MORPHOPATHOLOGICAL STUDIES OF STUMP CANCER FOLLOWING GASTRIC SURGERY

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Abstract. A distinction can be made between a precancerous condition and a precancerous lesion.The former is a clinical state associated with a significantly increased risk of cancer, whereas a precancerous lesion is a histopathological abnormality in which cancer is more likely to occur than in its apparently normal counterpart. Up to the present time atrophic gastritis, gastric ulcer,pernicious anaemia, gastric stumps, gastric polyps, and Menetrier's disease have all been considered as precancerous conditions and lesions of the stomach. Of these, only atrophic gastritis, pernicious anaemia, gastric stumps, and certain types of gastric polyp can now be regarded as having any really significant malignant potential. The precancerous lesion common to these is epithelial dysplasia which can occur in ordinary (foveolar) gastric epithelium as well as in intestinal metaplasia.The criteria for grading dysplasia in gastric epithelium into mild, moderate, and severe grades are given, and attention is drawn to the problems of differentiating inflammatory or degenerative change from mild dysplasia and intramucosal carcinoma from severe dysplasia.. Our study was related to morphological changes of gastric mucosa after partial gastectomy , followed by reconstruction with a gastroduodenostomy (Billroth I) or a gastrojejunostomy (Billroth II) to gastric stump cancer(GSC), with special reference to reliable early diagnostics. In particular, dysplasia can be considered as a dependable morphological marker. Therefore, close endoscopic surveillance with multiple biopsies of the gastroenterostomy is recommended. Screening starting at 15 years after the initial ulcer surgery can detect tumors at a curable stage..
Key words: Gastric stump cancer;(GSC) dysplasia,metaplasia,adenocarcinoma, Endoscopic surveillance

Rezumat. Se poate face o distinctie intre conditia precanceroasa si leziunea precanceroasa.Prima este o stare clinica asociata cu un risc semnificativ crescut pentru cancer,pe cand leziunea precanceroasa este o anomalie histopatologica in care cancerul are mai mare probabilitate sa apara decat in prima situatie aparent normala.Pana in momentul de fata,gastrita atrofica, ulcerul gastric,anemia pernicioasa ,cancerul de bont gasrtc ,polipii gastrici si boala Menetrier,toate au fost considerate drept conditii precanceroase si leziuni ale stomacului.Dintre acestea,doar doar gastritele atrofice ,anemia pernicioasa,cancerul de bont gastric si anumite tipuri de polipi gastrici pot acum considerate ca avand vreun potential semnificativ malign.Leziunea precanceroasa comuna acestor conditii patologice este displazia epiteliala care se poate produce la nivelul epiteliului gastric obisnuit(foveolar) ca si in metaplazia intestinala. Sunt prezentate criteriile pentru gradarea displaziei epiteliului gastric in forme usoare ,moderate si severe ,atentia fiind atrasa de problemele de diferentiere a schimbarilor inflamatorii ori degenerative din displazia usoara si carcinomul din mucoasa gastrica de displazia severa. Studiul nostru a fost legat de schimbarile mucoasei gastrice dupa gastrectomia partiala,urmata de reconstructie cu gastroduodenostomia(Billroth I)or,gastrojejunostomia(Billroth II)la cancerul de bont gastric(GSC) cu referire speciala la un diagnostic timpuriu eficient. In particular,displazia poate fi considerata,ca un marker morfologic dependent.De aceea , este recomandata o urmarire atenta cu multiple biopsii ale gastrostomei .Screeningul inceput la 15 ani de la operatia initiala a ulcerului gastric poate detecta tumori intr-un stadiu curabil.
Cuvinte cheie:Cancerul de bont gastric(GSC),displazie , metaplazie, adenocarcinom,evaluare endoscopica

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INTRODUCTION

During the first half of this century, partial gastrectomy became the predominant surgical treatment for peptic ulcer disease [[1,2]. This procedure involves the resection of the distal 50%-75% of the stomach, followed by reconstruction with a gastroduodenostomy (Billroth I) or a gastrojejunostomy (Billroth II). During the 1940s-1950s, truncal vagotomy and drainage (generally pyloroplasty or gastrojejunostomy) became popular as an alternative procedure.

