



## Pattern of Distribution of Residual Microscopic Disease Following Neoadjuvant Therapy for Rectal Cancer

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### Abstract

**Background:** Preoperative chemoradiotherapy is the standard of care for locally advanced rectal cancer. It results in significant macroscopic tumor response and pathological downstaging. Understanding the relationship between the Residual Gross Abnormality (RGA), the only visible mark of the disease that can be detected preoperatively or intraoperatively, and possible occult microscopic cancer is important for planning the ensuing surgical resections.

**Methods:** We retrospectively reviewed the medical records and pathology slides of patients undergoing rectal resection after neoadjuvant chemoradiotherapy in our center between 2011 and 2018. We observed the relationship between the RGA and residual microscopic cancer.

**Results:** Fifty-seven patients with locally advanced rectal cancer received neoadjuvant therapy followed by surgical excision. Two, 48 and 5 tumors were clinically staged as T2, T3, and T4, respectively. Two patients had missing clinical staging data. Sixteen patients (28%) had a complete pathological response and were excluded from further analysis. Of the remaining 41 tumors, ypT1 stage was noticed in 5, while ypT2, ypT3, and ypT4 were noticed in 14, 21, and 1 case, respectively. No microscopic disease was detected solely outside the Gross Mucosal Abnormality (GMA) or in the perirectal fat without involving the rectal wall directly underneath GMA. Occult microscopic disease extending outside GMA was seen only in 2/41 cases (5%) and extended by 1 cm.

**Conclusion:** When local excision is contemplated to confirm the residual tumor pathological response status without therapeutic intent, the surgical excisions need not extend beyond the borders of GMA and adjacent perirectal fat. The incidence of occult microscopic disease outside GMA is very low; when present, it extends by only 1 cm. This information is useful in planning surgical resection or the design of the radiation therapy boost.

**Keywords:** Chemoradiotherapy; Resection; Residual tumor; Tumor response

### Introduction

Neoadjuvant therapy with concurrent chemoradiotherapy is recognized as the standard of care for the management of locally advanced rectal cancer [1]. More recently, induction or consolidation multiagent systemic chemotherapy is increasingly used in the preoperative setting as well [2]. Preoperative treatment can often cause significant tumor response with either complete eradication of the tumor or substantial decrease in the post-treatment tumor volume and downstaging [3,4]. Surgeons, at the time of resection, will have to determine the extent of dissection in relation to the only visible abnormality, Gross Mucosal Abnormality (GMA). Successful resection requires complete eradication of all microscopic tumor cells without excessive removal of normal rectal tissues to minimize the post-treatment deterioration of the rectal function. It is therefore important to study the relationship between the GMA apparent to the surgeon intraoperatively and the extent and distribution of residual microscopic cancer cells.

### Methods

We conducted an IRB-approved retrospective review of the electronic medical records as well as pathology reports and slides of patients diagnosed with rectal adenocarcinoma treated with neoadjuvant chemoradiotherapy followed by surgical excision at Ascension St. John Hospital from 2011 to 2018. All patients were staged preoperatively by digital exam, flexible endoscopy, and endoscopic ultrasound and/or Magnetic Resonance Imaging (MRI). Computerized tomography was used to rule out distant metastases. Neoadjuvant therapy consisted of a course of radiation therapy to the pelvis given concurrently with either 5FU or capecitabine. The pathology reports

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**Table 1:** Patient clinical features.

Male	30
Female	27
cT2	2
cT3	48
cT4	5
Tx	2
N0	33
N+ve	20
Nx	4
Low rectal tumor	24
Mid rectal tumor	16
Upper rectal tumor	7

were re-evaluated to retrieve the description and size of the residual GMA. The pathology slides of these patients were also re-examined to evaluate the ypT and ypN status according to AJCC 8<sup>th</sup> edition guidelines and the presence and extent of microscopic cancer cells outside the GMA. The tumor response to neoadjuvant therapy was scored according to the modified Ryan scheme [5].

