Retrospective study of histological diagnoses of surgical resections from the GI-tractus as a basis for future selection to undergo endoscopic surgery.

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Foreword

The purpose of this paper is to elucidate the number of patients who underwent elective surgical organ resection at the University Hospital of Northern Norway's Department of Gastrointestinal Surgery during the years 2008-2010, and determine how many of these patients could have been operated with newly introduced endoscopic resection techniques instead. This number would then represent a basis for future planning of endoscopic surgery.

The assignment was a research question Dr. Rushfeldt had been pondering, as he himself is actively engaged in using gastrointestinal endoscopic techniques at the University Hospital of Northern Norway's Department of Gastrointestinal Surgery. After emailing Dr. Rushfeldt in January, 2015 regarding this topic and expressing my own interest in the field of gastrointestinal surgery we agreed upon a collaboration in order to answer his question.

No monetary aid was sought during any process of this paper's construction. With aid from Dr. Rushfeldt and University Hospital of Northern Norway pathologist Dr. Sonja Steigen, the findings and results in this paper were made possible, and therefore a great thanks must be extended to them both.

Work process

In January 2015 Dr. Rushfeldt, known to be engaged in the field of endoscopy, was contacted regarding the possibility of completing a 5th year paper/thesis under his supervision. Dr. Rushfeldt was asked if there were any questions within his field of study which he wanted answered that would allow for immersion and learning within the fields of histology, surgery and endoscopic techniques, to which he essentially answered the thesis-question of this paper. At that point, however, certain key questions remained unanswered. How do we discover which patients were operated at UNN's Department of Gastrointestinal Surgery 6-8 years ago? Which patients were to be included in the study, and which patients excluded, if any? What information would we gather from patients' electronic journals? What criteria would be used to select patients for endoscopic resection? This planning phase lead to the involvement of Dr. Sonja Steigen, and the acquisition of lists of all patients contained within this study. Several unsystematic searches on PubMed and Cochrane Library lead to a variety of background literature material, and to choosing the European Society of Gastrointestinal Endoscopy guidelines for the inclusion criteria which were retrospectively fitted to our Norwegian patient population. The last question posed above proved to be a pivotal one, as the most up-to-date guidelines contained information that lacked to some extent in UNN's pathology reports from 2008-2010, discussed later. From initial contact in January, 2015, to a finalized idea of what question this paper would attempt to answer, and how to answer it, a period of 4 months passed. The above questions had all been answered and the data collection was set to begin. Data collection proceeded arduously during the first days and weeks of August, 2015, but with gradually increasing ease in the months to come. These months coincided with days spent in hospital and general practitioner's office, and

thus took an extended period of time to accomplish. Finally, by March 2016 all the data currently in the excel spreadsheet had been accumulated, and analysis using excel functions began, which ultimately took one month to finish. The writing of this paper took approximately 2 months to finish.

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Abstract

Endoscopic resection (here meaning the use of flexible endoscope and not laparoscopic or otherwise) of superficial gastrointestinal lesions has gained a stronger foothold in Western medical institutions since its introduction in the 1990's. Pioneered by Japanese endoscopists who developed and tested the evidence of using techniques such as endoscopic mucosal resection and endoscopic submucosal dissection, this technology allows the operator to remove an invasive, or pre-invasive lesion depending on endoscopically observable characteristics judged intraoperatively. Final histological analysis by the pathologist leads to a conclusive determination of further recommended therapy.

With these endoscopic techniques gradually implemented at the University Hospital of Northern Norway's Department of Gastrointestinal Surgery since 2011, a retrospective analysis was performed to determine how many patients operated with surgical organ resection during the years 2008-2010 could instead have been operated using newly introduced endoscopic techniques, and thereof with curative result. The purpose of this project is to give some quantitative measure of future endoscopic activity at the abovementioned department. The European Society of Gastrointestinal Endoscopy's guidelines were used as retrospective inclusion criteria.

In all 278 patients were included in the study. Of these, 45 patients (16%) would have been referred to endoscopic resection based on T-status alone, and 27 (10%) patients would have met the criteria for curative endoscopic resection of their gastrointestinal lesion.

Introduction

The purpose of this paper is to determine what percentage of patients who underwent surgical resection of gastrointestinal (GI) organs including oesophagus, stomach, colon, rectum could have undergone endoscopic resection with a flexible endoscope after the introduction of new endoscopic resection techniques, and what percentage of these with curative result. All patients were electively surgically operated at the University Hospital of Northern Norway's Department of Gastrointestinal Surgery between the years 2008-2010 due to the presence of invasive, pre-invasive or benign lesions (herein generally referred to as 'lesions'). In order to plan the expected amount of endoscopic procedures in the years to come there was a necessity to first determine how many patients could have undergone endoscopic resection before these services were offered at UNN. Pathology reports of the aforementioned patients were analyzed and summarized in excel format in order to compare with inclusion-criteria for curative endoscopic resection using the most current European consensus guidelines - the European Society of Gastrointestinal Endoscopy (ESGE) guidelines published in 2015. Keep in mind that the ESGE's inclusion criteria are for *curative* endoscopic resection, and are therefore very limiting in how many lesions can be considered for inclusion.

Endoscopic resection with a flexible endoscope is a minimally invasive alternative to open or laparoscopic surgery for pre-invasive or superficially invasive lesions of the oesophagus, stomach, colon and rectum. At the Department of Gastrointestinal Surgery at the University Hospital of Northern Norway (Universitetssykehuset NordNorge - UNN) new endoscopic procedures have been gradually implemented since 2011. These techniques have been pioneered and implemented by endoscopists in Japan since the 1990's (1), and have resulted in a wealth of

knowledge on how to both correctly identify and treat superficial lesions based on a set of organ-specific criteria (2). A lesion of the oesophagus, stomach, colon or rectum is known as superficial when its morphological appearance suggests invasion no deeper than the submucosa (3). With a trained eye, and when caught early enough, superficial lesions in the oesophagus, stomach, colon and rectum can be targeted and removed using endoscopic techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) (4).

Before the acceptance of endoscopic resection techniques in Western institutions, largely around the middle to late 1990's - when papers began to be published on the subject in Europe and America - there was a significant difference between Eastern and Western definitions of invasiveness, or cancer. The Eastern histological analyses lead to far more diagnoses of cancer in superficial, endoscopically resectable, tissues, and thus lead to significant success rates in Eastern literature (2,5). Further, Eastern endoscopists had developed a method of morphological classification for gastrointestinal tumors, which Western endoscopists thought to be more a "botanical hobby" with no real practical application (2). The reconciliation of Eastern and Western methodological approaches to gastrointestinal histology and morphology are reflected in the publication of papers following two international conferences - the Vienna and Paris conferences in 2000 and 2002 respectively. Both the Vienna and Paris classifications have later been revised. Copies of the updated Vienna histological classification published in 2002 (6) and Paris morphological classification published in 2005 (3) can be found in Table 1 and Figures 1-5 respectively. A common definition of invasiveness (Vienna Conference papers) and Western recognition of the prognostic value of Japanese methods of morphological classification (Paris Conference papers) lead to a concerted international effort to develop and test the efficacy of endoscopic techniques, which has culminated in the ESGE guidelines for endoscopic resection,

largely based on publications from Eastern literature. Norwegian criteria for endoscopic resection are not as detailed as those of the ESGE's, and therefore Norwegian clinicians cannot rely on national guidelines to provide the most up-to-date information on a field of study, which can potentially save many patients from unwanted complications from partial or total surgical organ resections.

