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ORIGINAL ARTICLE – COLORECTAL CANCER

The Need for Consensus and Transparency in Assessing Population-Based Rates of Positive Circumferential Radial Margins in Rectal Cancer: Data from Consecutive Cases in a Large Region of Ontario, Canada

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ABSTRACT

Background. A positive circumferential radial margin (CRM) after rectal cancer surgery is an important predictor of local recurrence. The definition of a positive CRM differs internationally, and reported rates vary greatly in the literature. This study used time-series population-based data to assess positive CRM rates in a region over time and to inform future methods of CRM analysis in a defined geographic area.

Methods. Chart reviews provided relevant data from consecutive patients undergoing rectal cancer surgery between 2006 and 2012 in all hospitals of the authors' region. Outcomes included rates for pathologic examination of CRM, CRM distance reporting, and positive CRM. The rate of positive CRM was calculated using various definitions. The variations included positive margin cutoffs of CRM at 1 mm or less versus 2 mm or less and inclusion or exclusion of cases without CRM assessment.

Results. In this study, 1222 consecutive rectal cancer cases were analyzed. The rate for pathology reporting of CRM distance increased from 54.7 to 93.2 % during the study. Depending on how the rate of positive CRM was defined, its value varied 8.5 to 19.4 % in 2006 and 6.0 to 12.5 % in 2012. Using a pre-specified definition, the rate of positive CRM decreased over time from 14.0 to 6.3 %.

Conclusions. A marked increase in CRM distance reporting was observed, whereas the rates of positive CRM dropped, suggesting improved pathologist and surgeon performance over time. Changing definitions greatly influenced the rates of positive CRM, indicating the need for more transparency when such population-based rates are reported in the literature.

In rectal cancer, a positive circumferential radial margin (CRM) usually is defined as tumor cells 1 mm or less from the mesorectal fascia.[1] Such cells can be an extension of the main tumor, cells in a regional lymph node, or cells in neurovascular structures. A positive CRM in most series predicts a greater risk of local tumor recurrence and consistently predicts a worse patient survival.[2–7]

Quirke and Dixon[8] defined specific steps for rectal cancer pathology assessment including the painting of the intact mesorectal margin before fixation, axial serial sectioning after fixation, and then the taking of appropriate blocks for microscopic assessment. Most national bodies endorse the Quirke method and suggest that it is the best method for optimizing lymph node harvest counts and the provision of an accurate CRM distance.[1,9] Ideally, if such methods are consistently used in a given region, measures

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such as overall specimen quality and tumor-CRM distance would be available for all cases after rectal cancer surgery.

Recent reported rates of positive CRM in population-based series and large trials range from 6 to 28 %.[3,10–14] A number of factors likely influence such variations. First, rates may differ with surgical or pathologic quality. Second, the definition of a positive CRM may vary among jurisdictions. Traditionally, in many North American studies, a positive margin was defined as tumor cells 0 mm from the CRM. More recently, the 1-mm or less cutoff for a positive CRM has been endorsed by most stakeholder groups, although certain groups endorse a 2-mm cutoff.[2]

Finally, the method of data analysis may differ among regions, leading to marked differences in rates of positive CRM. The positive CRM rate will be dependent on which cases are included or excluded in both the numerator and denominator. As an example, Wibe et al.[15] in a Norwegian population-based study reported a positive CRM rate of 9.5 %. However, more than half of all rectal cancer cases were excluded from the analysis, including cases treated with preoperative radiation and cases involving a perforation during surgery. It should be noted that surgery on an advanced tumor still may result in a positive CRM despite aggressive neoadjuvant therapies and expert surgery. But it is unlikely that variations in tumor presentation can explain marked differences in positive CRM rates at a regional level. These comments suggest the need for consensus in the evaluation of population-based rates of positive circumferential radial margins or, at the least, the need for methodologic transparency to facilitate appropriate comparisons over time and among regions.

Since 2006 there has been an ongoing quality improvement project in the Local Health Integration Network 4 (LHIN4) region (population 1.3 million) of Ontario (population 14 million) called the Quality Improvement in Colorectal Cancer in LHIN4 (QICC-L4) project. Surgeons select markers of quality for assessment and interventions to improve marker scores. The markers selected to date include rates of CRM distance reported and positive CRM. For this study we used these latter markers to help assess positive CRM rates in LHIN4 over time and to inform future methods of CRM analysis in a defined geographic area.

