Sampling error in the diagnosis of colorectal cancer is associated with delay to surgery: a retrospective cohort study

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Abstract

Background Accurate histopathologic diagnosis of colorectal cancer is important for treatment decision-making and timely care. The aim of this study was to measure rates and predictors of sampling errors for biopsy specimens attained at flexible lower gastrointestinal endoscopy, and to determine whether these events lead to a delay in surgical care.

Methods This is a retrospective observational study of patients who underwent elective resection for colorectal adenocarcinoma between January 2007 and June 2020. Primary outcomes were proportion of incorrectly diagnosed colorectal adenocarcinomas at index endoscopy by histopathology, and time between endoscopy and surgery. Secondary outcomes were predictors of sampling error, and diagnostic yield of repeat endoscopy.

Results Sampling errors occurred in 217/962 (22.6%) flexible endoscopies for colorectal adenocarcinomas. Negative biopsies were associated with a longer median time to surgery (87.6 days, IQR 48.8–180.0) compared to true positive biopsies (64.0 days, IQR 38.0–119.0), p < 0.001. Controlling for lesion location, neoadjuvant therapy, endoscopist specialty, year, and repeat endoscopies, time to surgery remained 1.40-fold longer (p < 0.001) following sampling error. Repeat endoscopy occurred following 62/217 (28.6%) cases of sampling errors, yielding a correct diagnosis of cancer in 38/62 (61.3%) cases. On multivariable analysis, sampling errors were less likely to occur for lesions endoscopists described as suspicious for malignancy (OR 0.12, 95% CI 0.07–0.21) or simple polyps (OR 0.24, 95% CI 0.08–0.70) compared to endoscopically unresectable polyps.

Conclusions Colorectal cancers are frequently improperly sampled, which may lead to treatment delays for these patients. When cancer is suspected, surgeons should take care to ensure timely management.

Keywords Colonoscopy · Colorectal cancer · Endoscopy · Biopsy

Accurate diagnosis of colorectal neoplasms is of utmost importance. An accurate histopathologic diagnosis is crucial for timely and informed treatment decision-making between providers and patients. For benign disease, endoscopic or local excision alone may suffice. For malignant disease, oncologic resections are usually required, often combined with a variety of neoadjuvant or adjuvant therapy options [1, 2]. The provision of chemotherapy or radiation in the neoadjuvant setting requires histopathologic evidence of
malignancy, as diagnostic imaging, photographs, or clinical suspicion are not always sufficiently specific [3].

For both colon and rectal cancers, a tissue sample for diagnosis is usually achieved from biopsies obtained through flexible endoscopy. While the specificity of these biopsies in the diagnosis of colorectal malignancy approaches 100%, reported sensitivities vary widely between 50 and 100%, depending on technique, volume of tissue, and number of samples obtained [3–8]. Furthermore, repeat endoscopy is often necessary for the purposes of repeat tissue sampling, which is associated with procedural risks, uses valuable healthcare resources, and most importantly delays in definitive surgical resections [9, 10]. In most healthcare systems, triage of patients based on priority or disease severity is performed. This factor has increased in importance recently due to the COVID-19 pandemic [11]. Cancers are prioritized for treatment over seemingly benign disease. Thus, accurate tissue diagnosis is essential to timely and correct allocation of treatment resources.

Given the variable sensitivity of endoscopic biopsies reported in the literature, and the potential implications for treatment, the aim of this study was to measure the rates and predictors of sampling errors for biopsies of colorectal cancers at lower endoscopy, and to determine whether these events lead to a delay in surgical care for these patients.

Methods

Design and setting

This is a retrospective cohort study of all patients who underwent elective surgery for colorectal cancers at St. Boniface General Hospital (SBGH) in Winnipeg, Canada between January 1, 2007 and June 30, 2020. SBGH is the tertiary colorectal referral center for a region of over 1.4 million people.

Ethics

We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [12], and obtained approval from the University of Manitoba Health Research Ethics Board (REB) (HS21588, H2018:103) and the SBGH REB (RRC/2018/1770).

