

# Ioannina University Courses in Pathology (IUCP)

## *Gastrointestinal Pathology - Oncology*

9-11 March 2018

Palladion Hotel  
Ioannina

Organized by



Under the auspices of



**FINAL PROGRAMME & PROCEEDINGS BOOK**

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## Welcome Message

Ioannina University Courses in Pathology (IUCP) are organized in Ioannina, Greece every year. These are postgraduate courses on selected topics of Human Pathology and have been offered since 1996, after the unanimous decision of the Executive Committee of the European Society of Pathology (ESP) to give the ESP auspices to the organization of the IUCP. The official language is English.

Up to now 34 IUCP have been organized and Professor Niki J. Agnantis has been the Director and the Coordinator of the first 33 IUCP. The Hellenic Society of Pathology (HSP) acknowledges Prof. N.J. Agnantis's commitment to establishing these courses.

Since the beginning, the aim of the courses is to bring together young Pathologists and Tutors, experts in the various fields of Pathology, as well as to encourage active participation of all colleagues during the discussions following the Lectures and the Slide Seminars, providing an in-depth review of Diagnostic Surgical Pathology. An emphasis is given on morphologic features, newly recognized entities and modern techniques. The Courses have been designed for 45-50 Pathologists and Clinical Colleagues related to the subject. Over the years besides Greek Pathologists, expert Pathologists from all over Europe have contributed as Tutors. The participants' body has also been international, with the majority being not only from Greece but from the neighboring Balkan countries as well.

Starting from last year (2017), the organization of IUCP has been passed by Em. Prof. N.J. Agnantis to the HSP and she has been nominated Honorary President of IUCP. We are grateful for this educational gift to all Pathologists, offered continuously for 20 years, and we also commit to stay true to the scope and the high standards of IUCP.

HSP is devoted to training young Pathologists but also to continuing education of senior Pathologists, and is organizing the 35<sup>th</sup> IUCP on "Gastrointestinal Pathology-Oncology", in Ioannina, from 9-11 of March, 2018. An up-to-date and stimulating educational program has been formulated jointly by the Gastrointestinal Working Group, the Scientific Committee and the Advisory Board of HSP. We do hope that the presentations by experts on the field will meet your expectations and will increase your knowledge in this particular field of Pathology.

We are welcoming you to Ioannina and wishing you an enjoyable stay.

**Prof. Anna Batistatou**  
President of  
Hellenic Society of Pathology

**Dr. Kalliopi Patsiaoura**  
Secretary General of  
Hellenic Society of Pathology

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## IOANNINA UNIVERSITY COURSES IN PATHOLOGY

{ I U C P }

SECOND SERIES

## FINAL PROGRAMME & PROCEEDINGS BOOK

9-11 March, 2018

Hotel Palladion, Ioannina, Greece

## IN MEMORY



*Dedicated to the memory of*  
**Vassiliki Malamou-Mitsi**  
*Director of the Department of Pathology/Cytology*  
*University Hospital of Ioannina/University of Ioannina Medical School (2007-2014)*

**Friday 9/3/2018**14.00-15.00 **Registrations****Session 1**Chairpersons: Ass. Prof. **Mitselou A. (GR)**, Assoc. Prof. **Peschos D. (GR)**, Dr. **Zioga A. (GR)**

15.00-16.00 Normal Gastrointestinal Tract (oesophagus, stomach, small intestine, large intestine): Anatomy, Histology and Function **Ass. Prof. Galani V. (GR)**

16.00-16.45 Non-Neoplastic Oesophageal Diseases **Dr. Fotiadou A. (GR)**

16.45-17.15 **Coffee Break****Session 2**Chairpersons: Assoc. Prof. **Goussia A. (GR)**, Dr. **Kamina S. (GR)**, Dr. **Papoudou-Bai A. (GR)**

17.15-18.00 Carcinoma of the Oesophagus and Oesophago-gastric Junction. What's New in Diagnosis and Staging **Dr. Grekou A. (GR)**

18.00-18.45 **Slide Seminar: Non-Neoplastic and Neoplastic Oesophageal Pathology**

1. Eosinophilic Oesophagitis **Dr. Fotiadou A. (GR)**
  2. Barrett with Dysplasia **Dr. Poullos C. (GR)**
  3. Adenocarcinoma v/s Poorly Differentiated Squamous Cell Carcinoma **Dr. Milias S. (GR)**
  4. Metastatic Ovarian Carcinoma to Oesophagus **Dr. Gerasimidou D. (GR)**
- Comments: Dr. **Bouklas D. (GR)**, Dr. **Katsiki E. (GR)**, Dr. **Sourla A. (GR)**

18.45-19.15 The role of the Oncologists in GI Cancer **Dr. Zarkavelis G. (GR)**19.15-19.30 **Coffee Break****Session 3**Chairpersons: Prof. **Batistatou A. (GR)**, Assoc. Prof. **Goussia A. (GR)**, Prof. **Stefanou D. (GR)**  
Em. Prof. **Agnantis N. J. (GR)**

19.30-20.00 IUCP History

20.00 **Welcome Address****Saturday 10/3/2018****Session 4**Chairpersons: Dr. **Kafiri G. (GR)**, Prof. **Korkolopoulou P. (GR)**, Dr. **Tzaida O. (GR)**

09.00-09.45 Gastritis **Assoc. Prof. Tzardis M. (GR)**

09.45-10.35 Pathology of Precancerous Lesions in Gastrointestinal Tract **Dr. Demonakou M. (GR)**

