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# Patterns of bowel invisible microscopic endometriosis reveal the goal of surgery: removal of visual lesions only

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**Précis:**

Invisible microscopic endometriosis implants surround bowel macroscopic endometriosis nodule at variable distances, suggesting that complete surgical microscopic removal may be a challenging goal.


## Abstract

**Study objective:** To document the presence of bowel invisible microscopic endometriosis implants and their relationship with deep endometriosis macronodule infiltrating the bowel.

**Design:** A series of consecutive patients with deep endometriosis infiltrating the rectum and/or sigmoid colon.

**Design classification:** Canadian Task Force classification II-2.

**Settings:** University referral center.

**Patients:** Ten patients managed by colorectal resection.

**Interventions:** Microscopic study of endometriotic foci of the bowel involving 3,272 microsection slides was established using a unique method of step-serial sections using combined transversal and longitudinal macrosection. 2D reconstruction based on slide scanning highlighted the presence and localization of the deep endometriosis macronodule in contrast with bowel invisible microscopic endometriosis microimplants.

**Measurements and Main Results:** Distance separating the microimplants and the nodule and their histological characteristics. The mean length of colorectal specimens was 91 ± 19 mm. The maximum distance between the farthest microimplants was 7.2 cm. The maximum distance from the macroscopic nodule limit to the farthest microimplant was 31 mm. Bowel invisible microscopic endometriosis microimplants presented with similar features, independently of the type of spread. They had an active appearance, including stroma and glands, sometimes decidualized, free of fibrosis. They were found on the distal/rectal limit of the specimen in 3 patients and on both limits (distal/rectal and proximal/sigmoid colon) in one patient.

**Conclusions:** Invisible microscopic endometriosis implants surround the bowel macroscopic endometriosis nodule at variable distances, suggesting that complete surgical microscopic removal may be a challenging goal. These results may help to reconsidering the principles and feasibility of the surgical management of bowel endometriosis.

**Keywords:** microscopic endometriosis; invisible endometriosis; histology; segmental resection; surgery

## Introduction

Deep endometriosis infiltrating the rectum or sigmoid colon may present under various forms, such as deep posterior adenomyomas originating from the posterior uterine wall or isthmus and infiltrating the anterior wall of the rectum (1), endometriosis nodules infiltrating the sigmoid colon sometimes connecting with either ovarian endometriomas or uterosacral ligament nodules, or solitary nodules of upper rectum and sigmoid colon without contact with surrounding organs (2). In many cases, the digestive tract is infiltrated by multiple nodules, leading to debates about the most suitable surgical technique to propose (3, 4, 5, 6, 7, 8). Recent data suggest that colorectal endometriosis presents as a disseminated disease, with microscopic satellite implants or bowel invisible microscopic endometriosis (BIME) located outside the limits of macroscopic nodules (9, 10, 11, 12), which correspond to invisible endometriosis identified on the pelvic peritoneum (13, 14, 15). These findings concerning BIME are not without impact on both the choice of the most suitable management and the risk of postoperative recurrences. Thus, BIME raises questions about the goals of surgical treatment and the usefulness of adjuvant postoperative suppressive medical treatment.

Previous studies attempted an estimation of the frequency of microscopic implants spread around macroscopic bowel nodules, however their design was perfectible (9, 16). In a past study, we used systematic histological transversal sections separated by 3mm of healthy bowel, which could have underestimated the actual number of BIME implants and their distance from nodule limits (9). Thus, we planned a new study where histological examination is carried out using combined transversal and longitudinal sections, in order to improve the precision of BIME detection.

The aim of this study was to document the presence of BIME, to assess the distance separating microimplants and macroscopic nodules, and to seek a relationship between BIME spread and histological findings in colorectal specimens.

