GIPS-AGPS Recommendations For Pathologic Assessment And Reporting Of EMR/ESD Specimens From The GI Tract

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INTRODUCTION

Over the past decade, there have been significant advances in effective endoscopic therapies for patients with superficial neoplasia of the upper and lower GI tract. [1-6] The increasing application of advanced endoscopic resection techniques has ushered in a new era of interdisciplinary relations between pathologists and gastrointestinal endoscopists. As these techniques have evolved with more precision, progressively more detailed and meticulous pathology assessment is required. It is crucial that both groups understand each other's clinical perspective and technical approach to ensure that patient management is optimized.

Currently, in leading tertiary centers, endoscopic resection and surgery are non-competing but complementary therapeutic options. Endoscopic resection (ER) allows optimal staging with potential cure of early stage malignancies while maintaining organ preservation, avoiding major surgery and allowing for better stratification and guidance for additional treatment if appropriate. The curative status of an ER depends on adequacy of resection and the risk of lymph node metastasis. Although lymph node status (pN) cannot be determined, important pathological risk factors predictive of lymph node metastasis can be assessed in ERs. For instance, depth of tumor invasion is linked to risk of lymph node metastasis (Table 1).[7-11] Other histological risk factors include poor differentiation, lymphovascular invasion, and high grade tumor budding [8,11-14]. Complete resection with negative margins is critical to avoid local recurrences of both non-invasive and invasive neoplasms. Therefore, similar to the reporting of large surgical specimens, a systematic approach for handling and assessing ER specimens is recommended to evaluate all important pathological risk factors and the margin status appropriately .[15,16]

In the West, endoscopic resections are primarily used in the setting of Barrett's esophagus complicated by early intramucosal carcinoma or dysplasia, and endoscopic management is considered the standard of care. [1-4,11-19] Similarly, in the East, endoscopic resection represents the first-line therapy for early gastric cancer in lesions with very low likelihoods of lymph node metastasis.[20] In addition, endoscopic resections are increasingly advocated for curative treatment and staging of early esophageal squamous cell carcinoma, as well as low-risk submucosal invasive cancers (LR-SMIC) and large laterally spreading adenomas of the colon.

CLINICAL ASPECTS

1-Clinical developments that led to the use of endoscopic mucosal resection and endoscopic submucosal dissection.

The three main endoscopic resection techniques include simple polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). For most of the last century, advanced endoscopic tissue resection techniques were largely limited to the concept of 'polypectomy'. Except for pedunculated lesions, histologically advanced or large (>20 mm) mucosal neoplasms of the gastrointestinal tract could not be reliably excised 'en-bloc'. Piecemeal excision was often necessary, thus compromising histological assessment and often subsequently requiring surgery to ensure cure. In the late 1990s, as a result of screening programs and advancement of endoscopic techniques, asymptomatic early neoplasms were increasingly detected, and ushered in technical innovations for their management. The

advantages of minimally invasive endoscopic resection over surgical management were recognized, and proven in large prospective studies. [21,22]

Japan, with its high incidence of gastric cancer, is where the first advanced endoscopic tissue resection technique, i.e. endoscopic mucosal resection [EMR], was developed in the 1990s. EMR can provide for en-bloc resection of small lesions (up to approximately 10-15 mm), but removal of lesions measuring more than 15 to 20 mm in size can only be accomplished in a piecemeal fashion. It is difficult, if not impossible, to assess completeness of excision at the radiall resection margins in these piecemeal resections by pathological examination .[1] Furthermore, recurrences occur in the range of 15-20%, presumably due to incomplete removal. [23] Thus, EMR does not fully meet basic therapeutic principles and complete en bloc excision should be performed for the stated goal of cure for early stage invasive disease. Hence, in the early 2000s, endoscopic submucosal dissection was pioneered (in Japan again) as a method for en bloc excision of early gastric cancer (EGC). The invasiveness and morbidity of a standard surgical gastrectomy was a major driver for implementing this new technique. ESD allows for: 1) the resection of larger lesions; 2) tissue margins to be pre-defined and 3) for lesions to be excised en bloc, achieving complete/R0 excision without need for further surgery and therefore cure where histology is favorable.

Large Japanese cohort studies, although not randomized, confirm that ESD is associated with a very low rate of local recurrence during long-term follow-up. [24-26] However, ESD is technically demanding, with average procedure times of 2-4 hours, resulting in increased health resource utilization even for experts. There is also a greater incidence of complications, including

perforation. Thus, ESDs are ideally limited to situations where it may add a meaningful clinical benefit. Table 2 summarizes the endoscopic treatment selection between EMR and ESD for various mucosal pathologies at different sites in the gastrointestinal tract.

EMRs and ESDs have distinct advantages and disadvantages in the management of early neoplastic lesions throughout the GI tract (Table 3). Selection of one technique over the other depends greatly on location and characteristics of lesions as well as gastroenterologist's technical expertise.

2-*Technical Aspects of Performing EMR and ESD*

Simple Polypectomy

This common technique allows for removal of mucosal lesions using a snare, without any additional techniques and/or devices. Electrosurgical current may be used (e.g. hot snare polypectomy) to dissect through the tissue captured in the snare, but for smaller lesions, mechanical transection of the tissue without electrocautery can be achieved by tightening the snare (e.g. cold snare polypectomy).[27] Simple polypectomy is best suited for lesions protruding into the GI lumen (allowing capture with the snare) and measuring < 10 mm in diameter, facilitating *en bloc* resection, although piecemeal cold snare polypectomy is presently being evaluated for larger polyps > 10 mm in size.

Endoscopic Mucosal Resection (EMR)

This technique uses a snare and additional ancillary technique(s) or device(s).

1) Inject and lift EMR. The most commonly used EMR ancillary technique is to inject fluid in the submucosa with a needle in order to create a submucosal cushion.[28] The now-elevated lesion is captured and removed in one or more pieces using a snare. Electrocautery is typically used to dissect through the tissue.[29] The two suggested benefits of submucosal injection are that "lifting" the lesion may make it easier to capture in the snare and that the submucosal fluid cushion protects the muscularis propria layer and serosal surface from electrocautery-induced damage. Large mucosal areas can be removed by sequentially applying injection followed by snare capture and transection (aka wide-field EMR).
2) Cap EMR. The cap-assisted EMR utilizes a transparent distal attachment at the tip of the endoscope (cap), which creates a chamber.[30] The mucosa is suctioned up into this cap; the "pseudopolyp" thus produced is then captured at the base with a snare, and tissue is then transected by electrosurgical current. Cap EMR is predominantly used in the esophagus and rectum but can also be utilized in the duodenum and colon.
3) Band EMR. Band EMR is based on the use of variceal band ligator, but the concept is similar to the Cap EMR. A distal cap preloaded with rubber bands is fitted at the tip of the endoscope; after the "pseudopolyp" is sucked up into the cap, a rubber band is pushed off to create a polyp base, which can be transected.
4) Underwater EMR. The concept of Underwater EMR is based on the observation that the folds of a water-filled GI lumen consist of involutions of the mucosa and submucosa, analogous to the rugae of the stomach.[31] This technique allows for the mucosa and submucosa to 'float' away from the deeper muscularis layer, thus facilitating safe snare capture.

After the mucosal resection has been performed, the specimen(s) can be retrieved. To save on procedure time, esophageal and gastric EMRs are often allowed to collect in the stomach and multiple EMRs removed at the end of the procedure with a basket. Due to the risk of stricturing in the esophagus, it is uncommon to resect the entire circumference; generally, one half to one third of the circumference is treated in each session.

As noted above, lesions removed by EMR have a higher risk of local recurrence. This may be due to thin 'strips' of residual mucosa present between the approximately circular areas of multiple EMRs. Combining EMR with radiofrequency ablation (RFA) to eradicate residual mucosa in the area of the lesion can aid in eradication. [32]

Endoscopic Submucosal Dissection (ESD) (figure 1 and video)

ESD is a technique for en-bloc removal of superficial lesions regardless of size. Injection of fluid in the submucosa is first carried out. A circumferential mucosal incision around the lesion is then performed, followed by submucosal layer dissection. [28,33,34]A solution providing a longer-lasting submucosal cushion is typically used, and the procedure is performed with specialized knives. The technique is easier to perform in the esophagus, stomach and rectum and considerably more difficult in the colon and duodenum.

PATHOLOGIC ASPECTS

Intraepithelial lesions (dysplasia and adenomas) and early invasive carcinomas are two major groups of lesions evaluated by pathologists in assessing ERs of the GI tract. Less commonly encountered lesions are mesenchymal and neuroendocrine tumours (NETs).

Histological examination of an ER specimen serves 2 purposes: 1) Confirmation of pre-procedure diagnosis (pinch biopsy or endoscopic impression alone); 2) Prognostication, including staging (in invasive lesions). For non-invasive lesions, complete resection is curative. Therefore, confirmation and subtyping of lesions and a comment on radial margins are appropriate.

For invasive lesions, histological risk factors predict 2 main outcomes: 1) risk of lymph node metastasis; and 2) risk of residual disease at the ER site

Adverse histological risk factors for lymph node metastases are poor tumor differentiation, lymphovascular invasion (lymphatic or venous invasion), depth of infiltration and high tumor budding. In early neoplastic lesions, these factors are associated with higher risk of lymph node metastasis. [8,11-14] Margin involvement is associated with residual/recurrent disease. These factors determine the curability of endoscopic resections. There are also additional site-specific special issues that will be discussed further in subsequent sections.

Unlike in the lower GI tract, pT1 carcinomas of the upper GI tract are divided into pT1a and pT1b, as they show different behavior in terms of risk of nodal metastases.[7-11] Hence, accurate

pathology assessment is critical. Consequently, a systematic approach for handling, assessment and reporting of endoscopic resections similar to surgical resections should be adopted for accurate microscopic assessment.[15,16, 35,36]

Handling/grossing

There are several well-established, important steps to follow in order to facilitate the microscopic examination and optimize the reporting.

1. Pinning out specimen and fixation (Figure 2)

The specimens in the fresh status ought to be pinned out on a hard surface (e.g., corkboard, Styrofoam, wax block) immediately with the mucosal side up, to prevent curling and shrinkage. This can be done in the endoscopy suite by trained personnel or in the pathology laboratory. The specimen can then be floated upside-down in a vial of formalin and should be marked as to the presence of 'sharps' (pins). Alternatively, specimens can be received fresh in the laboratory immediately after the resection has been performed and then handled in the same manner. Polypoid pieces should be stretched and pinned; however, over-stretching will result in tears on the margins.

EMR specimens are often un-oriented, but ESDs may come with proximal/distal orientation. If orientation is provided, proximal/distal aspects (oral and anal ends) should be indicated. Measurement of the specimens is best performed before fixation. The specimens are placed in

neutral buffered formalin as soon as possible to avoid tissue degeneration. The recommended fixation time is 12-72 hours. An additional step, seldom performed, is to spray indigo carmine (on stomach or intestine specimens) or iodine staining (on oesophageal specimen) to highlight the contour of the lesion. Rolled edges may pose problems not only for the assessment of radial margins but also for depth of invasion, in particular when an invasive carcinoma is found close to the radial margins. This underscores the importance of satisfactory handling with pinning out the specimen in the fresh state.

Recently, endoscopic systems such as Captivator® have been developed to facilitate handling specimens by providing cassettes for direct placement of the tissues with the lid intended to flatten the specimen in a manner similar to pinning but lacking the pin-hole artifacts. Effectiveness is greatly dependent on how the tissue is initially placed in the cassette.

Identification of the ampulla in duodenal/ampullary specimens is helpful to allow visualization of and sectioning through the ampullary duct (Figure 3). Assessment of the ampullary duct resection margin is important to assess adequacy of excision. A pin or probe through the duct can be used as an indicator by the endoscopist, although it may be technically challenging (Figure 3a). However, with this method, there is a theoretical risk of dislodging any papillary fronds of the luminal component of a lesion involving the ampullary duct and artifactually pushing them into the deep portion of the specimen. Sectioning through the ampullary duct allows examination of the ampullary duct margin and the resection base. Careful sectioning of the ampulla is necessary to be able to visualize the bile duct margin. The ampulla can be sectioned like a cervical LEEP specimen, i.e. radially around the clock-face of the roughly circular specimen so that the area of the bile duct is seen in the inner edge of the slices, or by serially sectioning the

specimen so that the bile duct area appears in the middle and extends to the deep margin of the specimen, in a ‘volcano-like’ appearance. Evaluation is often complicated by cautery artifact at the deep margin.

2. Macroscopic examinations (after fixation)

The documentation of the size and the number of tissue fragments received is important. EMR specimens often tend to be multiple compared to en bloc ESDs (Figure 2). After adequate fixation, pins are carefully removed. With satisfactory pinning and fixation, a technically accurate ER specimen should appear as a flat piece of tissue without curled edges (Figure 4). The 2 dimensions of the lesion(s), maximum size and macroscopic type (polypoid, elevated, depressed, flat, etc.) should be recorded. Given that specimens tend to shrink after fixation, accurate measurements are optimally performed in the fresh state. However, identification of lesions, in particular the shape and borders, can often be better appreciated after fixation. If identifiable, the distance from the lesion to the nearest margin (cut edge/radial margin) must be recorded, especially for ESD, which have true radial margins. It should be noted that radial, circumferential and lateral are synonymous terms and the term radial is used throughout this text. If a lesion cannot be identified, it is important to correlate with the endoscopic notes and photographs to compare and match the subsequent sections and tissue blocking. In the case of EMRs, all pieces may not contain the lesion, as multiple EMRs are sometimes performed to achieve clearance. In contrast, an ESD should essentially contain the lesion in question.

3. Sectioning

After fixation, the specimen is dried off by gentle blotting and deep and radial margins painted with an ink/dye. Assessment of both radial and deep margins is essential in an en bloc ESD specimen, unlike in multi-piece EMRs.

In EMR specimens, a specific comment on radial margin may not be required unless there is a specific request by the endoscopist. However, inking of radial margins helps in confirmation of full-face sections at microscopic evaluation of an EMR. Sections targeting the closest point of any visible lesion to the radial margin or specified margin, or the deepest part of the specimen, should be included. If there is a visible lesion, the first incision may be made to include the part of the visible lesion with the minimum distance to the margin. Further incisions can be made parallel to the first at intervals of 2-3 mm (Figure 5). Slices that are too thin result in incomplete sections on the slides. The first slice may be flipped (embedded on the margin edge) to allow the margin to be sectioned first during histological evaluation. Depending on the size of the specimen (>10 mm), the first and the last slices may be wide and sectioned perpendicular to the margin for better assessment of the radial margins. This allows for perpendicular rather than 'en face' margin assessment. However, this is best for larger ESD specimens and is not recommended on small specimens. Sectioning may be difficult in technically unsatisfactory ERs such as those with ragged margins. One major issue in such samples is unsatisfactory margin assessment and the standard approach may be modified to achieve best outcomes. Excessive thermal cautery during the procedure also hampers accurate microscopic assessment, causing artifactual changes that hinder margin assessment (Figure 6 a and b). For ampullectomy specimens, a slice ideally will include the distal bile duct sectioned longitudinally. A diagram or photograph of specimen(s) and mapping showing the serial slices and a key to the blocks is most helpful.

4. Numbering and orientation of slices into cassettes

Tissue embedding is a critical step in producing high-quality diagnostically accurate sections. Poor orientation of tissue slices can result in the loss of superficial tumor tissue through trimming or loss of deep submucosal tissue, resulting in the inability to diagnose submucosal invasion and loss of the deep margin. Thus, to optimize this process, all sections should be embedded 'en face' or on edge. Optimally, the slices are also laid sequentially in the cassette, with a sponge to hold them in place (if needed) for better orientation. In cases of large specimens with multiple slices, no more than 2-3 slices should be placed in any one block, to allow for optimal orientation (Figure 5). Supervision of the embedding process by the pathologist is advisable in some cases, especially when the pieces are small.

Microscopic evaluation

Initially, two to three H&E-stained levels per block are sufficient for EMR (Figure 7). One section may be sufficient for ESDs as they are large specimens. Deeper levels can be requested on selected blocks, in particular to ensure accurate assessment of the level of invasion and the status of the margins. Careful, multiple deep or serial levels are mandatory if sections are incomplete and inked margins and submucosa are not included. The same is true if the lesion is not observed, as early invasive lesions can be very small.[37] However, one must be aware that excessive trimming at the time of sectioning may cut through small lesions. This approach is vital to identify foci of invasion as well as accurate assessment of crucial pathological prognostic features. When appropriate, the laboratory should be instructed to preserve ribbons in between

levels since they can be used for ancillary stains in instances where confirmation is required for foci of lymphovascular invasion, for assessment of detailed depth of invasion (see under esophagus) or for any other reason.

Recommended approach to reporting

Depth of invasion, presence of adverse microscopic features, and margin status are important risk factors relevant to the management of early neoplasia throughout the gastrointestinal tract. In order to assess these features, a systematic approach is advocated. These are essential elements that should be reported irrespective of the site. Site-specific details will be discussed later. Table 5 summarizes the criteria for cure.

1. Tissue layers present:

The resection plane for ERs is submucosa, meaning 3 layers (mucosa, muscularis mucosae and submucosa) should be clearly identified. The type of mucosa (e.g. squamous, glandular or mixed) and tissue layers (e.g. muscularis mucosae (mm)), submucosa (sm)) present need to be recorded. The presence of duplicated muscularis mucosae in Barrett's esophagus must be considered, as it can interfere with evaluation of depth of invasion. Implications are discussed below. Deep and radial margins ought to be identified and documented as well.

