Management of rectal cancer in Canada: an evidence-based comparison of clinical practice guidelines

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Background: Rectal cancer requires a multidisciplinary and multimodality treatment approach. Clinical practice guidelines (CPGs) provide a framework for delivering consistent, evidence-based health care. We compared provincial/territorial CPGs across Canada to identify areas of variability and evaluate their quality.

Methods: We retrieved CPGs from Canadian organizations responsible for cancer care oversight and evaluated their quality and developmental methodology using the AGREE-II instrument. Recommendations for diagnostic and staging investigations, treatment by stage, and post-treatment surveillance of stage I–III rectal cancers were abstracted and compared.

Results: We identified 7 sets of CPGs for analysis, varying in content, presentation, quality, and year last updated. Differences were noted in locoregional staging: 4 recommended magnetic resonance imaging over endorectal ultrasonography, 2 recommended either modality, and 3 specified scenarios for one over the other. Recommendations also varied for use of staging computed tomography of the chest versus chest radiography and for surgical management and indications for transanal excision. Recommendations for neoadjuvant therapy in stage II/III disease also differed: 3 guidelines recommended long-course chemoradiation over short-course radiation therapy alone, while 3 others recommended short-course radiation in specific clinical scenarios. Adjuvant chemotherapy for stage II/III disease was uniformly recommended, with variable protocols. The use of proctosigmoidoscopy and interval/duration of endoscopic post-treatment surveillance varied among guidelines.

Conclusion: Canadian CPGs vary in their recommendations for staging, treatment, and surveillance of rectal cancer. Some of these differences reflect areas with limited definitive evidence. Consistent guidelines with uniform implementation across provinces/territories may lead to more equitable care to patients.

Contexte: Le cancer rectal requiert une approche thérapeutique multidisciplinaire et multimodalité. Les guides de pratique clinique (GPC) procurent un cadre pour assurer la prestation de soins de santé constants reposant sur des données probantes. Nous avons comparé les GPC des provinces et des territoires canadiens pour identifier les secteurs où ils varient et pour en évaluer la qualité.

Méthodes: Nous avons obtenu les GPC des organisations canadiennes responsables des soins oncologiques et nous avons évalué leur qualité et la méthodologie de leur élaboration au moyen de l'outil AGREE II (Appraisal of Guidelines for Research & Evaluation). Nous avons extrait et comparé les recommandations en ce qui concerne les épreuves diagnostiques et la stadification, les traitements en fonction du stade et la surveillance post-thérapeutique du cancer rectal de stade I à III.

Résultats: Nous avons recensé 7 GPC aux fins de cette analyse; leur contenu, leur présentation, leur qualité et l'année de leur plus récente mise à jour variaient. Des différences ont été observées au plan de la stadification locorégionale : 4 recommandaient l'imagerie par résonnance magnétique plutôt que l'échographie endorectale, 2 recommandaient l'une ou l'autre et 3 précisaient des circonstances où utiliser l'une plutôt que l'autre. Les recommandations variaient aussi pour ce qui est de l'utilisation de la scintigraphie c. radiographie thoracique de stadification, de la prise en charge chirurgicale et des indications de l'excision transanale. Les recommandations variaient également en ce qui concerne le traitement néoadjuvant pour la maladie de stade II/III : 3 guides recommandaient un traitement par chimioradiothérapie à long terme plutôt qu'une brève radiothérapie seule, tandis que 3 autres recommandaient une radiothérapie brève dans certains cas particuliers. La chimiothérapie adjuvante pour la maladie de stade II/III était uniformément recommandée, mais les protocoles variaient. L'utilisation de la proctosigmoïdoscopie et l'intervalle/durée de la surveillance endoscopique post-thérapeutique variaient d'un guide à l'autre.

Conclusion: Les GPC canadiens varient quant à leurs recommandations pour la stadification, le traitement et la surveillance du cancer rectal. Certaines de ces différences témoignent du manque de données probantes concluantes dans certains secteurs. L'uniformisation des guides et de leur application entre les provinces et les territoires pourrait faciliter une prestation plus équitable des soins aux patients.