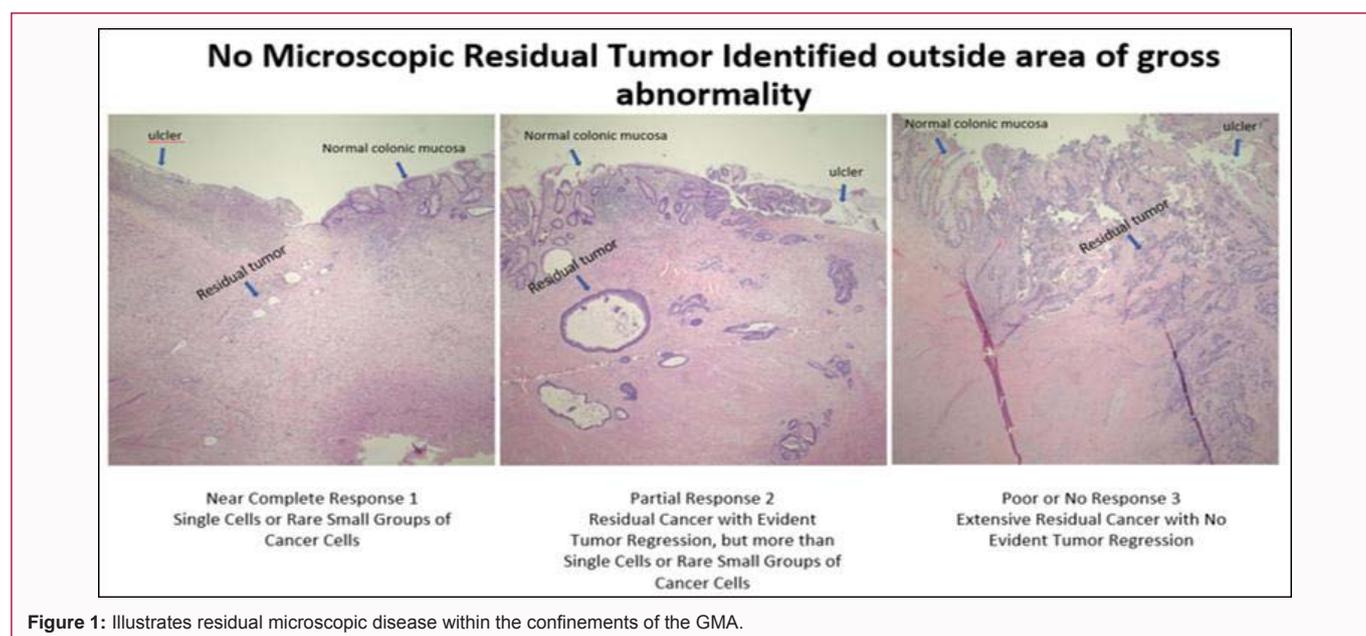
### Results

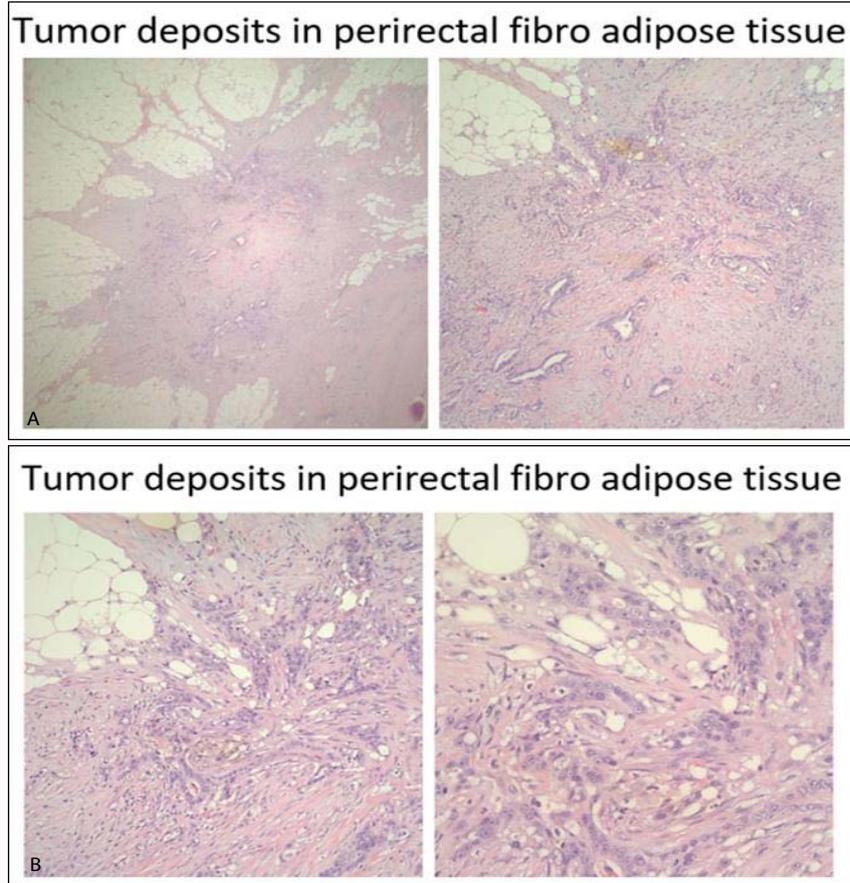
Fifty-seven patients met the selection criteria and were included in the study. Patient ages ranged between 32 and 86 years. The median length of the largest tumor dimension was 4.5 cm (range 1 to 15). Table 1 depicts the clinical features of the cohort. The radiation therapy dose was between 45 and 5.4 Gy. The time interval between completion of radiation therapy and surgical excision varied between 28 and 140 days with a median value of 68 days. Forty-three patients underwent low anterior resection, 12 patients had abdominoperineal surgery, and 2 patients had transanal local excision. The most common abnormality noticed in 31 patients (76%) on gross pathological examination was an ulcer. In 5 patients, the mucosa appeared normal and the tumor bed was determined by the presence of the preoperative tattoos. Other gross abnormalities

included nodules, mucosal thickening, loss of mucosal texture, and rectal perforation. As expected, there was a significant tumor response noticed on both gross and microscopic evaluations. The average size of the remaining gross abnormality was 2.8 cm (0.8 to 11.3). Figure 1 illustrates residual microscopic disease within the confinements of the GMA. Sixteen patients (28%) had no residual disease after neoadjuvant therapy and were excluded from further analysis. The average size of the microscopic residual malignant lesions was 1.2 cm (0.1 to 2.8). No microscopic disease was found solely outside the gross abnormality or in the perirectal fat without involving the bowel wall directly underneath the GMA. Microscopic disease extended outside