10.35-11.00 **Coffee Break**11.00-11.45 Gastric Polyps - Gastric Carcinoma - New Classification **Dr. Barbatis C. (GR)****Session 5**Chairpersons: Dr. **Patsiaoura K. (GR)**, Em. Prof. **Stathopoulos E. (GR)**

11.45-12.30 Small Intestine Pathology **Dr. Sourla A. (GR)**

12.30-13.00 Differential Diagnosis of Celiac Disease **Prof. Delladetsima I. (GR)**

13.00-13.45 Gastrointestinal Lymphomas **Ass. Prof. Foukas P. (GR)**

13.45-15.30 **Break****Session 6**Chairpersons: Dr. **Patsea E. (GR)**, Dr. **Zacharouli K. (GR)**, Prof. **Zolota V. (GR)**15.30-16.30 Gastrointestinal Stromal Tumours (GISTs) **Dr. Papadopoulos S. (GR)**16.30-17.45 **Slide Seminar: Gastric and Small Intestinal Pathology - Oncology**

1. Gastric Inflammatory Fibroid Polyp **Dr. Chliara E. (GR)**
  2. Clear cell Sarcoma of Small Intestine **Dr. Gerasimidou D. (GR)**
  3. Alkaline Gastritis in Coexistence with Autoimmune Gastritis **Dr. Sakellariou S. (GR)**
  4. Gastric Vascular Ectasia (GAVE) **Dr. Katafygiotis P. (GR)**
  5. Plexiform Fibromyxoma **Dr. Sakellariou S. (GR)**
  6. MMF- Related Coeliac-like Enteropathy **Dr. Sakellariou S. (GR)**
  7. Myofibroblastic Tumor of Small Intestine **Dr. Sotiriou S. (GR)**
  8. Methotrexate Related Gastroduodenitis **Dr. Katafygiotis P. (GR)**
  9. Ileal-Ileocecal Adenocarcinoma Developed in a Patient with Crohn Disease **Dr. Baliou E. (GR)**
  10. Primary Gastric Peripheral T-cell Lymphoma, NOS **Ass. Prof. Foukas P. (GR), Dr. Tsakiraki Z. (GR)**
- Comments: Dr. **Bouklas D. (GR)**, Dr. **Katsiki E. (GR)**, Dr. **Sourla A. (GR)**

17.45-18.00 **Coffee Break****Session 7**Chairpersons: Prof. **Batistatou A. (GR)**, Dr. **Kaklamanis L. (GR)**

18.00-18.45 Colitis **Prof. Langner C. (AT)**

18.45-19.15 Drug-associated Colitis **Prof. Delladetsima I. (GR)**

19.15-20.00 **Slide Seminar: GI Pathology - Oncology** **Prof. Langner C. (AT)**

21.00 **Get together cocktail**

## Sunday 11/3/2018

### Session 8

Chairpersons: **Dr. Arapantoni-Dadioti P. (GR)**, Ass. Prof. **Koletsa T. (GR)**, Dr. **Zizi A. (GR)**

- 09.00-09.45 New Insights in Colorectal Carcinogenesis **Dr. Bouklas D. (GR)**  
 09.45-10.30 Carcinoma of Large Intestine - New Classification - Biomarkers **Dr. Papaparaskeva K. (GR)**  
 10.30-11.15 Gastrointestinal Neuroendocrine Neoplasms **Dr. Giannikakis L. (GR)**

### 11.15-11.30 Coffee Break

### 11.30-12.15 Satellite Symposium - Sponsored by MSD

Chairpersons: **Prof. Batistatou A. (GR)**, **Dr. Patsiaoura K. (GR)**

PD-L1: A new biomarker for gastric cancer

**Dr. Kafiri G. (GR)**

### 12.15-13.30 Slide Seminar: Pitfalls in Large Intestinal Pathology - Oncology

1. Mucormycosis of Large Intestine **Dr. Fotiadou A. (GR)**
2. Eosinophilic Colitis **Dr. Tzigkalidis T. (GR)**
3. Perineural-like Proliferation in Serrated Polyp **Dr. Sourla A. (GR)**
4. Coexistence of Large Bowel Neuroendocrine Carcinoma with Villoglandular Adenoma with High Grade Dysplasia **Ass. Prof. Cheva A. (GR)**
5. Metastatic Gastric Carcinoma in Large Bowel **Dr. Milias S. (GR)**
6. Rectal Carcinoma after Neoadjuvant Treatment **Dr. Papaparaskeva K. (GR)**

Comments: **Dr. Bouklas D. (GR)**, **Dr. Katsiki E. (GR)**, **Dr. Sourla A. (GR)**

### 13.30-14.30 Conclusions - Examination in GI Pathology - Oncology

Chairpersons: **Dr. Bouklas D. (GR)**, **Dr. Katsiki E. (GR)**, **Dr. Sourla A. (GR)**

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## Proceedings Book

Important Notice: for the content of the abstracts the only responsible are the Authors

## GASTROINTESTINAL TRACT (OESOPHAGUS, STOMACH, SMALL INTESTINE, LARGE INTESTINE): ANATOMY-HISTOLOGY AND FUNCTION

### V. Galani

Assistant Professor of Anatomy-Histology-Embryology, Faculty of Medicine, University of Ioannina, Greece

The gastrointestinal system is primarily involved in reducing food for absorption into the body. The alimentary canal, which is about 9 meters long, is subdivided into morphologically recognizable regions: the esophagus, stomach, small intestine (duodenum, jejunum, and ileum), and large intestine (cecum, colon, rectum, anal canal and appendix).