olon and rectal cancers represent 15% of all newly diagnosed cancers in Canadian men, and 12% of all newly diagnosed cancers in Canadian women.1 The detection, staging and management of rectal cancer has evolved dramatically over the last 30 years, with improved surgical techniques, involvement of multidisciplinary cancer disease site groups, and the utilization of a multimodal approach to treatment.²⁻⁴ During this time, there has been an improvement of outcomes in locoregional control and overall survival.^{5,6} However, with the volume and pace of evidence being generated, there remains some uncertainty and controversy regarding several elements of care, including the optimal neoadjuvant protocol, use of local excision and utility of adjuvant systemic therapy.⁵⁻⁸ This leads to variability in decision-making and clinical practice as well as knowledge gaps among clinicians. Previous Canadian studies have highlighted such differences among surgeons managing rectal cancer across the country.9,10

Clinical practice guidelines (CPGs) are systematically developed statements that are meant to inform decision-making regarding specific clinical situations. ^{11,12} They have the ability to improve the quality and consistency of care provided by bridging the gap between clinicians' knowledge/practices and what is supported in the literature. ^{12,13} Ideally, CPGs should analyze and distil the best evidence to provide direction to health care providers. However, guidelines may contain flawed or inaccurate content, may be presented in a suboptimal fashion, or may be poorly generalizable to individual patients. ^{12,13} Other barriers to implementation include clinician factors such as lack of agreement with published guidelines or limited time and resources, or patient factors such as specific preferences and expectations. ¹⁴

The Appraisal of Guidelines for Research & Evaluation II instrument (AGREE-II) is a standardized and validated tool used to evaluate the quality and methodology of CPGs. ^{15,16} It is considered by many to be the gold standard for guideline appraisal. ^{17,18}

Given the potential variation in practice patterns among Canadian surgeons, our objective was to examine Canadian rectal cancer CPGs to evaluate their quality, developmental methodology, presentation and interprovincial concordance.

METHODS

We obtained CPGs from the websites and/or publications of the responsible organization within each province and territory. These included the British Columbia Cancer Agency, Alberta Health Services, Saskatchewan Cancer Agency, Cancer Care Manitoba, Cancer Care Ontario, Institut national d'excellence en santé et en services sociaux and Groupe d'étude en

oncologie du Québec, and Cancer Care Nova Scotia. The latest published guidelines from each organization were used for this study; these were separate from care pathways or care maps published by the same organizations. From these guidelines, 2 of us (Z.M.M. and D.Y.) independently extracted information regarding stage I, II and III (i.e., curable) rectal cancers. Accuracy of extracted information was verified by a third, independent assessor (S.V.P.).

Recommendations for diagnostic and staging work-up (locoregional staging, assessment for distant metastases), treatment by stage (neoadjuvant therapy, surgery, adjuvant therapy) and protocols for post-treatment surveillance (endoscopic evaluation, imaging, tumour marker assessment, clinical visits) were assessed.

Each English guideline was evaluated and scored independently by 2 reviewers (Z.M.M. and D.Y.) for quality using the Appraisal of Guidelines for Research & Evaluation II (AGREE-II) instrument. The domains of evaluation included scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence. In addition to these, there are 2 global rating items within the assessment that rate the overall quality of each guideline and whether they would be recommended for use; however, we chose not to make a recommendation for or against the use of each CPG. Scaled domain scores for each guideline were then calculated as per AGREE-II methodology; within each domain, a score from 1 to 7 was assigned by each reviewer. A score of 1 reflects either no information or poor reporting of an AGREE II item/ concept. Conversely, a score of 7 indicates exceptional reporting of an AGREE II item/concept. Each pair of scores was summed, and the total was scaled as a percentage of the maximum possible score for that domain. A Spearman rank correlation coefficient was calculated to determine interrater agreement.

It should be noted that the AGREE-II process does not have a set minimum domain score to delineate the difference between a guideline that is considered to be of higher quality versus one considered to be of lower quality; such decisions are subjective and left to the user of the instrument.

RESULTS

We obtained CPGs specific to rectal cancer management from 7 of the 13 Canadian provinces and territories (Table 1). Most were available as published documents, but the BC guidelines were published online only. Guidelines from New Brunswick, Newfoundland & Labrador, Prince Edward Island, Nunavut, Yukon, and the Northwest Territories were not available, despite our attempts to obtain them. The CPGs varied with respect to year of most recent update(s).

Guideline evaluation using AGREE-II

All English guidelines were rated across different domains using the AGREE-II instrument (Table 2 and Fig. 1). Guidelines from Manitoba, Ontario and Nova Scotia scored well; average domain scores were above 50%. Conversely, guidelines from Saskatchewan and British Columbia scored the lowest; their average domain scores were below 20%. The majority of differences were noted within the domains of applicability and rigour of development, as defined by the AGREE-II instrument. The Spearman rank correlation coefficient was 0.90, indicating a statistically significant agreement of domain scores between the 2 assessors.