Endoscopic resection of superficial lesions in the GI tract result in a net benefit for patients, in that those who were previously admitted for open or laparoscopic surgical procedures may now potentially be treated in the out-patient clinic without admission. Additionally, the patients' convalescence is shortened due to lack of abdominal wall wound closure and the anatomy and the function of the affected organ is preserved, in contrast to traditional surgery with organ resection.

Background

In Norway statistics regarding cancer such as incidence, prevalence, mortality and 5-year survival are gathered in a centralized public registry, called *Kreftregisteret*, the results of which are published annually. The most recently published version contains statistics from 2014. Statistics and information below is summarized from *Cancer in Norway 2014* (7).

In 2014 there were 31,651 incidences (new cases) of cancer; whereof 289 were oesophageal, 488 gastric, 2,801 colonic and 1,365 rectal. Colon cancer was the third leading site of cancer incidence in men (1,359 new cases), and second leading site in women (1,442 new cases). Rectum cancer was the seventh leading site of cancer incidence in men, and 8th in women. The remaining GI-cancers discussed in this paper (oesophagus, gastric) were not amongst the 10 highest incidence cancer sites in men or women in 2014. While the incidence of rectal cancer has stabilized in both sexes in the period 2010-2014 compared with the period 2005-2009, the incidences of colon cancer have increased for both sexes in the same period of time and are amongst the highest rates of all Nordic countries. For men, over 90% of cancers are diagnosed when 50 years and older, and nearly 50% of cancers are diagnosed when 70 years or older. For women the respective numbers are 85% and 45%. Of all cancer-types, colon cancer has the third highest mortality rate in both sexes, with 543 male deaths and 595 female deaths in 2014 in Norway. Norwegian colon cancer mortality rates are amongst the highest of all the Nordic countries. Increased rectal cancer survival rates and decreased 5-year mortality has been noted since approximately 2000, thought to be due to national implementation of pre-operative radiation and the total mesorectal excision technique in the early 1990s. Gastric cancer rates have

seen a protracted and gradual decline in incidence and mortality, proposed likely to be due to changes in dietary habits and decreased prevalence of *H. pylori* (7).

Both in the University Hospital of Northern Norway's pathology laboratory, and amongst pathologists internationally, there is a consensus regarding how to stage cancer, using the *American Joint Committee on Cancer's* TNM system. This system gives a description of the tumor cells' histological depth of invasion (T), involvement of regional lymph nodes (N), and distant metastasis (M). In the oesophagus and stomach a T1 tumor is defined as tumor tissue involving the lamina propria (the mucosa is composed of epithelium, lamina propria and muscularis mucosae in order of increasing depth) or submucosa, whereas a T2 tumor invades the muscularis propria. In the colon and rectum a T1 tumor is defined as tumor tissue invading the submucosa, and a T2 tumor invades the muscularis propria. There is also a stage known as Tis, carcinoma-in-situ, which is when cells possess architectural and cellular characteristics akin to their cancerous T1 counterparts, but have not yet penetrated deep enough to be labeled T1. Thus, oesophageal and gastric carcinoma-in-situ are localized intraepithelially, whereas colorectal carcinoma-in-situ can be localized in the epithelium or in the lamina propria. Finally, there is a diagnostic term called high-grade intraepithelial neoplasia (HGIN), which incorporates high-grade dysplasia and carcinoma-in-situ (5,8). Keep in mind that HGIN may refer to varying depths of lesion invasion, depending on the organ specified. Combined, these individual components can give the pathologist and clinician an idea of a patient's prognosis, as various treatment options depend invariably on the extent of the tumor/cancer's progression. This method of classification can be used for all gastrointestinal cancers, such as squamous cell carcinoma (SCC) and adenocarcinoma of the oesophagus, and adenocarcinoma of the stomach, colon and

rectum, which are the most typical cancers of each organ respectively, and those discussed in this paper.

The Japanese morphological description of GI cancer is based upon Bormann's four group system (9), with the addition of a fifth group labeled group 0, "superficial protruding or nonprotruding lesions," copies of which can be viewed in Figures 1-5 (10). The correlation between morphological type, depth of mucosal or submucosal invasion, and risk of lymph node metastasis was the guiding question at the Paris conference in 2002 (2). The results of the Paris Conference greatly influenced the ESGE's current guidelines for endoscopic resection, but will not be discussed in further detail in this paper.

The Vienna Conference of 2000 brought Eastern and Western pathologists together in regards to a common definitions of invasiveness, that is, *what is cancer under the microscope*. A copy of the updated *Vienna classification of GI epithelial neoplasm* is shown in Table 1 (6). Note that this classification system does not limit it's discussion to merely the epithelium. Important to note from the Vienna classification - high grade adenoma/dysplasia, carcinoma in situ and intramucosal carcinoma all belong to the same pre-invasive category 4, and are distinctly different from the invasive category 5 - submucosal invasion by carcinoma, as the chances of lymphatic invasion are dramatically increased when varying levels of the submucosa are involved, depending on organ specificity (2,11). The Vienna histological classification is in line with the World Health Organizations system, but organized to reflect degrees of endoscopic resectability.

For the remainder of this paper all non-invasive lesions displaying low-grade intraepithelial dysplasia will be referred to as low-grade intraepithelial neoplasia (LGIN). All pre-invasive

lesions containing either high-grade intraepithelial dysplasia or carcinoma-in-situ will be referred to as HGIN. Lesions containing carcinoma invading up to and including the submucosa are simply referred to as T1 tumors. Keep in mind that almost all intramucosal (LGIN and HGIN) lesions of the GI tract can be curatively resected endoscopically, and some T1 tumors as well, depending on a variety of factors that all correlate with risk for lymph node metastasis, discussed later.

The criteria for curative endoscopic resection of gastrointestinal lesions laid forth by the ESGE are the most up-to-date European guidelines for endoscopic surgery including all organs of the gastrointestinal tract discussed in this paper. ESGE guidelines form the retrospective inclusion-criteria used in this study to select patients operated surgically and electively in 2008-2010 at UNN's Department of Gastrointestinal surgery for invasive, pre-invasive, or benign lesions.

The ESGE's criteria for endoscopic resection is based largely upon risk for lymph node metastasis, for involvement of lymph node stations necessitates their removal, impossible with endoscopic techniques - leaving only the option of radical surgery. Prior to resection the endoscopist can judge visual characteristics such as size and location of the lesion, morphology according to the Paris classification, chromoendoscopic and narrow band imaging (NBI) findings, all of which correlate to a specific risk for invasiveness and lymph node invasion (2,3,12). The two latter technologies aid in properly identifying the lesion and its borders, and highlighting the "mucosal pattern and superficial vasculature" respectively (12). It is important to highlight the fact that the first characteristics to be judged are those seen by the endoscopist upon examination of the patient. If these factors suggest the lesion has not progressed far enough to invade local lymph nodes or the muscularis propria then endoscopic resection is deemed

advisable, and performed immediately. Following en-bloc endoscopic resection (removal of the entire specimen in one piece), the lesion is sent to the pathologist for examination, at which point histological details such as the lesion's depth of invasion, lymphovascular invasion and grade of cellular dysplasia/differentiation are elucidated and communicated to the endoscopist, who then determines what further action is required. Therapy beyond this point is without the scope of this paper, and not discussed further. For a full explanation of further therapy, and details regarding the pre-resection lesion characteristics suggestive of no lymph node involvement, see ESGE's guidelines (12).

The ESGE's summarized criteria for curative endoscopic resection of superficial neoplastic lesions of the gastrointestinal tract are shown in Table 2, with summarized Norwegian national guidelines in Table 3 for comparison. Supplemental comments are found below.