The entire specimen should be examined as lesions may be very small. Inked deep and radial margins should be identified in all sections. In addition, esophageal EMR specimens often

demonstrate significant artifact across the mucosal surface with denudation, hemorrhage and necrosis. Artefactual holes due to aggressive use of pins also can interfere with microscopic assessment. Scarring may be present in repeat endoscopic mucosal resections, which can distort the tissue and hamper accurate microscopic assessment, in particular assessment of depth of invasion. Fibrosis in particular may mimic desmoplasia, which generally is only present when there is submucosal invasion.

2. Type of lesion

The lesions may represent intraepithelial neoplasia, invasive carcinoma or other lesions, including neuroendocrine tumors or mesenchymal neoplasms.

3. Histological subtype.

Histological subtype of invasive carcinoma should be documented according to established criteria and guidelines (squamous, glandular, mesenchymal or other).

4. Size of lesion/s: When multiple/multifocal lesions are present, the size range in mm or sequential size of all lesions should be documented.

5. Presence of an invasive lesion

5.1 Depth of invasion:

Depth of invasion should be evaluated for either intramucosal carcinoma or submucosally invasive malignancy. Depth of invasion into the submucosa can be recorded in microns since this information will guide the need for surgical management and/or other forms of therapy as definitive treatment (Table 4).[1,38] Description of submucosal invasion in 3 levels into inner 1/3, middle 1/3 and outer 1/3 is possible only if muscularis propria is present, while generally endoscopic resections include only mucosa and submucosa. Therefore, measurement of the submucosal invasive component in microns is recommended. [38] The deepest level of invasion of a mucinous carcinoma is equated to the deepest level showing mucinous material. If a lympho-glandular complex is involved by carcinoma but otherwise the submucosa is not involved, the lesion ought to be staged as /pT1a in upper GI sites. Detailed assessment of level of invasion into muscularis mucosae is important in intramucosal adenocarcinomas of the esophagus (to be discussed in a later section). Similarly, guidance for measurement of invasive carcinomas associated with an adenomatous component in the colon and rectum will be discussed in the appropriate section below.

5.2 Margin status:

The margin status is cardinal and ought to be commented on and recorded separately both for deep and radial margins in oriented specimen. The report should clearly indicate if the margins are involved by carcinoma (radial and deep) or intraepithelial neoplasia (IEN)/dysplasia (radial). Currently there is no consensus or evidence-based data on the definition of the clear “deep margin” on endoscopic resections throughout the GI tract. The clearance between the invasive front of the neoplasm[s] and the deep margin is measured in microns in some centers but not universally recommended. Obviously, it is necessary to state when neoplastic tissue is present at

the deep margin. Radial margin status is not essential to be documented in multi-piece EMRs, unlike ESDs. However, the endoscopist may request specific pieces deemed to contain particularly concerning lesions to be assessed similar to an en bloc ESD. If specimens are oriented, specific margins should be commented on for adequacy of resection. Decision about margin assessment in specific situations needs clear communication with the endoscopists. Site specific issues related to margin status will be discussed later.

5.3 Lymphovascular invasion

The presence or absence of lymphatic/capillary (lymphovascular) and large (vein and artery) caliber vessels must be reported. Special histochemical (elastin stains such as Movat's, elastic trichrome etc.) stains are useful to demonstrate venous invasion. D2-40 immunohistochemistry is useful to demonstrate lymphatic invasion.

5.4 The presence or absence of perineural invasion may be recorded.

5.5 Tumor budding

Tumor budding, defined as the presence of single cells or small groups of less fewer than 5 undifferentiated cells at the invasive front of the carcinoma, should be reported in the colon and rectum using the international guidelines.[1,39-41] Currently there is insufficient evidence to support the routine reporting of tumor budding in other sites and, should be considered optional as well as investigational in upper GI lesions.[42-45]

6. Histologic grade

Histologic grade of intraepithelial neoplasia/dysplasia or invasive malignancy should be reported as appropriate for the various histologic subtypes according to established guidelines.[46]

7. Additional findings

The presence of additional pathologies and changes related to previous treatment must be reported. This includes the presence of Barrett's esophagus, the presence of chronic gastritis with intestinal metaplasia, the detection of *Helicobacter* organisms, and the presence of features of colitis in colonic specimens.

SITE-SPECIFIC ISSUES

ESOPHAGUS

Barrett's Esophagus

Endoscopic management has become the standard of care in patients with Barrett's dysplasia and early esophageal adenocarcinoma and has supplanted surgical resection, with its significant morbidity. [17,18,47-49] Cohort studies have shown that endoscopic therapy for IMCs have similar long-term disease-specific survival to surgery, but lower treatment-related morbidity and mortality rates.[50-52] It has not only resulted in cure for many, but also helped to accurately stage disease with improved measurement of depth of invasion and nodal metastatic risk.[53-58]
Long-term prospective studies have showed high efficacy, safety and cost benefit of EMR in the management of dysplastic Barrett's esophagus.[59-65] Depth of invasion and adequacy of resection dictate the curative success of endoscopic treatment of early Barrett's neoplasia as well as opportunity for accurate staging.[54-58]

For lesions with the high likelihood for submucosal invasion (i.e. > 20 mm in diameter) with a bulky intraluminal component, it may not be possible to resect 'en-bloc'. However, these lesions only represent <10% of cases of early esophageal neoplasia, and the advantages and disadvantages of EMR and ESD need to be considered.[66] Given the reported high risk of lymph node metastasis, early guidelines recommended surgical treatment for submucosal Barrett's cancer.[51-54] However, the suspected high risk of nodal metastases (thought to be up to 50% in cases of submucosal cancers) in retrospective surgical series was likely overestimated, since they often did not differentiate between different levels (i.e., depths) of submucosal infiltration. [38,56-58,67-70] Recent endoscopic series have reported a lower risk (0-2%) when superficial submucosal invasion is ≤500 μm (measured from the bottom of the muscularis mucosa) and there are no other associated histological risk factors[38,56,68-70]

There are special issues that need to be considered when evaluating Barrett's esophagus associated neoplastic lesions. Assessment of level of invasion is complicated by the well-recognized duplication and resulting distortion of muscularis mucosae.[71-73] (Figure 8) Given the importance of depth of invasion for further management and staging implications, this abnormality should be recognized and appreciated. The muscularis mucosae is duplicated and distorted in up to 92% of Barrett esophagus. This results in creating an inner and an outer layer of muscularis mucosae (Figure 9). These changes also result in thickening of muscularis mucosae and frequent prolapsing of fibers into the superficial lamina propria. The outer layer is thicker and organized and represents the true and original muscularis mucosae, while the inner muscularis mucosa is more disorganized and may blend with the lamina propria. The space in between the split muscle layers may resemble submucosa but can be identified by appreciating the presence of loose connective tissue with capillaries and dilated thin-walled blood vessels. In

contrast, submucosal vessels are different in that they are not only of large caliber and dilated but also show a characteristic thick wall (Figures 8 and 9). Submucosa also contains fat and submucosal glands (Figure 8b).

Appreciation of the concept of duplication of muscularis mucosae is vital to avoid pitfalls in the assessment of depth of invasion of Barrett's-related adenocarcinomas. Thickened muscularis mucosae may be misinterpreted as muscularis propria, resulting in over-staging of intramucosal carcinomas [pT1a] as muscularis propria invasion [pT2] (Figure 10). If the space between the duplicated muscularis mucosae is misinterpreted as submucosa, a pT1a lesion can be over-staged as pT1b. Both of these errors may result in unnecessary surgery. Differentiation of deep muscularis mucosae invasion from submucosal invasion may also be problematic, resulting in misinterpretation of pT1a and pT1b carcinoma. Duplicated muscle strips can also be seen among the noninvasive neoplastic glands, raising the suspicion of an invasive lesion (pTis/high grade dysplasia vs pT1a).

There is emerging evidence that the level of invasion within the muscularis mucosae also may have an impact on the behavior of pT1a adenocarcinomas.[58,71] There is also evidence suggesting that invasion into the space between the 2 layers portends a low risk of lymph node metastasis, similar to carcinomas that invade lamina propria only. It is possible that superficial muscularis mucosae invasion (into the inner layer and the space in between) has different implications than invasion into deeper/outer muscularis, although data is not consistent[71,72,74]

Another important recognition is that endoscopic ultrasound (EUS) examination is less accurate for staging of pT1 adenocarcinomas due to this issue of duplication and distortion of the muscularis mucosae. A recent study has established that EUS has no role in staging of early esophageal adenocarcinoma, as EUS often resulted in over-staging.[75,76]

The above issues have led to introducing 2 systematic methods of differentiating depth of invasion of pT1a carcinomas into different layers of mucosa in the Barrett setting (Table 5). The first method is based on recommendations by AJCC (8^{th} edition) into 3 levels; m1-m3, as described by Hölscher et al.[54,77] (Figure 11a). This method is generally more appropriate for use in squamous carcinomas of the esophagus (see below). The second method, the Vieth and Stolte system, is more comprehensive; this separates intraepithelial lesions from invasive carcinomas clearly and divides pT1a adenocarcinomas into 4 levels, taking the duplicated muscularis mucosae into consideration. This is therefore more appropriate for use in esophageal adenocarcinomas.[9,15,16,58] (Figure 11 b). Detailed assessment of the different layers helps appreciation of issues related to duplication of muscularis mucosae to avoid pitfalls. The method used should be recorded in the report.

In both systems, submucosally invasive carcinoma (pT1b) is sub-divided as sm1-3 (Figure 12). Generally, submucosal invasion is divided into 3 tiers (sm1 – superficial 1/3 submucosa; sm2 – intermediate one third of submucosa and sm3 – outer one third of submucosa). This division may be difficult, as it depends on the amount of submucosa included in the specimen (as in ER specimens). Since there is no muscularis propria for a landmark, the division is not accurate. The Paris endoscopic classification of superficial neoplastic lesions have recommended measurements in microns as an alternative.[38]

Currently, measurement of submucosal invasion in microns may be helpful due to recent suggestions that low risk submucosal invasive cancers (LR-SMIC), defined as pT1sm1,

submucosal invasion ≤500 μm) without any other histological risk factors for nodal metastasis may be managed by endoscopic therapy, followed by close endoscopic follow-up.[1]

Depth of invasion in the submucosa should be measured from the outermost extent of the outer (true) muscularis mucosa (Figure 12c). As this can be difficult to assess on H&E stained slides, special stains (ie trichrome, HPS) or immunohistochemistry (Desmin) may be of use to determine the lowest edge of the muscle layer. Some invasive carcinomas may be depleted of any appreciable muscularis mucosa (mm) in the invasive front. If neoplastic glands do not extend beyond the bottom aspect of the imaginary muscularis mucosa compared to that of the adjacent intact mm, they are best classified as intramucosal carcinoma (pT1a) with an explanatory note (Figure 12 d). If neoplastic glands are noted in the vicinity of submucosal large caliber vessels the lesion should to be classified as submucosally invasive carcinoma (pT1b) even if the location with respect to the muscularis mucosae cannot be defined. Accurate measurements require well-oriented specimens and the presence of intact muscularis mucosae somewhere in the specimen - absence of these factors will lead to inaccurate measurements.

Squamous cell carcinoma of esophagus (figure 13)

Invasive squamous cell carcinomas (SCC) that do not invade the muscularis propria are divided into pT1a (invasion of mucosa) and pT1b (invasion of submucosa). Since SCC generally do not develop the duplicated muscularis mucosae of Barrett's esophagus-associated adenocarcinomas, subdivision of intramucosal adenocarcinomas can be done by the M1-M3 methodology.Neoplastic squamous epithelium limited to the epithelium (m1) or lamina propria (m2) and completely resected on endoscopic resections are considered cured in the absence of risk factors such as poor differentiation and lymphovascular invasion .[78,79]

The risk of lymph node metastasis is increased for lesions invading into the muscularis mucosae (m3) and is significantly increased with involvement of the superficial submucosa (1); the latter has been estimated between 5-24% . This is also reflected in the definition for a smaller cut-off level for superficial submucosal invasion (200 µm for squamous sm1 versus 500 µm for Barrett's sm1). It is suggested that m3 and sm1 squamous cancers with submucosal invasion ≤200 µm without any other risk factors and negative deep resection margin be considered relative indications for endoscopic rather than surgical treatment. [70,80]

EMR is less suited to esophageal squamous neoplasia since small lesions [i.e., < 10-15 mm in size] that can be resected en-bloc are relatively rare. A further limitation is that from a theoretical standpoint, complete resection of the submucosal glands may not be achieved - they may harbor squamous neoplasia extending down the ductal shaft from the luminal epithelial layer. Thus, ESD is the preferred and commonest method of resection for esophageal squamous neoplasia.

STOMACH:

Endoscopy is an accepted first-line therapy for early gastric cancer in lesions with very low likelihood of lymph node metastasis.[20,81]

The 2016 Japanese guidelines divide the indications for endoscopic therapy of early gastric cancer into absolute and extended. [20,81]Endoscopic resection is absolutely indicated in macroscopically (clinically) intramucosal T1a (clinical T1a), differentiated carcinomas measuring less than 2 cm in diameter. The factors to consider are: size of lesion, presence of ulceration, histologic type, resection margin status, degree of differentiation, lymphovascular invasion, and depth of submucosal invasion (measured in microns).[10,12,13,20,81] (Figure 14-16) Therefore, these parameters should be clearly described in the pathology report.

When completely resected with absent vascular infiltration and no other unfavourable criteria, the risk of lymph node metastasis is extremely low and the procedure is deemed curative. (Table 6). [20,81]ER is considered non-curative if mucinous adenocarcinoma is found in the submucosal layer, regardless of the differentiation of the rest of the carcinoma, in the refined criteria described by the Japanese Cancer Association (Figure 16b). [20]

Due to the noted limitations of EMRs, the vast majority of all early gastric cancer lesions in Japan are now treated by ESD if the technical expertise is available. Once en-bloc endoscopic resection has been performed and the pathologist has evaluated the specimen, the resection can be considered as curative or non-curative.

DUODENUM

Historically, duodenal adenomas have been managed by radical surgery or more conservative local surgical excision, approaches respectively associated with increased morbidity/mortality and a high rate of local recurrence.[82] Additionally, in a small percentage of cases, duodenal adenomas can involve the ampulla, which presents an additional level of complexity when contemplating surgery. For these reasons, endoscopic management has become increasingly popular, offering considerable advantages in terms of organ preservation, risks, recovery and length of hospital stay. [83,84]

In capable hands, the overall success rates of EMR for complete removal of duodenal adenomas ranges from 59–100%, with an overall successful removal rate of 92% in 6 published series. [68] In most cases, this is achieved with a single attempt at endoscopic removal; however, with increasing size of lesion and circumference involvement over 25%, some patients require 1-2 additional procedures to achieved complete removal.

In contrast to the colon where similar endoscopic techniques are utilized for polypectomy, the extensive second-order arterial blood supply and thin duodenal wall contribute to intraprocedural bleeding (0%-29.2%), delayed bleeding (0%-16.7%), and thermal injury-related perforation (0%-4.3%)[81]

In comparison to early cancers of the stomach and colon, limited data are available regarding the risk of lymph node metastases in early duodenal cancer after endoscopic resection. It appears that IMC carries a very low risk of lymph node involvement, provided that there are no other adverse histological features, namely poor differentiation, signet ring cell type or lymphovascular invasion. In lesions with submucosal invasion (sm1 to sm3), the risk appears to be at least 5%[85-88] Therefore, those should be considered for radical surgery. This emphasizes the importance of accurate histologic staging and the need for excellent histologic evaluation and reporting.

With adenomas involving the ampulla, dysplastic lesions can spread along the ampullary or pancreatic ducts. Non-invasive involvement of the duct at the deep margin is a unique problem and a cause for local recurrence; hence the common bile duct/ampullary duct margin needs to be identified and assessed.

COLON AND RECTUM

In the last decade, there has been extensive technical development in endoscope design aimed at improved detection of colonic neoplasia and enhanced lesion characterization. These new features include high-definition endoscopes with push -button technologies including optical and digital zoom and electronic push-button electronic

chromoendoscopy (e.g. NBI, FICE, i-SCAN). These advances in optical diagnosis of polyps have resulted in accurate typing and enhanced prediction of submucosal invasion in a polyp.

There have also been equally significant advances in endoscopic management of advanced lesions > 20 mm, with surgical management no longer considered the treatment of choice[89-92] In the West, EMR is preferred due to its comparative technical ease, efficiency, effectiveness, low complication rate and excellent long-term outcomes.[90-92] Major limitations of piecemeal EMR for advanced lesions include recurrence and difficulty with assessment of margins in the setting of incidental early submucosal invasive cancer.[93,94]

En bloc excision by ESD offers more accurate histological assessment, in particular for early, low-risk submucosal invasive cancer (LR–SMIC) but has its inherent technical challenges[95-98] According to Western studies, given that only 8% of colorectal endoscopic mucosal resections show submucosal invasion, ESD is reserved for those lesions displaying endoscopic features predicting a higher risk of early cancer, with the majority of lower-risk lesions managed by piecemeal EMR[99,100]

In the lower gastrointestinal tract, in contrast to the upper tract, invasive adenocarcinomas are diagnosed only in the presence of submucosal invasion. Advanced neoplastic lesions that do not invade into the submucosa of the large intestine are regarded as having no risk for lymph node metastases and are commonly designated as low-grade or high-grade dysplasia, even in the rare cases where lamina propria invasion is demonstrated. Consequently, the term intramucosal carcinoma is discouraged.