Diagnosis and staging work-up

All 7 guidelines recommended measuring carcinoembryonic antigen (CEA) levels, complete colonoscopy (if possible), and computed tomographcy (CT) of the abdomen and pelvis as part of the initial staging work-up for rectal cancer. The primary difference was noted in the use of magnetic resonance imaging (MRI) versus endorectal ultrasound (ERUS) for local staging of tumours. Guidelines from British Columbia and

Table 1. Guideline avail province/territory	ability and yea	ar of publication, by
Province/territory	Availability	Year(s) of publication
British Columbia	Yes	2012
Alberta	Yes	2013, 2014, 2017
Saskatchewan	Yes	2011, 2013
Manitoba	Yes	2014, 2015, 2018
Ontario	Yes	2013, 2014, 2016
Quebec	Yes	2016
Nova Scotia	Yes	2016
Newfoundland & Labrador	No	_
New Brunswick	No	_
Prince Edward Island	No	_
Nunavut	No	_
Northwest Territories	No	_
Yukon	No	_

Saskatchewan did not indicate a strong preference for either MRI or ERUS, whereas guidelines from Alberta, Ontario, Quebec and Nova Scotia recommended MRI (Table 3). Ontario and Manitoba guidelines provided specific scenarios for the use of MRI and ERUS in staging. In addition, while the majority of guidelines suggested CT to stage the chest, the BC guidelines recommended chest radiography over CT, and the Manitoba guidelines did not declare a preference (Table 3).

Neoadjuvant recommendations by stage

Guidelines frrom British Columbia, Alberta, Manitoba, Ontario and Nova Scotia did not recommend neoadjuvant therapy for stage I rectal cancer (Table 4); however, guidelines from Saskatchewan and Quebec suggested neoadjuvant therapy in the setting of select T2N0 and low tumours to obtain better opportunities for sphincter preservation at the time of surgery. All guidelines recommended neoadjuvant therapy for stage II and III rectal cancers, but their recommendations differed for shortcourse radiotherapy versus long-course chemoradiotherapy as the protocol of choice (Table 4). Guidelines from Saskatchewan, Ontario and Nova Scotia recommended long-course neoadjuvant treatment, whereas the guideline from Manitoba recommended short-course. British Columbia recommended long-course for patients with fixed tumours, predicted positive circumferential margins, and distal rectal cancers versus short-course for nonfixed and middle/proximal rectal cancers. Alberta recommended long-course for patients "not amenable to resection." Overall, the neoadjuvant protocols themselves were fairly consistent (data not shown).

Surgery recommendations by stage

Surgical resection was recommended as the primary curative option for stage I rectal cancer in all of the guidelines. Transanal excision (TAE) in stage I disease was mentioned in most guidelines (British Columbia, Alberta, Quebec, Nova Scotia), whereas

	Province, score					
AGREE II Domain	British Columbia	Alberta	Saskatchewan	Manitoba	Ontario	Nova Scotia
Scope & purpose	0%	86%	17%	100%	94%	50%
Stakeholder involvement	8%	11%	6%	61%	58%	33%
Rigour of development	0%	19%	1%	86%	50%	30%
Clarity of presentation	81%	53%	56%	94%	94%	92%
Applicability	0%	0%	0%	65%	52%	42%
Editorial independence	0%	88%	0%	100%	75%	67%
Average domain score	15%	43%	13%	84%	71%	52%