The stump of the stomach after remote gastric resection because of benign ulcer disease is a well-defined premalignant condition. Many studies in the past have confirmed that, after remote partial gastrectomy, there is an increased risk for stomach cancer[3,4]. GSC is defined as a malignancy of the stomach occurring > 5 years after initial partial gastrectomy, to confusion with cancer recurrence after initial misdiagnosis. The risk for stump cancer is remarkable because most of these patients suffer from peptic ulcer disease prior to surgery. The relation between peptic ulcer disease and gastric cancer is not fully understood. Gastric cancer and peptic ulcer disease are inversely associated and they are accompanied by distinct patterns of acid secretion[5]; by contrast, gastric ulcers, non-peptic gastric ulcers, and gastric cancer partly share pathophysiological features[6,7]. The part of the stomach that is at the highest risk for gastric cancer is removed by surgery. Nevertheless, with an increasing postoperative interval, there is a steadily increasing risk for stomach cancer in the gastric remnant. After more than 15-20 years postoperatively, the risk is higher than can be expected for an age- and sex-matched general population, and it rapidly increases thereafter[8]. In line with the increased risk for stomach cancer, the post-gastrectomy stomach also harbors dysplasia relatively frequently[9;10]. The dysplasia is typically encountered around the gastric anastomosis, and similarly the cancers are almost exclusively found there. Both the dysplasia and the cancers can be multifocal and extensive mapping of the mucosa with endoscopic biopsies is warranted. Unlike primary gastric cancer, which is frequently resectable (resectability rate in Poland: 66%), gastric stump carcinoma once detected be-WJG Billroth antrectomy and its various modifications remove the part where the ulcer is located and that contains the gastrin-producing antral mucosa responsible for the stimulation of acid production through the oxyntic mucosa.It also induces biliary reflux, felt to be beneficial for healing due to its alkaline contents. The majority of patients with peptic ulcer disease will have an antrum-predominant*H. pylori* gastritis[11].

The biliary reflux creates a microenvironment that is not suitable for *H. pylori* and it will eradicate the microorganisms from the anastomosis after surgery.

Our study was related to morphological changes of gastric mucosa in different evolutionary stages of GSC, with special reference to reliable early diagnostics.

MATERIAL AND METHOD

Patients: This study is a randomized anatomopathological study performed on 320 patients on which it was pointed out the late modifications of gastric mucosa following gastroduodenal resections for benign lesion

Over 32 years(1980-2012) in Surgery Clinique of Tg.Mures,have been admitted and operated 59 patients (56 men and 3 women) aged between, 42-87 years old with a mean age of 59.The initial surgery has been performed in 30 cases for gastric ulcer and in 29 cases for duodenal ulcer,one of them being associated with a gastric polip without signs of hystopathologic malignancy and the other for double gastric and duodenal ulcer.

Out of 59 patients with primary stump gastric cancer,a patient has been externalized upon request in worst condition following surgery and to another

has been performed for biopsy of left laterocervical ganglia.32 were inoperable (42%) for 10 patients the surgery has a paleative purpose (16.9%), and only for 16 patients (27.1%) the surgery has a radical purpose.Have been performed the following types of surgeries:
31laparatomies,8 GEA,1 jejunoanastomy for feeding,3 subtotal resections and 14 total gastrectomies,majority with extended visceral sacrifices (left supramesocholic)
Postoperatory evolution
Has been generally favorable,3 patients have died during hospitalization(5%) and 5 have been externalized in aggravating state upon request of their relatives,the rate of death being 13.6% ie. 8 patients.The causes of death:haemoragic shock 1 case Cardiorespiratory stop-in two cases.
The mean time of hospitalization was 21 days with limits between 5 and 68 days.Neoplasm of gastrc stump is like a spider web,anchored by the neighbourhood organs.
Fragments of tumoral tissue taken during surgery from anastomosis have been processed using clasical hystopathological techinques of processing (fixing and embedding in parafin blocks) ,then have been taken serial sections from each blockTissue sections have been stained with haematoxilin-eosin and others with alcian blue and mucicarmin standard techniques.
Hystopathological aspects have been selected by means of Olympus CX31optical microscope, using the eyepiece 4. For immages have been used the objectives opticaly corrected X4, X10, X20 şi X40. The most significant immages have been processed by means of digital video camera LiveViewPro, introduced directly into computer by means of analySIS Pro programm FotoCanvas Lite v1.1 module from ACD programm.

