Surgical Endoscopy (2022) 36:4893–4902
https://doi.org/10.1007/s00464-021-08841-z

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

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Received: 5 April 2021 / Accepted: 21 October 2021 / Published online: 1 November 2021

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

This work has not been presented at any scientific meetings.

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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, abdominoperineal 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 removable 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

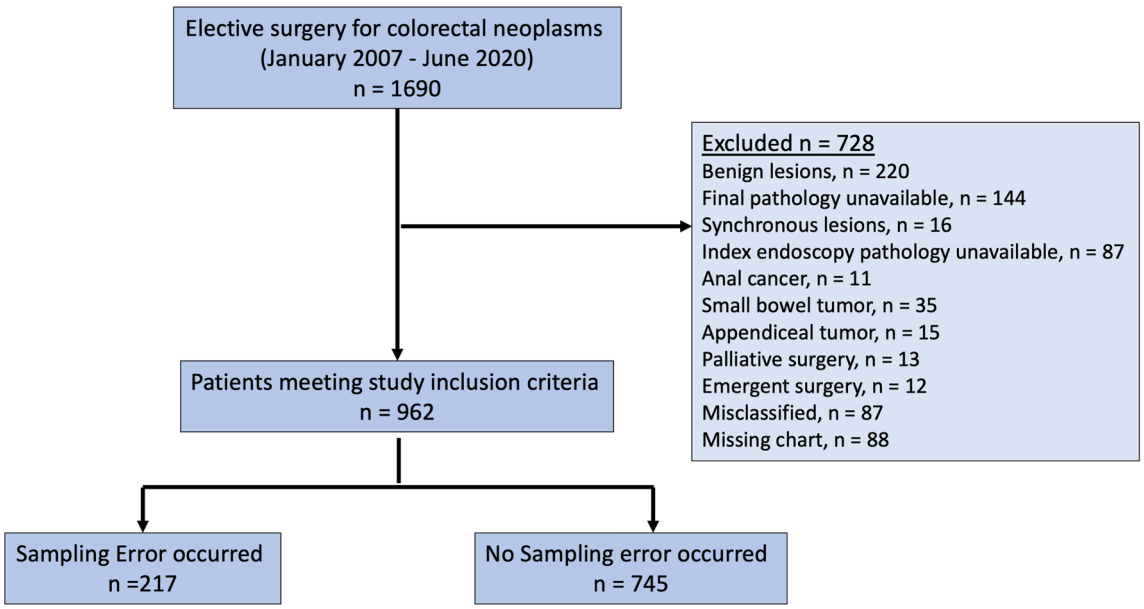


Fig. 1 Flow chart of included/excluded patients of charts reviewed for retrospective cohort study of patients who underwent elective surgical resection for colorectal cancer at St. Boniface Hospital from January 2007-June 2020

Table 1 Predictors of sampling error at index endoscopy (univariable)

Variable	True positive $N=745$. N (%)	False negative $N=217$. N (%)	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 history[a]				
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
IBD[b]	27 (79.4)	7 (20.6)	0.88 (0.38–2.06)	0.776
Past abdominal surgery[c]	346 (77.8)	99 (22.2)	1.01 (0.74–1.37)	0.953
Indication for endoscopy[d]				
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 site[e]				
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 specialty[f]				
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 endoscopist[g]	215 (73.9)	76 (26.1)	1.29 (0.94–1.78)	0.119
Index procedure type[h]				
Colonoscopy	701	208	Ref.	–
Flexible sigmoidoscopy	39	8	0.69 (0.32–1.50)	0.351
Bowel prep quality[i]*				
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 location[j]				
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 morphology[k]				
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.	–

Table 1 (continued)

Variable	True positive $N=745$. N (%)	False negative $N=217$. N (%)	OR (95% CI)	p
Sessile	39 (54.2)	33 (45.8)	3.23 (1.97–5.28)	**< 0.001**
Endoscopist impression[l]				
Unremovable polyp	21 (31.8)	45 (68.2)	Ref.	–
Simple polyp	15 (68.2)	7 (31.8)	0.22 (0.08–0.61)	**0.004**
Cancer suspicion	641 (82.5)	136 (17.5)	0.10 (0.06–0.17)	**< 0.001**
Median polyp Size in mm (IQR)[m]*	30 (6–50)	30 (10–40)	–	0.388

Bold indicates $p < 0.05$

* > 50% missing data, interpret with caution

Missing patient data: [a]4 in true positive group (TP), 1 in false negative group (FN). [b]5 TP, 1 FN. [c]11 TP, 8 FN. [d]10 TP, 4 FN. [e]30 TP, 14 FN. [f]16 TP, 4 FN. [g]15 TP, 0 FN. [h]5 TP, 1 FN. [i]514 TP, 163 FN. [j]2 TP, 1 FN. [k]23 TP, 5 FN. [l]64 TP, 127 FN. [m]635 TP, 196 FN