## Material and methods

We enrolled in the study consecutive patients who underwent surgical management for deep colorectal endometriosis between October – December 2015, in the Department of Gynecology and Obstetrics, Rouen University Hospital, France. Inclusion criteria were: women with symptomatic deep endometriosis infiltrating at least the muscular layer of the rectum or sigmoid colon, who were exclusively managed by segmental colorectal resection. Data regarding patients' characteristics, intraoperative findings, surgical procedures, and operative route were prospectively recorded using the CIRENDO database (the North-West Inter Regional Female Cohort for Patients with Endometriosis, NCT02294825), which is a prospective cohort financed by the G4 Group (The University Hospitals of Rouen, Lille, Amiens, and Caen) and coordinated by one of the authors (H.R.). Data management was carried out by a clinical research technician and was approved by the French authority CCTIRS (Advisory Committee on information processing in healthcare research). The surgical route was laparoscopic. Gynecologic surgeons performed dissection of the pelvis, treatment of endometriosis in extra-digestive localizations, while general surgeons carried out colorectal resection and colorectal anastomosis using a 28 or 31mm end-to-end circular anastomosis transanal stapler. To achieve complete radical removal of bowel endometriosis when colorectal resection was performed, the edges were generally >=2 cm outside macroscopic colorectal nodule limits.

The surgical specimens of bowel tract were immediately fixed in formaldehyde for 48 hours. Grossing was performed using the same method for all the specimens. The specimens previously fixed were sliced from the distal/rectal to the proximal/sigmoid colon side in step serial sections using combined transversal and longitudinal macrosection, each of 3mm thickness and all the sections were embedded in paraffin blocks. One microsection of 5μm was taken from each macrosection, and stained with Hematoxylin and Eosin. During specimen grossing, sections containing macroscopic nodules (visible with the naked eye during the grossing method) were distinguished from those surrounding the apparently healthy bowel wall on macroscopic examination. BIME implants were defined by the presence of both endometrioid glands and stroma on microscopic examination, in an area with healthy macroscopic appearance. The use of combined transversal and longitudinal microsection of whole specimens allowed a complete documentation of the presence of BIME implants on the specimens and an accurate representation of precise localization of BIME implants within the bowel wall. Finally, this accurate sampling allowed the mapping of the entire bowel area. A gynecologic pathology expert together with a gynecologist (S.S, A.B.) evaluated all the microsection slides using a multiheaded microscope (Nikon i55, Nikon GmbH) to document the presence of BIME implants, their distance from macroscopic nodule limits and specimen margins, their spread and the depth of rectal wall involvement. A reconstruction based on slide scanning was established for each specimen, highlighting the presence and localization of the macroscopic nodules and the precise localizations of the

BIME implants. Slides were scanned using Merlin Camera F-146C IRF MEDICAL (ALLIED Vision Technologies Medical) with MIRAX MIDI control software version 1.12.25.1. We performed a panoramic image reconstruction derived from the slide scanning, by stitching together the images containing both macroscopic nodules and microscopic implants and performing a rigid alignment, after spotlighting the microscopic endometriosis. The images were outputted in quadrates with yellow borders for macroscopic nodules and quadrates with red borders for BIME. The panoramic image stitching was realized using GIMP GNU Image Manipulation Program, 2.8.18. We connected by arrows each microsection containing endometriosis (BIME and macroscopic nodules) with the area of bowel it came from. Each figure was created to highlight the presence of endometriosis foci and to underline the precise localization of BIME within the digestive wall, and the distance to macronodules and specimen margins. Informed consent to use the specimens for histological examination was obtained from all patients. The study was approved by Rouen University Hospital IRB. Statistical analysis was performed using the Stata 9.0 software (Stat Corporation, 10 Lakeway Drive, TX, USA). Median values and range were obtained for continuous variables. We estimated the degree to which various variables are correlated by using Spearman's correlation.

