



Distal Margin Shrinkage Factor – A Consideration before Dividing the Specimen in Colorectal Cancer Surgery

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Abstract

Background: The risk of local recurrence in colorectal cancer has been associated with the length of clear distal margin in the specimen taken during original resection. It has been reported that there is significant specimen shrinkage. This study aimed to quantify the degree of shrinkage after fixation in formalin and to investigate the factors affecting specimen shrinkage.

Methods: This research was a single-center prospective study. All adult patients who underwent colorectal surgery for cancer had demographics, surgical details, and cancer staging and pathology recorded. Colonic specimens were measured immediately post resection including the total length, the mesenteric length and the distal length from the palpable tumor. Multiple logistic linear regression was applied to identify factors associated with distal margin shrinkage.

Results: Right-sided colectomy specimens had an inconsistent degree of shrinkage. Left-sided colectomy specimens showed an average shrinkage of 20% (CI 4% – 36%). The only other factor observed that had statistically significant association on the shrinkage of distal margins in specimens was increasing tumor size.

Conclusion: Specimens resected during anterior resection for colorectal cancer have a consistent level of shrinkage. Locally advanced tumors were observed to have an association with specimen distal margin shrinkage; however, the mechanism is unclear. This new evidence can assist intra-operative decision making to allow adequate distal margin resection.

Keywords: Colorectal neoplasm, Colorectal surgery, Formalin, Margins of excision

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Introduction

Achieving adequate distal margins in colorectal resections is a fundamental principle of colorectal surgery (1, 2). Inadequate margins often lead to local recurrence in the pelvis (3, 4). The National Cancer Institute currently states that

a distal margin of one centimeter is adequate in rectal cancers (5). There has however, been research suggesting that colorectal specimen may shrink by up to 57% in formalin (6). This substantial degree of tissue shrinkage does not seem to impact clinical practice. The purpose of this study was to verify the amount of shrinkage a specimen will undergo in

formalin and to determine whether tissue shrinkage has an impact in terms of the clinical setting.

There are three time points at which the specimen could be measured: *in vivo* prior to rectal division, *in vitro* fresh after rectal division, and *in vitro* after fixation. *In vivo* measurements have been described (7) but are not routine. It can also be difficult in rectal cases and the methodologies of measurement would be inconsistent between laparoscopic and endo-luminal approaches, as in a transanal total mesorectal excision. Furthermore, *in vivo* measurements may be unreliable as a result of the various intra operative tension on the tissues. We felt that the most reproducible measurement would be taken *in vitro* on the fresh specimen in the operating theatre with no tension applied. This measurement would be collected and compared to the macroscopic measurements in the histology report.

Methods

This prospective study was conducted in the Digestive Diseases Department at Royal Sussex County Hospital between July 2018 and March 2019. All patients aged 18 or over who underwent an abdominal surgery involving colectomy for colorectal cancer were included in the study. For each specimen, the following were recorded; patient basic demographics including age and sex, TNM staging, operative approach, neoadjuvant therapy, and operative site. Operative sites were classified as either right-sided or left-sided colectomies. Right-sided colectomies included right hemicolectomies and extended right hemicolectomies, with or without an anastomosis. Left-sided colectomies included left hemicolectomies, high and low anterior resections, sigmoid colectomies with or without an anastomosis, and subtotal colectomies. For fresh tissue measurements, the total specimen length, the length of the distal margin and the mesenteric length were measured. These measurements were performed after the specimen was divided and removed from the patient, prior to the application of formalin solution within thirty minutes after resection in operating theatres. The total specimen length was measured between one resection end to the other without further dissection or tensioning of the specimen. The length of the distal margin was measured between the distal palpable edge of the tumor and the distal resection edge. The mesenteric length was measured from the mesenteric intestinal edge to the ligated end of the colic artery. All the specimens were processed in the same pathology laboratory. The surgeon-recorded measurements were compared against the macroscopic measurements in the final histology report. The number of lymph nodes harvested, tumor differentiation, presence of mucin, presence of micro-satellite instability (MSI), and neurovascular invasions were recorded.