#### **Histological Layers of the Gastrointestinal tract:**

There are four broad layers: the mucosa, submucosa, muscularis externa, and serosa (or adventitia). Within the wall of gastrointestinal tract from the oesophagus to anal canal lies a series of ganglionated plexuses. In the wall of the gastrointestinal tract exists large amounts of unencapsulated lymphoid tissue, termed Mucosa-associated lymphoid tissue.

#### **ESOPHAGUS:**

The oesophagus conducts food from the oral cavity to the stomach where fragmentation is completed and digestion initiated. Attributes: Straight tube, ~25 cm long

**Mucosa:** It is composed of the three layers: stratified squamous non-keratinized epithelium, the lamina propria, and the thick muscularis mucosae (circular & longitudinal layer).

**Submucosa:** It is composed of dense, irregular fibroelastic connective tissue.

The esophageal glands (submucosal) secrete acidic mucous.

**Muscularis externa:** The upper third has striated muscle, middle third has mixed smooth and striated and the lower third has smooth muscle.

**STOMACH:** Mixes food with secretions to begin protein digestion.

It divided into (anatomically, histologically): cardia, fundus, body and pylorus.

-**Cardia:** Separate from esophagus by cardiac sphincter. Glands contain mucus-secreting cells, stem, enteroendocrine, and occasional parietal cells

-**Fundus and body:** Largest portion. Fundic glands contain parietal and chief cells with some stem cells, mucous and enteroendocrine cells.

-**Pyloric region:** Lower end that connects to duodenum; ends at pyloric sphincter. Glands primarily mucus-secreting cells and two special endocrine cells: gastrin-secreting (G) and somatostatin-secreting cells (D).

The inner surface of the stomach is thrown into folds called rugae that include both mucosa and submucosa. These folds form invaginations and the upper portion of these invaginations is called the gastric pits (foveolae gastricae). The epithelial lining of the pits consists of simple columnar epithelium of mucous secreting cells. The gastric glands of the stomach connect to the bottoms of the gastric pits. The cellular structure of these glands is different in the different parts of the stomach.

#### **SMALL INTESTINE:**

It, comprising the duodenum, jejunum and ileum, is the principal site for absorption of digestion products from the gastrointestinal tract. Digestion begins in the stomach and is completed in the small intestine in intimate association with the absorption process.

The luminal surface of the small intestine is modified to increase its surface area. Three types of modifications have been noted: plicae circulares (valves of Kerckring), villi and microvilli.

**Mucosa:** It is composed of the three layers: a simple columnar epithelium, the lamina propria, and the muscularis mucosae. The simple columnar epithelium covering the villi and the surface of the intervillar spaces is composed of surface absorptive cells, goblet cells, and enteroendocrine cells.

**Lamina propria:** The loose connective tissue of the lamina propria forms the core of the villi. The rest of the lamina propria, extending down to the muscularis mucosae, is compressed into thin sheets of highly vascularized connective tissue by the numerous tubular intestinal glands, the crypts of Lieberkuehn. These glands are composed of surface absorptive cells, goblet, regenerative, enteroendocrine, and Paneth cells. The muscularis mucosae is composed of an inner circular and outer longitudinal layer of smooth muscle.

**Submucosa:** It is composed of dense, irregular fibroelastic connective tissue. The submucosa of the duodenum contains glands, known as Brunner's glands.

**Muscularis Externa:** It is composed of an inner circular and an outer longitudinal smooth muscle layer. With the exception of the second and third parts of the duodenum, the entire small intestine is invested by a serosa.

**Secretory Activity of the Small Intestine:** Glands secrete mucus and a watery fluid in response to neural and hormonal stimulation.

**Movement of the Small Intestine:** The movement may be subdivided into two interrelated phases, mixing and propulsive. The hormones cholecystokinin, gastrin, motilin, substance P, and serotonin increase intestinal motility, whereas secretin and glucagon decrease it.

#### **Digestion**

The chyme that enters the duodenum is in the process of being digested by enzymes produced by glands of the oral cavity and of the stomach.

#### **Absorption**

Each day, approximately 6 to 7 L of fluid, 30 to 35 g of sodium, 0,5 kg of carbohydrates and proteins, and 1 kg of fat are absorbed by the surface absorptive cells of the small intestine.

#### **LARGE INTESTINE:**

It (~1,5 m long) is composed of the cecum, colon (ascending, transverse, descending, and sigmoid), rectum and anus. The first part of the large intestine is called the caecum.

**Colon:** It accounts for almost the entire length of the large intestine. It receives chyme from the ileum at the ileocecal valve, an anatomical sphincter that prevents backflow of the cecal content into the ileum.

**Histology of the Colon:** It has no villi but is endowed with crypts of Lieberkuehn that are similar in composition to those of the small intestine, except for the absence of Paneth cells. The number of goblet cells increases from the cecum to the sigmoid colon, but the surface absorptive cells are the most numerous cell type. A few enteroendocrine cells are also present. The muscularis externa is unusual in that the outer longitudinal layer is not continuous along the surface but is gathered into three narrow ribbons of muscle fascicles, known as taenia coli. The serosa displays numerous fat-filled pouches, called appendices epiploicae.

It absorbs water and electrolytes (approximately 1400 ml per day) and compacts and eliminates feces (~100 ml /day). Bacterial byproducts include riboflavin, thiamin, vitamin B12, and K.