**Results**

Between October to December 2015, 10 women having undergone colorectal resection for deep endometriosis infiltrating the rectum or sigmoid colon were enrolled in the study. The length of the colorectal specimens was 91 ± 19 mm. We examined 3,272 microsection slides (Fig. 1- Supplemental Figs. 1-9). Both BIME and macroscopic nodules were located in the muscularis layer in all specimens without involving the mucosal layer in any of the cases. Six nodules were connected with left ovarian endometriomas. Patients' characteristics and major intraoperative findings are presented in Table 1. Fig. 1 and Supplemental Figs. 1-9 present the location of the macroscopic nodules and BIME for each colorectal specimen. Multiple macroscopic nodules were revealed in 3 specimens (Fig. 1, Supplemental Figs. 3, 5). The spread of BIME implants was either concentrated around the nodules (5 patients) or far from their limits (5 patients). BIME implants presented with similar features, independently of the type of spread. They had an active appearance, including stroma and glands, sometimes decidualized, free of fibrosis. BIME concerned on average 25% of the area of colorectal specimens. Table 2 presents the findings of microscopic examination. The maximum length separating the farthest of the endometriosis implants in a specimen was 72 mm, while the largest distance from an implant to a nodule limit was 31 mm. Table 3 presents the statistical analysis between various characteristics of the specimens and histological findings. Significant correlations were found between the maximum distance between the farthest BIME implants (mm) and the length of the specimen (0.007) and between the maximum distance between the farthest BIME implants and the distance from the nodule limit to BIME (0.01). BIME was found on the margin in 3 specimens (Supplemental Figs. 2, 6, 9), and on both margins in one specimen (Supplemental Fig. 3). In 4 specimens BIME was found close to both margins, at an average distance of 3 mm and 13 mm from the distal and proximal margins, respectively (Fig. 1, Supplemental Figs. 4, 5, 8).



**Discussion**

Through an extensive histological analysis of colorectal specimens, we observed that BIME is spread into colorectal muscularis layer around and far from the macroscopic nodule limit, as microscopic implants can be found on the edges of the specimens. These findings suggest that microscopic implants may be left behind in the bowel wall in patients managed by segmental colorectal resection, and raises questions about the feasibility of microscopic complete resection of bowel endometriosis. The goal of surgery ought to be removal of visual lesions and it seems unreasonable to expect complete removal of microscopic disease. We do not know whether BIME foci are microscopically related to the macroscopic nodule, such as satellite endometriotic foci in an endometriotic network or if are completely isolated. The only different characteristic is their size. Clonality studies could demonstrate if they are identical or different, but neither do these studies demonstrate 100%, because as BIME develops, some clones may suffer transformation and so they may be different from the source. In the debate concerning bowel resection and shaving, a strong argument against shaving was the disease left behind after shaving. However, bowel resection, supposed to be radical, failed to show less recurrence of the disease. This could be due to BIME and then an important question come: should we remove BIME and so increase the length of the specimen? An increased of length of the specimen cannot necessary eradicate the disease, because BIME can be left behind. BIME is very common in women with colorectal endometriosis (9), BIME has no impact on 1- year outcomes (2) and should not affect treatment decision. In line with malignant disease).

The novelty of this study is understanding the disease and the meaning from the clinical point of view: the goal of surgery ought to be removal of visual lesions and it seems unreasonable to expect complete removal of microscopic disease. The major weakness of our study is related to the small group size, which may not allow revealing correlations between the characteristics of the specimens and identification of factors predicting incomplete resection of BIME. However, the high number of sections performed on each specimen makes the feasibility in large series of patients difficult. In our center, segmental colorectal resection is usually proposed to patients presenting with large nodules of upper rectum and sigmoid colon the diameter of which exceeds 3 to 4 cm, or with nodules responsible for severe stenosis of digestive lumen. In our practice, multiple nodules do not necessarily require colorectal resection, whether the association of multiple shaving or disc excisions may treat them (17).

Of the 121 patients with colorectal endometriosis we managed in 2015, only 52 had segmental resection (43%).