RESULTS

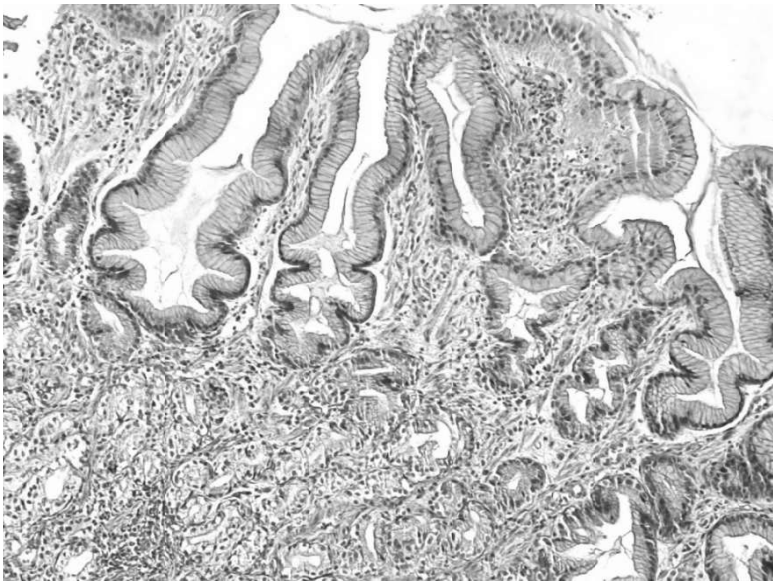

Fig.1 Chronic moderate gastritis (HE staining, ×400)

Antral mucosa with moderate foveolar hyperplasia, mild edema, prominent interfoveolar smooth muscle fibers, and no inflammation. This is highly suggestive of chemical gastropathy.

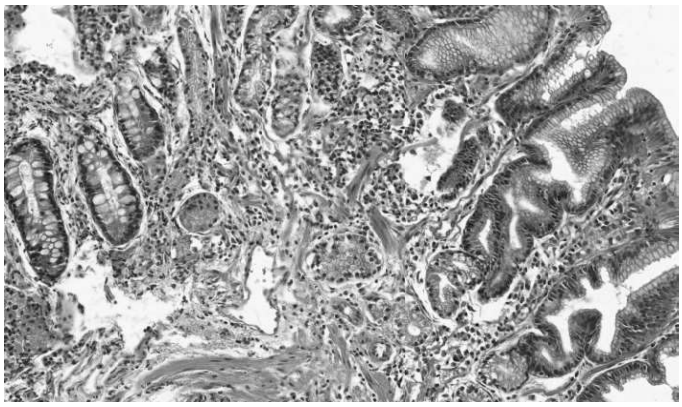

Fig. 2.Reflux gastritis with Intestinal metaplasia (HE staining, ×400)

Loss of parietal cells with the subsequent disappearance of the chief cells introduces an accelerated mucosal atrophy that is caused by the lack of the trophic hormone gastrin and the vagotomy that is mostly done simultaneously. The specialized glandular mucosa is replaced by intestinal metaplasia and pseudopyloric metaplasia [13]. Atrophy of the gastric mucosa may lead to vitamin B12 deficiency.

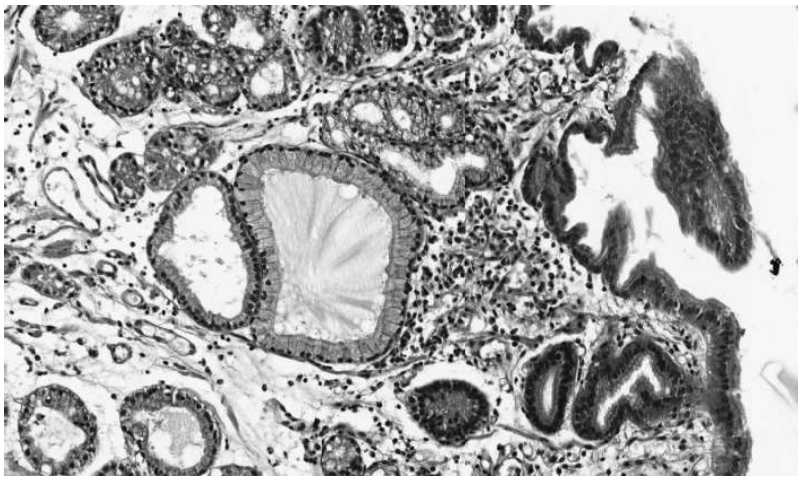

Fig.3 Cystic reflux gastropathy with intestinal metaplasia (HE staining, ×400)

Gastric glands cysticaly enlarged are delimited both by foveolar epithelium and by the epithelium with intestinal metaplasia.