the gross GMA only in 2 cases to a distance of 1 cm. In one case, tumor cells existed outside the bowel lumen, presumably a tumor deposit. In another case, a tumor was found in one section proximal to the gross abnormality. Five patients had ypT1 stage, while 14, 21, and 1 patient had ypT2, ypT3, and ypT4, respectively.

### Discussion

Our results show that in all cases, the residual microscopic disease lay directly in the bowel wall underneath the GMA. In no case did we observe the presence of microscopic disease confined only to the rectal wall outside the GMA. Similarly, we did not observe microscopic disease only in the deep perirectal fat without involving other parts of the rectal wall corresponding to GMA (Figure 2A, 2B). These two observations are important during organ preservation surgery with transanal full-thickness local excision when this procedure is used only as a biopsy to confirm the ypT0 status without any therapeutic goal. Our study demonstrates that in all cases, an accurate assessment of the pathological tumor response can be obtained by limiting the surgical resection only to the bowel wall corresponding to the GMA, without the need to resect a margin of normal-appearing rectal wall or dissection into the deep perirectal fat. This technique of Limited Local Excision (LLE) can avoid the reported severe and frequent postoperative surgical complications when more extensive resections were used [6-8]. Our findings are in agreement with the prospective comprehensive work of Guillem et al. [9], who detected occult tumor extension beyond the mucosal edge in only 2% of cases and, when present, were limited to 1 cm. The report of Smith et al.