TABLE 1 Periods for data collection

Iteration	Period	No. of cases
1	1–30 November, 2006	217
2	1 July 2007–30 June 2008	246
3	1 July 2008–30 June 2009	239
4	1 July–31 December 2009 & 1 July–31 December 2010	272
5	1 July 2011–31 December 2011	114
6	1 January 2012–30 June 2012	134

List of data collection time frames according to iteration and number of cases reviewed

METHODS

Study Setting

In LHIN4, colorectal cancer surgery is provided at eight community hospitals and three teaching hospitals. During any 1-year period, approximately 50 surgeons provide colorectal cancer services. All radiation therapy and most chemotherapy are provided at two regional cancer centers. The QICC-L4 project, a region-level initiative that began in 2006, is designed to propel quality improvement in colorectal surgical care and clinical outcomes at all LHIN4 hospitals. Annually, LHIN4 surgeons select quality markers targeted for improvement and interventions to facilitate such improvement. The initiative allows for large amounts of data to be collected on a population of consecutive rectal cancer patients undergoing surgical resection. Such data have included pathology measures relevant to this study including "CRM assessed—yes or no" and "closest distance from tumor cells to CRM."

Patients and Data Collection

Between November 2005 and June 2012, 11 LHIN4 hospitals provided yearly lists of patients who had undergone major colorectal cancer surgery linked to a diagnosis of colon or rectal cancer. The resulting case lists represented all patients undergoing major bowel surgery for primary colon or rectal cancer in a LHIN4 hospital. The annual periods of collection were determined by available abstractor resources, and for each year, the periods were either 6 or 12 months in duration (Table 1). Each year, a random sample of 5 % of cases was re-abstracted by a second abstractor to assess agreement for indicator scores. The agreement exceeded 95 % for all indicators.

Pathologic Analysis

The methods for histopathologic examination of resected rectal specimens were hospital specific. The QICC-L4 project did not attempt to mandate specific methods of rectal assessment. However, during the period under review, initiatives at the international, national, and provincial levels encouraged pathologists to incorporate Quirke methods. Synoptic pathology reporting was in use at all sites throughout the study period.

Study Outcomes, Analyses, and Ethics

For each year, we assessed CRM evaluation by considering the total number of cases, the availability of a pathology report, assessment of the CRM—yes or no, reporting of the closest distance from tumor cells to the CRM—yes or no, and the actual CRM distance. Our main outcomes were rates of CRM assessment, reporting of CRM distance, and positive CRM. The rate of positive CRM was defined in four ways to consider differing definitions of a positive CRM (i.e., ≤1 or ≤2 mm) as well as differing potential numerators and denominators (Fig. 1).These four ways included

Calculation A All cases with a CRM of 1 mm or less or deemed positive without a CRM distance reported over the denominator of all pathology reports ($e + g/b$)

Calculation B All cases with a CRM of 2 mm or less or deemed positive without a CRM distance reported over the denominator of all pathology reports ($e + f + g/b$)

Calculation C All cases with a CRM of 1 mm less or deemed positive without a CRM distance reported over denominator of all pathology reports with a CRM distance or deemed positive without a CRM distance reported ($e + g/d + g$)

Calculation D All cases with CRM of 2 mm or less or deemed positive without a CRM distance reported over the denominator of all pathology reports with a CRM distance or deemed positive without a CRM distance reported ($e + f + g/d + g$).

A priori, we selected calculation C as the definition of a positive CRM that reflects the growing consensus on distance (i.e., tumor cells ≤1 mm from the radial margin) and balances the inclusion and exclusion of cases (i.e., included cases must have an actual radial margin distance or a definite positive CRM; simply completing a field on a synoptic report that the radial margin was assessed is not adequate).

Data analyses were descriptive and performed using SPSS software, version 19.0 (SPSS, Inc., Chicago, IL, USA). The study received ethics approval from the Hamilton Health Sciences Research Ethics Board.