Submucosal invasion can be quantified by two methods - by measuring from below the last fiber of the muscularis mucosa in µm, or determining which third of the submucosa is invaded. Upper, middle or lower third of submucosal involvement correspond to sm1, sm2 or sm3 accordingly (12). The ESGE guidelines use both sm and depth in µm, however only depth in µm has been displayed in the ESGE summarized inclusion criteria for endoscopic resection, since division of submucosal invasion into thirds and analysis of which third is penetrated by invasive cells would necessitate a full-thickness resection, obtained only in tradition surgery with organ resection, and not through endoscopic resection techniques.

Pedunculated polyps of the GI tract are graded using Haggitt's classification, in which neoplastic cells confined to the head, neck, stalk and base of the polyp are classified Haggit 1, 2, 3, and 4 respectively (13).

It is assumed that the lateral margins of endoscopically resected specimens are free in order to avoid local recurrences. With the ESD technique used routinely in the stomach and partly in the oesophagus, colon and rectum, an en-bloc resection is obtained, making it possible for the pathologist to judge whether the lateral margins are free. With the EMR technique, usually applied in the colon and rectum, the resection is piece-meal (in individual pieces) and the lateral margins cannot be assessed by the pathologist. Therefore, it is the endoscopists' evaluation of lateral borders following resection which will determine the radicality of the endoscopic procedure. The routine control endoscopy a few months after the endoscopic resection may reveal a possible residual or recurrent lesion, but such findings indicative of insufficient primary resection are rare, and can be treated effectively with further endoscopic resection (14).

When dealing with Barrett's oesophagus with visible lesions, endoscopic resection is first carried out followed by radio frequency ablation (RFA) on the entire lesion, whereas in cases of HGIN without visible lesions, RFA is the only method of treatment. These are recommendations common to both ESGE and Norwegian national guidelines (12,15).

Method/Materials

The pathology reports of patients electively operated at UNN's Department of Gastrointestinal Surgery with resection of gastrointestinal organs (oesophagus, stomach, colon and rectum) in the years 2008, 2009, 2010 formed the basis for the population analyzed in this paper. Lists of patients operated surgically during these years was gained from pathologist Dr. Sonja Steigen. A search by Dr. Steigen yielded organ resections containing squamous cell carcinoma and adenocarcinoma of the oesophagus, adenocarcinoma of the stomach, colon, rectum, high and low grade dysplasia/neoplasia in all the above organs, as well as benign lesions such as fibroepithelial polyps and lipomas from all GI organs mentioned above.

The University of Northern Norway's eHealth systems DIPS was used to access the health records of each individual patient on the lists provided by Dr. Steigen. The following information from each patients' pathology report was organized into an excel spreadsheet: patient identification numbers, age, gender, date of operation, lesion location, main histological diagnosis, grade of dysplasia in biopsy, cellular differentiation in biopsy (only T1 lesions), pre-operative radiation therapy (only rectal resections), grade of dysplasia in resected specimen (only T0 and T1 lesions), cellular differentiation in resected specimen (only T1 lesions), histological infiltration of blood vessels, lesion morphology (only T0 and T1 lesions), TNM-status, sm-status and Haggitt's status. All analysis and processing of this data took place using excel functions.

There was one set of patients amongst those provided by Dr. Steigen who were excluded from this study. Those operated acutely with organ perforation or intestinal ileus due to advanced tumor progression were excluded, as their condition was considered life-threatening they were

operated surgically on vital indication, and would not have benefited from the techniques described in this paper. All the remaining patients included in the study were operated electively.

Information gained from the pathology reports of all resections stored in excel was cross-referenced with respect to that organ's specific inclusion-criteria, as set forth by ESGE guidelines. Patients' lesions were deemed curatively endoscopically resectable if the criteria set forth by the European Society of Gastrointestinal Endoscopy were met.

Results

In total 278 patients, and 289 lesions were included in the study. 171 patients were male and 107 female. Average age of men was 68 years, ranging from 40 to 91 years of age. Average age of females was also 68 years, ranging from 36 to 89 years of age. 11 lesions in the oesophagus, 26 lesions in the stomach, 118 lesions in the colon, and 134 lesions in the rectum were excised with surgical organ resection, displayed graphically in Figure 6. The annual distribution of these surgical resections can be seen in Figure 7. There were 9 patients with synchronous tumors, whereby one of the two lesions met the criteria for curative endoscopic resection. Two patients were operated twice for invasive lesions of two separate organs. Lesions occurred synchronously in separate parts of the colon in 4 instances, synchronously in the colon and rectum in 4 instances, and synchronously in the stomach and colon in 1 instance.

The distribution of the surgical resections' postoperative pathological T-status can be seen in Figure 8, all organs having a majority of T3 lesions.

A postoperative pathological diagnosis of carcinoma was given by UNN's pathologists in 11/11 surgical oesophagus resections, 25/26 surgical gastric resections, 112/118 surgical colon resections, and 128/134 surgical rectal resections, as shown in Figure 9.

Of 11 surgically excised oesophageal lesions, 4 met the criteria for curative endoscopic resectability, or 36%, as displayed in figure 10. Two were T1 adenocarcinomas with invasion of the lamina propria, and 2 were T1 adenocarcinomas with invasion of the submucosa.

Of 26 surgically excised gastric lesions, 2 met the criteria for curative endoscopic resectability, or 8%, as displayed in figure 10. One of these curatively endoscopically resectable lesions contained HGIN, the other was a T1 adenocarcinoma with invasion of the submucosa.

Of 118 surgically excised colonic lesions, 10 met the criteria for curative endoscopic resectability, or 8%, as displayed in figure 10. Of these curatively endoscopically resectable lesions, 4 contained LGIN, 2 contained HGIN, 1 pedunculated polyp contained adenocarcinoma in the head - staged Haggitt 1, 2 pedunculated polyps contained adenocarcinoma in the stalk - staged Haggitt 3, and 1 was a T1 adenocarcinoma with invasion of the submucosa.

Of 134 surgically excised rectal lesions, 11 met the criteria for curative endoscopic resectability, or 8%, as displayed in figure 10. Of these curatively endoscopically resectable lesions 1 had no identifiable viable tumor tissue following pre-operative chemoradiotherapy, 4 contained HGIN (of which 1 had received pre-operative chemoradiotherapy), 1 pedunculated polyp contained adenocarcinoma in the neck - staged Haggitt 2, and 3 were T1 adenocarcinomas with invasion of the submucosa.

In total, 27 out of 289 surgically resected lesions were judged to be curatively endoscopically resectable, or 10% of all lesions included in the study. See Figure 10 for a comparison of number of lesions that were curatively endoscopically operable versus those which were not, grouped by organ. See Figure 11 for numbers of lesions which met the criteria for endoscopic resection grouped by year.

These 27 curatively endoscopically resectable lesions translate to 27 individual patients who could have undergone curative endoscopic lesion resection instead of surgical organ resection.