Participants

Patients were identified from hospital records from visit data pertaining to elective resection of colorectal tumors. These patients were identified through search terms of a combination of diagnosis, procedure, and admission to one of the two elective general surgery services. Operations considered were: ileocolic resection, right hemicolectomy, extended right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoid resection, anterior resection, low anterior resection, abdominopereineal resection, total abdominal colectomy, and total proctocolectomy. Diagnoses included: colon or rectal polyps, colon or rectal cancer, and colon or rectal tumours. Patients were identified from medical record search as above, and corresponding outpatient clinic charts were reviewed. Patients were included if they had a final pathological diagnosis of colorectal adenocarcinoma following surgical resection. Patients with benign disease on final pathology were excluded. Patients with missing pathology reports, or complete pathologic response to neoadjuvant therapy were excluded, as final pathology report following surgical resection was used as the gold standard for comparison. Patients with synchronous cancers were also excluded. Emergency or palliative surgery patients were excluded. Surgery for genetic colon cancer predisposition, or inflammatory bowel disease, without a distinct polyp or tumor identified preoperatively were also excluded. All other cancers such as neuroendocrine, appendiceal or small bowel tumors, were excluded.

Data sources/variables

Charts were reviewed for patient, endoscopist, and surgeon demographic information. Endoscopy reports were examined to determine rates and rationale for repeat preoperative endoscopy. Patients’ postal code was used to determine their home location. For procedure site, a tertiary care hospital indicated procedure was performed at SBGH or Health Sciences Centre in Winnipeg. Community sites were other hospitals or clinics inside Winnipeg. Rural sites included all endoscopy locations in the province of Manitoba outside of Winnipeg. Lesion location was determined based upon final operative and pathology report. Endoscopy reports and consultation letters were used to determine rationale for endoscopy, clinical impression, and lesion characteristics including appearance, size and bowel preparation quality. Sampling errors (1 – biopsy sensitivity) were determined to have occurred if the final pathology report from surgery confirmed adenocarcinoma differed from the initial biopsies obtained from endoscopy.

Outcomes

Primary outcomes were 1. Rates of sampling errors at index endoscopy, and 2. Time between endoscopy and surgery. Secondary outcomes include predictors of sampling error, and diagnostic yield of repeat endoscopy.
Statistical analysis

Predictors of sampling errors were analyzed via univariable and multivariable logistic regression. To avoid overfitting of the multivariable model due to the large number of variables and relatively low number of sampling errors, variables were selected using a regularized (elastic-net) logistic regression model, with elastic mixing and penalization terms estimated via repeated cross-validation performed using R software (R Core Team, 2020 version 4.0.3) with packages “caret” (Version 6.0–86, 2020) and “glmnet” (Version 4.1. 2020) [13, 14]. Model fit was determined via area under the receiver operator curve (AUC).

Time between endoscopy and surgery was not normally distributed. In order to determine whether sampling error was associated with delay in care, Mann Whitney U test was performed. To account for possible confounders for time to surgery, non-parametric data were log-transformed, and analyzed using multiple linear regression. Patients with missing data had those parts excluded from analysis and are indicated alongside results where appropriate. For multiple linear regression to determine surgical delays, covariates were selected a priori based on factors hypothesized to affect time to surgery (laparoscopic surgery, neoadjuvant therapy, year, whether the surgeon was the endoscopist, lesion location, and repeat endoscopy) [15].

Results

Study sample

1690 consecutive patients were identified who underwent elective surgical resection between January 2007 and June 2020. Patients were referred from 97 endoscopists across Manitoba. 728 patients were excluded, primarily for benign disease on final pathology (Fig. 1). 962 patients with colon or rectal adenocarcinomas were included.

Sampling errors at index endoscopy

Sampling errors occurred for 217/962 (22.6%) flexible endoscopies for colorectal adenocarcinomas. This corresponds to a sensitivity of 77.4%. On univariable analysis (Table 1), sampling errors were less likely to occur for lesions endoscopists described as suspicious for malignancy (OR 0.10, 95% CI 0.06–0.17) or removably polyps (OR 0.22, 95% CI 0.08–0.61) compared to endoscopically unresectable polyps. Sessile polyps were more likely to be improperly sampled compared to other morphologies (OR 3.23, 95% CI 1.97–5.28). Sampling errors decreased in frequency over the past 5 years (Fig. 2).

