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Original Research Article

Changes in surgical margins following formalin fixation and the incidence of local recurrence of colorectal cancer

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ABSTRACT

Background: The surgical margin is an important prognostic factor in predicting the local recurrence of colorectal cancer. The current guidelines recommend a 5cm margin both proximally and distally for colon cancers and a distal resection margin of 1-2cm for mid and low rectal cancers. Although surgical margins are an important predictor for local recurrence, it is not routinely recorded in a fresh specimen prior to formalin fixation.
Methods: Retrospective analysis of prospectively collected data of patients undergoing colorectal surgery at the Gold Coast University Hospital from January 2012 to December 2021. Specimens were measured fresh by one surgeon immediately following extraction. This measurement was compared with measurement performed by the pathologist after formalin fixation. The remaining data were collected retrospectively.
Results: A total of 177 patients with a median age of 64 years old (range 27–87) underwent colorectal surgery at Gold Coast University Hospital. Following formalin fixation, the median total specimen length (TSL) shrinkage was 34.98% and distal resection margin (DRM) shrinkage was 40%. Following formalin fixation, 69.6% of colon cancer specimens met the recommended resection margin of 5 cm. On the other hand, 95.6% of rectal cancer specimens met the DRM recommendation of 1 cm. There were no local recurrences during the median follow up period of 202 weeks (range 33-523 weeks).
Conclusions: Marked shrinkage of colorectal cancer specimens can occur following formalin fixation. Documentation of surgical margins immediately following extraction is important to ensure adherence to current guidelines. Local recurrences are rare with current margin recommendations.

Keywords: Colorectal surgery, Rectal cancer, Colon cancer, Surgical margins

INTRODUCTION

The surgical resection margin is an important prognostic factor in predicting the local recurrence of colorectal cancer. The ideal extent of bowel resection for colon cancer requires removal of the blood supply and lymphatics at the level of the primary feeding artery of the tumour together with 5-10 cm proximal and distal margins.[1,2] Despite some studies proposing distal and proximal margins of >8 cm to include additional epicolic and paracolic lymph nodes, this may result in needlessly extensive surgery. Hence a margin of at least 5cm is commonly accepted.[1,3-5] For rectal cancers, international guidelines recommend a distal resection margin (DRM) of 1-2 cm for mid and low rectal cancers and a clear circumferential resection margin (CRM).[6,7] Although a distal margin of <1cm in rectal cancer have been shown to be safe particularly in early stage rectal cancer, it often

is a balance between oncologically safe surgery versus sphincter preserving surgery and hence a margin of at least 1cm is preferred in low rectal cancer.[8,9] In addition, the circumferential resection margin (CRM) in rectal cancer is a powerful predictor of local and distant recurrence.[10]

Although surgical margins are important, it is not routinely recorded in a fresh specimen prior to formalin fixation. There is often specimen shrinkage following formalin fixation, resulting in a smaller than expected margin when measured by the pathologist.[11]

This study aims to assess the degree of specimen shrinkage following formalin fixation and determine the rate of local recurrence of colorectal cancer with current surgical margin recommendations.

METHODS

Study design

Retrospective analysis of prospectively collected data of patients undergoing colorectal surgery at the Gold Coast University Hospital from January 2012 to December 2021.

Inclusion criteria

The inclusion criteria in this study are all patients who underwent surgery for colon or rectal cancer at Gold Coast University Hospital with specimens measured prior to formalin fixation. Patients are also required to have ongoing follow-up for cancer surveillance at Gold Coast University Hospital.

Exclusion criteria

Exclusion criteria included patients who had colon and rectal surgery for benign indications. The specimen was opened longitudinally along the antimesenteric border and measurements of the tumour size, proximal and distal resection margins were recorded prior to formalin fixation by a consultant colorectal surgeon. These measurements were then compared to the measurements made by the pathologist in the histopathological report.

Surveillance after surgery include 3-6 monthly outpatient follow-up with carcinoembryonic antigen (CEA) level measurements for up to 5 years. A computed tomography (CT) of the chest, abdomen and pelvis was routinely performed annually after surgery for 5 years or earlier if there was a suspicion of metastatic disease based on clinical or biochemical parameters.

A colonoscopy was performed 1 year after surgery or within 6 months if a complete colonoscopy was not performed prior to surgery. Local recurrence of tumour is defined as recurrence of disease at the anastomosis seen on imaging or diagnosed by colonoscopy. Confirmation of local recurrence can be made by biopsy or salvage surgery. Based on a conservative estimate of 10% local recurrence rate of colorectal cancer in 2 years, with a margin of error of 0.05 and confidence interval of 95%, we calculated a sample size of at least 139 patients.

Descriptive analysis included presenting categorical data as proportions and continuous data as median (range) values. All statistical analysis was performed using Microsoft Excel® 2021 for Mac® (Microsoft, Washington, USA).

Ethical approval

This study received approval by the Human Research Ethics Committee (HREC) board from Gold Coast University Hospital.

RESULTS

One hundred and seventy-seven patients with a median age of 64 years old (range 27 to 87 years) who underwent colorectal surgery from January 2012 to December 2021 at the Gold Coast University Hospital were included in this study. Overall, there were 132 colon and 45 rectum specimens. Clinical characteristics of patient and tumour are shown in Table 1.