Discussion

The ESGE guidelines provide a very strict set of criteria for when endoscopic resection can be recommended with curative result (meaning here < 5% risk for lymph node metastasis) and it is those criteria which have been applied to the Norwegian patient population in this study. The ESGE guidelines differentiate between inclusion criteria which lead to resections considered simply "curative" (box to the left in column labeled *Criteria for curative endoscopic resection* in Table 2) and expanded inclusion criteria which lead to resections considered curative "in most instances" or in "majority of cases" (box to the right, in italics, in column labeled *Criteria for curative endoscopic resection* in Table 2) (12). The latter two sets of criteria include lesions with under 5% risk for lymph node invasion (12), which is considered within an acceptable margin of error by surgeons at UNN, and therefore included as lesions endoscopically resectable with curative result. However, patients who undergo endoscopic resection under expanded inclusion criteria should be discussed in an interdisciplinary teams composed of surgeon, oncologist and radiologist who meet twice weekly at UNN's Department of Gastrointestinal Surgery to discuss complicated patient cases. In clinical practice there also exists a group of patients who are considered for inclusion to undergo endoscopic resection with the foreknowledge that the result will not necessarily be curative. These patients include those with significant comorbidities and/or advanced age, who are unable to undergo open/laparoscopic surgery, or those with expressed wishes against radical surgery. It went beyond the scope of this paper to determine a patient's operability based on comorbidities, general health and individual expressed wishes, and these patients are therefore not accounted for in this study. In addition to the 27 lesions from this study which met the ESGE's criteria for curative endoscopic resection, all lesions with a T-status

of T1, Tis, and T0 could also have been resected endoscopically for diagnostic, and potentially therapeutic purposes. Depending on the analysis of the pathologist (grade of dysplasia / cellular differentiation, depth of mucosal/submucosal invasion, lymphovascular invasion, etc) several of these patients would not have been directed to further supplementary surgical organ resection due to consideration of the individual patient's age and comorbidity. In other patients however, endoscopic resection could prove therapeutic, as the criteria for curative endoscopic resection could have been met, which was the case for 27 patients in this study. In total 45 patients would have been referred to endoscopic resection based on the T-status of their lesion alone.

In more recent years there have been increasing numbers of patients operated with endoscopic techniques at UNN's Department of Gastrointestinal Surgery, proposed by Dr. Rushfeldt to be due to the public's increasing use of health services such as public and private endoscopists in Norway. In reality, if the endoscopic resection technology and ESGE guidelines had been fully implemented at UNN in 2008 - 2010, more than 45 patients would likely have undergone endoscopic resection. As mentioned earlier, it is the endoscopist who first examines the patient though the endoscope, and performs EMR or ESD on a lesion based upon visual characteristics alone, but also depending upon gross invasion of the middle and deeper aspects of the submucosa upon instrumentation. The 27 patients in this study met the criteria for curative endoscopic resection with the hindsight of all information from their pathology reports in hand. This excludes the possibility of an endoscopist endoscopically resecting a lesion judged to have low likelihood for lymph node invasion based on visual characteristics alone, which later turns out has a significant risk for lymph node invasion, a degree of human error one can eliminate from the picture in a retrospective study, and hence a large benefit of a study such as this one.

It is important to understand the results described above within the context of the method used in this study, namely that of a retrospective study. Criteria for endoscopic resection from 2015 were retrospectively fitted to patient profiles from 2008-2010. These patient profiles and their histological data were not collected in 2008-2010 with regards to future endoscopic techniques, and thus information in some reports were lacking in this respect. During the course of writing this paper, several unsystematic searches of PubMed were performed in order to identify retrospective studies similar to this one, aimed at determining the proportion of patients previously operated with radical surgery who could have been curatively operated endoscopically judged by updated inclusion criteria. No such studies were found, and thus our data cannot be directly compared to any published literature, which is interesting in its own right, as this paper will be the first of its kind in the field of endoscopy.

Of the 27 patients selected for curative endoscopic resection, 8 pathology reports lacked the exact depth of the lesion's submucosal invasion. These 8 reports labeled the deepest layer of invasion simply as "submucosa", and not according to one of the two ways of quantifying depth of submucosal invasion mentioned earlier. This is of course a potential source of error, as it is unbeknownst to the author of this paper which of these lesions penetrated so deep, as to exclude them from the category of curatively endoscopically resectable lesions.

Furthermore, lymphovascular invasion was inconsistently labeled in the gathered pathology reports, and it was therefore decided that this criteria was not to be applied, as it would have to done so only for rectal and colon surgical resections, but not oesophageal and gastric surgical resections. Worthy of mention, however, none of the T0, Tis or T1 colon or rectal resections had any invasion of tumor cells into extramural veins.

It has been agreed with UNN pathologist Dr. Sonja Steigen that if this paper should be pursued towards publication, these histology slides can be retrieved from the UNN archival system for analysis to determine both the exact depth of submucosal invasion, or at least sm-depth, and status of lymphovascular invasion.

Of the lesions which met the criteria for curative endoscopic resection, 5 were synchronous lesions of the GI tract. In these patients there were two lesions separated either by an entire organ (e.g. endoscopically resectable lesion in rectum and surgically resectable lesion in colon) or distanced far enough apart within the same organ, the colon, so that surgical resection of one lesion with standard resection margins did not necessitate surgical excision of the endoscopically resectable lesion. In the case of synchronous lesions in the colon, Norwegian surgical guidelines for the colon (4) were consulted to determine whether or not the second, endoscopically resectable lesion, fell within the standard resection margins of the lesion which necessitated surgical resection.

As can be seen in Figure 9 there were 128 carcinomas excised surgically from the rectum, and only 112 carcinomas excised surgically from the colon between the years 2008-2010. This stands in contrast to the higher incidence of colon cancer diagnosed versus rectum cancer in the years 2008-2010 (16,17,18), but can be attributed to the fact that UNN and the hospital in Bodø serve as centralized centers for rectum surgery in northern Norway. Therefore, the amount of rectum surgeries was accordingly higher than the amount of colon surgeries in 2008-2010, even though more colon cancers were diagnosed in the same years. One can also see the effect of this centralization in an increased number of surgical rectum resections per year from 37 to 56 in the years 2008-2010, as shown in Figure 7.

The novel solution of endoscopic resection of one of two synchronous tumors provides logistic problems for the hospital teams who are to operate these patients. It is logical that the endoscopist should be allowed to operate first, as the potential exclusion from endoscopic resection based on morphological features suggestive of lymphatic invasion would mean the lesion would need to be excised surgically. A second, open/laparoscopic procedure would need to be scheduled to take place shortly after the endoscopic procedure in order to meet the deadlines of the '*Pakkeforløp'* system currently in use in the Norwegian healthcare system. Patients known to have synchronous tumors should therefore be scheduled for two separate surgical procedures upon admission to hospital. One could theorize that ideally the endoscopist would be capable of performing the necessary radical surgery by converting to open, or laparoscopic surgery, however endoscopic and open/laparoscopic operations are performed in two separate operating fields at UNN, without the ability of moving patients from the endoscopy operating theatre to the radical operating theatre, except upon vital indication, due to issues of capacity. These issues, and most likely several more, will need to be anticipated and accounted for before eventual implementation of a fully functioning and coordinated system to tackle the issue of endoscopically resecting synchronous GI lesions.

There are additionally two related issues in incorporating and implementing endoscopic resection techniques using ESGE guidelines in Norwegian hospitals. One issue, which the Norwegian guidelines for oesophagus and gastric surgery both address, is that in order to achieve the same success rates as those found in the literature - these patients need to be concentrated to centers that specialize in their treatment. As shown in Figure 11, there was an average of 9 patients each year, varying between 8 and 10, who were curatively endoscopically operable. The latter issue could be due to errors in sampling, discussed in the paragraph below. The second issue of

implementing this new system is that of adopting methodologies that allow endoscopists to gain data upon examination of a patient that allows them to immediately calculate the relative risk of lymph node involvement, and thus which therapeutic avenue to pursue. It may prove challenging for some endoscopists, particularly those towards the middle or end of their careers, to suddenly set about learning the morphologies of the Paris classification system, colonic pit-patterns, and more visual characteristics which are instrumental in applying ESGE guidelines effectively to clinical practice.