Similar to the rest of the gastrointestinal tract, pathological risk factors predict for 2 main outcomes of an invasive carcinoma: 1) risk of lymph node metastasis and 2) risk of residual disease at the EMR/ESD site.

Similar to the previous discussions, in the colon there are 2 groups of pathological risk factors, with some additional factors not utilized in the foregut.

1) Qualitative factors

These include poor tumor differentiation; high or intermediate tumor budding, lymphatic and venous vascular invasion, positive margin status and microsatellite instability status (see ancillary stains below). Of these, poor tumor differentiation and vascular invasion (lymphatic and venous) are the best predicators of lymph node metastases. [101-103] There is now evidence that tumor budding, a manifestation of dedifferentiation at the invasive tumor edge, is an adverse risk factor.[39,40,41,101,102,104]A recent consensus paper has suggested that tumor budding is assessed by counting the number of foci in one hotspot (in a field measuring 0.785 mm^2) at the invasive front. It is suggested that the number of buds be divided into a 3 tier grading system with 0–4 buds=low budding (Bd 1); 5–9 buds=intermediate budding (Bd 2); and 10 or more buds=high budding (Bd 3).[41] Poorly differentiated clusters represent a probably related phenomenon of dedifferentiation and are characterized by tumor cell collections of more than 5 cells. There is emerging evidence that poorly differentiated clusters may be an adverse prognostic feature.[105]

2) Quantitative factor (large invasive tumor size)

This is best assessed by direct measurement, in microns, of tumor thickness below the level of the anatomically normal muscularis mucosae or from the ulcer base if the lesion is ulcerated (Figure 17 and c). When the muscularis mucosae is obscured or destroyed by tumor, it is measured from the surface of the lesion (figure 17 b and d). [106]

Submucosal tumor thickness ≥ 1000 μm is associated with increased risk of required lymph node metastases.[11,101-103] This may be because vessels conductive of tumor emboli only exist deeper to this level. Kikuchi levels, which involve determining the relative extent of invasion of the submucosa(into the inner 1/3 is level 1, into the middle 1/3 is level 2 and into the outer 1/3 is level 3) have been described in relation to the risk of invasive carcinomas.[11] However, this evaluation is possible only if muscularis propria is present. Therefore, measurement in microns of the submucosal invasion is recommended. [38] The width of submucosal invasion is also important, with increasing risk for lymph node metastases from ≥ 2000 μm. [11,101,102]

Margin involvement by invasive tumor predicts only for local recurrence (Figure 18 a and b). It does not predict for lymph node metastases. The distance of carcinoma from the margin that confers low risk for local recurrence is still a matter of debate, with some studies showing a clearance of >1 mm to be adequate while others accept 'not at cautery margin', yet others require a 2 mm clearance. [40,,107-111] However, it is generally agreed that clearance of >2 mm is not associated with local recurrence.[101]. Location in the distal rectum has also been associated with an increased risk for local spread.[112] Rectal location may pose a slightly higher risk of lymph node spread in T1 tumors compared to the rest of the colon.[112] The reason for this has not been established.

In conclusion, resection of submucosal low-grade invasive carcinoma with no lymphovascular invasion or tumor budding with invasion <1000 μm and adequate clearance of deep margin is considered curative (Figure 19). When present, the adverse factors are summative in their risk for lymph node metastases. In general, when two or more factors are present, then the risk is particularly high and follow up surgical resection is warranted.[109,113]

ANCILLARY STUDIES

Ancillary tests are of little use to support the diagnosis of classic neoplasia but can occasionally be helpful in some situations as described below.

1. Immunohistochemistry

Cytokeratins:

In rare cases, immunohistochemistry for cytokeratin, particularly AE1/AE3, may be useful for the detection of single infiltrating cells and for demonstration of a subtle infiltrating poorly cohesive carcinoma (stomach) or tumor buds. It can be helpful in delineating the extent of the carcinoma and demonstrating submucosal invasion where it is subtle (ie diffuse type gastric adenocarcinoma) or obscured by inflammatory cell infiltrates. Spindle cell (squamous) carcinoma may express cytokeratin, aiding distinction from primary sarcomas and spindle cell melanoma.

In the case of poorly differentiated carcinoma, high molecular weight cytokeratin (e.g. CK5/6), p63 and/or p40 (which are all typically positive in squamous cell carcinoma) may help differentiate squamous cell carcinoma from adenocarcinoma and basaloid squamous carcinoma esophagus from as the rare adenoid cystic carcinoma.

Smooth muscle markers: Immunohistochemistry for desmin (or another smooth muscle marker) is often helpful. It can help demonstrate the smooth muscle of vessel walls when venous invasion is suspected. It is also useful for highlighting and delineating the muscularis mucosae in areas with suspected submucosal invasion (particularly in the setting of duplicated muscularis mucosae in Barrett esophagus). Some pathologists have also found desmin immunohistochemistry helpful when evaluating neoplasias arising in the ampulla of Vater, as it helps demonstrate the muscle of the sphincter of Oddi.

Vascular markers: Immunohistochemical stains for endothelial cells are helpful in detecting lymphovascular vessel invasion and may demonstrate this feature when it is not seen on H&E-stained sections (e.g. D2-40, CD34, CD31, ERG). ERG nuclear stain is clean and increasingly used to demonstrate vascular endothelium; however, in cases of venous invasion with considerable vessel damage, the endothelium will often be lost. Anti-lymphatic endothelial antibodies (D2-40) for lymphatic vessels can be useful to confirm lymphatic invasion.

2. Histochemical stains:

Stains that highlight the muscularis mucosae (trichrome, hematoxylin phloxine saffron) can be useful aids in evaluating depth of invasion with respect to the muscularis mucosae. Elastic stains (e.g., orcein, Movat's, elastic van Gieson or Victoria blue-H&E) are useful to detect venous invasion. While EMRs and ESDs will not allow for the assessment of extramural venous invasion, recent studies suggest that even intramural venous invasion is clinically relevant.[114] Simple mucin stains such as alcian blue, periodic acid-Schiff or mucicarmine may aid in the differentiation of adenocarcinoma from poorly differentiated squamous cell carcinomas.

Table 7 summarises mandatory features that should be included in reports of endoscopic resections, with site specific comments.

Conclusion:

Mucosal resection specimens offer a viable treatment alternative to invasive surgery for early gastrointestinal cancers; however, their pathological processing and evaluation must be carefully undertaken to allow optimal patient care. This document provides detailed information on mucosal resection specimens from various areas of the luminal gastrointestinal tract to aid and instruct endoscopists and pathologists.

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Table 1: Risk of Lymph node metastases in early GIT cancer

DEPTH OF INVASION		**ESOPHAGUS**		**STOMACH**	**COLON**
		ADENOCARCINOMA	*SQUAMOUS*		
MUCOSA		0-2%[7]	0-5%[9]	0-3%[10]	0%
SUBMUCOSA	OVERALL	26%[8]	45%[8]	19%[10]	5-10%
	SM1	10%[8]	24%[8]	7%[9]	<3%[11]
	SM2	21%[8]	37%[8]	16%[9]	8%[11]
	SM3	49%[8]	48%[8]	26%[9]	23%[11]

Endoscopic resection technique selection for Large (≥ 20mm) and advanced mucosal lesions and early cancer

Site	Histological sub type	Lesion features and size	Technique	Comments
Oesophagus	Squamous	≤ 10mm > 10mm	EMR / ESD ESD	En bloc excision is optimal due to high LNM risk
Oesophagus	Barrett's	Flat demarcated HGD even extensive Nodular or bulky (> 10-15mm) lesions or those with possible minimal SMI	EMR ESD	LNM risk is low. Piecemeal excision is effective and efficient. Enbloc excision is preferred for more accurate histology and reduced local recurrence.
Stomach	Demarcated mucosal dysplasia	Flat, depressed or focally superficially ulcerated lesion of any size. Not obviously deeply invasive cancer.	ESD	All lesions should be treated as cancer with risk of LNM due to presence of gastric mucosal lymphatics. Surgery can always be offered to a fit patient if pathology is unexpectedly advanced.
Duodenum	Adenoma	Any size	EMR	Invasive disease is readily detected and infrequent, even in very extensive laterally spreading lesions. En bloc excision for lesions > 20mm by ESD offers no clinical advantage as any degree of submucosal invasive disease confers a significant risk of LNM and requires surgery for cure.
Right Colon	Laterally spreading adenoma or serrated adenoma	Any size or morphology without high risk endoscopic features for deep SMI.	EMR	Non-invasive lesions of all sizes can be cured by piecemeal EMR. Structured surveillance is necessary to detect and treat recurrence. Covert invasive cancer is infrequent.
Left Colon & Rectum	Laterally spreading adenoma or serrated adenoma	Any size or morphology without high risk endoscopic features for deep SMI. Includes lesions with suspected superficial SMI (Pit pattern Vi), best managed by ESD.	EMR Consider ESD in certain situations where resources are adequate	Same as for right colon. Some infrequent lesion morphologies may contain covert SMI (eg NG LSL with 1s component) and may benefit from enbloc excision by ESD to reduce the need for distal colonic surgery and protectomy and it's perioperative and long term morbidity risks.

Table 3: Endoscopic mucosal resections (EMR) VS. endoscopic submucosal dissection (ESD)

	EMR	ESD
Type of specimen received	Piecemeal	En bloc
Determination of curative resection	Limited	Accurate
Determination of resection margins	Limited	Accurate
Accuracy of assessment of pathological risk factors	+++/++	+++
Technical precision	+/++	+++
Technical challenge	+/++	+++
Resource utilization	+/++	+++
Procedure related complications	+/++	+++

Table 4: Pathological criteria for cure

	ABSOLUTE CRITERIA	EXTENDED CRITERIA
ESOPHAGUS-SQUAMOUS	**pT1a, m1 and m2** with no other risk factors for lymph node metastasis and radial resection margins.	**pT1a m1- m3-and pT1b sm1 (i.e. submucosal invasion ≤200 µm)** with no other isk factors for lymph node metastasis and radial l resection margin.
ESOPHAGUS-GLANDULAR	**pT1a** with no histological risk factors for lymph node metastasis and completely resected.	**pT1bSm1 (i.e. submucosal invasion ≤500 µm**) with no other histological risk factors for lymph node metastasis and radial resection margin
STOMACH	**pT1a**, < 2 cm in diameter, with noother histological risk factors and with no ulceration	No histological risk factors except **1. size >2cm only** **2. Ulceration but < 3 cm** **3. Undifferentiated only** **4. <3 cm, pT1b (SM1, ≤500 µm)** only
COLON & RECTUM	pT1, with noother risk factors, submucosal invasion ≤1000 µm and without tumor budding, completely resected and clear margins	

Table 5: Desirable microscopic features to be included in endoscopic resections

Microscopic features					
	Special site-specific features/comments				
	esophagus- glandular	esophagus-squamous	stomach	duodenum	colon
TISSUE LAYERS PRESENT	Mucosa/ Muscularis mucosa/ submucosa.				
TYPE OF LESION Invasive/Intraepithelial	IEN/Invasive carcinoma				Adenoma, Invasive ca
Histological type	According to established criteria				
Histological grade	Low and high		Differentiated and undifferentiated	Low and high	
Size of lesion (mm)			Determinant for curative resection		
Level of invasion					
Lamina propira/ Muscularis mucosa	pT1a Stolte (m1-m4) AJCC 8th[h] edition (m1-m3)	pT1a AJCC 8th edition (M1-M3)	pT1a	pT1a	pTis
SM invasion Cut off for cure	pT1b ≤500 μm	pT1b ≤200 μm	pT1b ≤500 μm		pT1 ≤1000 μm
Lymphovascular Invasion	Lymphatics, Capillaries, Venous				
Ulceration	Not applicable		Present/absent	Not applicable	
SURGICAL MARGIN STATUS*	Deep, radial* Type of mucosa on lateral margins				
Tumor budding	Optional				Absent/Present Low/high grade
Comments	e.g. residual Barrett mucosa		Intestinal metaplasia, *H pylori*		
MMR proteins	Optional [but recommended]				Lost /Preserved
Phenotype markers	Useful				

*Not required if piecemeal unless specifically indicated and no consensus on the distance of margin clearance; measurement in microns may be given.

Guidelines for endoscopic management of EGC

	Intramucosal T1a (clinical T1a)				Submucosal Cancer	
	Not Ulcerated		Ulcerated		SM1	SM2
	≤20mm	>20mm	≤30mm	>30mm	≤30mm	Any size
Differentiated						
Undiff.						

Classic indications

Expanded Indications

Extended criteria for ESD

Surgery

MOFFITT CANCER CENTER

TABLE 7: SUBDIVISION OF MUCOSAL INVASION IN PT1A ADENOCARCINOMA OF ESOPHAGUS

<table>
<tr><td></td><td>AJCC 8 TH EDIITON</td><td colspan="2">STOLTE METHOD</td></tr>
<tr><td>LEVEL OF INVASION</td><td>SUBDIVISION</td><td>LEVEL OF INVASION</td><td>SUBDIVISION</td></tr>
<tr><td>INTRAEPITHELIAL /DYSPLASIA ONLY</td><td>M1</td><td colspan="2">INTRAEPITHELIAL NEOPLASIA/DYSPLASIA</td></tr>
<tr><td>LAMINA PROPRIA (PT1A)</td><td>M2</td><td>LAMINA PROPRIA (PT1A)</td><td>M1</td></tr>
<tr><td rowspan="3">MUSCULARIS MUCOSA

(PT1A)</td><td rowspan="3">M3

(IRRESPECTIVE OF LEVEL OF INVASION WITHIN THE DUPLICATED MUSCULARIS MUCOSAE)</td><td>INNER MUSCULARIS MUCOSAE (PT1A)</td><td>M2</td></tr>
<tr><td>SPACE IN BETWEEN THE DUPLICATED MUSCULARIS MUCOSAE (PT1A)</td><td>M3</td></tr>
<tr><td>OUTER/TRUE MUSCULARIS MUCOSAE (PT1A)</td><td>M4</td></tr>
<tr><td colspan="4">SUBMUCOSA (PT1B)</td></tr>
<tr><td>SM1</td><td colspan="3">SUPERFICIAL ONE THIRD OF SUBMUCOSA</td></tr>
<tr><td>SM2</td><td colspan="3">INTERMEDIATE ONE THIRD OF SUBMUCOSA</td></tr>
<tr><td>SM3</td><td colspan="3">OUTER ONE THIRD OF SUBMUCOSA</td></tr>
</table>