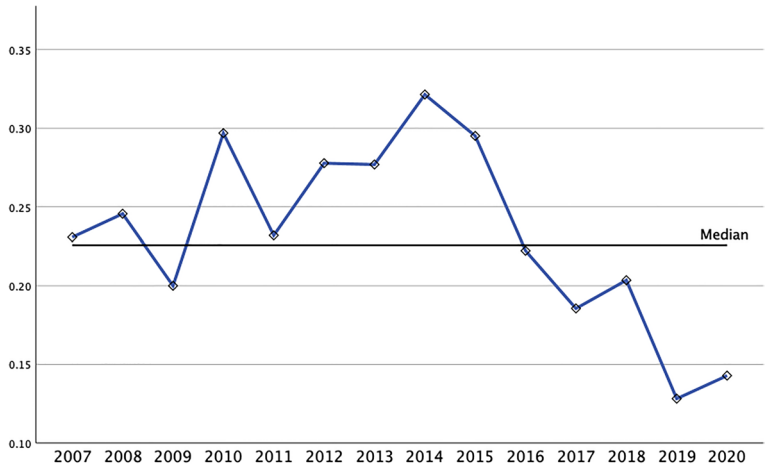


Fig. 2 Proportion of cancers improperly sampled at index endoscopy per year

Table 2 Predictors of sampling error at index endoscopy (multivariable)

Variable	OR (95% CI)	p
Year		
2007–2010	Ref.	–
2011–2015	1.24 (0.78–1.96)	0.365
2016–2020	0.64 (0.40–1.02)	0.059
Endoscopist impression		
Unremovable polyp	Ref.	–
Simple polyp	0.24 (0.08–0.70)	**0.009**
Cancer	0.12 (0.07–0.21)	**< 0.001**
Sessile polyp type	1.80 (0.97–3.34)	0.062

Variables selected via elastic-net logistic regression model, with elastic mixing and penalization terms estimated via repeated cross-validation, with an AUC = 0.66

Bold indicates p < 0.05

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

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 (28.57)	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]0TP, 1FN. [e]2TP, 2FN

Bold indicates $p<0.05$

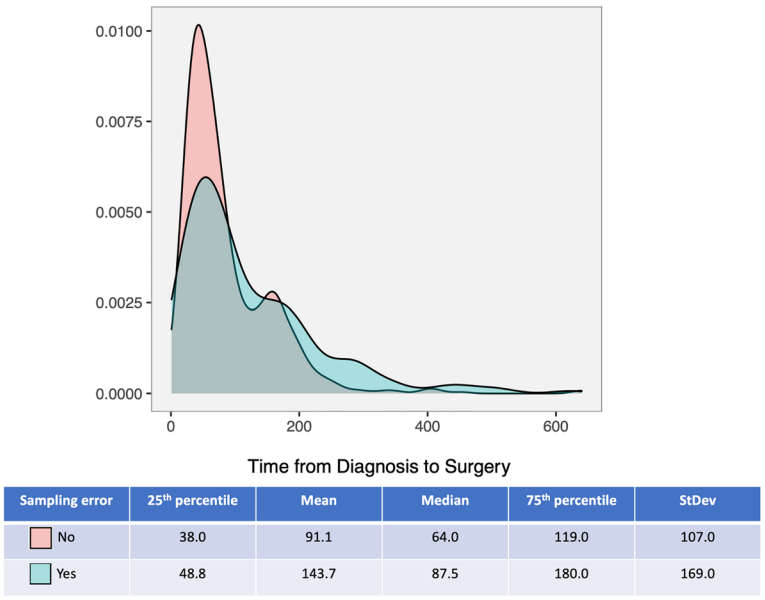
*Sample size too small for meaningful comparison. Excluded from univariate analysis

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



Sampling error	25th percentile	Mean	Median	75th percentile	StDev
No	38.0	91.1	64.0	119.0	107.0
Yes	48.8	143.7	87.5	180.0	169.0

Fig. 3 Time (days) from index endoscopy to surgery stratified by sampling error

Table 4 Multiple linear regression model for time between index endoscopy and surgery

Variable	Time estimate	95% CI lower	95% CI upper	*p*
Sampling error	1.40	1.26	1.56	**< 0.001**
Laparoscopic surgery	0.88	0.79	0.97	**0.013**
Neoadjuvant therapy	1.80	1.54	2.11	**< 0.001**
Years 2011–2015	1.04	0.92	1.17	0.542
Years 2016–2020	1.04	0.923	1.163	0.552
Index endoscopist was the surgeon	0.74	0.67	0.81	**< 0.001**
Rectal lesion	1.35	1.14	1.59	**< 0.001**
Rectosigmoid lesion	1.20	0.77	1.87	0.432
Right sided lesion	0.92	0.82	1.04	0.179
Transverse	0.92	0.76	1.11	0.382
Repeat preoperative endoscopy	1.33	1.19	1.50	< 0.001

Bold indicates $p < 0.05$

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-biopsies" 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 minority 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.