There must also be some mention as to whether or not the data included in this paper is representational of the actual patients operated with surgical resection of GI organs during the years 2008-2010. The number of patients surgically operated was determined by ascertaining lists of organ specific resections with a determined histopathological type, e.g. adenocarcinoma in rectal resections, or high grade intraepithelial neoplasia in tubulovillous colonic resections. This, in turn, depends on the pathology reports being properly labeled in the data software, as such. This is a potential source of error, as no alternative search method was used to determine how many patients were electively surgically operated for benign, pre-invasive or invasive lesions at UNN's Department of Gastrointestinal Surgery in the years 2008-2010. Ascertaining such a list and cross-referencing it with the GI organ resection list gained from the pathology department would elucidate in some detail the accuracy of the population selected for study in this paper. However, it is assumed that these numbers most likely accurately reflect the number of patients surgically operated by the Department of Gastrointestinal Surgery at UNN between the years 2008-2010.

Finally, 262 patients in this study were not curatively operable by endoscopic techniques, meaning these lesions were of such an advanced histological character that the risk of spread to regional lymphatic structures was judged to be too high and/or that these lesions had already invaded the muscle wall of their organ, making it impossible to remove with a standard mucosal resection or submucosal dissection without injurious contact with the muscularis propria. It becomes tempting to think that if these same lesions were merely caught earlier in their progression towards invasiveness, then the same inclusion-criteria for curative endoscopic resection discussed in this paper could be met, and the lesions could have been curatively resected endoscopically. In Norway there are currently no national screening programs in place for oesophageal or gastric cancer, and only a pilot project to be completed in 2018 for screening of colorectal cancer (19). With colon cancer claiming the third highest number of lives amongst both sexes per year of all cancers, it seems a perfect marriage of convenience that these endoscopic techniques and guidelines should become available at this point in time.

Conclusion

In summary, 45 out of 278 patients (46 out of 289 lesions) who underwent elective surgical resection of gastrointestinal organs due to presence of invasive, pre-invasive or benign lesions in the oesophagus, stomach, colon or rectum at UNN's Department of Gastrointestinal Surgery between the years 2008-2010 would have been referred to endoscopic resection based on T-status alone, and 27 out of 278 patients (27 out of 289 lesions) met the ESGE's criteria for curative endoscopic resection using endoscopic techniques such as EMR and ESD. It is not certain that the 18 patients who did not undergo curative endoscopic resection would necessarily have received further surgical treatment, as their risk for recurrence, age, comorbidities and own personal expressed wishes would have to be taken into account, something that is impossible to judge in such a retrospective study. ESGE's inclusion-criteria to undergo curative endoscopic resection were fitted retrospectively to our sample population. In hindsight, and with histologically analyzed surgical resected lesions in hand, it is easy to say which, and how many patients should have undergone endoscopic resection with curative result. In reality there would likely have been more than 45 patients referred to endoscopic resection, based on two factors. Firstly the endoscopists must evaluate organ-specific endoscopically observable criteria (morphology, lesion size, chromoendoscopy and NBI etc.) associated with low risk for lymph node invasion, and as such this visual method of inclusion is prone to human error and could lead to over-inclusion, albeit one that can be reduced with practice and seeing which endoscopic observations in fact correspond to the according morphology suggested by the pathology report. Secondly, as alluded to above, there are some patients who are not capable of undergoing

surgical procedures due to advanced age and/or significant comorbidities, or expressed wishes, who could benefit from endoscopic resection, not included in this study.

The correlation between endoscopically observable characteristics and histological verification of a lesions malignancy (or lack thereof) lends itself to the design of a prospective study, and such studies should be performed at any institution planning on implementing endoscopic resection techniques.

It is the natural progression of the medical profession to learn, too oft with hindsight, how to improve on techniques of the past, and to attain the same level of treatment results or better with less harm done to the human body. Endoscopic techniques present an opportunity to remove superficial and some invasive lesions from the oesophagus, stomach, colon and rectum, yet the main problem in its effective implementation is discovering superficial lesions while still curatively resectable. This highlights the main future challenge within the field of endoscopic surgery - designing and implementing effective screening protocols.

The field of endoscopic surgery is a relatively new one in the field of general surgery, and must therefore continue to be tried and tested by the same strict codes that govern all medical research. It is only by collecting data on results that the true power of a medical tool can be judged and, through international cooperation, shared. Hopefully this study has shed some light onto the possibilities that this new and exciting field of medical surgery has to offer. With the willingness of endoscopists to learn new and challenging ways of thinking regarding GI superficial lesions, a whole host of new and potentially life-saving therapies will be available to the Norwegian population. With endoscopic techniques already pioneered and tested by the international community, it becomes a question of *when* future patients in Norway, similar to the 27 found in

this study, can be spared surgical organ resection in favor of the curative, and far less damaging endoscopic mucosal resection or endoscopic submucosal dissection.

Tables

Table 1: The updated *Vienna Classification of gastrointestinal epithelial neoplasia*, copied from Dixon's Vienna Revisited (3) for display purposes.

Category	Diagnosis	Clinical management
1	Negative for neoplasia	Optional follow up
2	Indefinite for neoplasia	Follow up
3	Mucosal low grade neoplasia Low grade adenoma Low grade dysplasia	Endoscopic resection or follow up*
4	Mucosal high grade neoplasia 4.1 High grade adenoma/dysplasia 4.2 Non-invasive carcinoma (carcinoma in situ) 4.3 Suspicious for invasive carcinoma 4.4 Intramucosal carcinoma	Endoscopic or surgical local resection*
5	Submucosal invasion by carcinoma	Surgical resection*

*Choice of treatment will depend on the overall size of the lesion; the depth of invasion as assessed endoscopically, radiologically, or ultrasonographically; and on general factors such as the patient's age and comorbid conditions. For gastric, oesophageal, and non-polypoid colorectal well and moderately differentiated carcinomas showing only minimal submucosal invasion (sm1) without lymphatic involvement, local resection is sufficient. Likewise, for polypoid colorectal carcinomas with deeper submucosal invasion in the stalk/base but without lymphatic or blood vessel invasion, complete local resection is considered adequate treatment.

Table 2: summarized ESGE guidelines for endoscopic resection of superficial GI lesions (12)

Organ	Lesion type	Recommended procedure	Criteria for curative endoscopic resection		Indication for surgery or chemoradiotherapy
Oesophagus	SCC (20,21)	ESD (EMR if diameter <10 mm)	no deeper than lamina propria, L0V0	well differentiated, ≤ 200 µm into submucosa, L0V0	> 200 µm into submucosa, poorly differentiated, L1 or V1, positive vertical margins[1]
	Adenocarcinoma (22,23,24,25,26,27,28)	EMR (ESD if diameter >15 mm, poorly lifting, risk of submucosal invasion)	well or moderately differentiated, no deeper than muscularis mucosae, diameter < 30 mm, L0V0	well or moderately differentiated, ≤ 500 µm into submucosa, L0V0	> 500 µm into submucosa, poorly differentiated, L1 or V1, positive vertical margins[2]
Stomach	Adenocarcinoma (29,30,31,32,33,34,35,36,37,38)	ESD (EMR if diameter <15 mm and Paris 0-IIa)	LGIN or intestinal-type adenocarcinoma no deeper than muscularis mucosae, without ulceration, L0V0	intestinal-type adenocarcinoma with ulceration no deeper than muscularis mucosae or adenocarcinoma ≤ 500 µm into submucosa, both diameter ≤ 30 mm, L0V0	> 500 µm into submucosa, ulceration when diameter > 30 mm or submucosal invasion, L1 or V1, positive vertical margins[2]
Colorectal	Adenocarcinoma (13,14,39,40,41,42,43)	EMR (ESD if Paris 0-IIc, irregular/nongranular surface pattern, and diameter > 20 mm)	well differentiated, ≤ 1000 µm into submucosa, L0V0	pedunculated polyp - adenocarcinoma no deeper than stalk (Haggitt's 3)	> 1000 µm into submucosa, poorly differentiated with submucosal invasion, L1 or V1, positive vertical margins[2]

note: L0 and V0 mean no lymphovascular involvement, L1 and V1 mean lymphovascular involvement respectively (Ref AJCC 7th edition)