Figure 1

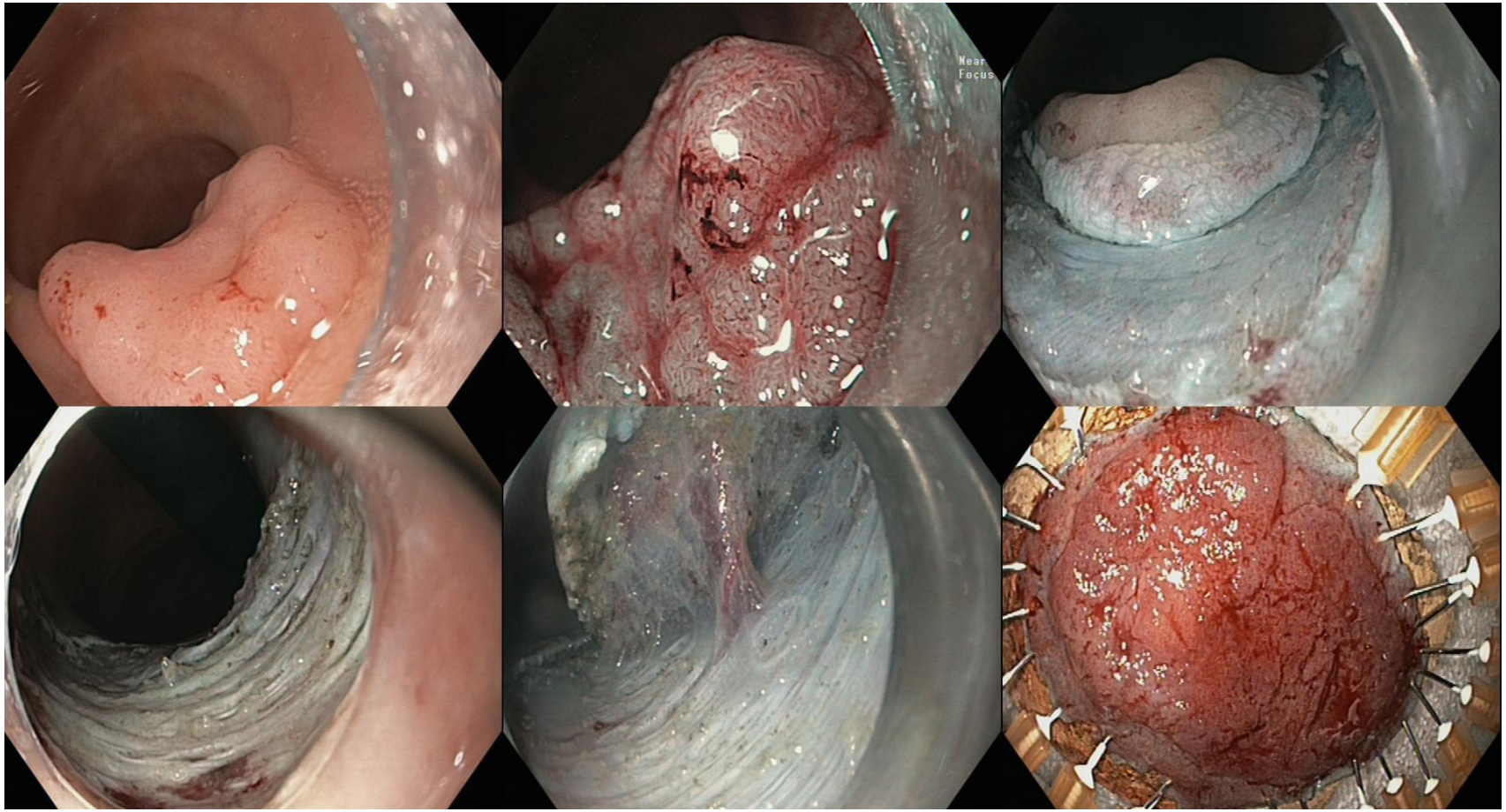

Figure 2

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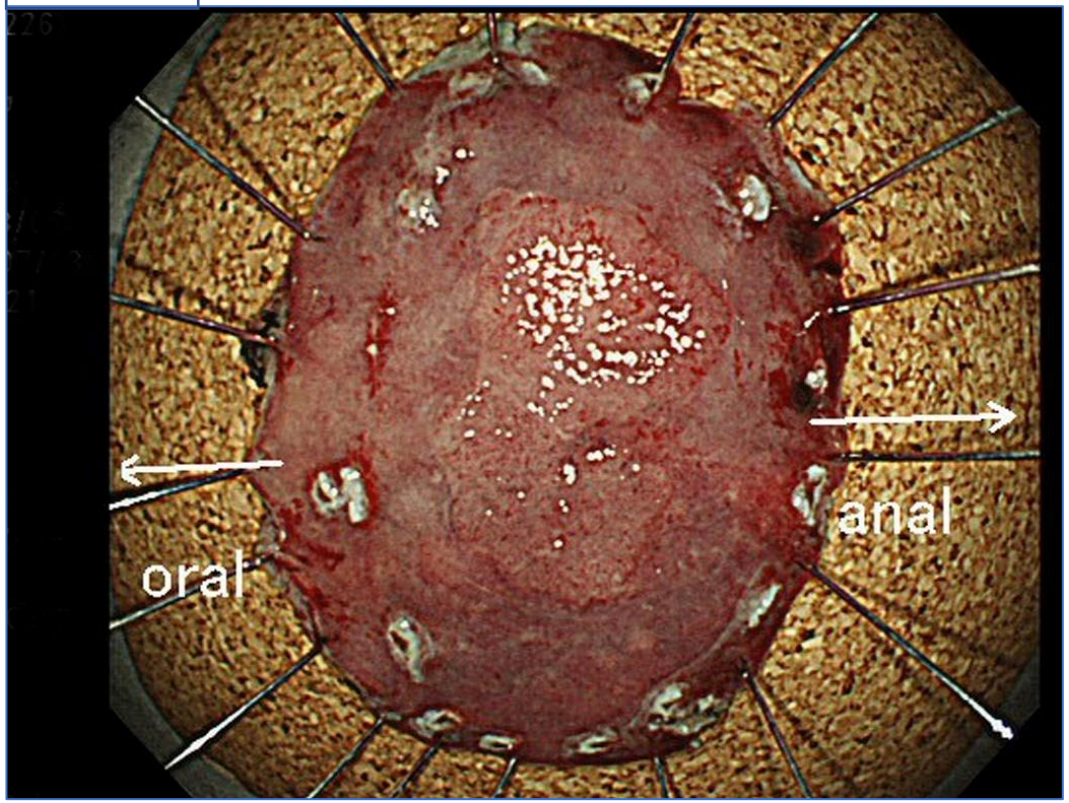


b

Figure 3

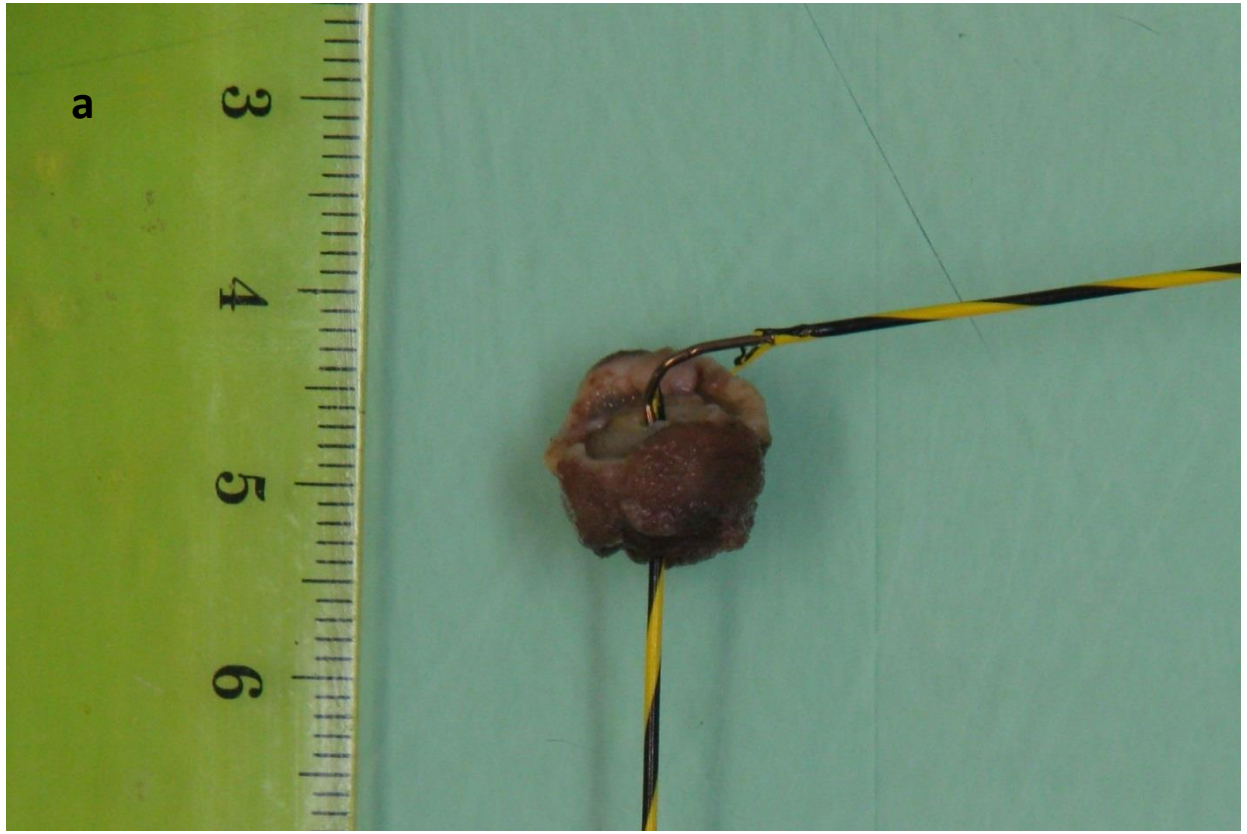


Figure 4

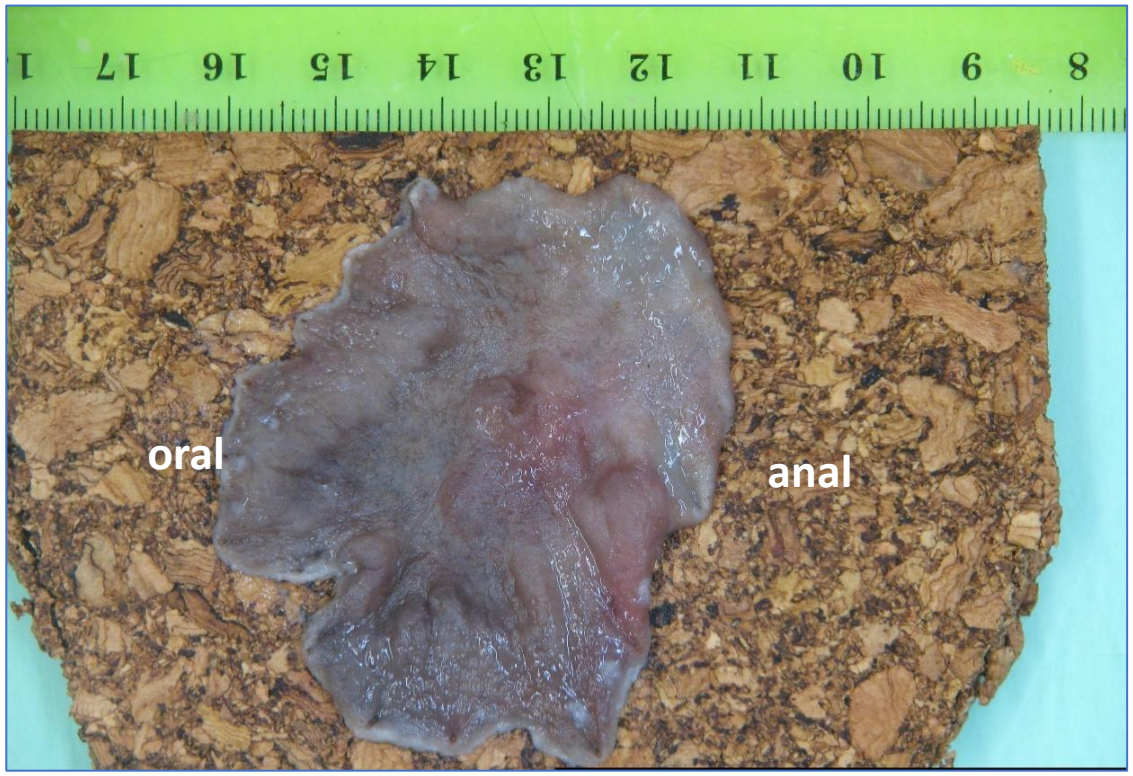


Figure 5

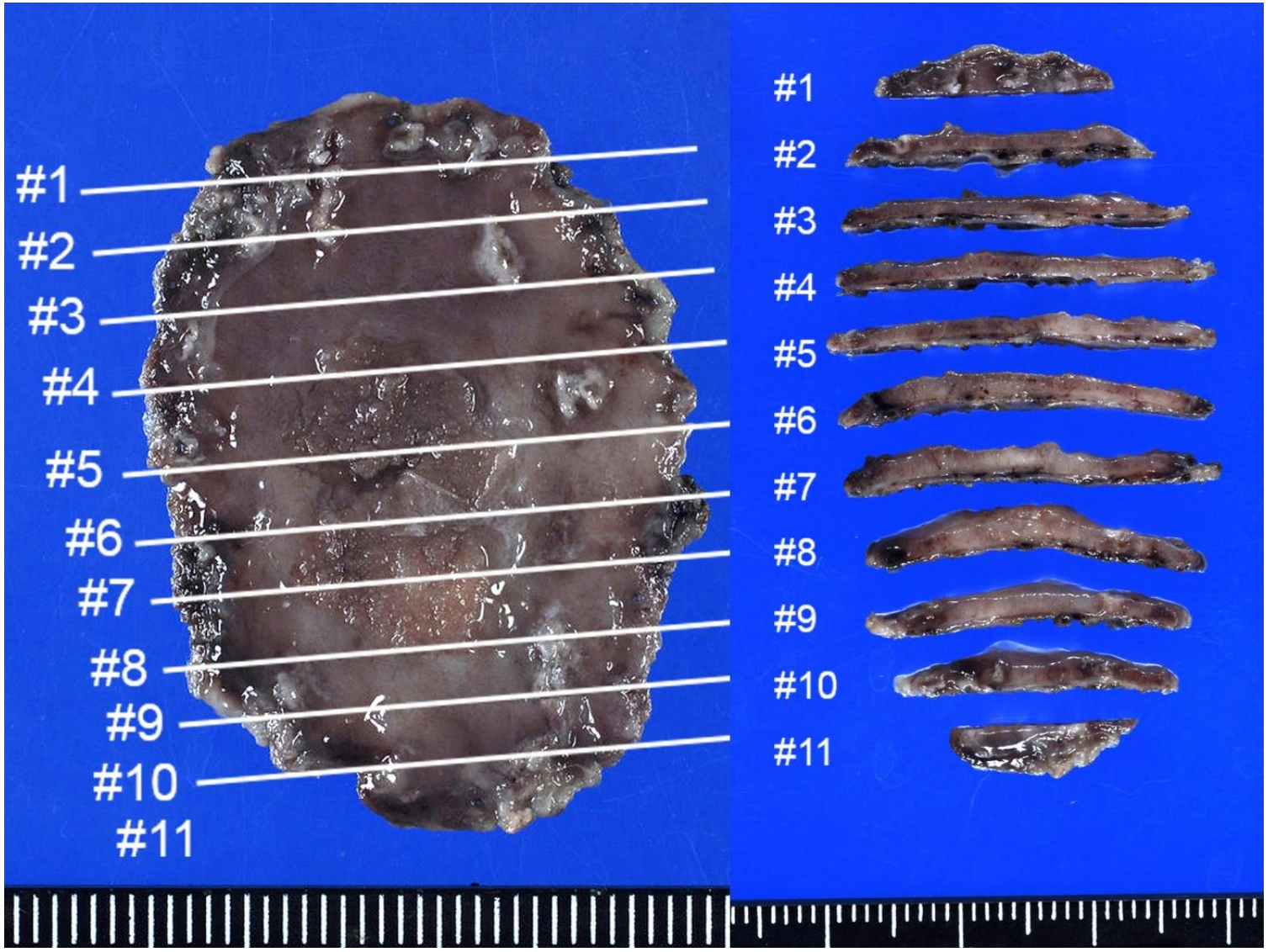
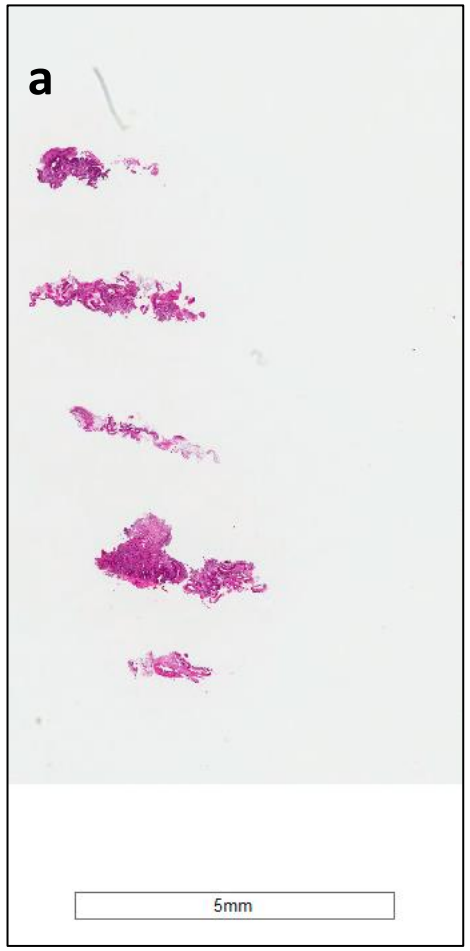
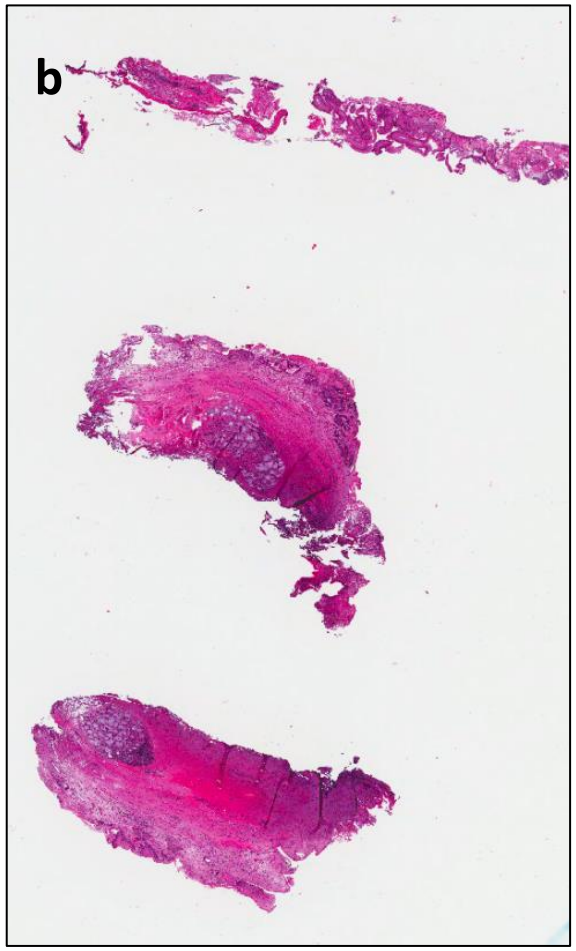