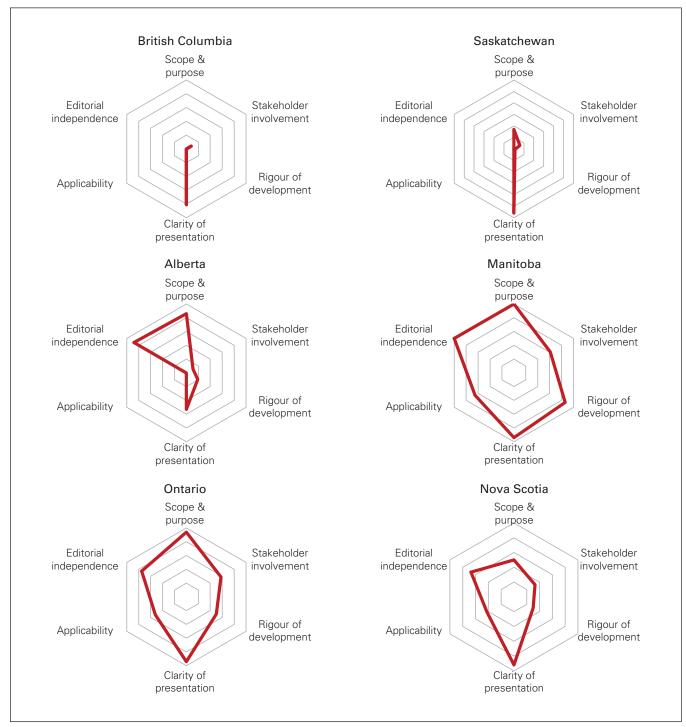


Fig. 1. Appraisal of Guidelines for Research & Evaluation II instrument (AGREE-II) domain scores of each provincial guideline.

Manitoba and Ontario guidelines did not comment specifically on TAE (Table 5). Specific considerations for TAE eligibility include node-negative cancers, absence of lymphovascular or perineural invasion, and tumour size < 3 cm. The guideline from Saskatchewan did not discuss surgical technique in any great detail.

For stage II and III disease, surgical recommendations were within the context of neoadjuvant protocols, and radical resection was recommended with a focus on total mesorectal excision (TME). The time between completion of neoadjuvant therapy and surgery was similar in all assessed guidelines (i.e., time from short-course to surgery 7–10 days; time from long-course to surgery 4–6 weeks or 6–10 weeks).

Province	MRI v. ERUS	Abdominal staging	Chest staging
British Columbia	No preference	CT abdomen/ pelvis	CXR preferred
Alberta	MRI preferred (especially if SC planned)	CT abdomen/ pelvis	CT preferred
Saskatchewan	No preference	CT abdomen/ pelvis	CT preferred
Manitoba	ERUS preferred (especially for small or low tumours) MRI for all stenotic tumours	CT abdomen/ pelvis	CXR or CT
Ontario	MRI preferred ERUS for low tumours	CT abdomen/ pelvis	CT preferred
Quebec	MRI preferred	CT abdomen/ pelvis	CT preferred
Nova Scotia	MRI preferred	CT abdomen/ pelvis	CT preferred

Table 4. Neoad	juvant therapy red	commendations, by stage
Province	Stage I	Stage II & III
British Columbia	_	SC for non-fixed, upper 2/3 location LC for fixed or predicted +CRM
Alberta	_	SC for "amenable to resection" LC preferred for stage II/III, and if "not amenable to resection"
Saskatchewan	Chemoradiation for select T2N0 and low tumours	LC standard
Manitoba	_	SC preferred
		LC for down-staging, sphincter preservation
Ontario	_	LC Preferred
Quebec	For sphincter preservation	No specific preference but states that majority of clinicians use LC
Nova Scotia	_	LC preferred
CRM = circumferentia short-course radiother		y-course chemoradiotherapy; SC =

Adjuvant protocols by stage

Adjuvant systemic therapy was not recommended for stage I rectal cancer in any of the CPGs. Manitoba, Ontario and Quebec guidelines did discuss adjuvant therapy for stage I disease if there was pathological upstaging postresection (Table 6). The BC guideline recommended adjuvant radiotherapy if local excision was carried out.

For stage II and III disease, all guidelines recommended some form of adjuvant systemic therapy,

Table 5. Surgica	al treatment reco	mmendations, by stage
Province	Stage I	Stage II & III
British Columbia	TAE offered	For SC, surgery within 10 d
		For LC, surgery within 6-10 wk
Alberta	TAE offered	For SC, surgery within 1 wk
		For LC, surgery within 6-8 wk
Saskatchewan	No details	For SC, surgery within 7–10 d
		For LC, surgery within 6-8 wk
Manitoba	Highlights	For SC, "immediate" surgery
	importance of TME technique	For LC, surgery within 6–8 wk
Ontario	Highlights	For SC, surgery within 10 d
	importance of TME technique	For LC, surgery within 4–6 wk
Quebec	TAE offered	For SC, "immediate" surgery
		For LC, does not specify time to surgery
Nova Scotia	TAE offered	For SC, surgery within 10 d
		For LC, surgery within 6-10 wk
	moradiotherapy; SC = sh 1E = total mesorectal ex	nort-course radiotherapy only; TAE = cision.