1: chemoradiotherapy and/or surgery

2: surgery

Table 3: summarized Norwegian guidelines for endoscopic resection of superficial GI lesions (4,15,44)

Organ (histopathology)	**Recommended procedure**	**Criteria for recommended procedure**	**Indication for surgery or chemoradiotherapy**
Oesophagus (adenocarcinoma) (45,46,47)	EMR	no deeper than muscularis mucosae	(not specified)
Stomach (adenocarcinoma) (48,49,50)	ESD	well or moderately differentiated, without ulceration, < 20 mm diameter, limited to upper part of submucosa (cT1b), not pathologically enlarged lymph nodes	criteria not met[1]
Colorectal (adenocarcinoma) (13, 51, 52, 53, 54, 55)	EMR	well or moderately differentiated, invasion no deeper than stalk of pedunculated polyp (Haggitt's 3), L0V0	poorly differentiated, Haggitt's 4, L1 or V1, or positive resection margins[2]
	EMR	pedunculated polyp and flat polyp < 15 mm diameter	positive resection margins[2]
	EMR	flat polyp 15 - 20 mm diameter	
	ESD	broadbased polyp > 20 mm diameter	

note: L0 and V0 mean no lymphovascular involvement, L1 and V1 mean lymphovascular involvement respectively (8)

1: surgical gastric resection, weighed against risk of recurrence

2: TEM resection if rectal lesion, formal surgical resection if colonic lesion.

Figures

Figures 1-5 and text for these figures are copied from *Update on the Paris Classification* for display purposes (3).

Figure 1

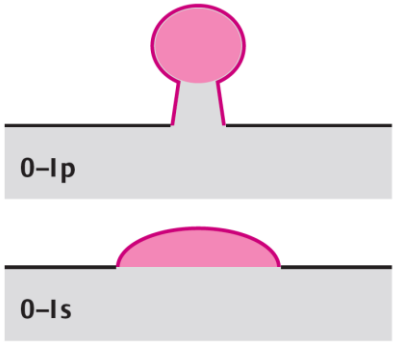

Figure 1: "Endoscopic appearance of a superficial neoplastic lesion at the surface of the digestive tract mucosa: protruding type, pedunculated (0-Ip) and sessile (0-Is). The distinction between a sessile (protruding) lesion and a slightly elevated (nonprotruding) lesion is based on the extent of the elevation from the adjacent mucosa. The cut−off limit is 2.5mm in the columnar epithelium and 1.2mm in the stratified epithelium of the esophagus" (3).

Figure 2

Figure 2: "Endoscopic appearance of a superficial neoplastic lesion on the surface of the digestive tract mucosa: nonprotruding and nonexcavated types, slightly elevated (0-IIa), completely flat (0-IIb), or slightly depressed (0-IIc). The distinction between a slightly depressed lesion and an excavated lesion is based on the depth of the depression from the adjacent mucosa. The cut−off limit is 1.2mm in the columnar epithelium and 0.5mm in the stratified epithelium of the esophagus" (3).

Figure 3

Figure 3: "Endoscopic appearance of a superficial neoplastic lesion on the surface of the digestive–tract mucosa: excavated type (0-III). An ulcer is seen" (3).

Figure 4

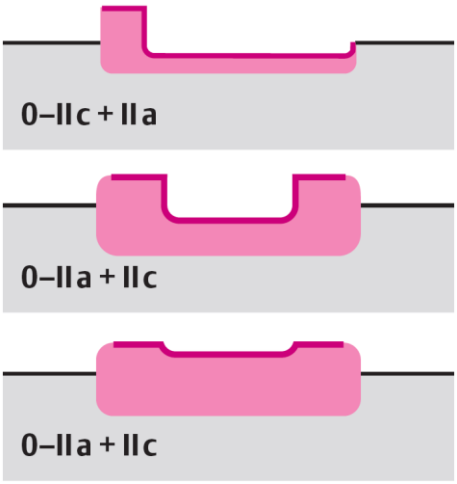

Figure 4: "Endoscopic appearance of a superficial neoplastic lesion on the surface of the digestive tract mucosa: elevation plus depression. Type 0-IIc + IIa is a depressed lesion with an elevation in part of the peripheral ring. Type 0-IIa + IIc is an elevated lesion with a central depression. The central depression is surrounded by an elevated ring. When the level of the depression is higher than the mucosa adjacent to the lesion, it is a relatively depressed lesion" (3).

Figure 5

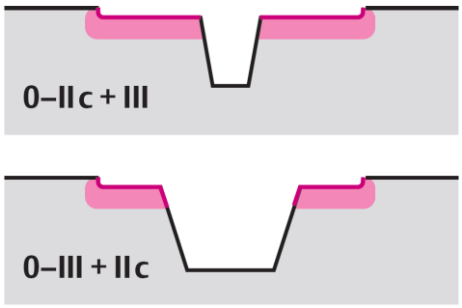

Figure 5: "Endoscopic appearance of a superficial neoplastic lesion on the surface of the digestive–tract mucosa; ulcer plus depression. Type 0-IIc + III is a depressed lesion with a central ulcer. Type 0-III + IIc is an ulcer with short depressed margins" (3).

Figure 6

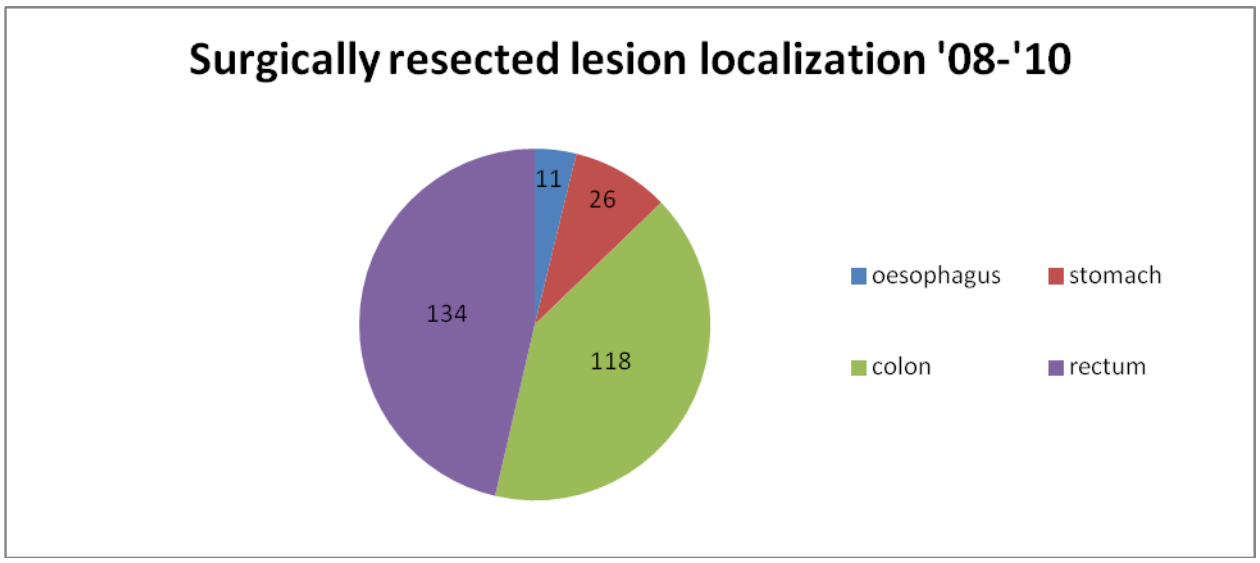

Figure 6: The distribution of surgically resected lesions within the GI tract based on location, 2008-2010.