Figure 6 a-c





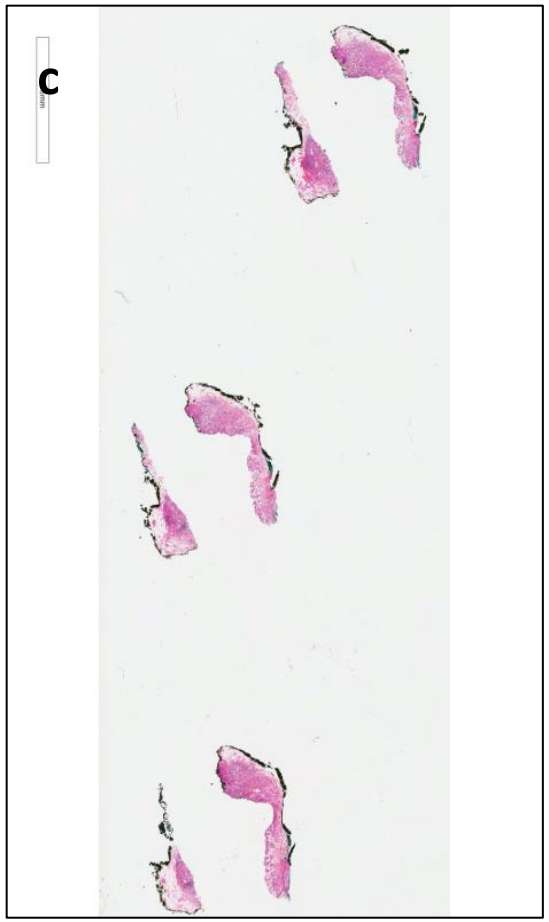
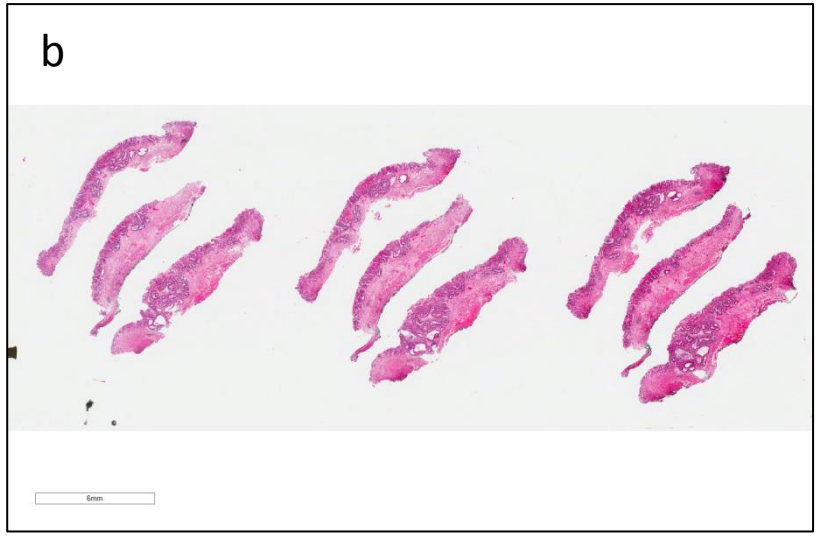


Figure 7



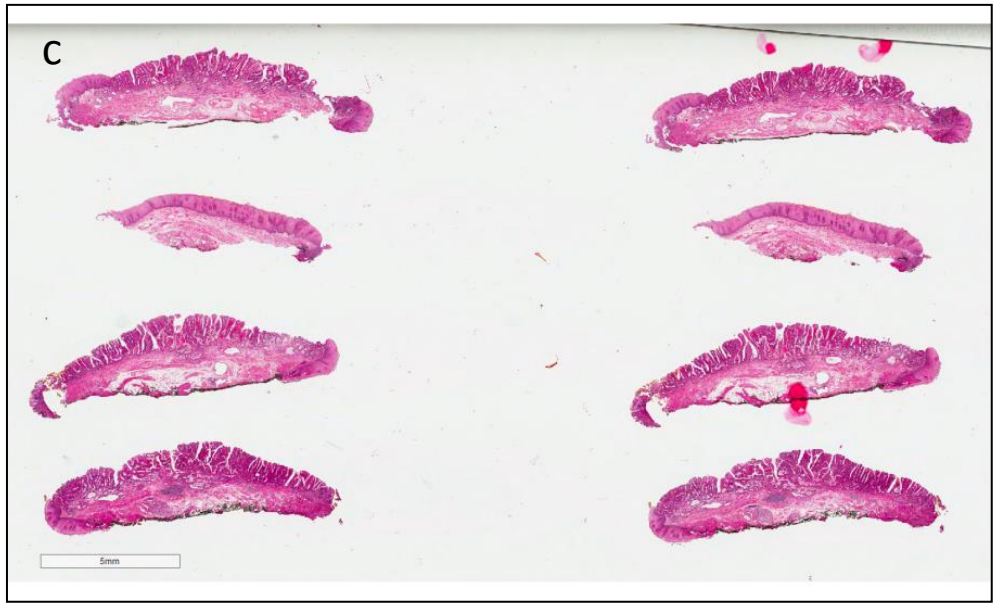
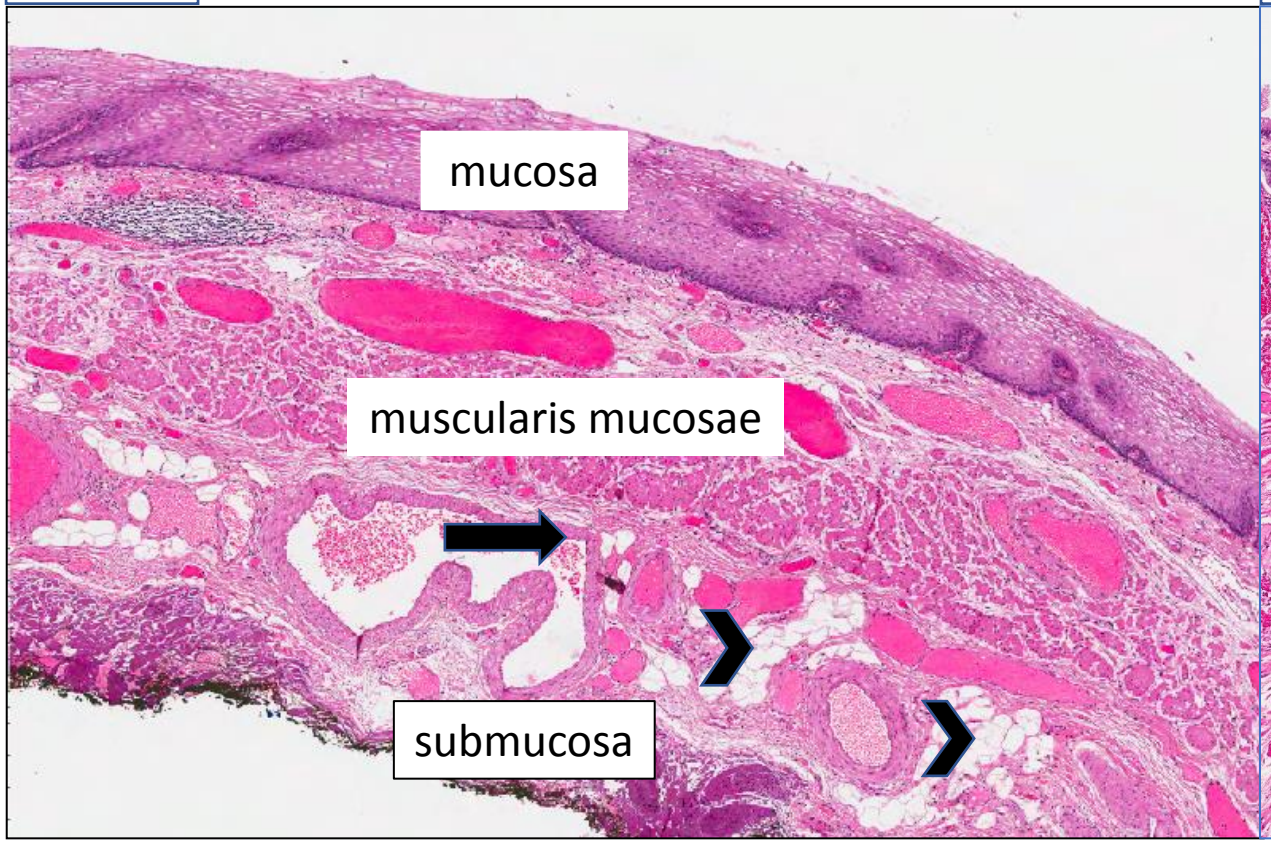


Figure 8

a


mucosa
muscularis mucosae
submucosa

b

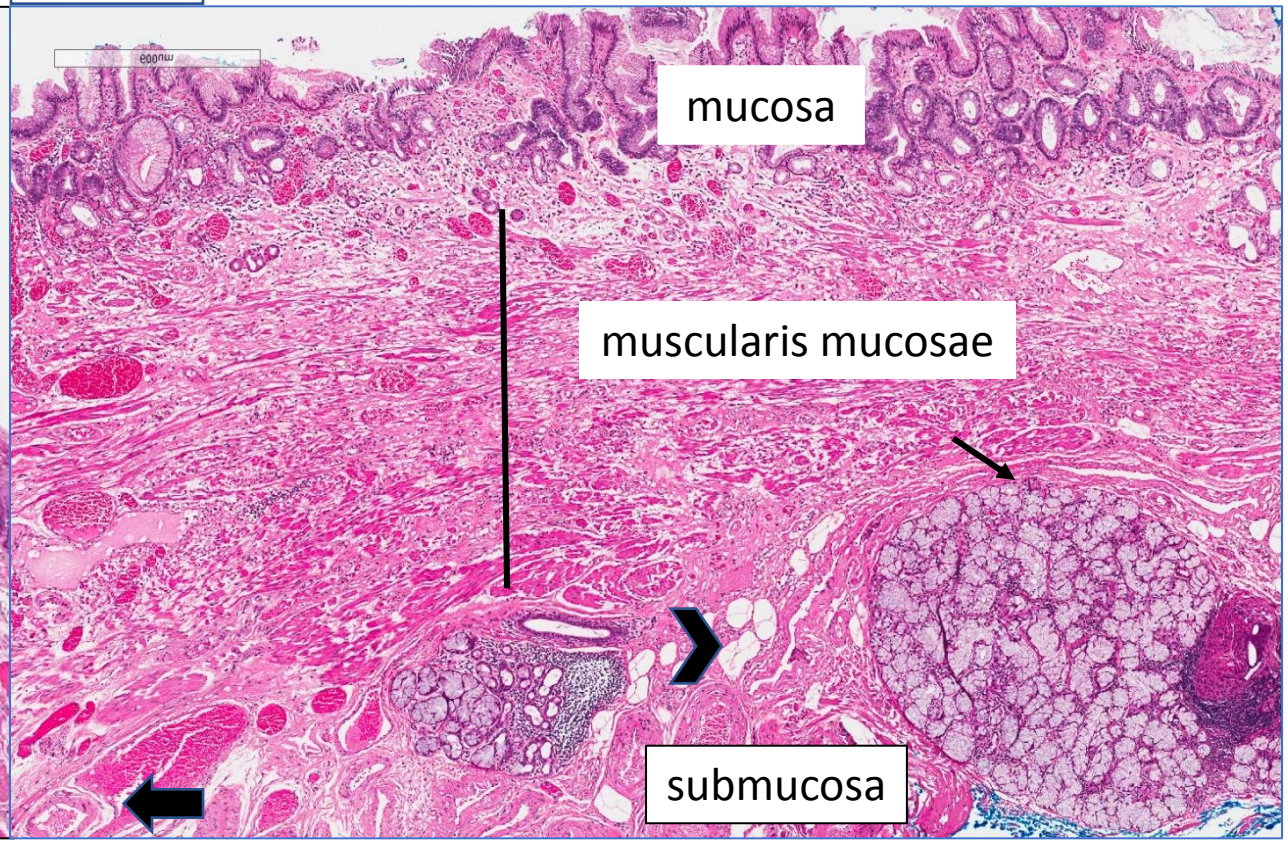

mucosa
muscularis mucosae
submucosa

Figure 9

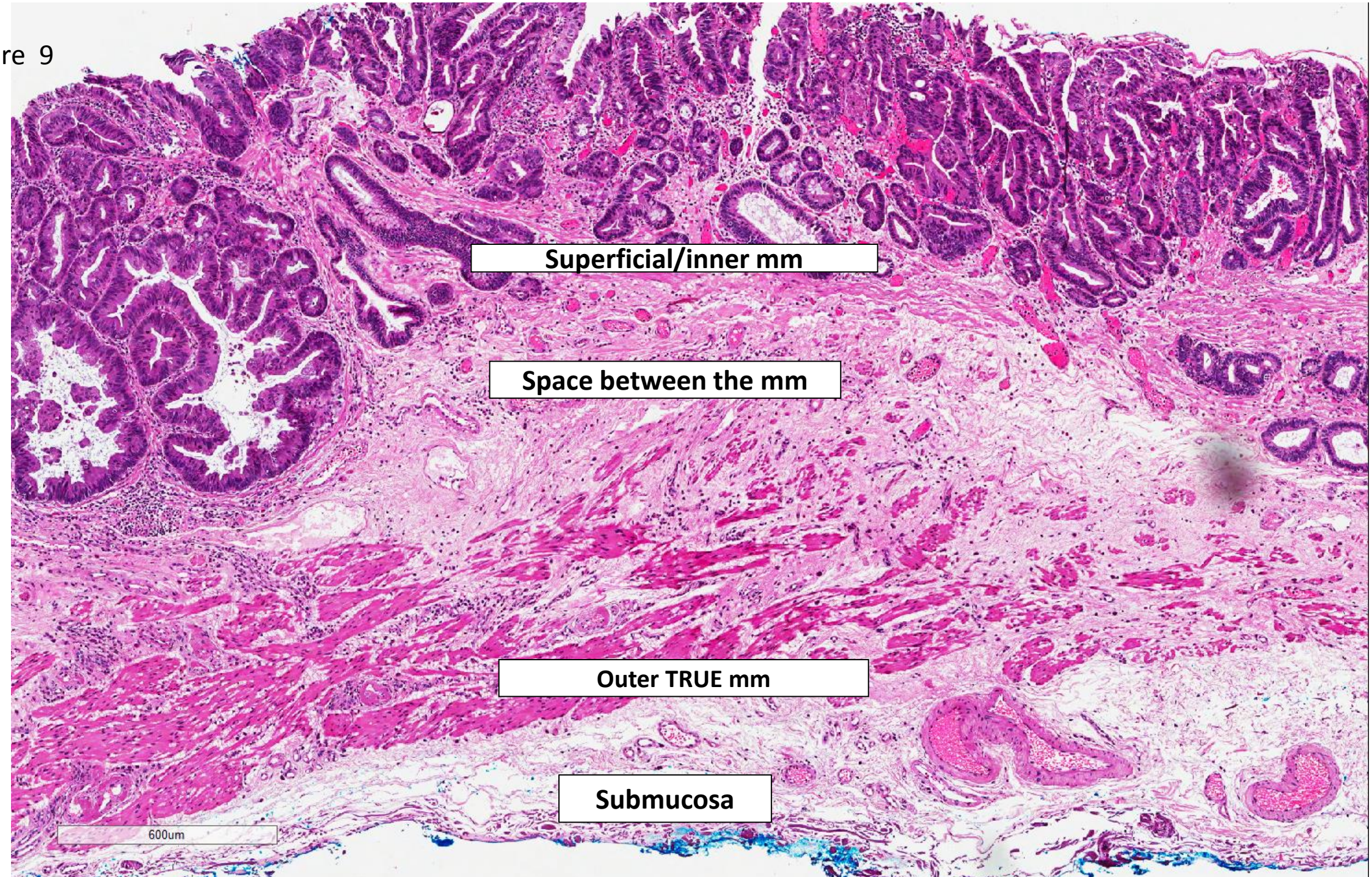

Superficial/inner mm
Space between the mm
Outer TRUE mm
Submucosa
600um

Figure 10 **T1a adenocarcinoma that should not be mistaken as T1b (submucosal invasion) or pT2 (muscularis propria invasion)**