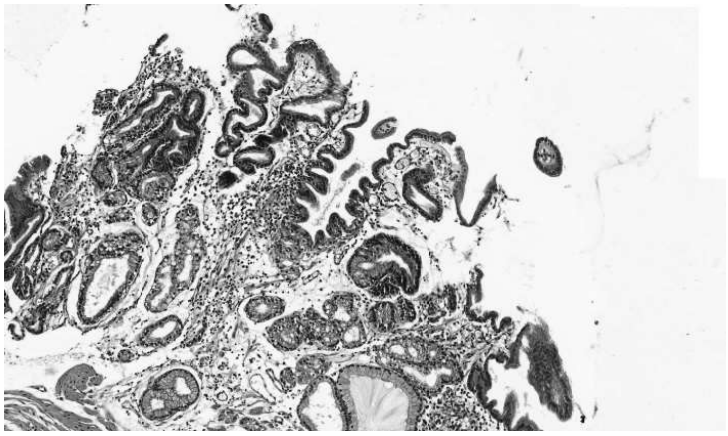

Fig.4. Foveolar hyperplasia (HE staining, ×400)

Epithelial foveolar cells have enlarged round and unistratified nuclei ,slightly hyperchromic. Modifications of reactive type.

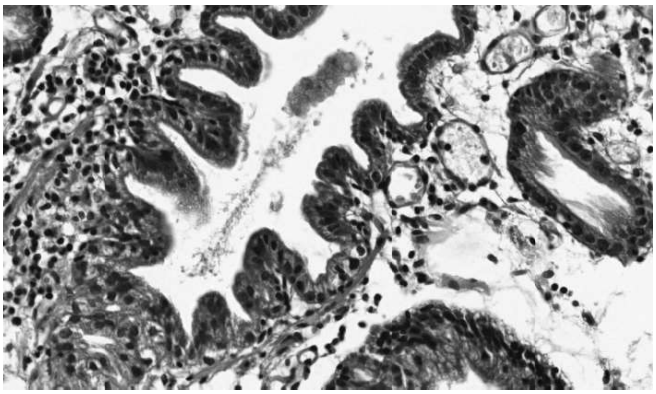

Fig.5 Foveolar hyperplasia with regenerative athipy (HE staining, ×400)

Epithelial foveolar cells have enlarged round and unistratified nuclei slightly hyperchromic.Modifications of reactive type.

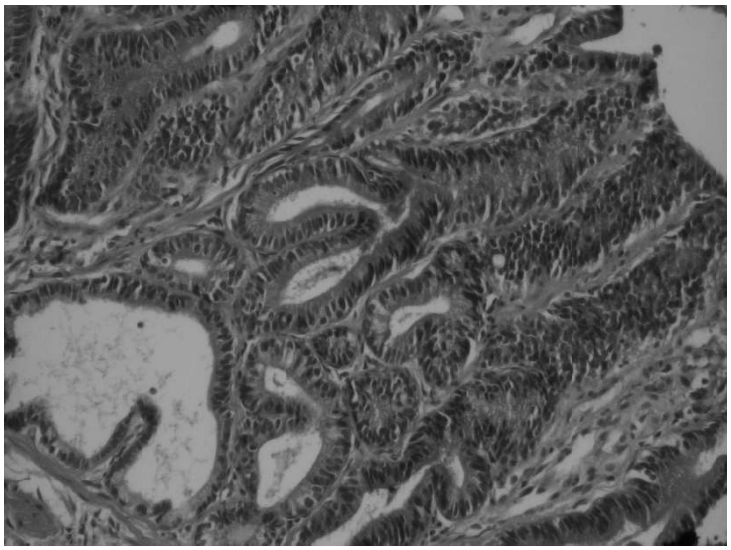

Fig.6 Mild dysplasia of gastric mucosa (HE staining, ×400)

Gastric mucosa with cystic dilatations , delimitated by epithelium with signs of dysplasia, cells have elongated, hyperchromic and pseudostratified nuclei, which keep their basal polarity (signs of light dysplasy or of low grade).