Figure 7

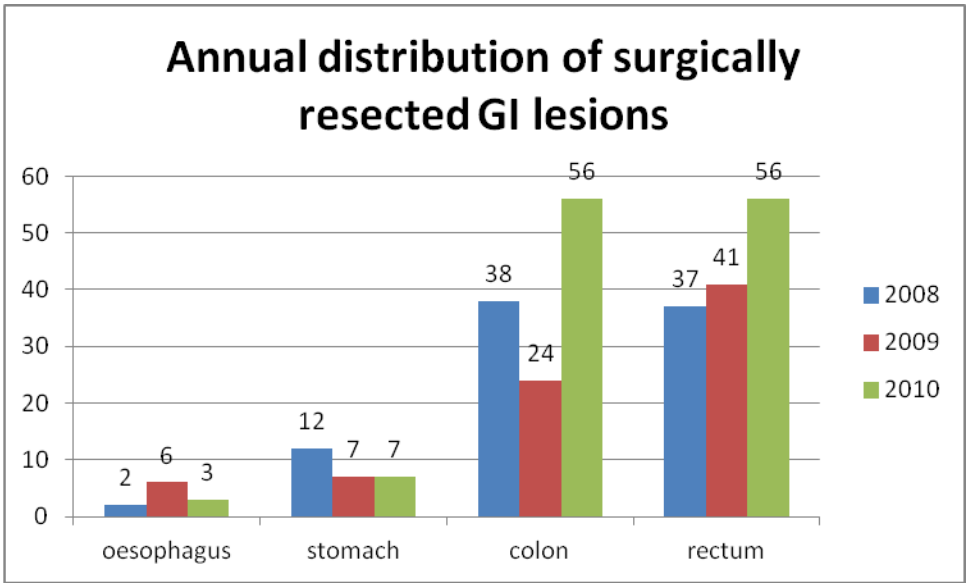

Figure 7: The annual distribution of surgically resected lesions within the GI tract grouped by organ, 2008-2010.

Figure 8

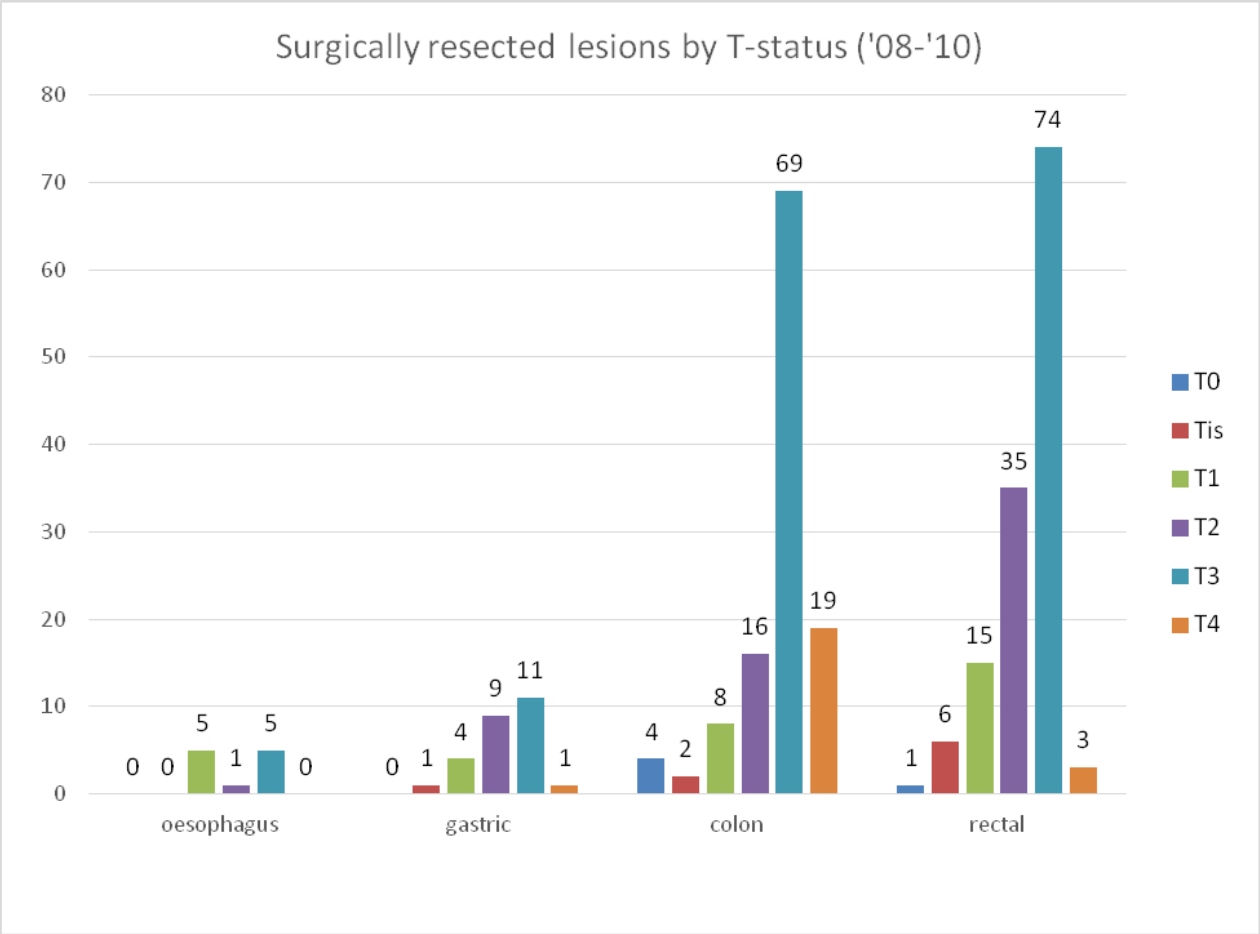

Figure 8: The T-status distribution of surgically resected lesions within the GI tract grouped by organ, 2008-2010.