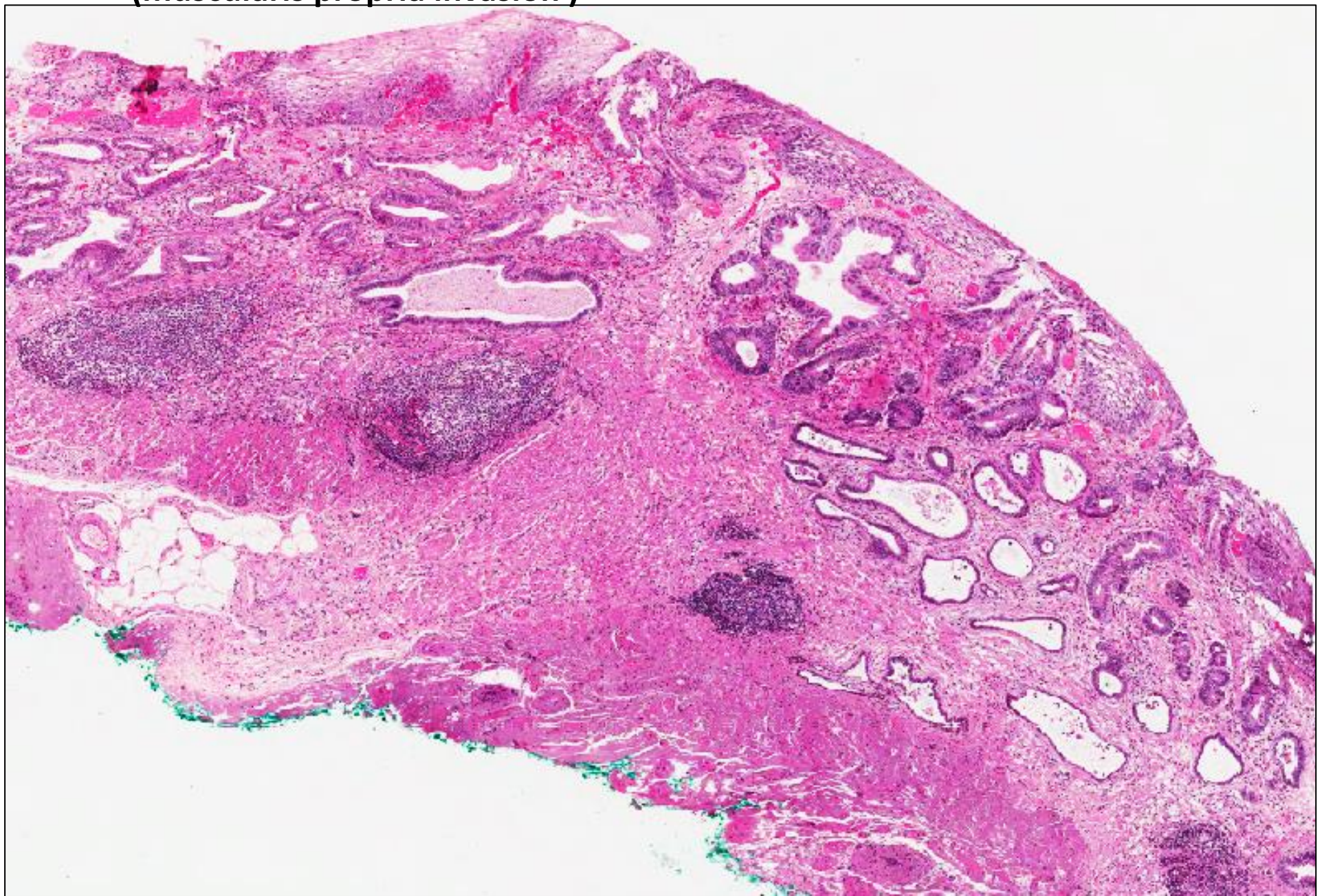


Figure 11a

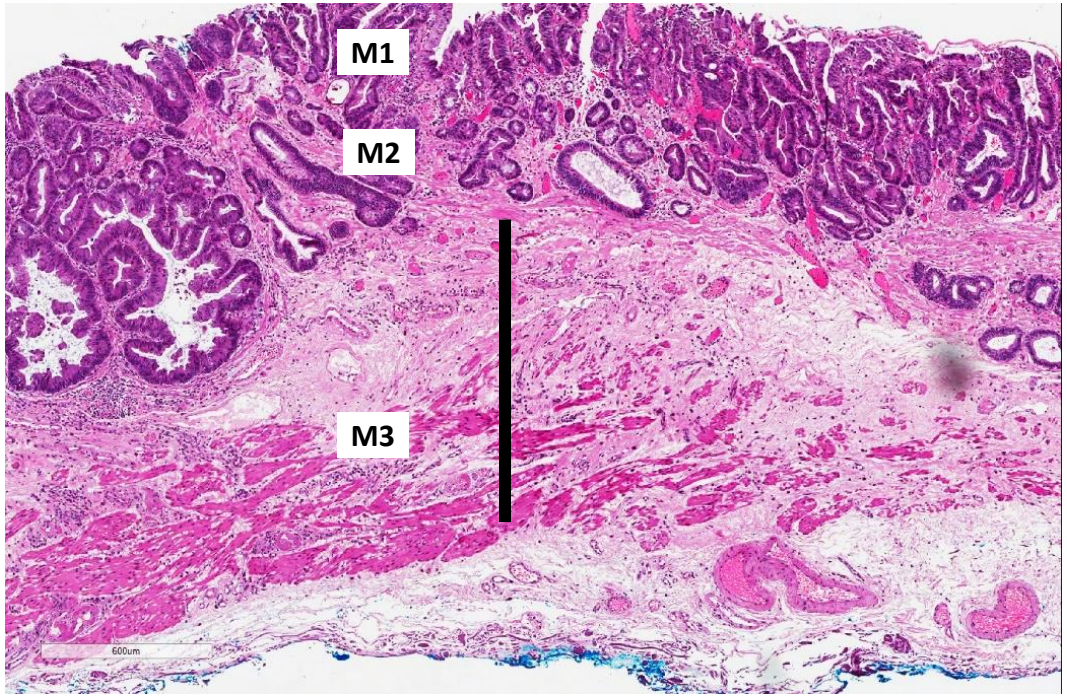
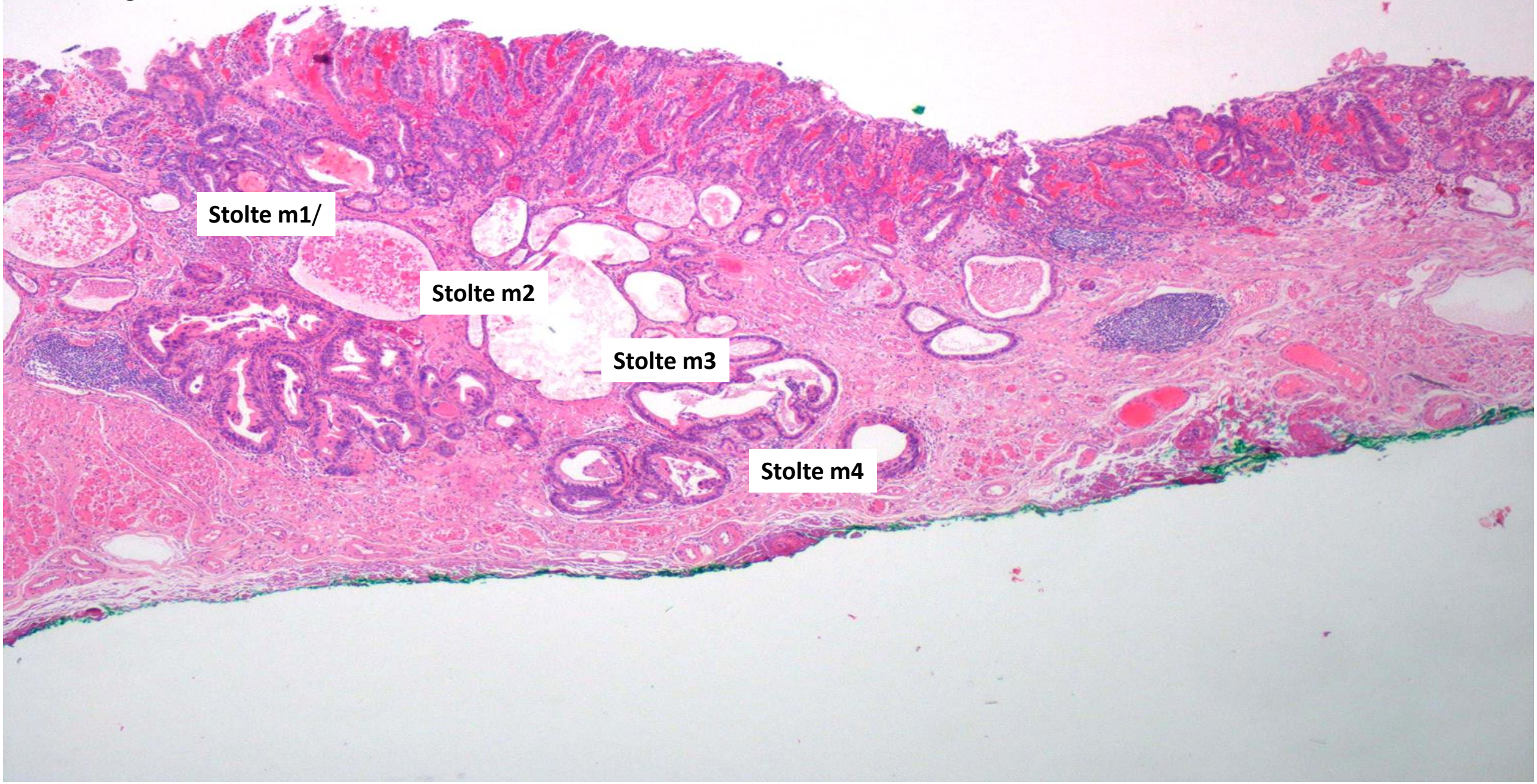


Figure 11b



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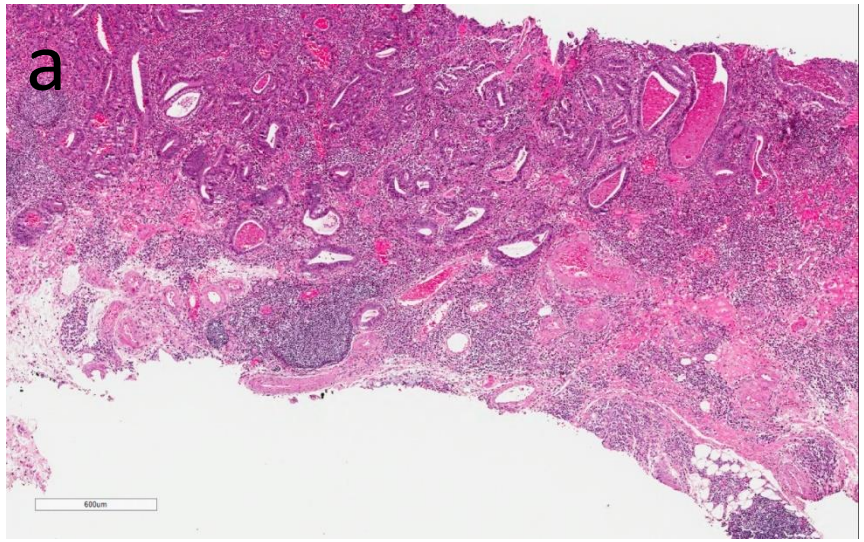

