•		•		•		•				•				•
		Colonoscopy				•				•				•								
	Stage III	DRE		•		•		•		•		•		•								
		Chest-abdomen-pelvis CT scan		•		•		•		•		•		•		•		•		•		•
		Colonoscopy				•				•				•								
Australian	Stage II-III	CEA	•	•	•	•		•		•		•		•				•				•
		Chest-abdomen-pelvis CT scan				•				•				•				•				•
		Colonoscopy[c]				•																

Abbreviations: CEA: carcino-embryonic antigen; CRM: circumferential resection margin; CT: computed tomography; DRE: digital rectal examination.
[a] Colonoscopy every 5 years up to the age of 75 (if a complete colonoscopy was not performed before surgery, it should be done within the first year).
[b] Complete colonoscopy 1 year after surgery (3–6 months after surgery if it was not performed in the initial workup), 3 years afterwards and then every 5 years.
[c] To be performed after 6 months if a complete colonoscopy was not done before surgery; further endoscopic follow up to be done every 5 years until year 11 (subsequent follow-up by either fecal occult blood test or colonoscopy).

inhabitants but extend their influence on decision-making far beyond their geographic boundaries. Using a question & answer model allowed us to make a pragmatic comparison of clinical recommendations, while regular reporting of the highest LoE existing in support of recommendations for each of the topics provided an opportunity to better understand potential reasons of inter-guideline disagreement.

While some degree of disagreement was anticipated, we were surprised to find that this occurred for almost two thirds of the topics. By analysing more in detail the results of our study, we noticed quite an interesting clustered distribution of the areas of disagreement. With the

	A/D	ESMO	NCCN	JSCCR	AUSTRALIA	ONTARIO	LoE
1. Definition		□□	■	-	▫	■	5
2. Topographic classification		□□	□	-	□	□	5
3. Baseline local staging		□□	□	-	□	□	2a
4. Baseline MRI pro-forma reporting		□□	□	-	□	□	2a
5. Baseline staging work-up		□□	□	-	□	▫	2b
6. Baseline circulating tumour markers		□□	□	-	-	□	5
7. Baseline risk stratification		□□	▪	■	■	■	1b
8. Criteria for neoadjuvant treatment		□□	▪	▪	▪	▪	1b
9. Types of neoadjuvant treatment		▪	□□	■	▪	■	1a
10. LCRT to surgery interval		▫	□	▪	□□	▫	1b
11. SCRT to surgery interval		▪	□□	-	-	▪	1b
12. Restaging after neoadjuvant treatment		□□	□	-	■	■	1a-
13. Salvage neoadjuvant treatment		▫	□□	-	-	■	4
14. Watch and wait		▪	□□	-	▫	▪	2a
15. Total mesorectal excision		□□	□	□	□	□	2b
16. Assessment of TME quality		□□	□	-	□	□	1b
17. Lateral lymph node dissection		■	■	□□	-	■	1b
18. Laparoscopic surgery		□□	□	□	□	-	1b
19. Local excision		□□	□	□	□	-	1a-
20. Pathology reporting after surgery		□□	□	-	▫	-	2a
21. Adjuvant chemotherapy		■	□□	▫	■	□	1a
22. Adjuvant chemotherapy regimen		▪	□□	▪	▪	□	1a
23. Adjuvant (chemo)radiotherapy		□□	▪	▫	▪	▪	1b
24. Follow-up		■	▪	□□	▪	-	2a-
25. Isolated local recurrence		□□	▫	▪	▪	-	2b
26. Synchronous metastases		▪	□□	■	■	-	2b

Comparison		Agreement/disagreement		Level of evidence	
□□	Reference guideline		Substantial/complete agreement	1a to 5	According to Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009)
□	Identical/very similar		Partial agreement		
▫	Similar		Partial disagreement		
▪	Slightly different		Substantial/complete disagreement		
■	Different	-	-		

Fig. 1. Agreement/disagreement between clinical guidelines and highest level of evidence for each of the study questions. Abbreviations: A/D: agreement/disagreement. LoE: level of evidence. LCRT: long-course chemoradiotherapy. SCRT: short-course radiotherapy. TME: total mesorectal excision.

only exception of some aspects of the surgical management, disagreement existed for all the treatment-related recommendations. On the other hand, agreement prevailed for topics such as diagnosis, staging, and radiology/pathology pro-forma reporting. The most surprising and counterintuitive result, however, was a trend towards an inverse association between the degree of inter-guideline agreement and the level of available evidence. According to our results, large consensus exists in areas which suffer the lack of high-quality supporting data, while the presence of randomised evidence is not sufficient in most cases to generate unequivocal views among groups of international experts.