Figure 9

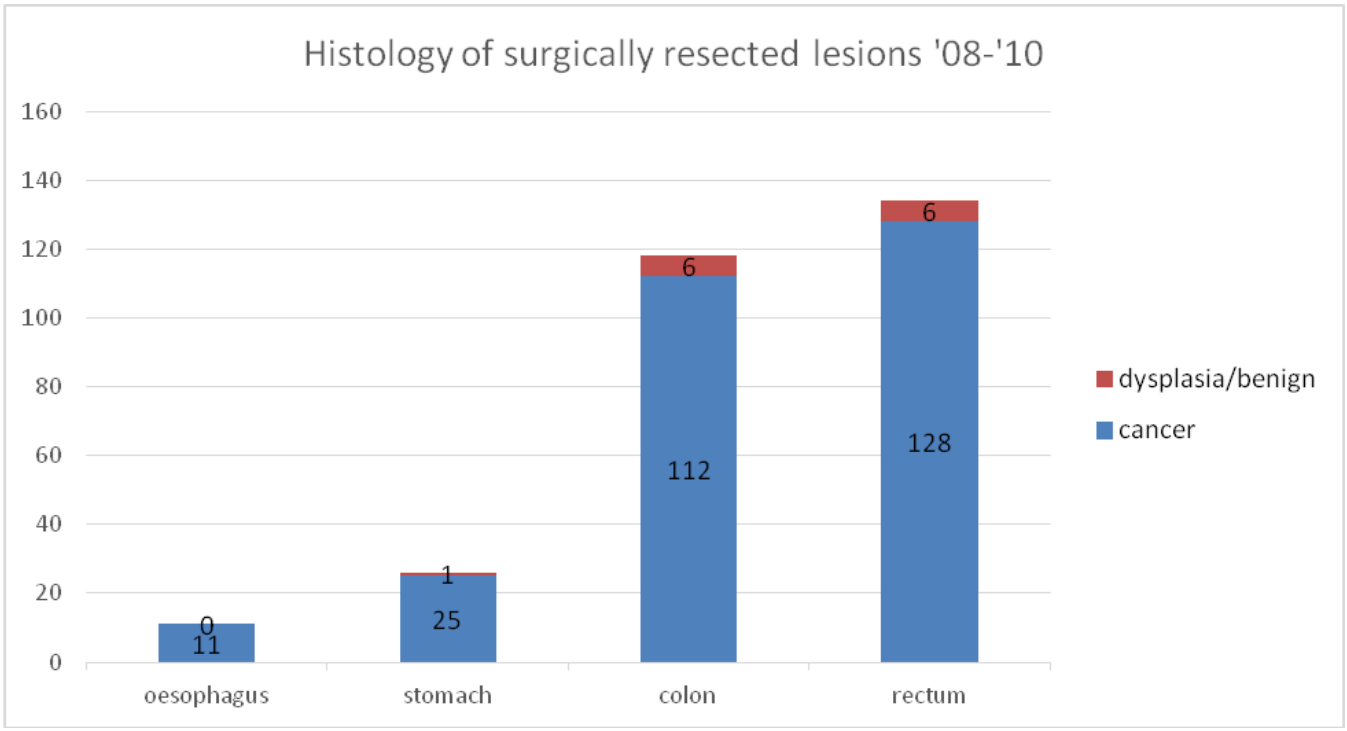

Figure 9: Number of surgically resected lesions which received diagnosis of cancer (blue) and dysplasia (red) from UNN pathologists, grouped by organ, 2008-2010.

Figure 10

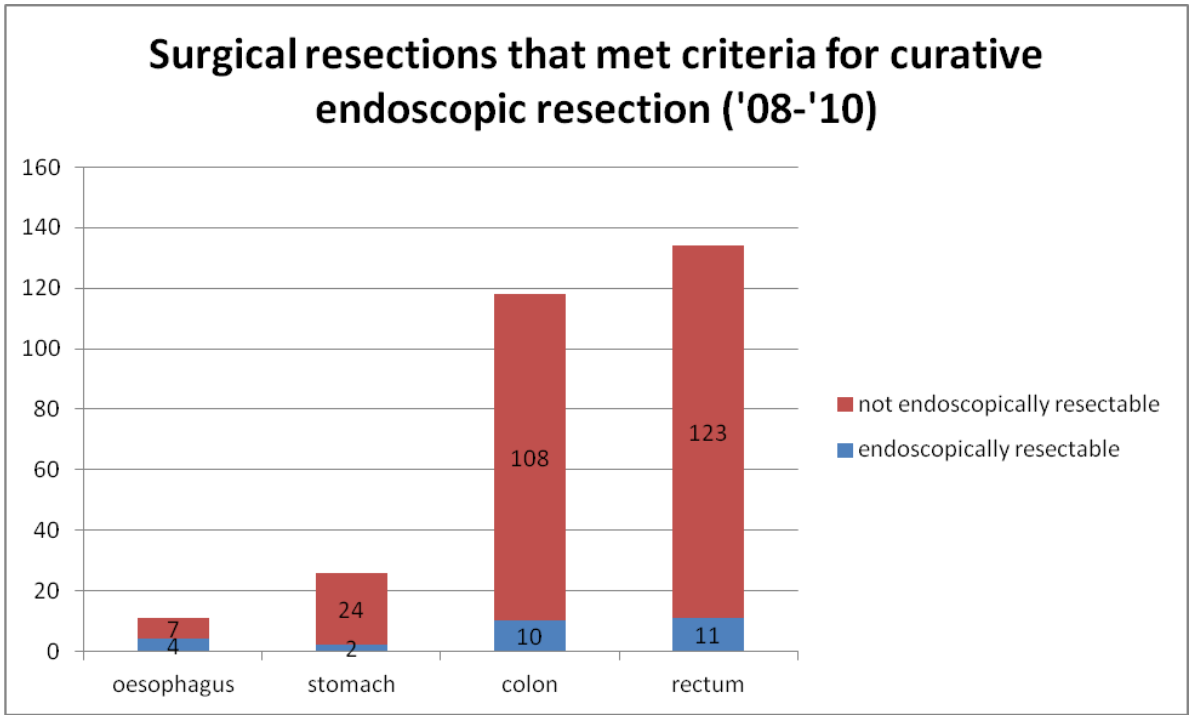

Figure 10: Number of surgically resected lesions that met ESGE criteria for curative endoscopic resection (blue) and those resections which did not meet the criteria (red), 2008-2010.

Figure 11

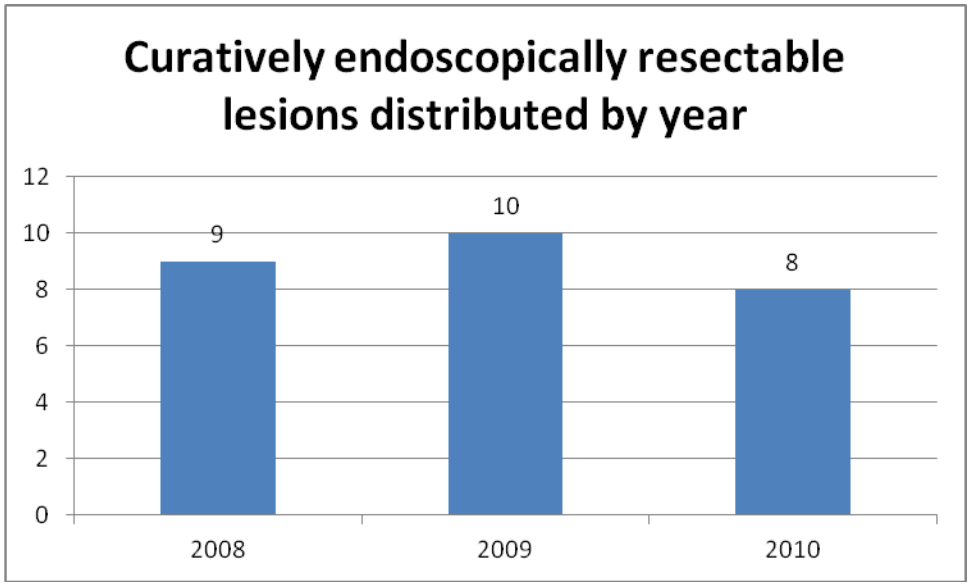

Figure 11: Distribution of surgically resected lesions that met ESGE criteria for curative endoscopic resection grouped by year of operation.

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