Variables for multivariable analysis were selected using an elastic-net logistic regression model, with elastic mixing and penalization terms estimated via repeated cross-validation, with an AUC = 0.66. On multivariable analysis, there were no significant predictors of sampling

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Fig. 1 Flow chart of included/excluded patients of charts reviewed for retrospective cohort study of patients who underwent elective surgical resection for colorectal cancer at St. Boniface Hospital from January 2007-June 2020
Table 1  Predictors of sampling error at index endoscopy (univariable)

| Variable                                | True positive | False negative | OR (95% CI) | p   |
|-----------------------------------------|---------------|----------------|-------------|-----|
| Median age (IQR)                        | 69.6 (60.4–78.0) | 70.6 (62.2–77.7) | –           | 0.331 |
| Year                                    |               |                |             |     |
| 2007–2010                               | 168 (75.7)    | 54 (24.3)      | Ref. –     |     |
| 2011–2015                               | 233 (72.1)    | 90 (27.9)      | 1.20 (0.81–1.78) | 0.357 |
| 2016–2020                               | 343 (82.5)    | 73 (17.6)      | 0.66 (0.45–0.99) | 0.042 |
| Males (Ref = Females)                   | 401 (76.8)    | 121 (23.2)     | 1.08 (0.80–1.47) | 0.615 |
| Home location                           |               |                |             |     |
| Rural                                   | 205 (78.8)    | 55 (21.2)      | Ref. –     |     |
| Urban                                   | 540 (76.9)    | 162 (23.1)     | 1.12 (0.79–1.58) | 0.526 |
| Medical historya                        |               |                |             |     |
| Polyposis syndrome                      | 7 (70.0)      | 3 (30.0)       | 1.48 (0.38–5.76) | 0.574 |
| FAP                                     | 0 (0)         | 2 (100)        | 0           | 0.051 |
| HNPCC                                   | 18 (85.7)     | 3 (14.3)       | 0.57 (0.17–1.94) | 0.364 |
| HPS                                     | 0 (0)         | 2 (100)        | 0           | 0.051 |
| IBDb                                    | 27 (79.4)     | 7 (20.6)       | 0.88 (0.38–2.06) | 0.776 |
| Past abdominal surgeryc                 | 346 (77.8)    | 99 (22.2)      | 1.01 (0.74–1.37) | 0.953 |
| Indication for endoscopyd               |               |                |             |     |
| Screening                               | 15 (78.9)     | 4 (21.1)       | Ref. –     |     |
| Diagnostic                              | 667 (79.0)    | 117 (21.0)     | 0.99 (0.33–3.04) | 0.993 |
| Surveillance                            | 53 (62.4)     | 32 (37.6)      | 2.26 (0.69–7.42) | 0.177 |
| Endoscopy sitee                         |               |                |             |     |
| Rural                                   | 94 (81.7)     | 21 (18.3)      | Ref. –     |     |
| Community                               | 404 (78.6)    | 110 (21.4)     | 1.22 (0.73–2.05) | 0.545 |
| Tertiary                                | 217 (75.1)    | 72 (24.9)      | 1.49 (0.86–2.56) | 0.153 |
| Endoscopist specialtyf                  |               |                |             |     |
| Non-surgeon                             | 332 (77.9)    | 94 (22.1)      | Ref. –     |     |
| Surgeon                                 | 397 (76.9)    | 119 (23.1)     | 1.06 (0.78–1.44) | 0.716 |
| Operating surgeon is the endoscopistg   | 215 (73.9)    | 76 (26.1)      | 1.29 (0.94–1.78) | 0.119 |
| Index procedure typeh                   |               |                |             |     |
| Colonoscopy                             | 701           | 208            | Ref. –     |     |
| Flexible sigmoidoscopy                  | 39            | 8              | 0.69 (0.32–1.50) | 0.351 |
| Bowel prep qualityi                     |               |                |             |     |
| Excellent                               | 83 (80.6)     | 20 (19.4)      | Ref. –     |     |
| Good                                    | 86 (81.1)     | 20 (18.9)      | 0.97 (0.48–1.92) | 0.920 |
| Fair                                    | 25 (77.8)     | 5 (16.7)       | 0.83 (0.28–2.44) | 0.735 |
| Poor                                    | 28 (77.8)     | 8 (22.2)       | 1.19 (0.47–2.99) | 0.718 |
| Inadequate                              | 9 (90.0)      | 1 (10.0)       | 0.46 (0.05–3.85) | 0.475 |
| Lesion locationl                        |               |                |             |     |
| Left colon                              | 144 (76.6)    | 44 (23.4)      | Ref. –     |     |
| Rectosigmoid                            | 8 (80.0)      | 2 (20.0)       | 0.82 (0.17–4.00) | 0.804 |
| Rectum                                  | 215 (82.1)    | 47 (17.9)      | 0.72 (0.45–1.14) | 0.156 |
| Right colon                             | 325 (75.2)    | 107 (24.8)     | 1.08 (0.72–1.61) | 0.716 |
| Transverse colon                        | 51 (76.1)     | 16 (23.9)      | 1.03 (0.53–1.98) | 0.937 |
| Lesion morphologyk                      |               |                |             |     |
| Completely flat                         | 3 (60.0)      | 2 (40.0)       | Ref. –     |     |
| Flat depressed                          | 2 (50.0)      | 2 (50.0)       | Ref. –     |     |
| Flat slightly elevated                  | 5 (100)       | 0 (0)          | Ref. –     |     |
| Ulcerated                               | 92 (85.2)     | 16 (14.8)      | Ref. –     |     |
| Pedunculated                            | 2 (40.0)      | 3 (60.0)       | Ref. –     |     |
| Mass NOS                                 | 579 (78.8)    | 156 (21.2)     | Ref. –     |     |
errors (Table 2). Protective factors against sampling error were lesions endoscopists described in their reports as suspicious for malignancy (OR 0.12, 95% CI 0.07–0.21) or simple polyps (OR 0.24, 95% CI 0.08–0.70) compared to unresectable polyps.