RESULTS

Within LHIN4, data were collected on 1222 consecutive patients who underwent surgical resection for primary rectal cancer during the intervals under review between November 2005 and June 2012. There were no obvious differences in tumor or treatment measures, including stage, over time, as shown in Table 2. Missing data points within the table reflect information not collected during the period in question.

Pathology reports were available for 1207 (98.8 %) of the 1222 patients analyzed. The CRM was assessed in 1134 cases (94.0 %), and during the years of the study, the rate increased from 92 to 100 % (Table 3). An actual CRM distance was reported in 927 cases (77 %) and increased over time from 55 to 93 %. Using calculation C, the positive CRM rate decreased over time from 14 to 6 %. We used definitions A, B, C, and D to calculate a range of rates for positive CRM in each iteration of data (Fig. 2). The range of positive CRM rates was 9–19 % for iteration 1 (2005) and 6 to 13 % for iteration 6 (2012). Thus, for each iteration, a two-fold difference in the rate of positive CRM was observed depending on the definition of the positive margin used and the inclusion and exclusion criteria used.

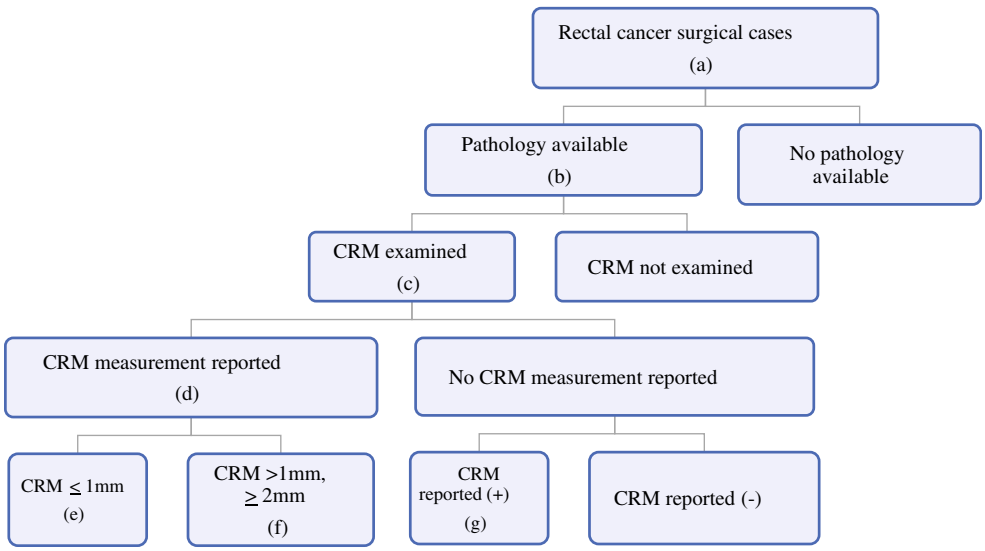

FIG. 1 Flow chart of pathology and circumferential radial margin (CRM) assessment for each iteration. (+) positive; (–) negative

TABLE 2 Tumor stage and treatment measures, including disease stage, over time

Iteration	1	2	3	4	5	6
No of cases	217	246	239	272	114	134
TNM stage 2/3 cases	–	–	136	160	63	71
Preoperative radiation (%)[a]	–	–	–	29.4	36.8	33.6
Postoperative radiation (%)[a]	–	–	–	7.0	6.1	5.2
Type of operation performed						
Low anterior resection	157	173	172	196	70	88
Abdominoperineal resection	49	53	57	61	35	33
Hartmann	7	18	10	13	9	9
Pelvic exenteration	2	1	0	0	0	0
Other	2	1	0	2	0	4

No obvious differences in tumor or treatment measures, including stage, were observed over time. TNM stage was collected for iterations 3–6 only, and use of radiation was collected for iterations 4–6 only

TNM tumor-node-metastasis

[a] Percentages are based on the total number of cases within the iteration

TABLE 3 Rates of assessment, reporting, and positive circumferential radial margin over time