**Rectum and Anal Canal:** The histology of the rectum resembles that of the colon, except that its crypts of Lieberkuehn are deeper but fewer per unit area.

The anal canal (~3 to 4 cm long) is the constricted continuation of the rectum. Its crypts of Lieberkuehn are short, few, and no longer present in the distal half of the canal. The mucosa also displays longitudinal folds, the anal columns (rectal columns of Morgagni).

**Anal Mucosa:** The epithelium is simple cuboidal from the rectum to the pectinate line (at the level of the anal valves), stratified squamous nonkeratinized from the pectinate line to the external anal orifice, and stratified squamous keratinized (epidermis) at the anus. **The lamina propria**, a fibroelastic connective tissue, houses anal glands at the rectoanal junction and circumanal gland at the distal end of the anal canal.

**The muscularis externa** consists of an inner circular and an outer longitudinal smooth muscle layer. The inner circular layer becomes thickened as it encircles the region of the pectinate line to form the internal anal sphincter muscle.

#### **REFERENCES**

1. Kierszenbaum A., Tres L. *Ιστολογία με Στοιχεία Κυτταρικής Βιολογίας. Εκδόσεις Πασχαλίδης, 2013*
2. L.P. Gartner and J.L.Hiatt: *Histology. Editions Williams, Wilkins, 2003*
3. *Gray's Anatomy: Editions Churchill Livingston. 1995*
4. Martini, Timmons, Tallitsch..*Human Anatomy. 6<sup>th</sup> edition, 2012*

## NON-NEOPLASTIC OESOPHAGEAL DISEASES

### A. Fotiadou

Pathologist, Laboratory of Diagnostic Histopathology, Thessaloniki, Greece

Non-neoplastic diseases of the oesophagus include: inflammatory disorders (reflux oesophagitis, infectious oesophagitis, eosinophilic oesophagitis, Barrett's oesophagus, sloughing oesophagitis, lymphocytic oesophagitis, acute necrotizing oesophagitis due to ischaemia), "iatrogenic oesophagitis" (pill-, drug- and toxin related oesophagitis, radiation-chemotherapy induced oesophagitis), *mechanical and neuromuscular disorders* (achalasia, diverticula, acquired hiatus hernia, scleroderma, primary muscle disorders, diffuse oesophageal spasm), *systemic diseases involving oesophagus* (Crohn's disease, Graft-versus-Host Disease, dermatological diseases: lichen planus, pemphigus vulgaris, pemphigoid, epidermolysis bullosa, toxic epidermal necrolysis), *tumor like-lesions* (glycogenic acanthosis, heterotopic tissue).

Oesophagus -related symptomatology is a common indication for endoscopic evaluation.

Histopathological features often overlap due to the limited range of oesophageal responses to various physical, chemical and infectious agents. Eosinophilic oesophagitis and gastro-oesophageal reflux disease are the most prevalent chronic oesophageal inflammatory conditions in children and adults in the western world. Distinguishing both disorders is important because of their different aetiopathogenesis, natural history and monitoring.

*Gastro-oesophageal reflux disease- (GORD)*, also known as peptic oesophagitis, is very common (prevalence of 20-40%). Clinically GORD can be classified as non-erosive and erosive based on endoscopic/pathologic features. Due to the lack of correlation between histological and endoscopic findings, and to exclude the presence of other conditions (such as Barrett's oesophagus), infection or neoplasia, oesophageal biopsies are usually warranted in symptomatic patients. Linear erosions, surrounded by a red halo and covered by a yellow exudate, initially occur on the longitudinal folds of the posterior wall 10-20 mm proximal to the Z-line. With *increasing severity* erosions are multiple and confluent and may involve the whole circumference of the lower oesophagus. Chronic GORD can result in nodular appearance of the mucosa, decreased distensibility of the wall, strictures and ulceration. More than half of the patients with reflux symptoms have normal mucosa or only mild hyperemia at endoscopy. Histology may show inflammatory changes whereas endoscopic findings may appear normal. There is better correlation between endoscopic and histological findings, when erosions or ulcers are found at endoscopy. Biopsies should be obtained 20 mm above the gastrooesophageal junction because mild squamous hyperplasia and reactive epithelial changes may occur normally in the lowermost segment as a result of "physiological" reflux. Histological changes of GORD are non-specific and include: - Basal cell hyperplasia (>15% of the thickness of the epithelium) - Elongation of the lamina propria papillae, extending more than 2/3 of the distance to the surface -Lack of surface maturation - Intercellular oedema -Ballooning degeneration of keratinocytes - Dilatation of capillaries in the lamina propria.

The inflammatory cells include neutrophils, eosinophils and lymphocytes. Occasional intraepithelial eosinophils may be found in asymptomatic adults in the distal oesophagus, without diagnostic value. Differential diagnosis includes infection, eosinophilic oesophagitis, drug-induced injury and involvement by systemic diseases. An accurate diagnosis requires correlation with the clinical, endoscopic, manometric and histologic data. The gold standard of diagnosis for GORD in the recent years is the multichannel intraluminal impedance-pH (MII-pH) monitoring. In the absence of clinical information a diagnosis of "active oesophagitis consistent with reflux" rather than "reflux oesophagitis" should be used.