Table 6. Adjuva	ant treatment	recommendations, by stage
Province	Stage I	Stage II & III
British Columbia	Radiotherapy if LE	Capecitabine x 6 mo post-SC Capecitabine x 4 mo post-LC For stage III disease, mFOLFOX6 may be considered, especially if N+
Alberta	_	6 mo of adjuvant therapy recommended for stage II with "high-risk features" and all stage III (CAPOX/XELOX, mFOLFOX6, or capecitabine)*
Saskatchewan	_	Capecitabine, 5-FU, mFOLFOX, or CapeOX x 6 mo
Manitoba	If upstaged	Fluoropyrimidine-based therapy offered postoperatively
Ontario	If upstaged	No adjuvant therapy if upstaged to II/III Fluoropyrimidine-based therapy, post-op Oxaliplatin-based therapy, or capecitabine for high risk of systemic recurrence
Quebec	If upstaged	5FU/LV or FOLFOX for 8–12 cycles (FOLFOX preferred if upstaged)
Nova Scotia	_	5FU or capecitabine; FOLFOX if high risk of recurrence
LC = long-course che only. *Extrapolated from c		= local excision; SC = short-course radiotherapy

although there was variability in recommendations among the guidelines (Table 6). Adjuvant radiotherapy was not routinely recommended in any CPG.

Post-treatment surveillance recommendations

Post-treatment surveillance for stage I disease was limited to routine screening colonoscopy in all provinces. For stage II/III disease, surveillance included routine clinical visits, CEA testing, abdomen/pelvic imaging and

ry 3–6 mo for 3 yr ery 6 mo for 2 yr Not specified ry 3–6 mo for 3 yr y 6–12 mo for 2 yr mually thereafter ery 3 mo for 3 yr ery 6 mo for 2 yr	At each visit Every 3 mo for 3 yr Every 3–6 mo for 3 yr Every 6–12 mo for 2 yr Every 3 mo for 3 yr	Annually for 3 yr Annually for 2 yr (± third year) Annually for 3 yr Annually for 3 yr	At 1 & 4 yr post-op Every 5 yr thereafter At 1 & 4 yr post-op Every 5 yr thereafter At 1 yr post-op If no polyps, every 3–5 yr thereafter Flexible proctosigmoidoscopy ever 6 mo for 5 yr* At 1 & 3 yr post-op Every 5 yr thereafter Flexible sigmoidoscopy every 6 mo for 3 yr post-op*
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ery 6 mo for 5 yr	At each visit	Annually for 3 yr	At 1 yr post-op
			Every 5 yr thereafter
			Rectosigmoidoscopy every 6 mo for 2-5 yr post-op*
ry 3–6 mo for 3 yr	At each visit	Annually for 3 yr	At 1 yr post-op
nually thereafter			If no polyps, every 3–5 yr thereafter
ery 3 mo for 3 yr	At each visit	Annually for 3 yr	At 1 yr post-op
ery 6 mo for 2 yr			No specific surveillance recommendation thereafter
			Rigid or flexible sigmoidoscopy at 6, 18, 24 and 36 mc post-op
	nually thereafter ery 3 mo for 3 yr ery 6 mo for 2 yr	nually thereafter ery 3 mo for 3 yr At each visit	nually thereafter ery 3 mo for 3 yr At each visit Annually for 3 yr ery 6 mo for 2 yr

colonoscopy. The various recommendations by province are shown in Table 7. While we noted minor differences across most of these domains among the guidelines, the main variation existed in evaluation of the colon and rectum. Only 4 of the guidelines (Saskatchewan, Manitoba, Ontario, Nova Scotia) explicitly advised clinicians to perform proctosigmoidoscopy postoperatively, in addition to colonoscopies, to assess anastomoses. The duration of endoscopic surveillance postoperatively also differed among guidelines.

DISCUSSION

The management of rectal cancer is a complex and evolving area that relies on accurate diagnosis, staging and multidisciplinary treatment for optimal patient outcomes. Clinical practice guidelines play an important role in synthesizing the latest literature and subsequently disseminating evidence-based recommendations to clinicians. We present the assessment and comparison of Canadian provincial CPGs for the management of rectal cancer. Of the 13 provinces and territories, we obtained and analyzed 7 guidelines (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia); guidelines from the remaining provinces/ territories were not readily available. We noted that available CPGs were not all current and had been updated at variable intervals. Using the validated AGREE-II instrument for guideline evaluation, we noted varying quality, developmental methodology and

presentation among the CPGs. In addition, there was notable interprovincial variation in clinical recommendations. These differences were within the areas of imaging for locoregional staging, assessment for pulmonary metastases, neoadjuvant therapy protocols (short-course v. long-course), recommendations for transanal excision, adjuvant therapy indications and protocols, and post-treatment surveillance algorithms.