Multiple logistic linear regression was applied to

determine the factors that were associated with the percentage of distal margin shrinkage. Data with statistical significance was defined by $P < 0.05$.

Results

A total of 24 colectomies were recorded during the study period, including 11 right-sided colectomies and 13 left-sided colectomies. The average patients age was 68 years, and 46% were female. One rectal cancer case in the cohort received neoadjuvant chemoradiation therapy. All specimens showed adenocarcinoma on histopathology. The average reduction in specimen distal margins for right-sided colectomy after fixation was 4% (confidence interval (CI): 40–47%). The average reduction of distal margins for anterior resection specimens was 20% (CI: 4–36%). Given that the degree of shrinkage in right-sided colectomy was highly variable, only the distal margin shrinkage in the left-sided colectomy group was further analyzed in multiple logistic linear regression. Patient factors including age and sex, operative approach, and the use of neoadjuvant therapy were not found to be associated with distal margin shrinkage. Pathological characteristics of the specimens including lymph node status (number of lymph nodes harvested and the N stage of the tumor), and tumor characteristics (including tumor differentiation, presence of neurovascular invasion, and MSI) were also not found to be associated with the shrinkage. Total specimen length and the T stage were associated with increased distal margin shrinkage ($P < 0.025$ and $P < 0.009$, respectively).

Discussion

The importance of the length of clear distal margin in anterior resection is currently under debate (8). There was early evidence that an inadequate distal margin is associated with local recurrence (9). The National Cancer Institute currently states that a distal margin of one centimeter is adequate in rectal cancers, and that margins greater than one centimeter do not reduce local recurrence (10, 11). However, recent evidence suggests that the distal margin can be further reduced to sub-centimeter levels without compromising oncological outcomes in patients who undergo neoadjuvant radiation (12, 13), and this has triggered questions over the current one-centimeter guideline (14). Despite the lack of consensus on the distal margin, in an event of a less than adequate margin, it is not uncommon to hear the comment that formalin had shrunk the specimen. Formalin shrinkage of specimens has been demonstrated for a wide range of tissues (15, 16), including colorectal specimens (6, 17). According to Goldstein, the degree of shrinkage was believed to be as significant as to 57%; however, this seems to have no clinical impacts. We have two major concerns in obtaining extra margins

without first quantifying the shrinkage. Firstly, an extra margin in rectal cancer means a rectum would be further excised and sphincter function could be compromised. It has been clearly demonstrated that the lower the resection, the poorer the functional outcome would be (18). An extra margin might, though yet to be proven, potentially benefit the local control; however, it will certainly impact the function. Secondly, an extra margin may mean a lower anastomosis, which, in turn, can lead to a high anastomotic leak rate.

Our study demonstrated that the fresh in vitro distal margin of anterior resections shrunk consistently by approximately 20%. Clinically, this is not a significant amount of tissue shrinkage when considering the current one-centimeter guideline. We found that the degree of distal margin shrinkage in specimens was positively associated with the clinical tumor stage. Tumors with a higher T score also have a higher local recurrence rate (19) and, therefore, obtaining extra distal margin might be considered. None of the other recorded observations, including the presence of perineural invasion and lympho-vascular invasion, were associated with specimen shrinkage, despite being suggested to be associated with positive distal margins (20). Right-sided colonic specimens were much less consistent in length and we believe that this was likely due to measurement error as they were often folded at the time of surgery.

The inclusion of one neoadjuvant specimen was

only possible due to only moderate regression in response to therapy on imaging. If there had been good or total response, it would be challenging for the operating surgeon to distinguish the palpable tumor from residual fibrosis in the specimen.

This was a prospective observational study and we acknowledge the statistical limitations that come with a small sample size in a single center. The association between tumor T score and the distal margin shrinkage might be due to sampling, and this finding must be verified with further research. There was no logical pathophysiological explanation for the association.

Conclusion

The shrinkage factor of the distal margin in anterior resection specimens is approximately 20%, which is not as substantial as previously described. There are suggestions that the distal margin shrinkage might be related to tumor T-score, though this must be verified. Clinical practice is unlikely to be affected by the degree of tissue shrinkage.

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Conflicts of interests: None declared.

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