*Eosinophilic oesophagitis* is a relatively new entity with overlapping features with GORD, affecting typically children and adolescents, with a strong male predominance (3-4:1). Patients often have co-existing or a history of allergic conditions. The current definition is "chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation". Some patients may show combined features of both GORD and EO. Eosinophilic oesophagitis typically involves longer lengths of the esophagus, affects the proximal equally or even more than the distal esophagus, and the pathologic findings are often patchy in distribution. Biopsies taken from the upper and mid-portions of esophagi from patients with EO more often contain increased eosinophils than do samples from patients with GORD. Endoscopic findings correlate poorly with histologic severity. *The major histologic features* of EO, although non-pathognomonic are: - Intraepithelial eosinophils  $\geq 15$ /HPF (peak density areas) - Eosinophilic microabscesses (>4 eosinophils) - Surface layering of the eosinophils - Surface sloughing of squamous cells mixed with eosinophils - Extracellular eosinophilic granules.

Management of EO typically consists of corticosteroid administration and/or dietary modification. Treatment response is best assessed using a combination of eosinophil counts and clinical findings, as well as comparison with prior biopsies.

*Achalasia* is an uncommon disorder (1 per 10,000 persons). The majority of cases are idiopathic. It is a primary esophageal motor disorder of unknown etiology characterized manometrically by insufficient relaxation of the lower oesophageal sphincter (LES) and loss of peristalsis. Achalasia is commonly misdiagnosed initially as GORD especially in the early stages of the disease. Elevated intraepithelial eosinophils have been documented in the biopsies of a proportion of patients with achalasia. The diagnosis of idiopathic achalasia is relatively straightforward with a well-documented medical history, radiography and esophageal motility testing. Pretreatment biopsies help exclude pseudoachalasia (such as neoplasms in the gastric cardia). High-resolution manometry has allowed for the differentiation of achalasia into 3 subtypes with

therapeutic implications.

*Barrett's oesophagus* is an acquired condition characterized by the presence of metaplastic columnar epithelium in the distal oesophagus which replaces normal stratified squamous mucosa. It is now widely accepted that all columnar mucosa located proximal to the anatomic gastro-oesophageal junction is metaplastic, and is formed secondary to chronic injury from reflux disease. It is associated with a risk of development of adenocarcinoma of the oesophagus. The diagnosis requires a combination of endoscopic and histopathologic findings. A quality endoscopic examination documents the location of the GOJ and the squamocolumnar junction as measured in cm from the incisors and obtains biopsy specimens from any proximal displacement of the SCJ (suspected BO). Guidelines recommend at least four biopsies for every 2 cm segment of BO. The criteria used to diagnose BO varies worldwide.

The commonest non-neoplastic oesophageal disorders that lie in the differential for the pathologist have overlapping clinical and histologic features. Histologic evaluation has a complementary role in diagnosis of gastro-oesophageal reflux disease, eosinophilic oesophagitis, Barrett's oesophagus and achalasia. The pathologist can exclude neoplasia, make the follow-up of patients and assess treatment adequacy. A combination of clinical, endoscopic, histological and monitoring findings should be evaluated for final diagnosis.

### REFERENCES

1. A. Maguire & Sheahan. *Pathology of eosophagitis. Histopathology* 2012; 60, 864-79
2. R. Odze. *Pathology of eosinophilic esophagitis: what the clinician needs to know. Am J Gastroenterol* 2009; 104, 485-90
3. S. Almashat et al. *Non-reflux esophagitis: a review of inflammatory diseases of the esophagus exclusive of reflux esophagitis. Semin Diagn Pathol* 2014; 31, 89-99
- A. Naini et al. *Barrett's oesophagus diagnostic criteria: endoscopy and histology. Best Pract Res Clin Gastroenterol* 2015; 29, 77-96
4. F. Ates and M. Vaezi. *The pathogenesis and management of achalasia: current status and future directions. Gut and Liver* 2015; 9, 49-63

## CARCINOMA OF THE ESOPHAGUS AND ESOPHAGOGASTRIC JUNCTION (EGJ) WHAT'S NEW IN DIAGNOSIS AND STAGING

### A. Grekou

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The pathologist's role in patients with esophageal Ca is to examine the available material, being biopsy, endoscopic mucosal resection (EMR), submucosal dissection (ESD) or surgical specimen, in order to determine the parameters that influence patient's survival and guide therapeutic approaches, including targeted therapies.

Pathologic diagnosis and staging must be signed out according to the guidelines from the College of American Pathologists and the 8<sup>th</sup> ed of AJCC/UICC staging.

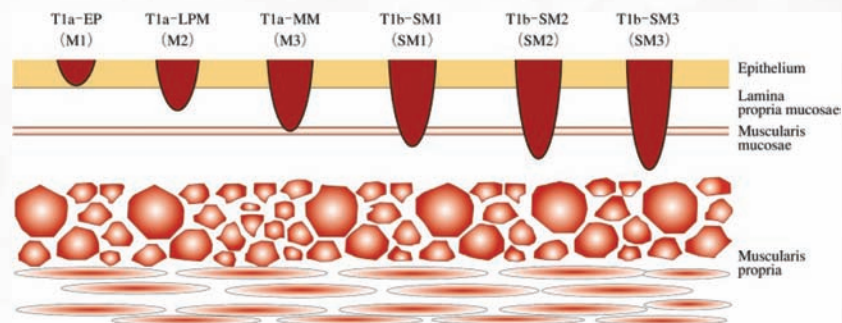
### ENDOSCOPIC BIOPSY

Endoscopy and biopsy is the first - and in cases of inoperable tumors the only - diagnostic approach to the patient with esophageal Ca. Pathologic examination confirms the malignancy and determines the histologic type and grade of the tumor. HER2 testing can be performed on bioptic material to select patients candidates for targeted therapy.