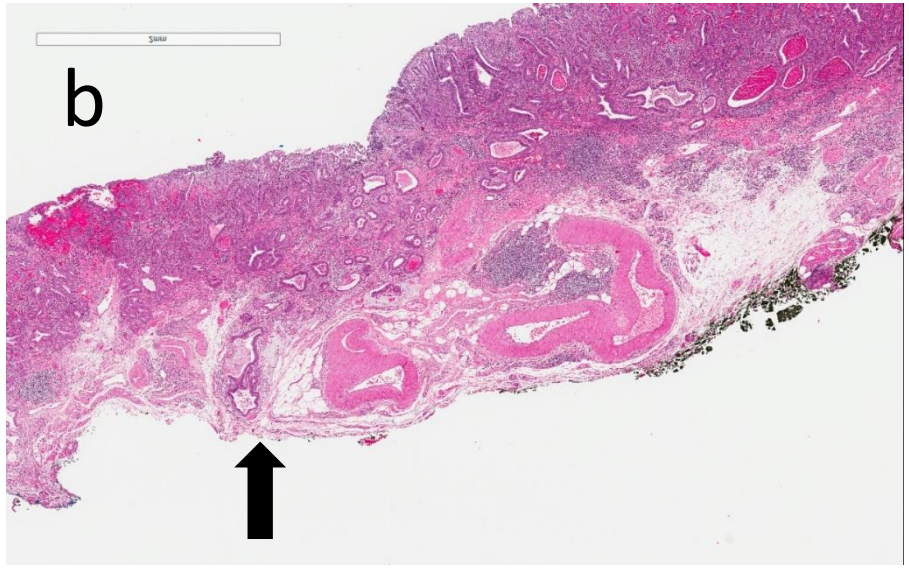

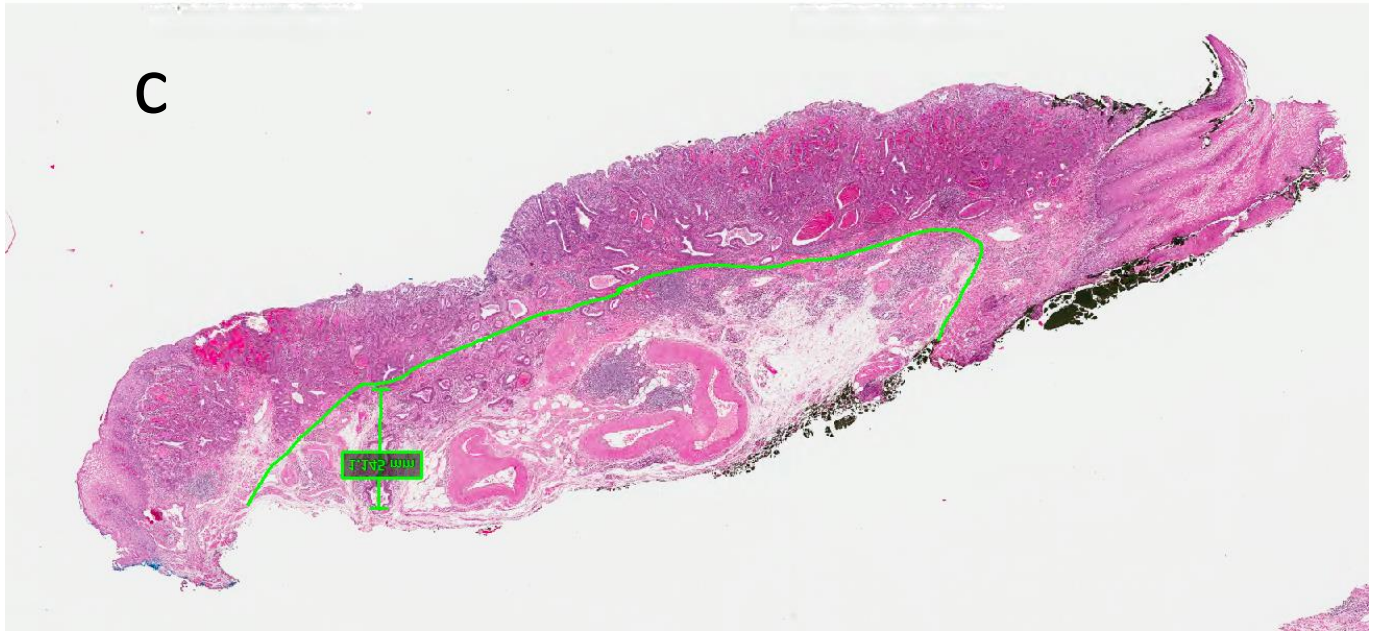

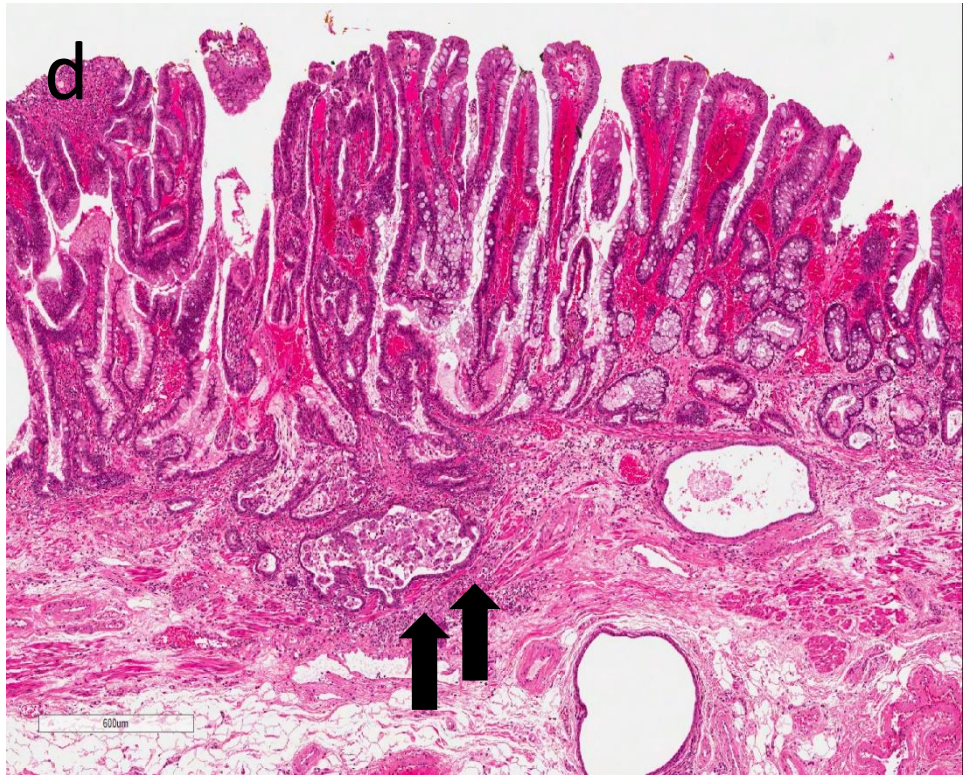

Figure 13

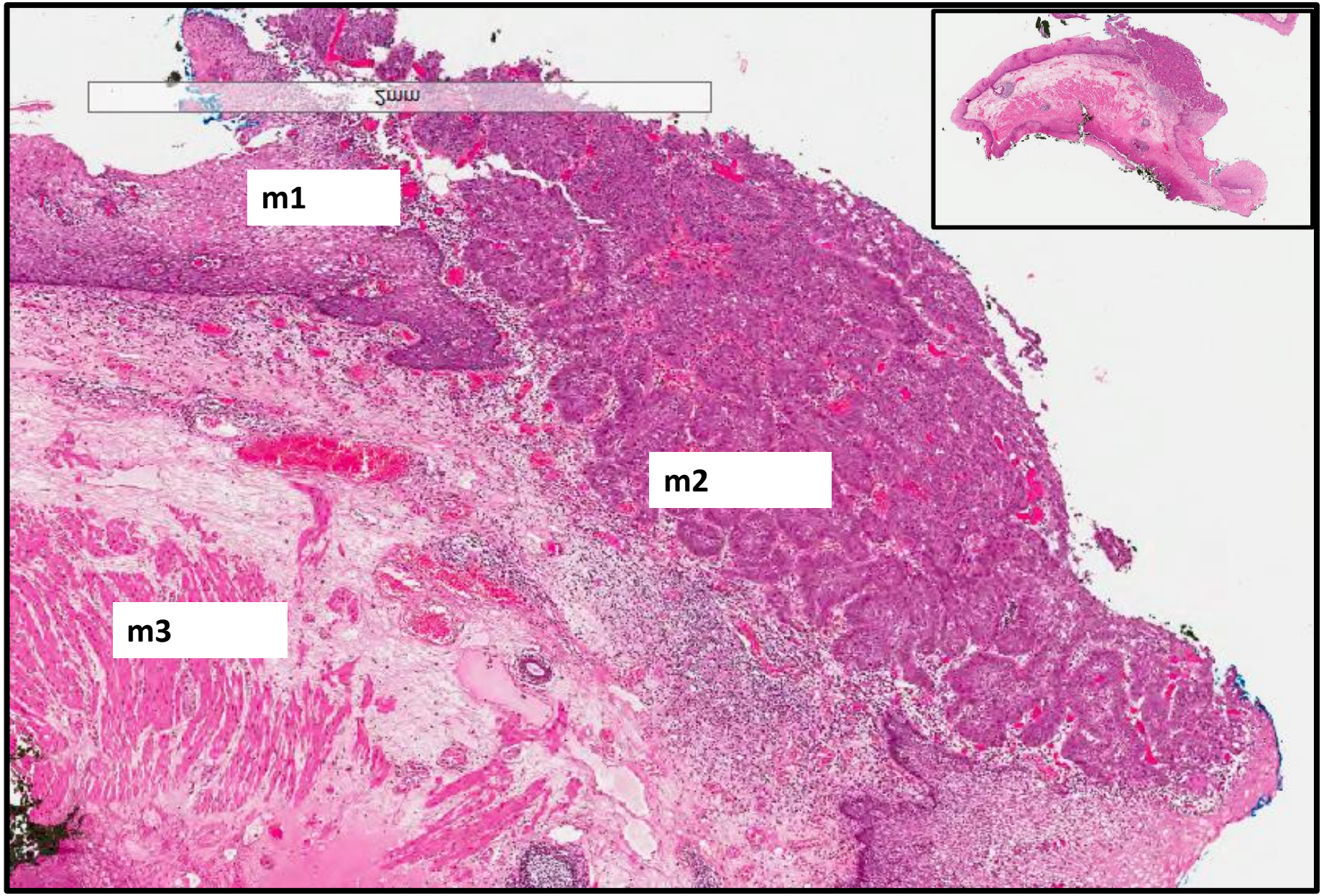

Figure 14

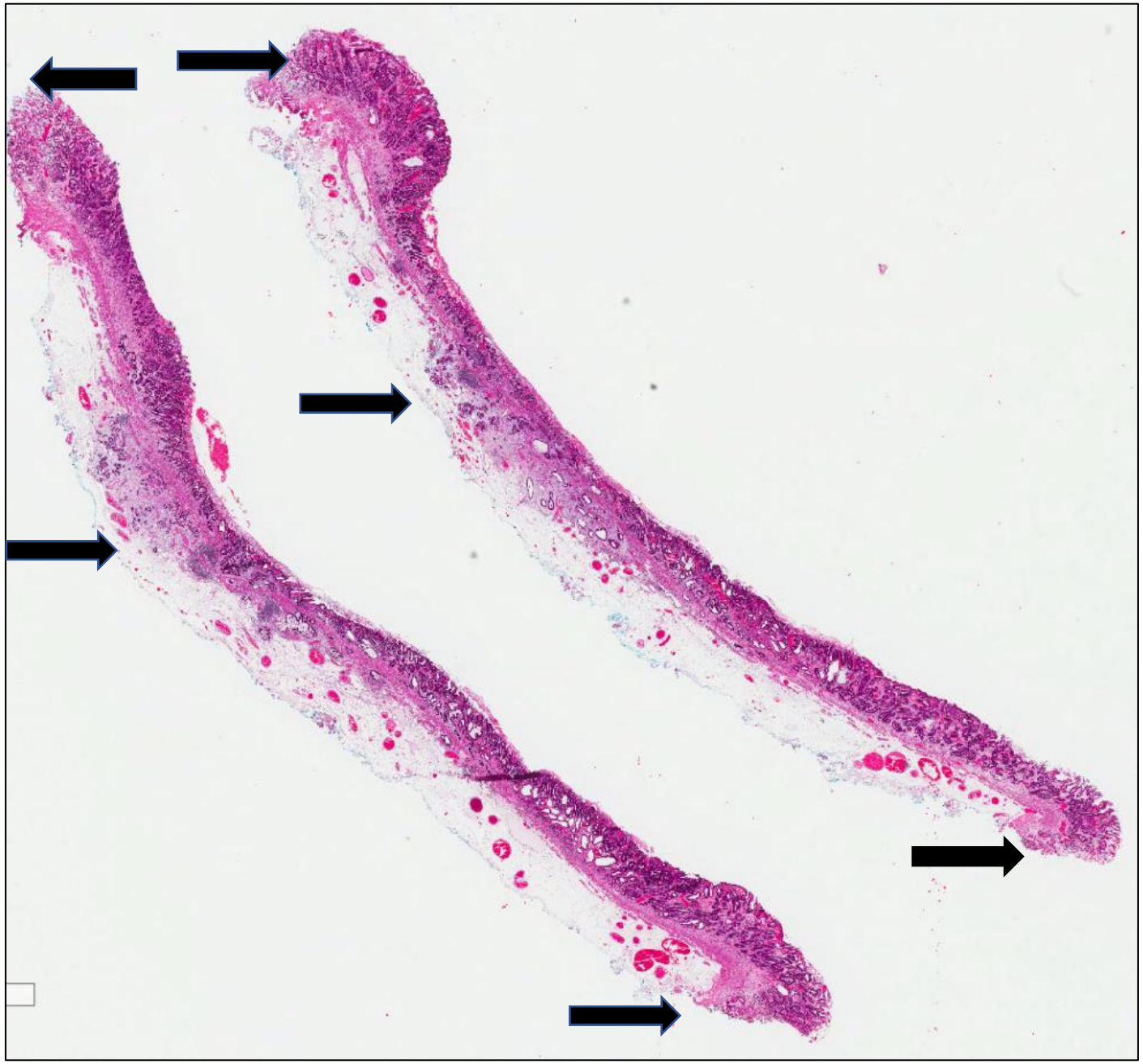

Figure 15

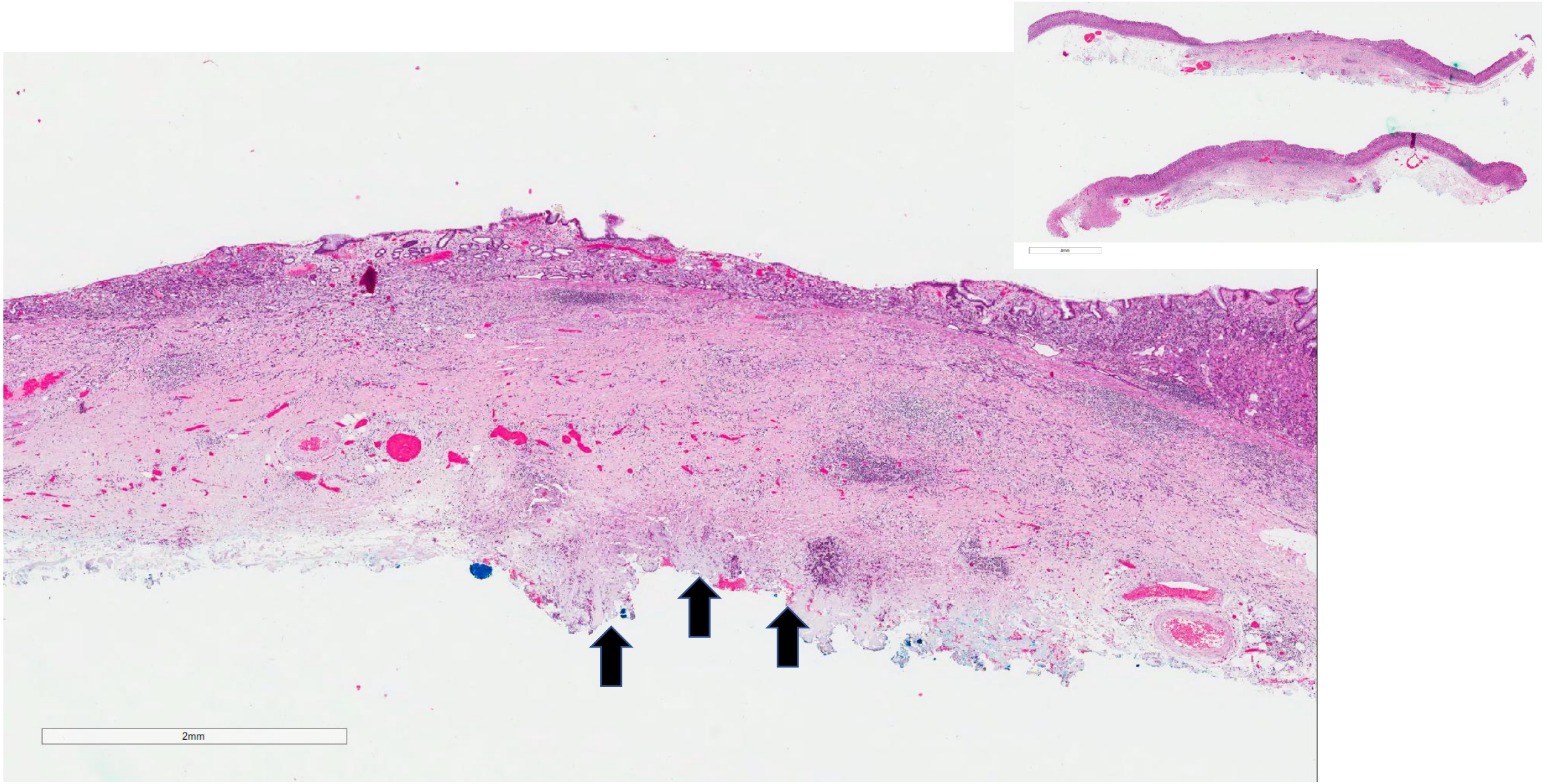

Figure 16:

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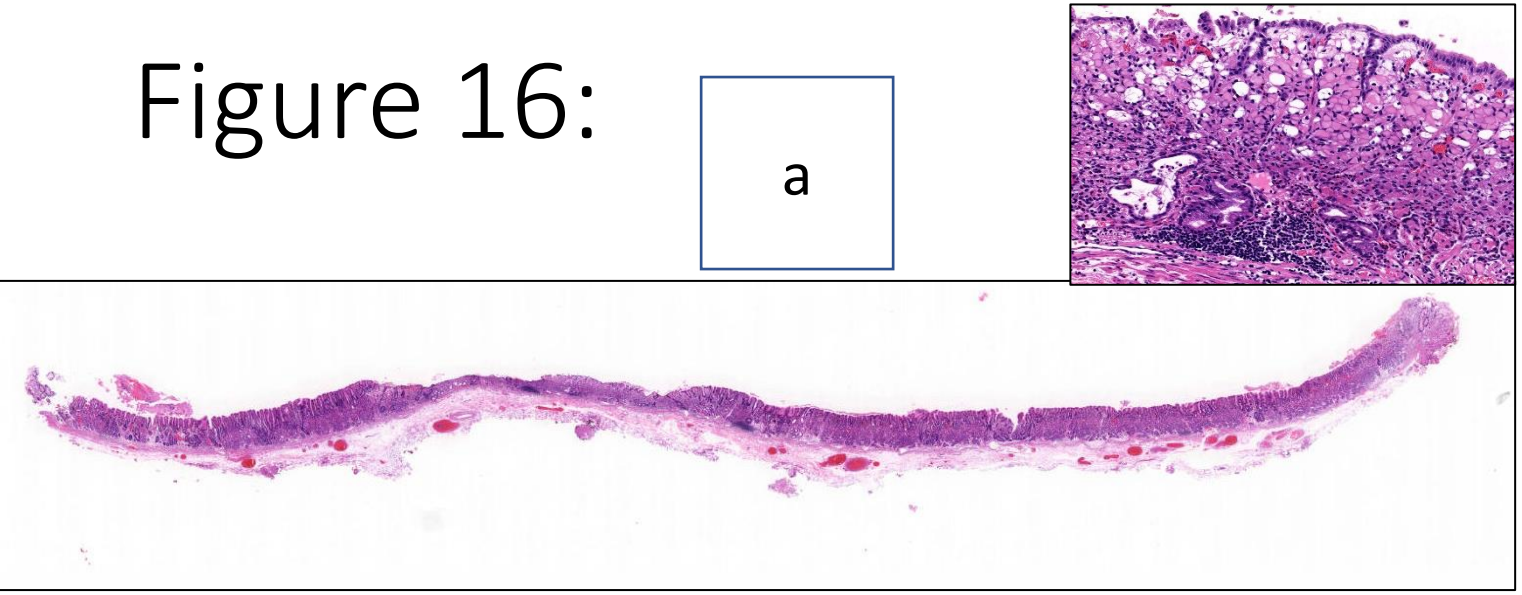

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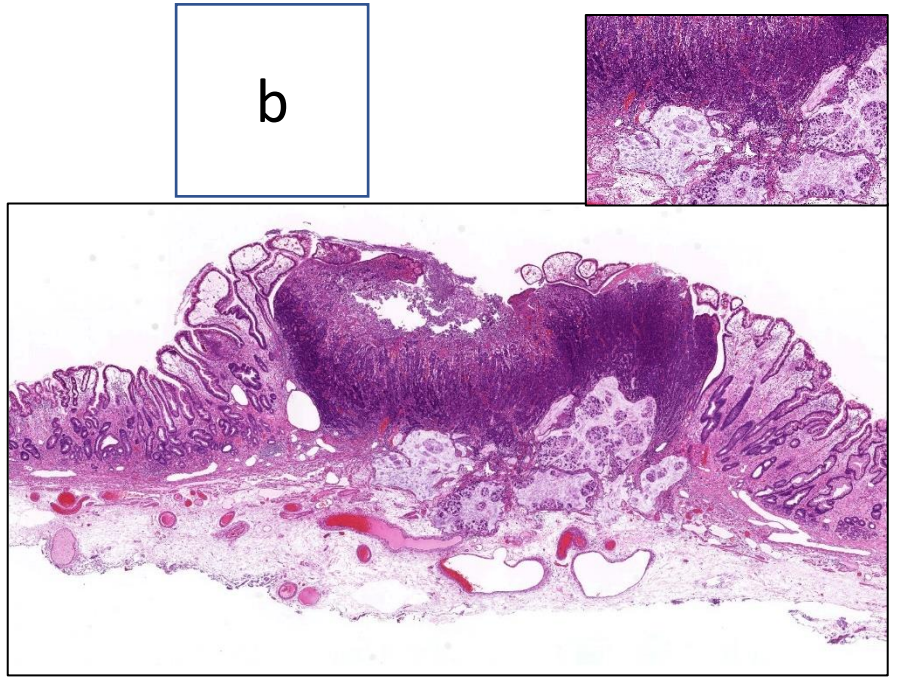