Iteration	1	2	3	4	5	6
No. of cases (a)	217	246	239	272	114	134
Pathology available (b): *n* (%)	212 (97.7)	242 (98.4)	237 (99.2)	269 (98.9)	114 (100.0)	133 (99.3)
CRM assessed (c): *n* (%)	195 (92.0)	224 (92.6)	218 (92.0)	250 (92.9)	114 (100.0)	133 (100.0)
CRM measure reported (d): *n* (%)	116 (54.7)	182 (75.2)	178 (75.1)	223 (82.9)	104 (91.2)	124 (93.2)
CRM $\leq$1 mm (e)	5	14	12	14	10	4
CRM >1 mm and $\leq$2 mm (f)	7	8	8	12	9	8
CRM positive, no measurement (g)	13	14	7	3	1	4
Positive CRM rate (%)[a]	14.0	14.3	10.3	7.5	10.5	6.3

CRM circumferential radial margin

For letters (a)–(g) refer to Fig. 1

[a] Positive CRM rate using calculation $C\ (e + g/d + g)$, where the numerator includes cases with CRM distance <1 mm (e) + cases deemed CRM positive without actual distance given (g); the denominator includes cases with CRM distance reported (d) + cases deemed CRM positive without a measurement reported (g)

DISCUSSION

Our study examined pathology measures related to the CRM after rectal cancer surgery in the LHIN4 region of Ontario. We observed a near doubling (54.7–93.2 %) between 2005 and 2012 in the proportion of cases for which CRM distance was reported. Also, using an a priori definition of positive CRM, the positive CRM rate decreased from 14.0 to 6.3 %. These improvements are likely a reflection of improving pathology and surgical standards.

The positive margin rate of 6.3 % in 2012 compares favorably with those from other jurisdictions and randomized trials. For example, the Dutch TME and Medical Research Council (MRC) CR07 trials were two large randomized controlled trials (RCTs) that measured the utility of preoperative radiation therapy before surgery.[12,16] In both trials the intention was to include patients with resectable non-metastatic disease, although a small percentage of stage 4 cases were included in the Dutch trial. Both trials also encouraged participating surgeons to use optimal total mesorectal excision surgical techniques.

The rates of positive CRM in the Dutch TME and MRC CR07 trials, respectively, were 18.8 and 9.9 %. The current study included consecutive patients undergoing resective surgery during set periods. Patients were not excluded due to tumor fixation at presentation or presence of metastatic disease. We are unaware of other studies that have presented in detail markers such as "CRM assessed" and "tumor-CRM distance reported," and thus could not compare these measures in our study with those from other regions. Furthermore, although some studies reporting

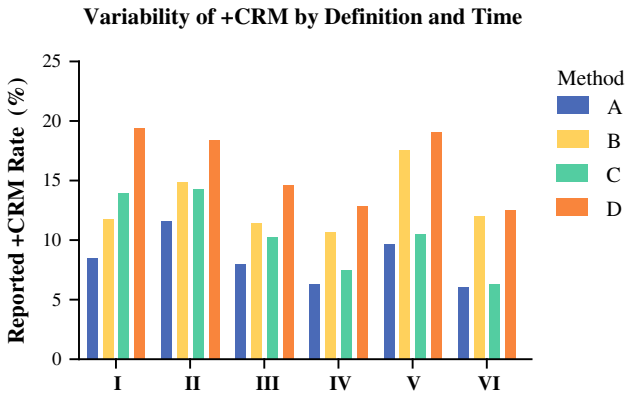

FIG. 2 Variability of the positive circumferential radial margin (CRM) rate by definition and iteration. Definitions *A*, *B*, *C*, and *D* were used to calculate a range of rates of positive CRM for each iteration of data (iterations 1 through 6). Depending on the method used, the rates of positive CRM varied between 9 and 19 % for iteration 1 (2005–2006) and between 6 and 13 % for iteration 6 (2012). $A = e + g/b$; $B = e + f + g/b$; $C = e + g/d + g$; $D = e + f + g/d + g$. For *letters* **a**–**g**, refer to Fig. 1

outcomes after rectal cancer surgery have considered the positive CRM rate, to our knowledge, this is the first study to investigate issues related to the pathology reporting of the CRM status.