### EMR AND ESD

EMR and ESD are performed by endoscopists and are indicated for en bloc removal of localized high grade dysplastic lesions or superficial (T1) carcinomas, measuring up to 2 cm. The resulting specimen is stretched and fixed pinned on cork and the horizontal and vertical margins are marked with ink. The whole specimen is cut in parallel sections and embedded in paraffin blocks.

Pathologic examination determines the histologic type and grade of tumor, the depth of invasion, the presence or absence of lymphovascular invasion and the adequacy of resection (margins). For these specimens a novel subclassification of T1a and T1b tumors was introduced.



Japanese Classification of Esophageal Cancer, 11<sup>th</sup> Edition,  
Japan Esophageal Society, Matsubara H et al: *Esophagus* 2017; 14:1-36

Duplication of the muscularis mucosa (MM) in Barrett's esophagus poses problems in determining the depth of invasion in T1 Barrett's associated adenocarcinomas. Smoothelin immunohistochemistry is helpful for the discrimination between native and duplicated MM.

### ESGE recommendations for management according to technical and histological outcomes:

#### Squamous cell carcinoma

- En bloc R0 resection of m2 tumor, without lymphovascular invasion is considered curative.
- En bloc R0 resection of G1-2 m3/sm1 tumor ( $\leq 200\mu\text{m}$ ) without lymphovascular invasion has a low risk of lymph node metastases and is curative in the majority of cases. The risk of further therapy should be balanced against the risk of lymph node metastasis in a multidisciplinary discussion.
- In the presence of G3 >sm2 (>200 $\mu\text{m}$ ) tumor, with lymphovascular invasion, or positive vertical margins, further treatment is recommended (chemoradiotherapy and/or surgery) depending on patient status.
- If the horizontal margin is positive and no other high risk criteria are met, endoscopic surveillance/re-treatment is an option.

### Barrett's esophagus-associated adenocarcinoma

- En bloc R0 resection of m tumor is considered curative.
- En bloc R0 resection of G1-2 sm1 lesion ( $\leq 500\mu\text{m}$ ) without lymphovascular invasion is potentially curative. The risk of surgery should be balanced against the risk of lymph node metastasis in a multidisciplinary discussion.
- In the presence of G3 >sm1 (>500  $\mu\text{m}$ ) tumor with lymphovascular invasion or positive vertical margins surgery is recommended.
- If the horizontal margin is positive or there is piecemeal resection with no other high risk criteria, endoscopic surveillance/re-treatment is recommended rather than surgery.
- Further treatments are necessary (EMR, RFA) in order to remove residual metaplastic epithelium.

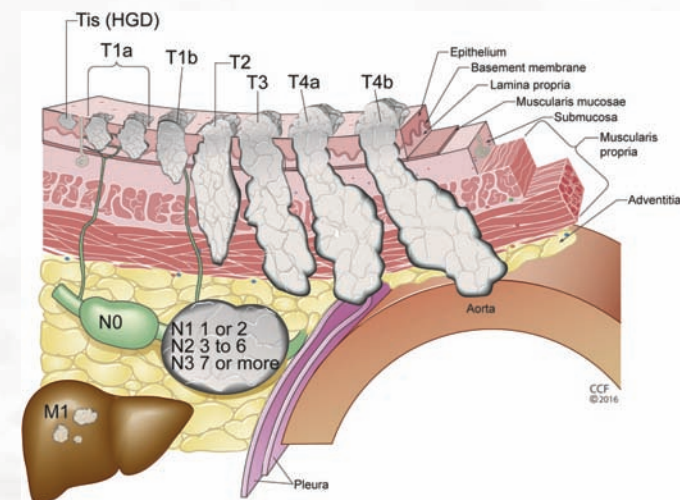
### SURGICAL SPECIMEN - ESOPHAGECTOMY

The specimen accompanied by detailed clinical information should be promptly sent to the pathology laboratory and fixed pinned on cork. Measurements must be taken before fixation.

The pathology report should include the following data elements:

- Location - Relation to GEJ
- Size and gross morphology
- Histologic type - Grade
- Extension (pT) - Lymph nodes (pN)
- Surgical margins (proximal, distal, radial)
- Vascular or nerve invasion
- Pathologic staging (pTNM)

### AJCC 8<sup>th</sup> ed TNM CATEGORIES



Rice TW et al: *J Thoracic Oncol* 2016;12:36-42

### PATHOLOGIC EVALUATION AND STAGING IN RELATION TO THE INTRODUCED MODIFICATIONS

**Relationship of the tumor to the EGJ:** If the tumor midpoint in proximal stomach/cardia in relation to GEJ is < 2 cm the tumor should be staged and treated as esophageal Ca. If it is > 2 cm the tumor should be staged and treated as gastric Ca.

**Histologic typing:** Undifferentiated Ca with squamous or glandular component should be classified as G3 squamous and G3 adenoCa respectively.

**Grading:** If there are variations in the differentiation within the tumor, the highest grade is recorded. Every effort should be made to avoid signing out a histologic grade as "undifferentiated". If this cannot be resolved, the cancer should be staged as a G3 squamous cell carcinoma.