While recent work has shown significant variation in recommendations between North American, European, and Japanese rectal cancer guidelines, it focused on describing the differences without an actual appraisal of each CPG.³⁹ To our knowledge, our study is the first such evaluation of rectal cancer CPGs in Canada, and we provide an objective comparison as well as an appraisal of the recommendations within these guidelines. While we endeavour to highlight the differences between these CPGs as well as the scientific standards surrounding their development, the evaluation of the actual clinical content within them is outside of the scope of this study. Nonetheless, the strengths of our study lie in its comprehensive examination of national CPGs, thereby providing useful feedback for stakeholders involved in guideline development to consider as they update, improve and disseminate their recommendations.

From a pragmatic standpoint, an important question is whether there are differences in the care received by patients with rectal cancer. Previous Canadian studies have highlighted self-reported differences in practice patterns among rectal cancer surgeons through the use of national and provincial surveys, suggesting that this may be the case. 9,10,32 These differences are attributed to factors such as level of training (i.e., subspecialty v. nonfellowship), participation in continuing professional development, length of time in practice, location of practice, and access to clinical resources (e.g., MRI, ERUS). Whether or not these self-reported differences in practice patterns translate to variability in patient-level outcomes is unclear at this time. It is possible that differences in CPGs may contribute at least in part to variations in clinical practice, but there are likely multiple causative factors.

Unlike variation among surgeons and clinicians, it is harder to discern specific factors contributing to the variation among CPGs. Certainly, the resources available to each provincial/territorial cancer agency as well as the volume and size of institutions within each province dictate the amount of time and expertise that can be devoted toward the development of CPGs. ^{12,13} As a result, we assume recommendations are made taking each province's respective health care context (i.e., health care funding, clinical volume, technology, number of specialists) into account.

Another consideration relates to the body of evidence on which CPGs are based. In the context of rectal cancer, this is best illustrated by recommendations for neoadjuvant therapy. Owing to the amount of ongoing research comparing and evaluating neoadjuvant chemoradiotherapy protocols (e.g., short-course, delayed short-course, long course), recommendations continue to evolve, and certainly there remains equipoise in this area.^{5,7,33-35} This is reflected in the guidelines we examined, which differed in their endorsement of specific neoadjuvant protocols, as there is no definitive evidence yet for clinical practice.

When trying to reconcile the observed variations across Canada in clinical practice guidelines and selfreported practice patterns for rectal cancer, what ultimately matters most is whether these translate into worse outcomes for patients. If yes, then philosophically this highlights the notion of acceptable and unacceptable variations in clinical practice. When there is uncertainty in the literature about a particular intervention, then variations in recommendations and practice are expected and may be acceptable as long as the care is competent.³⁶ Conversely, if there is no equipoise, or if there is a lack of consistency due to modifiable provider and system factors, then we may consider differences in clinical guidelines and practice patterns to be unacceptable. From our study, the majority of variability in CPGs reflected areas with either limited or evolving evidence. Explaining the relationship between CPG variability and outcomes in patients with rectal cancer is beyond the scope of our investigation, and is also a complex relationship to disentangle.

Limitations

Our study is not without limitations; some of these relate to our use of the AGREE-II instrument for guideline evaluation. Despite being a validated and frequently used tool for guideline appraisal, the instrument does not provide a context for interpreting the scaled domain scores of a guideline. 16,37,38 Therefore, once domain scores have been determined, the evaluator must interpret these scores on their own when considering whether or not to recommend a guideline for use. While it stands to reason that higher domain scores suggest higher-quality guidelines, this lack of context introduces an element of subjectivity into the entire appraisal process. For this reason, we felt compelled to present only the scaled domain scores for each guideline rather than subjectively assess whether or not we would recommend them for use.

Conclusion

We found that rectal cancer CPGs in Canada vary in their presentation style, content, quality and recency. We know from previous studies that self-reported practice patterns within this area already vary among Canadian surgeons, and given the rapidly evolving evidence surrounding rectal cancer management, CPGs can serve to provide vetted and clear recommendations for clinicians to follow. Thus, there may be a role for uniform CPGs in the management of rectal cancer, and further research is necessary to determine if and how this might affect patient outcomes.

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Contributors: Z. Mir and S. Patel designed the study. Z. Mir, D. Yu and S. Patel acquired the data, which all authors analyzed. Z. Mir, D. Yu and S. Patel wrote the article, which all authors reviewed and approved for publication.

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