Thus, the findings reported in our series were particularly representative for patients with severe colorectal endometriosis. The strengths of the study are having a surgeon dedicated only to performing the seriate sections (A.B.) under supervision of a senior pathologist trained in gynecological pathology (S.S.), the care taken to exhaustively analyze the section slides and the complete mapping for each specimen of BIME implants. Although time-consuming, our analysis of 327 slides on average per specimen allowed accurate description of BIME implants through the muscularis layer of the specimen, as well as the distance separating them from the nodule limits and specimen margins.

BIME implants could be spread in a longitudinal path (Supplemental Figs. 3-6, 8, 9) similar to that reported by Anaf et al. The authors supposed that endometriotic lesions infiltrate the large bowel preferentially along the nerves, sometimes far from macroscopic nodules (6), however we did not particularly observe this tropism for nerve fibers. Nevertheless, BIME implants could also spread concentrically being concentrated around the macroscopic nodule as observed in this study. Although high effectiveness of prolonged postoperative therapy is demonstrated, there is still a debate focused on hormonal medical treatment and surgery and on the most adequate surgical technique to be used (18, 19) taking into consideration that digestive symptoms are not related only to the infiltration of the rectum by macroscopic deep endometriosis nodules (20). A recent study indicates regression of the inflammatory microenvironment in the pelvis of women with endometriosis after GnRH treatment (21). The question remains whether BIME implants left behind may be active at a point to lead to bowel recurrences (22). The answer may be affirmative, as we previously reported a macroscopic recurrence on the stapled line in a patient with BIME identified on the distal margin of the colorectal specimen (2).

The debate on the BIME was also concerning the existance and the clinical relevance of microscopic endometriosis (23). Kahn's methodology of normal peritoneum visualization was refuted by Redwine which claims that every endometriotic implant can be seen intraoperatively with enough magnification during laparoscopy (23).The goal of surgery in endometriosis management should be avoiding the symptoms not removing all the implants. The reported percentage of BIME vary from study to study because increasing the number of biopsies will increase the number of lesions and the accuracy of detection (24). However, Kahn's paper and Redwine's editorial are both concerned with the topic of invisible endometriosis on the peritoneal surface whereas our current paper is concerned with impossible-to-see endometriosis embeded in colonic muscularis beneath the serosal surface of the bowel.

Another question may concern further malignant transformation of residual implants, due to subsequent intervention of various unknown factors. A hypothesis of the origin of the endometriosis reveals the importance of advancing the search for discriminatory cellular or molecular markers that identify patients at risk for progressive disease (25). Another key question is whether BIME implants differ, from a molecular point of view, from the tissue contained in macroscopic nodules, which can explain a different risk of development. This latter hypothesis is at the origin of an ongoing study the results of which may be reported in the near future.

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Figure 1. Distribution of endometriosis lesions through microsections in the first patient along with the macroscopic view of the colorectal specimen; macroscopic nodules are represented by the yellow quadrates and BIME implants by the red quadrates. The arrows connect BIME with the area of bowel it came from.

Supplemental Figure 1. Distribution of endometriosis lesions through microsections in the first patient along with the macroscopic view of the colorectal specimen; macroscopic nodules are represented by the yellow quadrates and BIME implants by the red quadrates. The arrows connect BIME with the area of bowel it came from.

Supplemental Figure 2. Distribution of endometriosis lesions through microsections in the first patient along with the macroscopic view of the colorectal specimen; macroscopic nodules are represented by the yellow quadrates and BIME implants by the red quadrates. The arrows connect BIME with the area of bowel it came from.

Supplemental Figure 3. Distribution of endometriosis lesions through microsections in the first patient along with the macroscopic view of the colorectal specimen; macroscopic nodules are represented by the yellow quadrates and BIME implants by the red quadrates. The arrows connect BIME with the area of bowel it came from.