Table 1: Patient and tumour characteristics.

Variable	N	%
Patients	177	
Age	64 (Range 27-87)	
Gender (M:F)	94:83	
ASA		
1	6	3.4
2	85	48
3	70	39.5
4	6	3.4
Missing	10	5.7
Tumour location		
Right colon	56	31.1
Transverse	25	13.9
Left colon	54	30
Rectum	45	25
Upper	23	51.1
Middle	10	22.2
Low	12	26.7
T stage		
1	13	7.2
2	37	20.6
3	94	52.2
4	36	20
N stage		
0	108	60
1	45	25
2	27	15

Table 2: Changes in specimen after formalin fixation.

Changes following formalin fixation	Total specimen length (TSL) Median, (%)	Distal resection margin (DRM) Median, (%)
All specimens	215 mm, (-34.98)	53 mm, (-40)
Colon specimens	205 mm, (-35.47)	65 mm, (-38.5)
Rectal specimens	240 mm, (-30.6)	26 mm, (-38.3)

Total specimen length (TSL) and distal resection margin (DRM) was measured in all specimens. Following formalin fixation, there was a median TSL shrinkage of 215 mm (34.98%) and DRM shrinkage of 53 mm (40%). In colonic specimens, the median TSL shrinkage was 205 mm (35.47%) and median DRM shrinkage was 65mm (38.5%). In rectal specimens, median TSL and DRM shrinkage was 240 mm (30.6%) and 26 mm (38.3%) respectively. The median lymph node harvest was 15.5 (range 6-26). These findings are summarized in Table 2.

Using 5 cm as the recommended distal resection margin for colonic resections, 100% of specimens met the recommended margin prior to formalin fixation. Following formalin fixation, only 69.6% (92/132) met the recommended margin of 5 cm. Using 1 cm as the distal resection margin for rectal resections, 100% (45/45) of specimens met the recommended margins prior to formalin fixation, and 95.5% (43/45) met the recommended margins after formalin fixation. In the median follow up period of 202 weeks (range 33-523 weeks), there were no local recurrences on endoscopy or imaging. Thirty-four (19.2%) of patients developed metastatic disease during the study period.

DISCUSSION

Surgical margins are an important predictor of local recurrence and a measure of the quality of surgery in colorectal cancer. In the literature, multiple studies have shown surgical margins to be a predictor for local and distant recurrence and may influence disease free survival and overall survival.[9,10,12,13] Specimen shrinkage following formalin fixation is a well-known phenomenon in surgery.[14-17] Formalin results in alteration in specimen size and shape by rapid diffusion into tissues stabilizing tissue infrastructure and cell shrinkage from potential tissue damage.[18] The observed shrinkage can play a significant role in determining the need for further adjuvant treatment. Despite this, routine measurement of fresh specimen is not performed.

At present, most studies do not specify whether specimen measurement is performed in vivo or ex vivo. In the literature, the shrinkage a colorectal cancer specimen can range from 14% to 57%.[11,18,19] Moreover, formalin may also result in a 10-20% shrinkage of pelvic side wall lymph nodes following resection in colorectal cancer.[20] Interestingly, the majority of specimen shrinkage (70%) occurs in the first 10–20 minutes after removal alone.[11]

Most specimen shrinkage from formalin tends to occur in the first 24 hours.[21] The median TSL shrinkage of 35% and DRM shrinkage of 38% is in line with that of the literature. A similar study performed by Lam et al, showed a mean shrinkage in TSL of 14.99% and DRM of 14.7%.[19] The larger specimen shrinkage following specimen fixation in the current study can be attributed to the timing of specimen measurement where the specimen in this study is measured immediately after extraction. The use of a single colorectal surgeon to measure all specimens in this study also minimizes the variability from measurement techniques.

The current practice of a colon cancer resection margin of at least 5 cm in this study has shown that local recurrence at anastomotic site is rare. The significant reduction in (DRM >5 cm) in colon cancer specimens following fixation highlight the importance of measuring and documenting specimen following extraction to ensure compliance with current standards. This is particularly important in low rectal cancers where narrow margins after formalin fixation can be interpreted as an inadequate, resulting in overtreatment with adjuvant therapy or further surgery. Inaccurate documentation of distal resection margin may also have medicolegal implications.

There are several limitations in this study. We did not record the length of time the specimens were fixed with formalin before measurements were made by the pathologist, however given the majority of specimen change occurs in the first 24 hours, this may not have a significant effect on shrinkage.[21] There is also significant inter-observer variability when measuring specimens, the use of a single pathologist may potentially help yield more accurate results. The actual DRM for rectal cancer in this study may be larger than recorded as we did not consider the margin from donuts obtained from the use of a circular stapling device.

To date, this is the largest study showing differences in surgical margin following formalin fixation. Marked shrinkage is seen following formalin fixation in both colon and rectal cancer specimens.

CONCLUSION

Routine documentation of resection margins as soon as possible following specimen extraction is recommended particularly when margins of resection are small and may impact decision for adjuvant therapy or further surgery.

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