Our study results demonstrate the need for consensus in evaluating population-based rates of positive circumferential radial margins, or at the least, the need for methodologic transparency to facilitate appropriate comparisons over time in a given region or among regions. For our iterations of data, we used four calculations to determine rates of positive CRM. In a transparent manner, each calculation varied the distance defining a positive margin (i.e., $\leq$1 or $\leq$2 mm) as well as the inclusion and exclusion of cases in the numerator and denominator. For each iteration, the rates of positive CRM varied greatly depending on the method of calculation. For example, in the final iteration (year 2012), the rate of positive CRM varied from 6 to 13 % and was largely influenced by the distance used to define a positive margin. In the first iteration (year 2005), the positive CRM rate varied from 9 to 19 % and was influenced by both the distance used to define a positive CRM and the choice of cases for inclusion.

We suggest that among our four presented methods, it is reasonable to use the distance of 1 mm or less to define a positive CRM and to include in the denominator all cases with a reported CRM distance or with evidence of cancer cells at the resected edge of the specimen. Other researchers may disagree, but this reinforces our main interest in encouraging consensus and transparency in the assessment of positive CRM rates.

Most studies related to CRM status do not present data on the completeness of pathology reports (e.g., number of cases with a reported CRM distance), but such data are important when results are compared across studies.

A Norwegian national study reported a positive CRM rate of 9.3 %.[15] However, only 686 (32 %) of 2121 cases were included in the evaluation. Cases were excluded because CRM was not assessed, although it is not known whether cases with CRM assessment have a higher or lower risk of a positive CRM than those without CRM assessment. Also, cases were excluded due to the use of preoperative radiation and whether a bowel or tumor perforation occurred at surgery. Factors such as perforation or the use of preoperative radiation likely predict for a higher risk of a positive CRM. A study using data from the U.S. National Cancer Database for the years 1998–2007 reported a positive CRM rate of 5.2 %.[17] Patients with stage 4 disease or unknown CRM status were excluded from the study, and it is not clear whether a positive CRM required a pre-specified tumor cells-CRM distance.

If the rate of positive CRM is to be used as an indicator of surgical quality at a surgeon, hospital, or region level, we suggest that stakeholders should agree on methods to define and assess rates of positive CRM. Such methods should present data that also allow an evaluation of the adequacy of pathology assessment. Without such data, presented rates of positive CRM may mean little. With regard to rates of positive CRM, the approach used in the current study, although detailed, likely is necessary to allow appropriate comparisons over time within or between jurisdictions.

The causes for the observed improvements in pathology reporting and positive CRM rates in LHIN4 are likely multifactorial. First, we have reported on efforts by our group to improve colorectal cancer surgical performance in LHIN4.[18] Second, Cancer Care Ontario and national pathology groups have expended considerable energy to encourage pathologists to properly assess the CRM in rectal cancer .[1] Finally, as observed in most clinical areas, care does improve over time, although stakeholders are unable to ensure at a population level that new care standards are adopted rapidly and accurately.

Our study had weaknesses. For the LHIN4 region, we were unable to evaluate the adequacy of pathology grossing and microscopic techniques and final reporting. But this is similar to most other studies that present pathology measures for large regions. There is an assumption of a homogeneous and acceptable standard of care, although this may not be the case. A consensus process to determine which pathology measures should be entered into a pathology report likely is only the first step in optimizing pathology practice, and optimal pathology practice greatly informs optimal surgical oncology practice.

Another weakness of our study was the varying length of periods for data collection. However, within each 6- or

12-month period, data were collected for consecutive patients undergoing rectal cancer resection in every LHIN4 hospital. Re-abstraction studies also demonstrated 95 % or higher rates of agreement among abstractors. Also, no patients were excluded due to neoadjuvant therapies or advanced disease. We did not attempt to differentiate between curative and noncurative cases. Thus, our results are an accurate reflection of CRM positivity over time among patients surgically treated in LHIN4 for rectal cancer.

This study was unique in that it performed a detailed temporal population-based assessment of CRM positivity. We observed marked increases in CRM distance reporting, whereas rates of positive CRM dropped dramatically, suggesting both improved pathology and surgeon performance over time. Changing definitions greatly influenced rates of positive CRM, indicating the need for consensus, or at least methodologic transparency, when such rates are reported in the literature.

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CONFLICT OF INTEREST The authors declared that they have no conflict of interest.

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