Discrimination between squamous and adenoCa in cases of undifferentiated Ca is important, especially for patients with inoperable tumor and for the selection of patients candidates for targeted therapy. Immunohistochemical markers usually used for squamous Ca are CK5/6, SOX2, p63

and p40, whereas markers used for adenoCa are CK7, MUC5AC, CDX2 and AGR2. As far as no single marker is absolutely specific and sensitive, a panel of markers should be examined.

**Extension of the tumor (pT):** HGD is regarded equal to In Situ Ca for staging purposes. pT1 tumors are divided in pT1a (invasion of the lamina propria or muscularis mucosa) and pT1b (invasion of submucosa). pT4 tumors are divided in pT4a (invasion of pleura, pericardium, diaphragm or peritoneum) and pT4b (invasion of aorta, vertebral body or airway).

**Lymph nodes (pN):** For staging the total number of positive nodes is taken into account irrespective of their anatomic site.

**Staging:** There is different staging for SqCCa and adenoCa. Grade is included in staging in both types, whereas location (lower, mid, upper esophagus) is included only in SqCCa.

A pTNM Adenocarcinoma		B pTNM Squamous Cell Carcinoma				
		N0				
		N0	N1			
		N2	N3			
		N4	M1			
Tis	0					
T1a	G1	IA	IB	IIA	IVA	IVB
	G2	IB	IB	IIA	IVA	IVB
	G3	IC	IB	IIA	IVA	IVB
T1b	G1	IB	IB	IIA	IVA	IVB
	G2	IB	IB	IIA	IVA	IVB
	G3	IC	IB	IIA	IVA	IVB
T2	G1	IC	IIA	IIIB	IVA	IVB
	G2	IIA	IIA	IIIB	IVA	IVB
	G3	IIA	IIA	IIIB	IVA	IVB
T3	IIIB	IIIB	IIIB	IVA	IVB	
T4a	IIIB	IIIB	IVA	IVA	IVB	
T4b	IVA	IVA	IVA	IVA	IVB	

Rice TW et al: J Thoracic Oncol 2016;12:36-42

**Modified Ryan Scheme for regression scores after neoadjuvant radio and/or chemotherapy:**

- Score 0: No viable cancer cells (complete response).
- Score 1: Single cells or rare small groups of cancer cells (near complete response).
- Score 2: Residual cancer with evident regression, but more than single cells or rare small groups of cancer cells (partial response).
- Score 3: Extensive residual cancer with no evident regression (poor or no response).

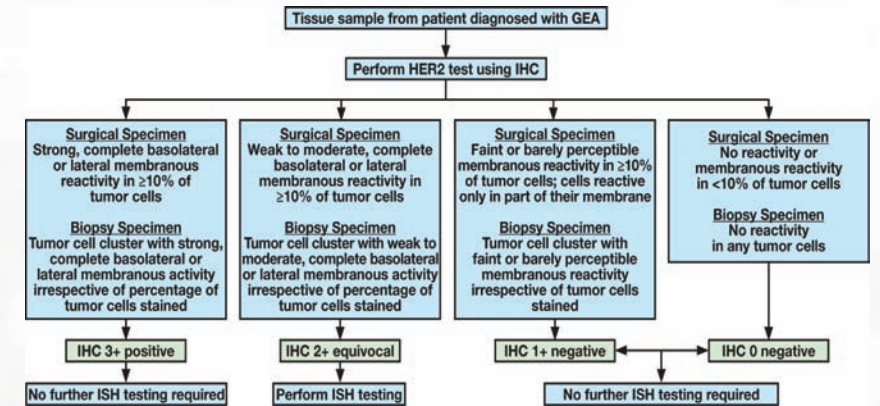
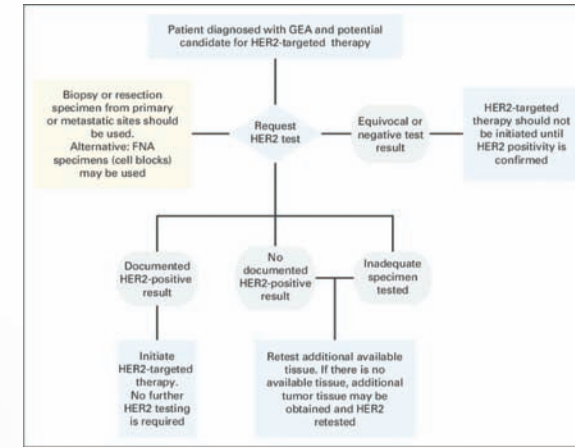
**ypTNM staging:** It is common for SqCCa and adenoCa. Grading is not taken into account.

ypTNM		N0	N1	N2	N3	M1
T0	I	IIIA	IIIB	IVA	IVB	
Tis	I	IIIA	IIIB	IVA	IVB	
T1	I	IIIA	IIIB	IVA	IVB	
T2	I	IIIA	IIIB	IVA	IVB	
T3	II	IIIB	IIIB	IVA	IVB	
T4a	IIIB	IVA	IVA	IVA	IVB	
T4b	IVA	IVA	IVA	IVA	IVB	

Rice TW et al: J Thoracic Oncol 2016;12:36-42

**HER2 TESTING**

HER2 testing and clinical decision making in gastroesophageal adenocarcinoma. Guideline from the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology.