**Repeat endoscopy**

Repeat endoscopy occurred in 62/217 (28.6%) cases following sampling errors, still failing to achieve a correct diagnosis of cancer in 24/62 (38.7%) instances. On univariable analysis (Table 3), surgeons were less likely to make a sampling error compared to gastroenterologists on repeat endoscopy (OR 0.15, 95% CI 0.03–0.79). Rectal lesions (OR 0.18, 95% CI 0.06–0.58) and lesions biopsied via flexible sigmoidoscopy (OR 0.18, 95% CI 0.05–0.60) were also less likely to have sampling errors. Sensitivity of biopsy at rigid sigmoidoscopy was 100%, (3/3) but occurred too infrequently for statistical comparison.

**Delays to surgery**

On univariable analysis median time to surgery was 1.36-fold longer (95% CI 1.20–1.54, \( p < 0.001 \)) following sampling errors (87.6 days, IQR 48.8–180.0) compared to
positive biopsies (64.0 days, IQR 38.0–119.0) (Fig. 3). After log-transformation to account for non-parametric data, multiple regression controlling for lesion location, neoadjuvant therapy, endoscopist specialty, year, and repeat endoscopies, time to surgery remains 1.40-fold longer ($p$ < 0.001) following sampling error (Table 4).

### Discussion

Endoscopic tissue biopsy remains the standard of care in the preoperative diagnosis of colorectal neoplasms. Multiple methods of obtaining tissue have been described, and there is no current accepted standard for the number of tissue samples to obtain, nor the ideal biopsy technique. Therefore, there are expected to be a variety of practices employed in usual care, and similar variation in diagnostic accuracy. While many studies have examined the sensitivity of one particular biopsy technique or number of specimens, the actual sensitivity of samples obtained from typical practice is infrequently described [3–8]. This study measures the proportion of colorectal adenocarcinomas that eventually went on to surgical resection that had been improperly sampled at index endoscopy. The sensitivity of a single flexible endoscopy in this current study for the correct preoperative histopathologic diagnosis of colorectal adenocarcinoma is 77.4%. This sensitivity is similar to those reported previously [3–8].