Supplemental Figure 4. Distribution of endometriosis lesions through microsections in the first patient along with the macroscopic view of the colorectal specimen; macroscopic nodules are represented by the yellow quadrates and BIME implants by the red quadrates. The arrows connect BIME with the area of bowel it came from.

Supplemental Figure 5. Distribution of endometriosis lesions through microsections in the first patient along with the macroscopic view of the colorectal specimen; macroscopic nodules are represented by the yellow quadrates and BIME implants by the red quadrates. The arrows connect BIME with the area of bowel it came from.

Supplemental Figure 6. Distribution of endometriosis lesions through microsections in the first patient along with the macroscopic view of the colorectal specimen; macroscopic nodules are represented by the yellow quadrates and BIME implants by the red quadrates. The arrows connect BIME with the area of bowel it came from.

Supplemental Figure 7. Distribution of endometriosis lesions through microsections in the first patient along with the macroscopic view of the colorectal specimen; macroscopic nodules are represented by the yellow quadrates and BIME implants by the red quadrates. The arrows connect BIME with the area of bowel it came from.

Supplemental Figure 8. Distribution of endometriosis lesions through microsections in the first patient along with the macroscopic view of the colorectal specimen; macroscopic nodules are represented by the yellow quadrates and BIME implants by the red quadrates. The arrows connect BIME with the area of bowel it came from.

Supplemental Figure 9. Distribution of endometriosis lesions through microsections in the first patient along with the macroscopic view of the colorectal specimen; macroscopic nodules are represented by the yellow quadrates and BIME implants by the red quadrates. The arrows connect BIME with the area of bowel it came from.

Table 1. Intraoperative findings

| | N=10 (%)<br>Median (range) |
|---|---|
| Length of colorectal specimen removed (mm) | 90.5 (70; 120) |
| Operative time (min) | 223 (120; 420) |
| AFS score | 52 (39; 130) |
| Douglas pouch complete obliteration | 3 (30) |
| Multiple colorectal nodules | 3 (30) |
| Right ovarian endometrioma | 3 (30) |
| Left ovarian endometrioma | 6 (60) |
| Left uterosacral ligament | 6 (60) |
| Right uterosacral ligament | 6 (60) |
| Bilateral uterosacral ligaments + rectovaginal septum | 4 (40) |
| Bladder nodule | 5 (50) |
| Stenosis of the ureter | 1 (10) |