Acknowledgements The authors would like to thank Mr. Brenden Dufault for his contribution to the statistical analysis portion of the study.

Author contributions Data were collected by OH and GJ. Manuscript was drafted and data were analyzed by GJ. All authors contributed to study design, critical revision, and final approval of manuscript and agree to be held accountable for all aspects of the work.

Funding This research has been funded in part by a GFT Research Grant from the Department of Surgery, University of Manitoba.

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.

References

1. NCCN (2020) National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines): Rectal Cancer (Version 1.2021). https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. accessed 24 Jan 2021
2. NCCN (2021) National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines): Colon Cancer (Version 2.2021). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. accessed 24 Jan 2021
3. Bökkerink GMJ, van der Wilt G-J, de Jong D, van Krieken HHJM, Bleichrodt RP, de Wilt JHW, Bremers AJA (2017) Value of macrobiopsies and transanal endoscopic microsurgery in the histological work-up of rectal neoplasms: a retrospective study. World J Gastrointest Oncol 9:251–256. https://doi.org/10.4251/wjgo.v9.i6.251
4. Brouwer R, MacDonald A, Matthews R, Gunn J, Monson JR, Hartley JE (2009) Brush cytology for the diagnosis of colorectal cancer. Dis Colon Rectum 52:598–601. https://doi.org/10.1007/DCR.0b013e3181a0ad44
5. Colleypriest BJ, Marden PF, Linehan JD (2009) What is the optimal number of biopsies to diagnose a tumor found during colonoscopy? J Clin Gastroenterol 43:1012–1013. https://doi.org/10.1097/MCG.0b013e31819fcd0a