**Figure 2A, 2B:** Illustrate tumor deposits in perirectal fat.

[10] agrees with our findings in this regard, as they determined that the maximum tumor infiltration is directly underneath the GMA in 98% of patients, supporting the concept of LLE. The relationship of the residual microscopic disease and GMA is important in other clinical scenarios such as when TME is considered for low rectal cancer to avoid unnecessary large proctectomy which can result in severe symptoms of low anterior resection syndrome. Understanding this relationship is also important for the surgeon to decide when to proceed with either sphincter-saving procedures or abdominoperineal resection and when local excision is intended to have a therapeutic aim with the removal of all residual cancer cells when patients cannot undergo or decline completion TME. Accurate delineation of the clinical target volume of the radiation therapy boost, especially when brachytherapy is used, also requires appreciating the degree of spread of microscopic cancer outside the GMA. The incidence of residual disease outside the GMA and the degree of extension varied among reported studies. While we and Guillem et al. [9,10] report a very low incidence and limited extension of microscopic disease outside the GMA, other investigators have reported a much higher rate and longer average distance of spread. Hayden et al. [11] reported a high incidence of occult microscopic disease (49%) outside the boundaries of the visible ulcer with spread up to 3 cm from the edge of GMA. In 7 of 55 cases (13%), microscopic disease was found underneath a discolored mucosa without grossly identifiable ulcer or normal-appearing mucosa. Smith et al. [10] reported that the majority of patients (71%) had tumors extending outside GMA but up to a distance of only 9 mm. Mezhir et al. [12] found 55% of their patients to have microscopic disease extension outside GMA up to a distance

of 2.5 cm. Perez et al. [13] studied the pattern of microscopic disease spread following neoadjuvant radiotherapy +/- chemotherapy and wide local excision. They detected microscopic cancer cells outside GMA in 53% of cases with a mean distance of spread of 4.8 mm and a maximum spread of 7.2 mm.

The variation in describing the pattern of residual microscopic cells following neoadjuvant therapy may be related to the small number of cases studied in each report, the retrospective analysis in many studies having inconsistent techniques of pathology evaluation. The difference in the intervals between completion of radiation therapy and surgical excision is of particular interest, as there is more interest now to wait for a relatively long time to achieve optimal tumor downstaging before patients undergo surgical resection [14]. Waiting up to 3 months is currently within the standard of care [2]. We are not able at present to discern reliable predicting factors for the presence and extent of microscopic disease outside GMA, although the studies of Smith et al. [10] and Perez et al. [13] suggested a possible correlation with the degree of tumor downstaging after neoadjuvant therapy. The common use of preoperative MRI provides an opportunity to study the tumor MRI response grade, which would be available to the surgeon before the planned surgical resection, in relation to the extent and distribution of any residual cancer cells. In addition, it is not clear if the increasing use of upfront or consolidation systemic chemotherapy will affect the pattern of microscopic spread. Our study is limited because of the small number of patients and its retrospective nature, but it adds to the relatively scant literature addressing this issue. Larger prospective studies are needed for a

better understanding of the relationship between the GMA and the residual microscopic disease.

## Conclusion

Our data suggest that the confirmation of the pathological complete response status by LE following preoperative treatment does not require surgical dissection beyond the borders of GMA and adjacent perirectal fat. More extensive dissection will not add to the accuracy of the assessment of the pathological response and may well add to the postoperative morbidity. The incidence of occult microscopic disease outside GMA, in our series, is very low and, when present, it extends only to a distance of 1 cm.

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