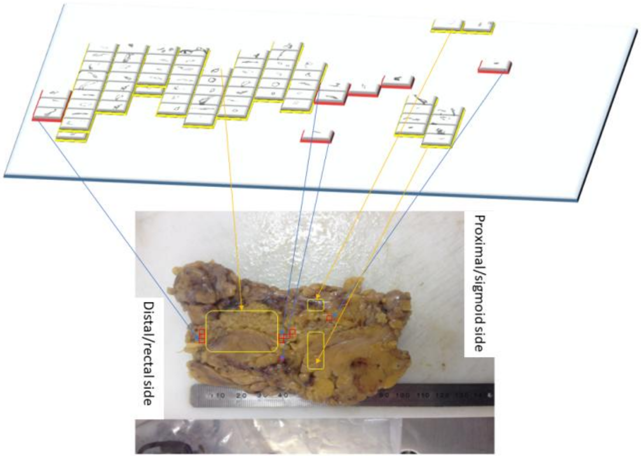
Table 2. Histological findings

| Specimen | Bowel segment removed | Length of colorectal specimen removed (mm) | Diameter of the largest nodule (mm) | Diameter of the second nodule (mm) | Number of sections including BIME | % of the specimen with endometriosis | Spread of endometriosis (mm) | Distance from nodule limits to the farthest BIME (mm) |
|---|---|---|---|---|---|---|---|---|
| 1 | Rectum | 70 | 24 | 18 | 10 | 23 | 45 | 10 |
| 2 | Rectum | 80 | 57 | | 12 | 32 | 69 | 10 |
| 3 | Rectum | 120 | 21 | 19 | 76 | 34 | 108 | 36 |
| 4 | Sigmoid | 111 | 24 | | 24 | 16 | 84 | 45 |
| 5 | Rectum | 105 | 12 | | 11 | 13 | 90 | 48 |
| 6 | Sigmoid | 105 | 10 | | 43 | 12 | 93 | 60 |
| 7 | Sigmoid | 81 | 24 | | 22 | 20 | 30 | 27 |
| 8 | Rectum | 70 | 24 | 6 | 12 | 26 | 45 | 10 |
| 9 | Rectum | 100 | 33 | | 17 | 21 | 90 | 51 |
| 10 | Sigmoid | 70 | 45 | | 23 | 38 | 63 | 12 |
| Median (range) | | 91 (70 ; 120) | 24 (10 ; 57) | 0 (0 ; 19) | 66 (10 ; 76) | 22 (12 ; 38) | 76.5 (30 ; 108) | 31.5 (10 ; 60) |

Table 3. Correlations between features of the diseases

| Correlations between various specimens' characteristics | Correlation coefficient | P |
|---|---|---|
| Nodule size and spread of endometriosis | -0.22 | 0.1 |
| Nodule size and distance from nodule limit to the farthest BIME implant | -0.60 | 0.1 |
| Nodule size and length of colorectal specimen removed | -0.48 | 0.1 |
| Spread of endometriosis and length of specimen | 0.8 | 0.007 |
| Spread of endometriosis and distance from nodule limit to BIME implant | 0.7 | 0.01 |
| Distance from nodule limit to BIME implant and the length of the specimen | 0.83 | 0.01 |

Spread of endometriosis: BIME extension on the specimen in relation to macroscopic nodule and distal and proximal margins

377 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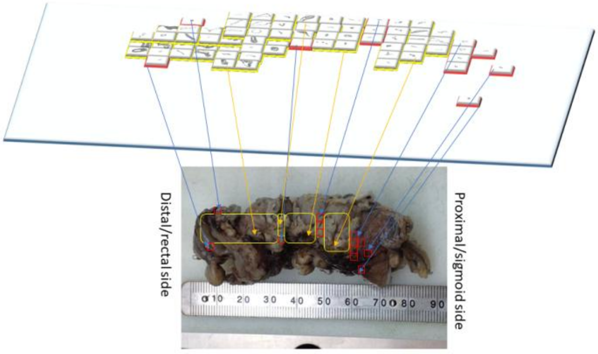


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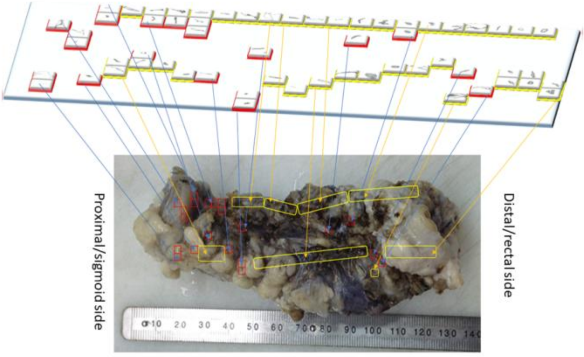


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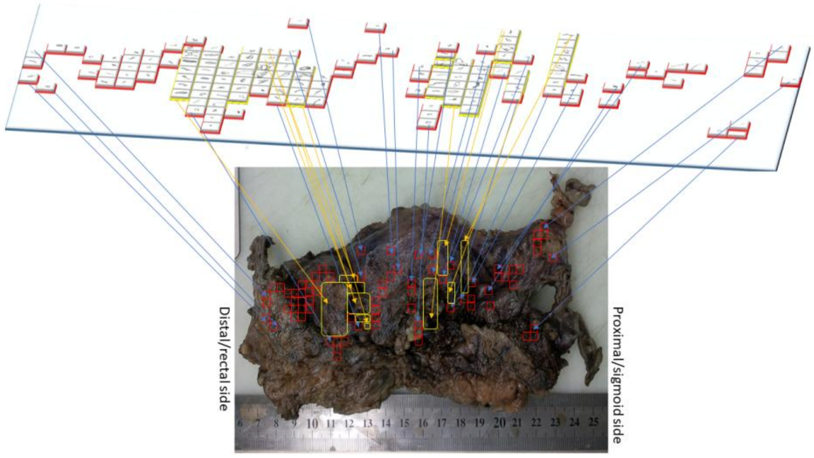