6. Gado A, Ebeid B, Abdelmohsen A, Axon A (2011) Improving the yield of histological sampling in patients with suspected colorectal cancer during colonoscopy by introducing a colonoscopy quality assurance program. Gastroenterol Res 4:157–161. https://doi.org/10.4021/gr334w
7. Marshall JB, Diaz-Arias AA, Barthel JS, King PD, Butt JH (1993) Prospective evaluation of optimal number of biopsy specimens and brush cytology in the diagnosis of cancer of the colorectum. Off J Am Coll Gastroenterol ACG 88:1352–1354
8. Winawer SJ, Leidner SD, Hajdu SI, Sherlock P (1978) Colonoscopic biopsy and cytology in the diagnosis of colon cancer. Cancer 42:2849–2853. https://doi.org/10.1002/1097-0142(197812)42:6%3c2849::aid-cncr2820420646%3e3.0.co;2-u
9. Azin A, Jimenez MC, Cleghorn MC, Jackson TD, Okrainec A, Rossos PG, Quereshy FA (2016) Discrepancy between gastroenterologists" and general surgeons" perspectives on repeat endoscopy in colorectal cancer. Can J Surg 59:29–34. https://doi.org/10.1503/cjs.005115
10. Abbasi Al T, Saleh F, Jackson TD, Okrainec A, Quereshy FA (2014) Preoperative re-endoscopy in colorectal cancer patients: an institutional experience and analysis of influencing factors. Surg Endosc 28:2808–2814
11. Fligor SC, Wang S, Allar BG, Tsikis ST, Ore AS, Whitlock AE, Calvillo-Ortiz R, Arndt KR, Gangadharan SP, Callery MP (2020) Gastrointestinal malignancies and the COVID-19 pandemic: evidence-based triage to surgery. J Gastrointest Surg 24:2357–2373
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, Initiative STROBE (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 370:1453–1457. https://doi.org/10.1016/S0140-6736(07)61602-X
13. Zou H, Hastie T (2005) Regularization and variable selection via the elastic net. J R Stat Soc Ser B (Stat Methodol) 67:301–320. https://doi.org/10.1111/j.1467-9868.2005.00503.x
14. Zhu X, Hou R, Li X, Jiang C, Xia W, Fu X (2020) Predictive model of the first failure pattern in patients receiving definitive chemoradiotherapy for inoperable locally advanced non-small cell lung cancer (LA-NSCLC). Radiat Oncol 15:2342. https://doi.org/10.1186/s13014-020-1467-x
15. Hershorn O, Park J, Singh H, Clouston K, Vergis A, Helewa RM (2020) Rates and predictors of repeat preoperative endoscopy for elective colorectal resetion: how can we avoid repeated procedures? American Society of Colon and Rectal Surgeons Annual Meeting
16. Singh H, Khan R, Giardina TD, Paul LW, Daci K, Gould M, El-Serag H (2012) Postreferral colonoscopy delays in diagnosis of colorectal cancer: a mixed-methods analysis. Qual Manag Health Care 21:252–261
17. Lee Y-H, Kung P-T, Wang Y-H, Kuo W-Y, Kao S-L, Tsai W-C (2019) Effect of length of time from diagnosis to treatment on colorectal cancer survival: a population-based study. PLoS ONE 14:e0210465. https://doi.org/10.1371/journal.pone.0210465
18. Helewa RM, Turner D, Park J, Wirtzfeld D, Czaykowski P, Hochman D, Singh H, Shu E, McKay A (2013) Longer waiting times for patients undergoing colorectal cancer surgery are not associated with decreased survival. J Surg Oncol 108:378–384. https://doi.org/10.1002/jso.23412
19. Delisle M, Helewa RM, Ward MAR, Hochman DJ, Park J, McKay A (2020) The association between wait times for colorectal cancer treatment and health care costs: a population-based analysis. Dis Colon Rectum 63:160–171. https://doi.org/10.1097/DCR.0000000000001517
20. Choi Y, Choi HS, Jeon WK, Kim BI, Park DI, Cho YK, Kim HJ, Park JH, Sohn CI (2012) Optimal number of endoscopic biopsies in diagnosis of advanced gastric and colorectal cancer. J Korean Med Sci 27:36–39. https://doi.org/10.3346/jkms.2012.27.1.36
21. Hatfield AR, Slavin G, Segal AW, Levi AJ (1975) Importance of the site of endoscopic gastric biopsy in ulcerating lesions of the stomach. Gut 16:884–886
22. Misumi A, Mori K, Ikeda T, Misumi K, Ookubo F, Shimamoto M, Nakashima K, Fujishima K, Yagi Y, Takano S, Shiraishi Y, Akagi M (1978) Evaluation of fibergastroscopic biopsy in the diagnosis of gastric cancer: a study of 339 cases. Gastroenterol Jpn 13:255–263. https://doi.org/10.1007/BF02774048
23. Hershorn O, Park J, Singh H, Restall G, Clouston K, Vergis A, Helewa RM (2020) Variability in communication and reporting practices between Gastroenterologists and Surgeons contributes to repeat preoperative endoscopy for colorectal neoplasms: a qualitative analysis. pp 387–e468
24. Azin A, Jimenez MC, Cleghorn MC, Jackson TD, Okrainec A, Rossos PG, Quereshy FA (2016) Discrepancy between gastroenterologists' and general surgeons' perspectives on repeat endoscopy in colorectal cancer. Can J Surg 59:29–34. https://doi.org/10.1503/cjs.005115
25. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, Amato A, Berr F, Bhandari P, Bialek A, Conio M, Haringsma J, Langner C, Meisner S, Messmann H, Morino M, Neuhaus H, Piessevaux H, Rugge M, Saunders B, Robaszkiewicz M, Seewald S, Kashin S, Dumonceau J-M, Hassan C, Deprez P (2015) Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 47:829–854. https://doi.org/10.1055/s-0034-1392882
26. Li M (2014) Kudo's pit pattern classification for colorectal neoplasms: a meta-analysis. World J Gastroenterol 20:12649. https://doi.org/10.3748/wjg.v20.i35.12649
27. Patrun J, Okreša L, Iveković H, Rustemović N (2018) Diagnostic accuracy of NICE classification system for optical recognition of predictive morphology of colorectal polyps. Gastroenterol Res Pract 2018:1–10. https://doi.org/10.1155/2018/7531368
28. Kothari ST, Huang RJ, Shaukat A, Agrawal D, Buxbaum JL, Abbas Fehmi SM, Fishman DS, Gurudu SR, Khashab MA, Jamil LH, Jue TL, Law JK, Lee JK, Naveed M, Qumseya BJ, Sawhney MS, Thosani N, Yang J, DeWitt JM, Wani S (2019) ASGE review of adverse events in colonoscopy. Gastrointest Endosc 90:863-876.e33. https://doi.org/10.1016/j.gie.2019.07.033
29. Rajendran A, Pannick S, Thomas-Gibson S, Oke S, Anele C, Sevdalis N, Haycock A (2020) Systematic literature review of learning curves for colorectal polyp resection techniques in lower gastrointestinal endoscopy. Colorectal Dis 22:1085–1100. https://doi.org/10.1111/codi.14960
30. Grimm IS, McGill SK (2019) Look, but don't touch: what not to do in managing large colorectal polyps. Gastrointest Endosc 89:479–481. https://doi.org/10.1016/j.gie.2018.10.008