On multivariable analysis sampling errors were independently associated with substantial delays to surgical treatment for these patients. While it has been previously

### Table 3  Predictors of sampling error at repeat endoscopy (univariable)

| Variable                        | True positive N=38. N (%) | False negative N=24. N (%) | OR (95% CI)      | $p$  |
|---------------------------------|---------------------------|----------------------------|------------------|------|
| Pathology at index endoscopy    |                           |                            |                  |      |
| Tubulovillous                   | 9 (56.3)                  | 7 (43.8)                   | Ref.             | –    |
| Non-diagnostic                  | 10 (71.4)                 | 4 (28.6)                   | 0.51 (0.11–2.36) | 0.392|
| Non-differentiated              | 11 (64.7)                 | 6 (35.3)                   | 0.70 (0.17–2.85) | 0.620|
| Other                           | 8 (53.3)                  | 7 (46.7)                   | 1.13 (0.27–4.63) | 0.870|
| Median age (IQR)                | 65.5 (60.3–82.6)          | 70.9 (64.5–75.0)           | –                | 0.149|
| Males                           | 23 (63.9)                 | 13 (36.1)                  | 0.77 (0.27–2.17) | 0.621|
| History of abdominal surgery    | 15 (55.6)                 | 12 (44.4)                  | 1.27 (0.44–3.61) | 0.658|
| Year                            |                           |                            |                  |      |
| 2007–2010                       | 5 (55.6)                  | 4 (44.4)                   | Ref.             | –    |
| 2011–2015                       | 15 (51.7)                 | 14 (48.3)                  | 1.17 (0.26–5.25) | 0.851|
| 2016–2020                       | 18 (75.0)                 | 6 (25.0)                   | 0.42 (0.08–2.08) | 0.286|
| Repeat endoscopy site$^a$       |                           |                            |                  |      |
| Rural*                          | 3 (100)                   | 0 (0)                      | *                | –    |
| Community                       | 13 (61.9)                 | 8 (38.1)                   | Ref.             | –    |
| Tertiary                        | 18 (56.3)                 | 14 (43.8)                  | 1.26 (0.41–3.89) | 0.683|
| Endoscopist specialty$^b$       |                           |                            |                  |      |
| Non-surgeon                     | 2 (22.2)                  | 7 (77.8)                   | Ref.             | –    |
| Surgeon                         | 31 (66.0)                 | 16 (34.0)                  | 0.147 (0.027–0.794) | 0.027|
| Repeat endoscopy type$^c$       |                           |                            |                  |      |
| Colonoscopy                     | 12 (40.0)                 | 18 (60.0)                  | Ref.             | –    |
| Flexible sigmoidoscopy          | 19 (79.2)                 | 5 (20.8)                   | 0.18 (0.05–0.60) | 0.005|
| Rigid sigmoidoscopy*            | 3 (100)                   | 0 (0)                      | *                | –    |
| Lesion location$^d$             |                           |                            |                  |      |
| Colon                           | 13 (43.3)                 | 17 (56.7)                  | Ref.             | –    |
| Rectum                          | 25 (80.7)                 | 6 (19.4)                   | 0.18 (0.06–0.56) | 0.004|
| Lesion morphology$^e$           |                           |                            |                  |      |
| Other                           | 33 (67.3)                 | 16 (32.7)                  | Ref.             | –    |
| Sessile                         | 3 (33.3)                  | 6 (66.7)                   | 4.12 (0.91–18.7) | 0.066|

Missing patient information: $^a$0 from true positive group (TP), 2 from false negative group (FN). $^b$1 TP, 2FN. $^c$0TP, 1FN. $^d$OTP, 1FN. $^e$2TP, 2FN

Bold indicates $p$ < 0.05

$^a$Sample size too small for meaningful comparison. Excluded from univariate analysis
observed that repeat endoscopy and post-referral colonoscopy delays care, the delays associated with errors in endoscopic tissue sampling have not been described [16]. In our center, many repeat endoscopies were performed for the purposes of re-biopsy. However, 71.4% of patients with false negative histopathology went on to surgical care without a preoperative tissue diagnosis of adenocarcinoma. These patients still had significant delays to care, signifying that the absence of a preoperative tissue cancer diagnosis independently delays surgical treatment. This is likely because patients with known cancers are prioritized for more urgent surgical intervention by their providers over those with benign disease. However, many of these patients with seemingly benign lesions went on to eventually have cancer diagnoses. Therefore, triage based on index endoscopy pathology reports may not be adequate. This study was not designed to detect whether delays in treatment related to sampling error led to worse healthcare outcomes. However, prior research has suggested an ideal time to treatment initiation for both colon and rectal cancers at less than 30 days to improve outcomes [17]. The median increased wait time imparted by a sampling error was 23.6 days, making this 30-day benchmark unattainable following sampling error. Fortunately, longer wait times for colorectal cancer have previously not been demonstrated to translate to increased morbidity and mortality [18]. However, increased healthcare utilization by those patients awaiting surgery does show a substantial increase in healthcare expenditures [19].