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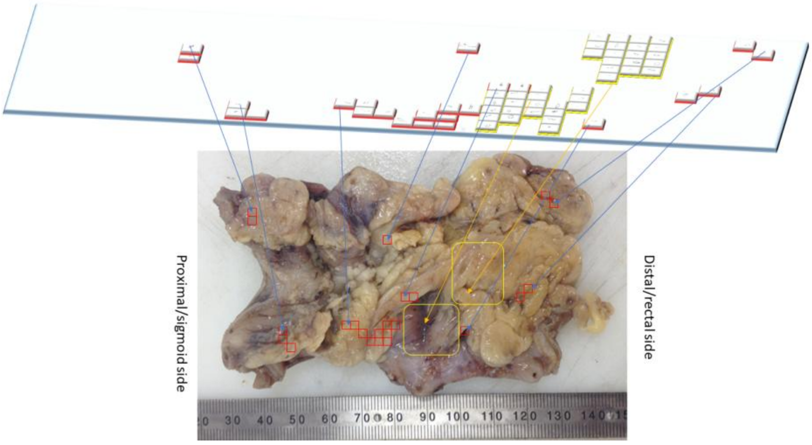
389 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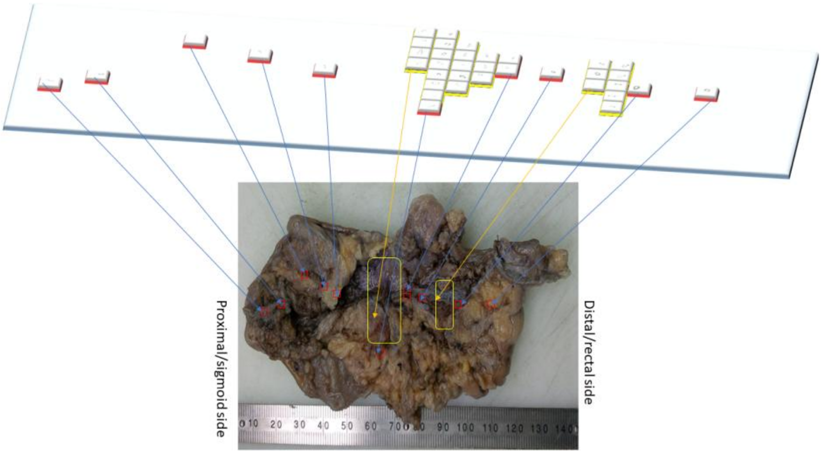
392 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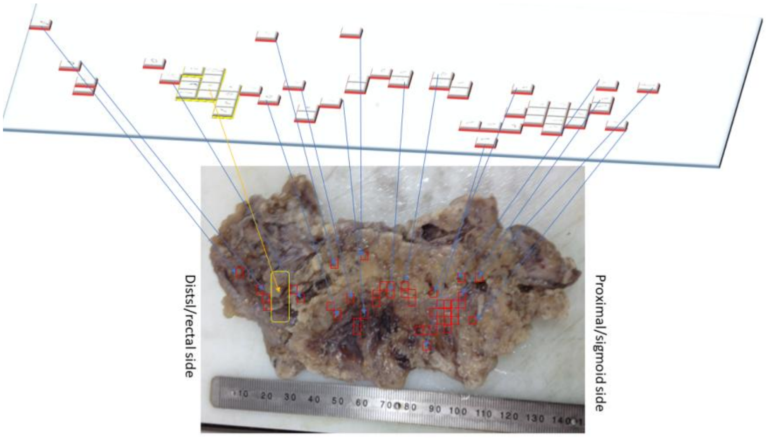