One of the reasons for the mismatch between level of existing evidence and inter-guideline agreement is the limited generalisability of certain randomised trials. A clear example of this is the JCOG0212 trial [38]. While this trial failed to formally demonstrate non-inferiority of total mesorectal excision alone versus total mesorectal excision plus lateral lymph node dissection, the participation of Japanese centres only (where lateral lymph node dissection has long been a standard procedure) and the design of the study (upfront surgery for all patients with no use of neoadjuvant treatment) suggest caution when translating these results into routine recommendations for Western populations. Unexpected inconsistency between guidelines may also be the result of some reluctance by physicians to accept evidence-based indications which largely contrast with their own perceptions or general historical assumptions, this reluctance being often reinforced by concerns regarding the risk of patient under- or over-treatment. This is the case of adjuvant chemotherapy after neoadjuvant (chemo)radiotherapy. Despite the negative results of randomised clinical trials and an individual patient data meta-analysis [44], systemic chemotherapy is still routinely recommended by some guidelines. Not surprisingly given the lack of robust supporting data, substantial heterogeneity across guidelines also exists with regards to the criteria for patient selection or the type of chemotherapy regimen. Paradoxically, disagreement between guidelines can also be caused by the opposite scenario, i.e., full endorsement by the panel of experts of treatment approaches that have not yet been properly validated in randomised phase III trials. Emblematic is the case of neoadjuvant treatment, where most of the observed discordance is due to the inclusion by some guidelines of systemic chemotherapy, either before or after (chemo)radiotherapy, among the recommended treatment options for patients with locally advanced tumours.

Diversity of clinical guidance is not necessarily negative value especially if this is meant to best address specific clinical needs of individual populations or unique regulatory frameworks. The findings of our study, however, may have important implications in terms of clinical practice and research. Bearing in mind that equivalent results can be achieved by adopting different management approaches, heterogeneous recommendations from clinical guidelines, especially if not supported by high-quality evidence, may potentially translate into suboptimal outcomes for under-treated patients or unnecessary treatment-related toxicities for over-treated patients. Inconsistent views across panels of experts may create confusions among physicians who have to make treatment decisions, as well as patients who would like to feel reassured that they are being managed in accordance with recommended standards. Also, the existence of substantially different practices across the globe may itself in a vicious circle undermine the ability to generate new evidence through international data sharing initiatives or clinical trials, and limit the generalisability and clinical applicability of results from smaller studies conducted in certain geographic areas.

We acknowledge that our study has many limitations. First of all, clinical guidelines and questions were arbitrarily selected. Our topic-by-topic comparison was based on subjective, and as such poorly reproducible and therefore potentially questionable, evaluation criteria. As a result, it is possible that, if the same analysis was conducted by a different research group (possibly practicing in a different country and following different guidelines), the conclusions could have been different. Also, the distinction between “similar” and “slightly different” was very subtle but decisive in the categorisation of the level of agreement. Nevertheless, it is very unlikely that such analysis could have been done using a methodology that was not affected by a certain degree of subjective interpretation. Second, we cannot exclude that some of the observed disagreements may actually be secondary to the comparison of guidelines that were issued at different times, this possibly precluding the revision of certain recommendations based on the latest evidence. The guidelines selected for this study, however, were reviewed during a time period spanning from 2017 to 2019, this reducing the risk of “falsely discordant cases”. Actually, it should be noted that in up to 65% of cases (i.e., 80% of the topics where agreement was found), no specific recommendation was provided by one or more guidelines, and this could have potentially caused an underestimation of the disagreement rate. Finally, the results of our study are not entirely new. The lack of consistency across clinical guidelines for rectal cancer was previously highlighted by Luzietti et al who compared the ESMO, NCCN and JSCCR guidelines [55]. Nevertheless, by extending the analysis to the Australian and Ontario guidelines, consulting updated versions of the ESMO, NCCN and JSCCR guidelines, widening the discussed topics, scoring recommendations using a systematic analytic approach, and comparing these against the highest available LoE, we added substantially to the existing literature providing the most comprehensive analysis of global rectal cancer guidelines.

In conclusion, we showed that substantial variation exists across national and international guidelines regarding clinical recommendations for the management of nonmetastatic or oligometastatic rectal cancer. This variation is multifactorial and only partly explained by the lack of supporting, high-quality data. The findings of our study should urge clinical guideline expert panels, whenever feasible and appropriate, to reappraise their recommendations in light of the available evidence. This will allow smoothing over some of the differences and inconsistencies that still fuel variation in clinical practice. Academic groups should also encourage the development of studies aiming to reduce the grey areas that still exist in this disease setting such as, for instance, the role of adjuvant chemotherapy after neoadjuvant (chemo) radiotherapy or the value of pre-operative systemic chemotherapy before or after standard (chemo)radiotherapy. While some unanswered questions may be difficult to address in randomised clinical trials due to poor patient/physician compliance, global collaborative initiatives such as the International Watch and Wait Database Consortium [56] or the Lateral Node Study Consortium [57] should be taken as good examples of how to put efforts together and take advantage of current diversity in clinical practice to fill evidence gaps and possibly shape future clinical guidelines.

Declaration of Competing Interest

All the authors declare no conflicts of interest.

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