In the current study, sessile appearance was the only lesion characteristic found to significantly predict sampling error, on univariable but not multivariable analysis. Synoptic endoscopy reports currently utilized at the study institution do not contain sections dedicated to the documentation of lesion appearance or size, therefore lesion characteristics...
were frequently missing on retrospective chart review. Given the frequency of missing data for these variables, the lack of association between sampling errors and lesion morphology or size in the current study should be interpreted with caution. Evidence extrapolated from gastric malignancies suggest that more advanced lesions such as those with ulceration, central necrosis, or a large adenomatous component may be more difficult to sample adequately [20–22]. Advanced lesions may benefit from expedited care rather than surgical delays, therefore malignant appearing lesions should be treated with a high degree of suspicion regardless of histopathology following endoscopy. In the present study, endoscopists frequently documented their impression whether they suspected a lesion was a malignancy or simply an unresectable polyp. This impression highly correlated with successful biopsy, implying that endoscopists may have taken more care to biopsy highly suspicious lesions compared to less suspicious ones. Removable polyps were also more accurately sampled, likely as these polyps were removed entirely during the procedure.

For the 62 patients who underwent repeat endoscopy, repeat biopsy had a diagnostic yield of only 61.3%. The majority of these repeat procedures were performed by surgeons, and correct sampling was predicted by lesion location in the rectum and by flexible sigmoidoscopy. This finding reflects the increased importance of a correct preoperative diagnosis for the rectal lesions, which are likely to undergo neoadjuvant therapy and therefore require a tissue diagnosis. Providers may take histopathologic diagnosis of these lesions more seriously compared to colon cancers where upfront surgical resection may take place regardless of histopathology. An alternate explanation is that rectal lesions are more accessible for adequate tissue sampling. Repeat flexible endoscopy is not the only option for tissue diagnosis in these patients. 3/34 repeat endoscopies used rigid sigmoidoscopy to attain tissue. 3/3 rigid sigmoidoscopies returned positive histopathology. Previously, an escalating protocol for preoperative diagnosis of seemingly benign rectal lesions incorporating rigid sigmoidoscopy with larger biopsies demonstrated a reduction in false negative diagnoses from 32 to 9% [3]. While biopsy by rigid sigmoidoscopy was rarely employed at our institution, and therefore our study was underpowered to determine its effects, the data supports previous findings of the utility of “macro-biopsy” in suspicious rectal lesions with benign histopathology. With the expanding role of neoadjuvant regimens for rectal cancer, including total neoadjuvant treatments, the accuracy of preoperative biopsy for these lesions will likely increase in importance, and perhaps biopsy via rigid proctosigmoidoscopy should be more frequently considered.

At repeat endoscopy, surgeons in our study were also less likely to make sampling errors compared to their gastroenterologist colleagues. This phenomenon was not observed following the initial endoscopy. Unfortunately, from the available data we are unable to identify a reason for this discrepancy. However, this observation highlights the importance for surgeons who operate on the colon and rectum to have dedicated and protected endoscopy time.

Notably, repeat endoscopy to re-biopsy a colon or rectal lesion was performed after the majority of false negative biopsies (28.6%). Although repeat endoscopy was not independently associated with delayed surgery in this current cohort in multivariable analysis, it may plausibly represent an effect modifier that could have magnified the effect of sampling errors on the delay to surgery observed here. Repeat preoperative endoscopy has previously been associated with a delay to surgical resection for colorectal cancers [15]. Therefore, we contend that repeat endoscopy to re-biopsy should only be performed when absolutely required to alter patient management. For example, approximately half of the repeat endoscopy cases in the present study were for rectal cancers, where accurate histopathology is mandatory in our institution before neoadjuvant chemoradiation can be provided to these patients. For the re-biopsied colon cancers, only 30 cases were included during the study period of the past 14 years. This is therefore a rare occurrence at our institution. Endoscopist rationale for repeat endoscopy has been examined previously by ourselves and others [23, 24]. One possible reason to repeat the endoscopy would be to try and avoid surgery altogether if a diagnosis of cancer was uncertain. There are multiple options for management of large adenomatous polyps, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) [25].