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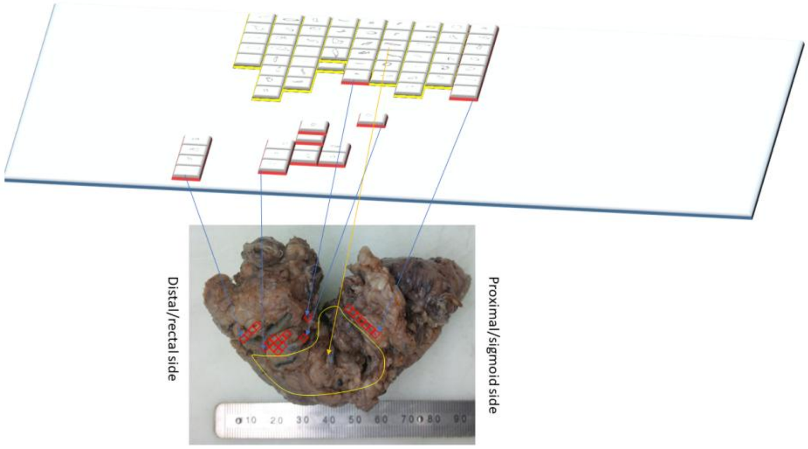


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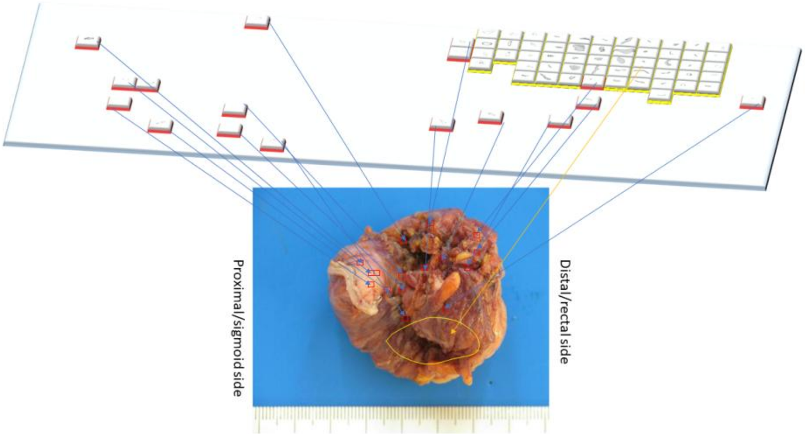


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402 Suppl.Fig.8_bestsetConverted.png

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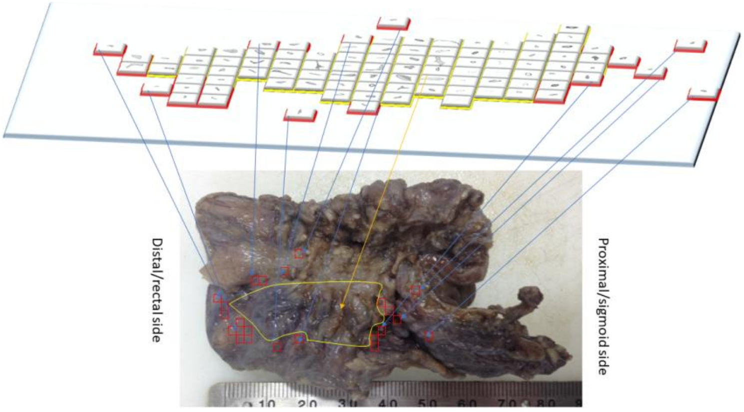


Suppl.Fig.9_bestsetConverted.png