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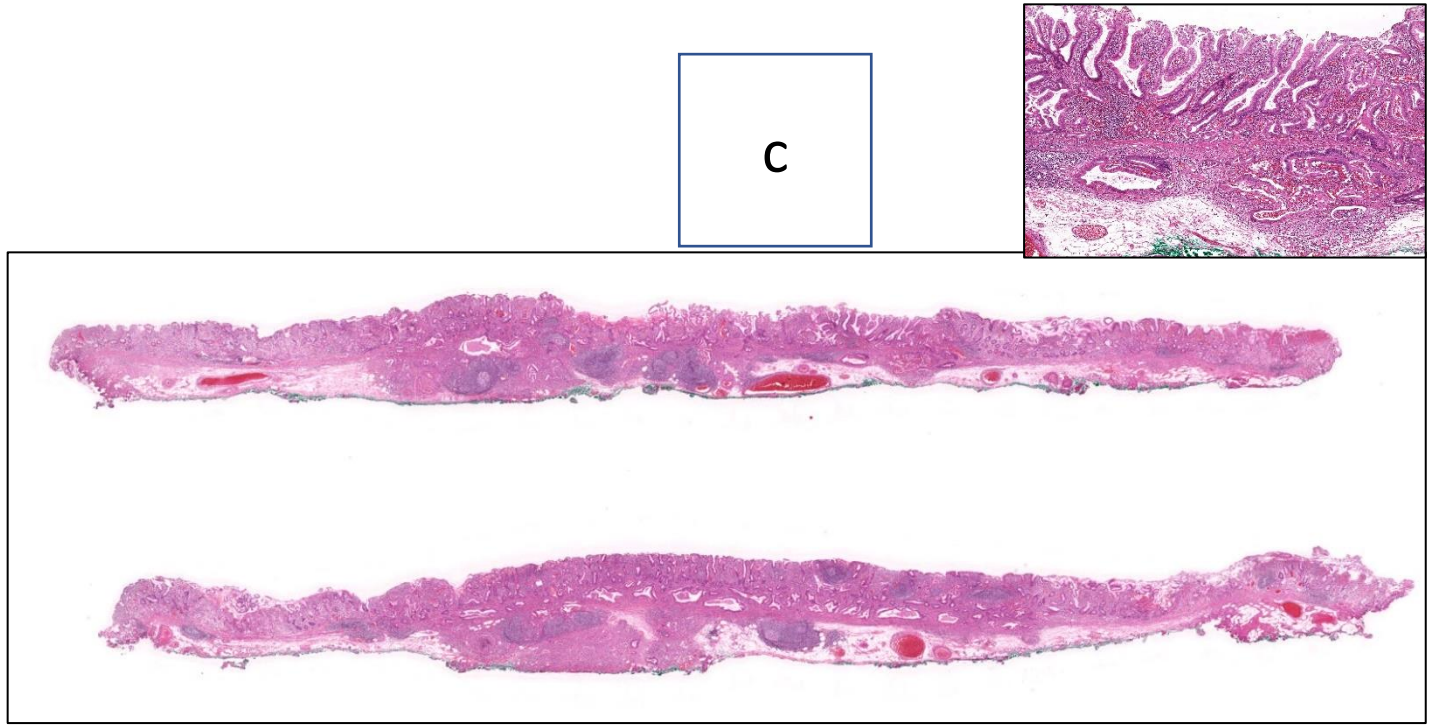


d

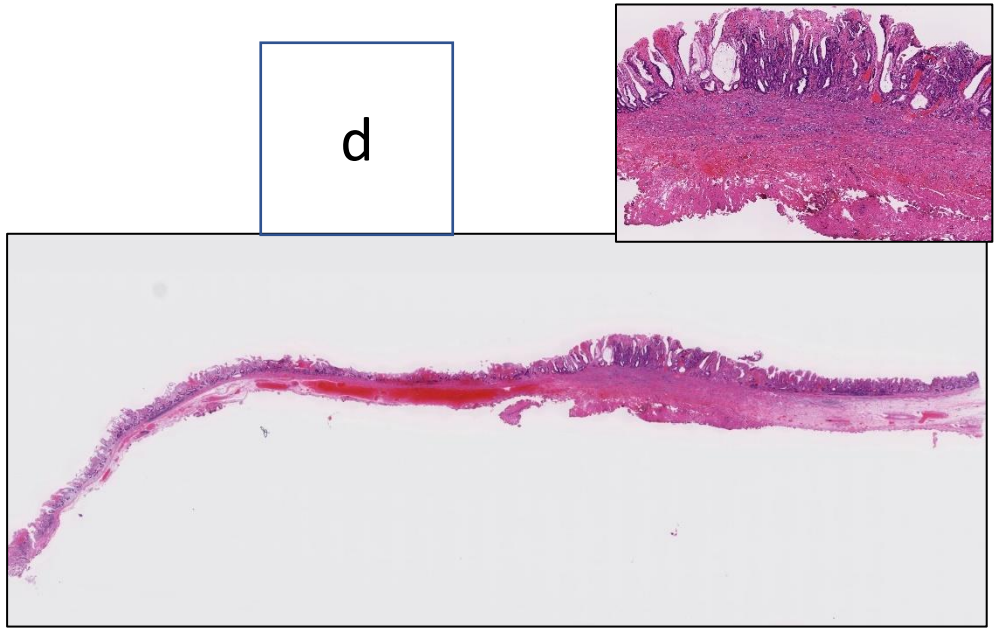
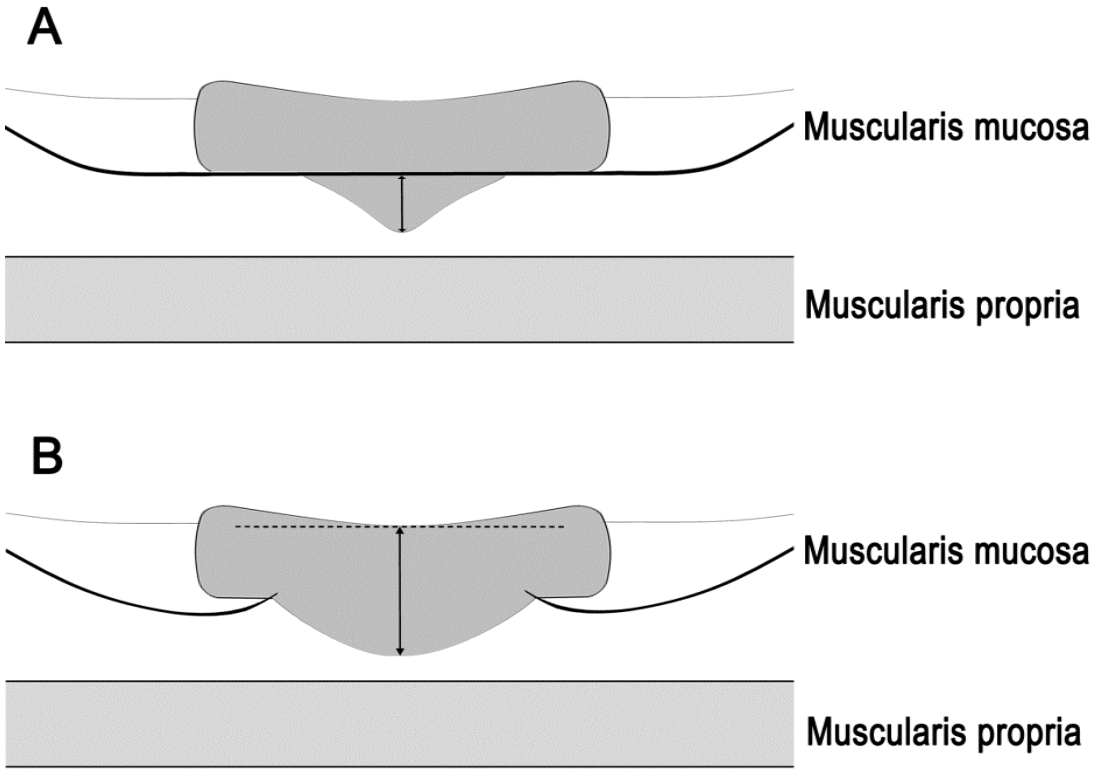
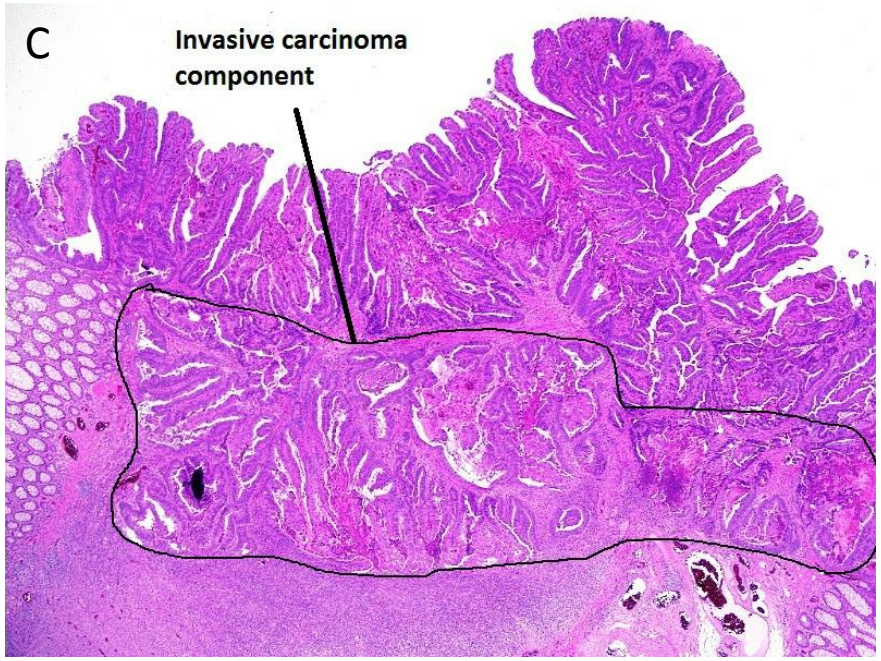


Fig 17


A
Muscularis mucosa
Muscularis propria
B
Muscularis mucosa
Muscularis propria


C
Invasive carcinoma component

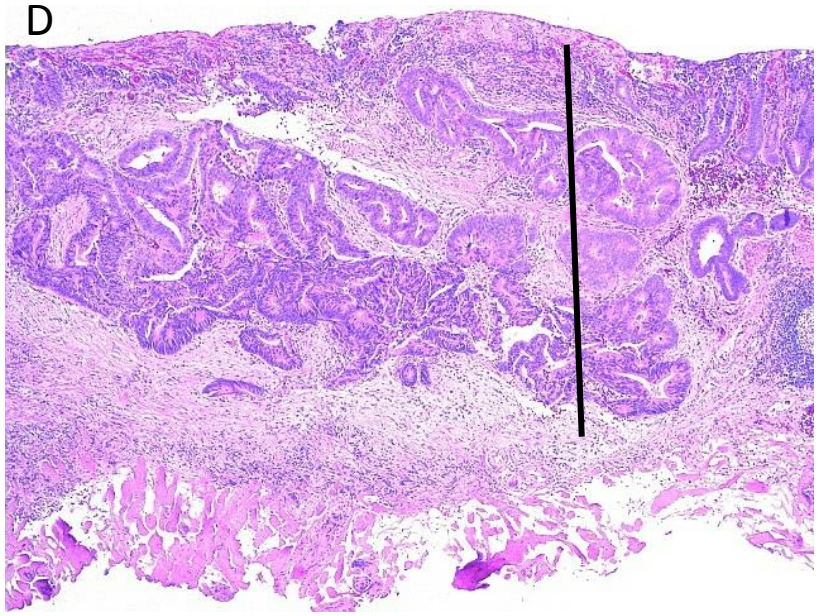
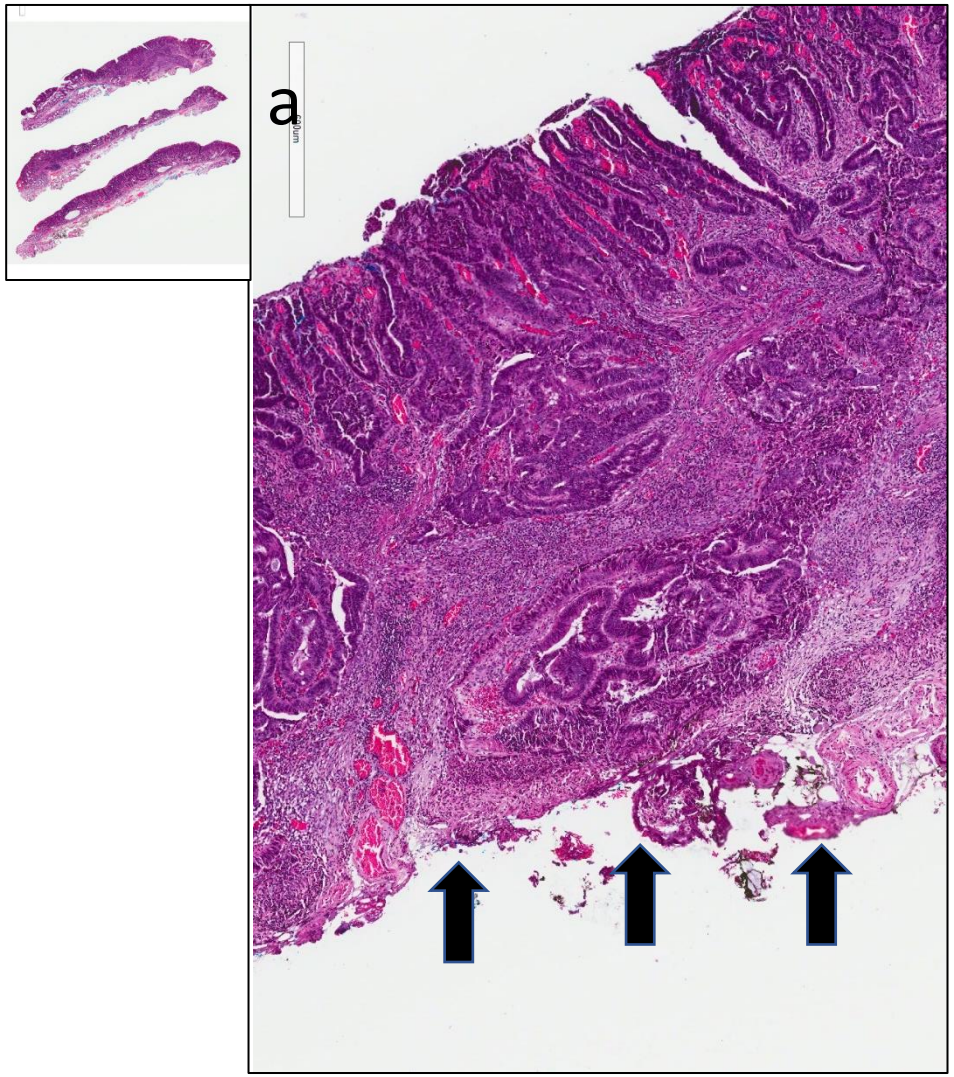

D

Fig 18



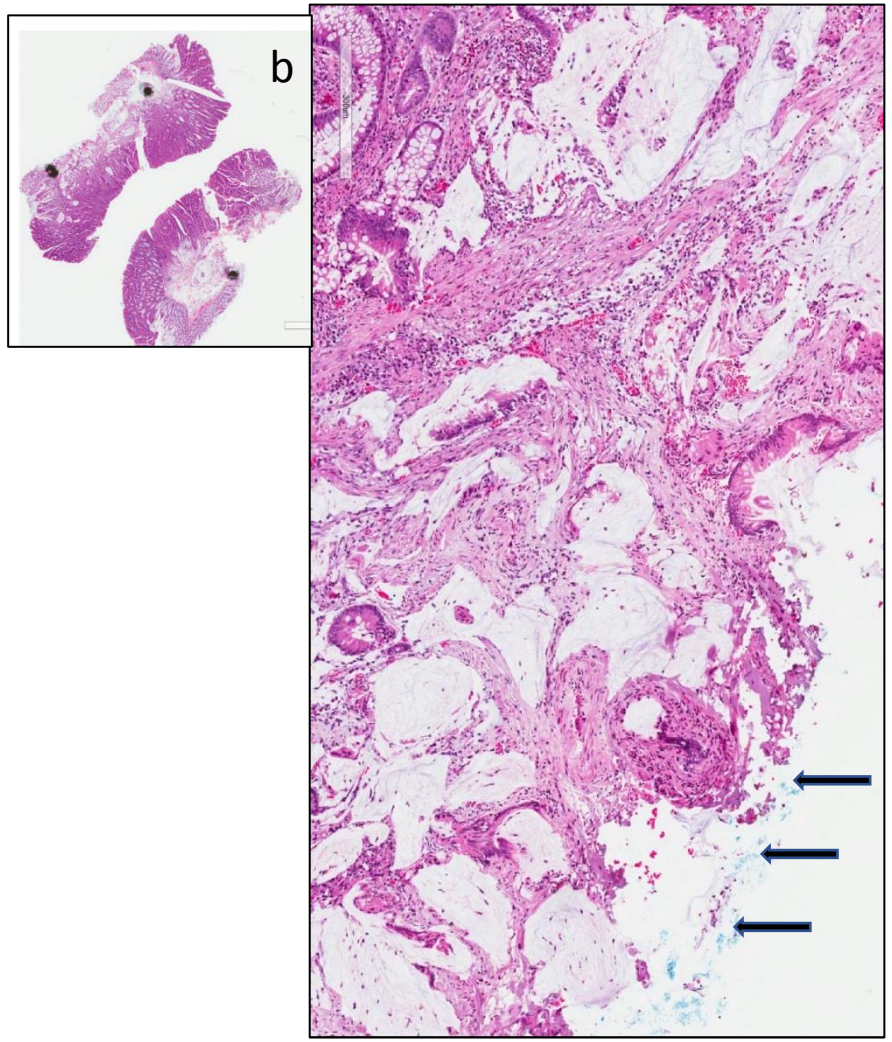


Figure 19