Despite the importance of our findings there are some notable limitations. First, this is a non-randomized retrospective study, which is subject to potential unknown confounders. For example, patients who never underwent surgery after a false negative biopsy would not have been included in this study and therefore lead to an over-estimate of biopsy sensitivity. Similarly, patients for which a repeat endoscopy to re-biopsy had led to avoidance of surgery altogether would not have been captured in our database. Therefore, we cannot evaluate how effective repeat endoscopy for the purposes of re-biopsy is for avoiding surgery. Some variable data were also missing. Lesion size, appearance and bowel preparation score were rarely reported, and therefore their effect on lesion sampling errors must be interpreted cautiously. Furthermore, some variables were not available for collection. The local synoptic endoscopy reporting system does not have a section to document the number of biopsies performed, nor the method of biopsy employed, so this data were not recorded at all for this chart review. Structured categorization of lesion phenotype, such as the NICE criteria and Kudo pit patterns are also important predictors of underlying malignancy [26, 27], but are not captured in...
our institution’s synoptic report and are therefore not available for analysis. The impact of lesion physical characteristics, number and method of biopsy samples obtained would be better evaluated through prospective study, or through retrospective review of reports where this information was systematically documented. Second, the population sample was obtained from a single institutions’ hospital records and derives from a relatively homogenous population with a public single-payer universal healthcare system. Therefore, the results may not necessarily be generalizable to other centers or healthcare models.

Despite these limitations, this study highlights some of the issues in current practice for biopsies attained at flexible endoscopy for suspected colorectal cancers. Past literature clearly demonstrates that more biopsies increase diagnostic accuracy, with samples ≥ 10 approaching 100% sensitivity [3]. Complete endoscopic excision of the lesion when possible should provide adequate tissue in most cases. However other studies show less tissue, fewer biopsies or alternate techniques are sufficient, which causes confusion [3–8]. Endoscopists may harbor legitimate concerns towards excessive biopsies due to bleeding or perforation risks [28]. Furthermore, endoscopist experience may play a role. An attempt at endoscopic excision for more advanced adenomas for an inexperienced endoscopist is a risky venture, and the resultant piecemeal or incomplete excision may condemn a patient to surgery who might otherwise have avoided it [29]. Conversely, inadequate tissue sampling and subsequent repeat endoscopy for re-biopsy is also less than ideal. Benign lesions may be distinguished from malignancies based on endoscopic appearance using Kudo pit pattern or NICE classification [26, 27]. Some argue benign appearing lesions shouldn’t be biopsied excessively, if at all, if advanced endoscopic resection is to be considered due to the possibility of fibrosis [30]. Therefore, the optimal technique of endoscopic biopsy for colorectal lesions remains unclear. Guidelines incorporating thorough literature review and consensus between advanced endoscopists and surgeons are needed in order to standardize preoperative management pathways including biopsy techniques and referral for endoscopic excision. Quality improvement programs at individual institutions are another potential solution [6].

Conclusions

This study demonstrates that sampling errors continue to commonly occur in usual endoscopy practice for patients with colorectal adenocarcinoma. Many of these patients proceed to surgery without a preoperative cancer diagnosis on histopathology. Sampling errors were associated with substantial delays in care, even when accounting for lesion location, neoadjuvant therapy, endoscopist specialty, year, and repeat endoscopies. While lesions endoscopists report as clinically suspicious for cancer were often biopsied correctly, lesions reported as unresectable polyps were frequently subject to sampling errors. Care should be taken by endoscopists to ensure adequate tissue sampling is done at the index procedure. Surgeons should guard against delays in management for patients based purely on benign histopathology obtained at endoscopy.

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Declarations

Disclosures Garrett Johnson, Olivia Hershorn, Harminder Singh, Jason Park and Ramzi Helewa all indicate that they have no conflicts of interest or financial ties to disclose.

Ethical approval Obtained approval from the University of Manitoba Health Research Ethics Board (REB) (HS21588, H2018:103) and the SBGH REB (RRC/2018/1770). This work is original and is not under consideration elsewhere.

Patient consent No patient consent was sought for this retrospective chart review.

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