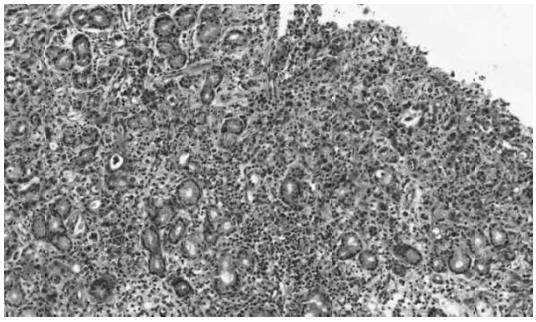

Fig.7. Reflux gastropathy with adenocarcinoma (HE staining, ×400)

The fragment from anastomosis tumor which shows an epithelial proliferation with a tubular architecture with small glandular and confluent structures which infiltrate and destroies normal glands architecture.

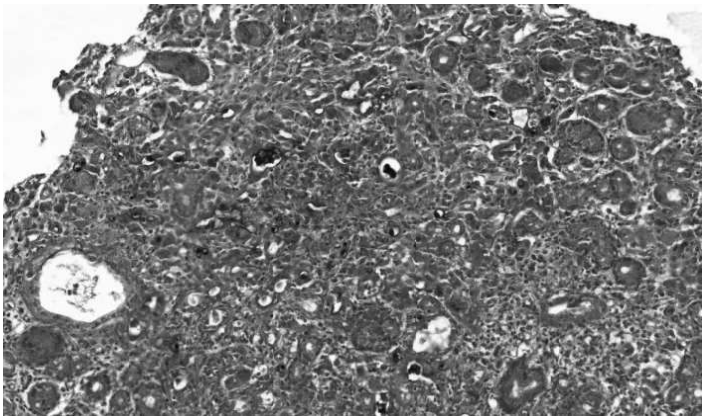

Fig.8. Reflux gastropathy with adenocarcinoma slightly differentiated Alcian Blue stained.
(HE staining, ×400)

The presence of mucin alcian positive (blue colour) both in tumor glands lumen and in cytoplasm of some isolated cells.

DISCUSSION

Following partial gastric resection antral mucosa presents moderate foveolar hyperplasia, mild edema, prominent interfoveolar smooth muscle fibers, and no inflammation. This is highly suggestive of chemical gastropathy [Fig.1].

The microscopy of the anastomosis following surgery have changed from the chronic active *H. pylori* gastritis picture into that of the typical reflux gastritis Loss of parietal cells with the subsequent disappearance of the chief cells introduces an accelerated mucosal atrophy that is caused by the lack of the trophic hormone gastrin and the vagotomy that is mostly done simultaneously [Fig2].

The specialized glandular mucosa is replaced by intestinal metaplasia and pseudopyloric metaplasia[13]. Atrophy of the gastric mucosa may lead to vitamin B12 deficiency.

Gastric glands cysticaly enlarged are delimited both by foveolar epithelium and

by the epithelium with intestinal metaplasia [Fig3].

The most important features of reflux gastritis are foveolar hyperplasia, congestion, paucity of inflammatory infiltrate, reactive epithelial change and smooth muscle fiber proliferation associated to intestinal metaplasia where calciform cells replace normal gastric glands from this region. [Fig.2,3] These changes are already apparent shortly after surgery; less so when a Roux-en-Y conversion is carried out to avoid reflux[12;13].

Stomal gastropathy in a patient who underwent a Billroth II resection two decades earlier. The pits are tortuous and the epithelial lining has a regenerative appearance, with large nuclei but a regular architecture that helps exclude dysplasia; the glandular component is somewhat hypertrophic, with several dilated cystic glands. These features give the mucosa its characteristic polypoid aspect seen at endoscopy .Epithelial foveolar cells have enlarged round and unistratified nuclei ,slightly hyperchromic.Modifications of reactive type. (Fig.4)

Foveolar hyperplasia is the elongation and increased tortuosity ("corkscrew appearance") of gastric pits resulting from hyperplasia of the foveolar cells. Hyperplasia (a visual surrogate for increased epithelial cell turnover) is accompanied by hyperchromatic nuclei and mitotic activity reaching an increased height of the pit and by signs of cellular immaturity,such as mucin depletion, a cuboidal shape, and an increased nucleo-cytoplasmic ratio [Fig.5].

Foveolar hyperplasia is a cardinal feature of chemical gastropathy.[14] Lesser degrees are commonly seen in *H.pylori* gastritis, but marked hyperplasia suggests coexistent chemical injury.

Gastric mucosa with cystic dilatations , delimitated by epithelium with signs of dysplasia, cells have elongated, hyperchromic and pseudostratified nuclei, which keep their basal polarity (signs of light dysplasy or of low grade) [Fig.6].

Patients who have had a partial gastrectomy for benign peptic ulcer are at increased risk for carcinoma in the gastric stump many years after the operation. There is evidence that such patients form a clinical risk group and should be monitored in order to detect precancerous changes but further research is required. Gastric stump carcinomas usually develop close to the anastomosis on the gastric side. Polypoid lesions are common in the same area, but their significance has not yet been established; many are hyperplastic or regenerative polyps, and others may be pseudopolyps resulting from the construction of the anastomosis

"Intestinal"-type carcinoma[15] are characterized by the presence of pseudoglandular carcinomatous structures made up of potentially malignant cells, disposed in one or more layers, with endoluminal papillary projections; . The fragment taken from anastomosis tumor which shows an epithelial proliferation with a tubular architecture with small glandular and confluent structures which infiltrate and destroies normal glands architecture. [Fig.7].Tumoral cells are generally well or moderately differentiated, cuboid or columnar.

When mucin secretion is present, it is mainly extracellular, tumoral cells rarely containing inflammatory infiltrate formed of lymphocytes, plasmocytes and eosinophils. The presence of mucin alcian positive (blue colour) both in tumor glands lumen and in cytoplasm of some isolated cells. [Fig.8].

Attention has so far been concentrated on the above precancerous conditions and much less emphasis has been placed on epithelial dysplasia in the stomach as a marker for increased cancer risk. It is important that dysplasia should be defined and its significance evaluated as a possible marker common to all the above precancerous conditions including Stump gastric cancer.The main histological and

cytological features of epithelial dysplasia are cellular atypia, abnormal differentiation, and disorganised mucosal architecture. These can occur in ordinary gastric (foveolar) epithelium as well as in intestinal metaplasia, both ofwhich may be the source of carcinoma.

Changes in the gastric mucosa exposed to biliary and duodenopancreatic reflux after Billroth II operations were described in the 1960s and 1970s as postoperative gastritis[15];the possible premalignant nature of such changes was later noted in cohorts of operated patients.[16,17]

The frequency of gastric stump carcinoma after gastric resection varies from 2 to 8% [17].

In the present series it was 5Y% after gastrectomy for duodenal ulcer and 4%Yo after gastrectomy for gastric ulcer.

However, evidence is accumulating that the frequency of stump carcinoma is higher than the incidence of gastric cancer in the general population [18].

The interval between gastric resection and stump cancer diagnosis varies in different series

It seems likely that it depends on the age of the patient when he had the initial operation: the younger the patient, the shorter the interval.Controversy exists regarding the relative incidence of gastric stump carcinoma after resection for gastric and for duodenal ulcer. There are those who claim that after gastrectomy for gastric ulcer the incidence of gastric carcinoma is three times greater than in the general population,while among those who have had gastrectomy for duodenal ulcer no increased incidence can be detected [17]. In contrast, other authors have been unable to find any such difference [19]. Our findings in this series of patients support those of the latter group; much the same percentage of our patients developed gastric stump carcinoma after total gastrectomy regardless of whether they had been operated on for gastric or duodenal ulcer. It is more than clear that after gastric resection, whatever the reason for it, atrophic changes develop in the gastric mucosa [20]. It has also been proved that the mucosal changes of intestinal metaplasia, cystification of the gastric glands, papillary hyperplasia, and adenomatous transformation are present after gastrectomy and that they are localised to the anastomosis area, where the incidence of neoplastic infiltration is increased [21]. This is in accordance with our finding that in 8o% of cases the cancer was located in the anastomosis area. Moreover, our gastroscopic biopsies provided evidence of changes in the mucosa analogous to the picture of atrophic gastritis.

CONCLUSION

It can be postulated that after gastric resection combined with gastroenteroanastomosis the resulting atrophic gastritis and reflux of bile and intestinal and pancreatic juices into the stomach are the main factors contributing to the increased risk of cancer development.

The stump carcinomas are preceded by well defined preinvasive precursor lesions and evolve as the end result of a series of mutagenic cell transformations, leading to stepwise tumor progression from atrophic gastritis with metaplasia *via* dysplasia to invasive carcinoma.

Dysplasia can be considered a dependable morphological marker, amenable for early detection by endoscopic surveillance.

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