**REFERENCES**

- Bartley AN et al: HER2 testing and clinical decision making in gastroesophageal adenocarcinoma. Guideline from the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. Arch Pathol Lab Med 2016;140:1345-1363
- Matsubara H et al: Japanese Classification of Esophageal Cancer, 11th Edition, Japan Esophageal Society, Esophagus 2017; 14:1-36
- Pimentel-Nunes P et al: Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2015;47:829-854
- Rice TW et al: Cancer of the esophagus and esophagogastric junction: An eighth edition staging primer. J of Thoracic Oncology 2016;12:36-42
- Shi C et al: Protocol for the examination of specimens from patients with carcinoma of the esophagus. College of American Pathologists, 2017 www.cap.org/cancerprotocols

## MEDICAL ONCOLOGIST AND GI NEOPLASMS; MOLECULAR TESTING AND PERSONALIZED MEDICINE

### G. Zarkavelis

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In the era of an expanding armory against cancer, a gradual shift towards the molecular characterization of neoplasms is taking place. Personalized medicine remains the main goal in cancer therapeutics but continues to be a major challenge for medical oncologists who are in need of robust biomarkers in order to make the right choice for each patient. Colorectal cancer, one of the leading causes of death, is an evolving field as far molecular diagnostics is concerned [1]. Testing for RAS and BRAF mutations is applied in every day clinical practice as well as testing for MSI (microsatellite instability) providing information which are prognostic but also predictive of the patients' outcome. Based on the results of the testing, patients may or may not be candidates for anti-EGFR monoclonal antibodies as well as immunotherapy administration. Anti-PD1 and anti-PDL-1 antibodies have shown promising results in clinical studies and are already approved for a variety of neoplasms. Metastatic colorectal cancer patients derive benefit while on immunotherapy once first line chemotherapy has failed. However, choosing the ones who will benefit the most is still under research and comes out as far more complicated than expected [2]. On the other hand, metastatic gastric cancer, less common than colon cancer, continues to carry poor prognosis. Although efforts have been made in classifying patients based on the tumors' molecular profile, the overall survival has not changed dramatically. Targeted therapies are administered in patients with metastatic disease, mainly anti-HER2 therapy, once tumor is shown to overexpress HER2. However, for gastric cancer patients immunotherapy may also be a possible choice in further lines of therapy based on MSI testing. It was not until recently that the molecular characterization of both colorectal and gastric cancer has been published with specific genetic alterations and prognosis recognized for each subtype [1,3]. The genetic and molecular basis of these gastrointestinal neoplasms is a field of active research and novel targeted therapy testing in order to achieve the maximum benefit for cancer patients with safety and without the expense of exposing them to inefficient and costly therapies [4].

### REFERENCES

1. Guinney J, Dienstmann R, Wang X, de Reyniès A, Schlicker A et. al. The consensus molecular subtypes of colorectal cancer. *Nat Med.* 2015 Nov;21(11):1350-6
2. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR et. al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science.* 2017 Jul 28;357(6349):409-413
3. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature.* 2014 Sep 11;513(7517):202-9
4. Smyth EC, Wotherspoon A, Peckitt C, Gonzalez D, Hulkki-Wilson S et. al. Mismatch Repair Deficiency, Microsatellite Instability, and Survival: An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial. *JAMA Oncol.* 2017 Sep 1;3(9):1197-1203

## IUCP HISTORY (1996-2016)

### N. J. Agnantis

MD, PhD, FRCPath, A.G.E. Emeritus Professor, University of Ioannina

The Ioannina University Courses in Pathology (IUCP) are postgraduate courses on selected topics of Human Pathology that have been offered since 1996, after the unanimous decision of the Executive Committee (Brussels, June 1995) of the European Society of Pathology, to give the ESP auspices to the organization of the IUCP, within the frame of the European Institute for Continuing Medical Education (EICME).

Two courses (or Part I and Part II) have been offered each year. The aim of the Courses has been to bring together young Pathologists or 4<sup>th</sup> and 5<sup>th</sup> year residents with Tutors, experts in the various fields of Pathology and to encourage active participation of all colleagues during the discussions following the lectures and the slide seminars, providing an in-depth review of Diagnostic Surgical Pathology. An emphasis has been given to morphological features, newly recognized entities and modern laboratory techniques. A limited number of didactic lectures, given by established and distinguished investigators, cover each topic theoretically. After the experience gained from the first course (May 1996), a number of distinguished Clinicians were gradually incorporated in the list of invited speakers. A tradition has been established, where the Opening Lecture is offered by a distinguished Clinician, Specialist on the subject, The Opening Lecture has always been dealing with "The challenge for co-operation with the Pathologist".

Until 2008, individual lectures regarding imaging and therapeutic approaches (chemotherapy, radiotherapy, surgery) were also offered by specialized Clinicians distinguished in the field. During the last years Clinicians incorporate their talks in multidisciplinary Sessions. Furthermore, the Scientific Programme is enriched with many Slide Seminars, which are offered in the form of interactive case presentations. The duration of each Course (or each Part) has been approximately 2 days (~14 credit hours). Each course has been designed for 40-50 Pathologists and Clinical Colleagues related to the subject. Over the years, besides the Greek students we also had Participants from: Cyprus, Balkan Countries, Hungary, Czech Republic, Russia, Georgia, Italy, Spain and Jordan, who accounted for approximately 25% of the student body. A brief curriculum vitae stating particular experience or interest in the topic of the Course is always required for the preparation of the final list of Tutors and Participants, and for the archives of the Institute. Diplomas are given for regular attendance only and include the number of credit hours, always according to the criteria of the Royal College of Pathologists. At the end of each Course students are asked to complete an evaluation questionnaire, with the scope to test the quality and effectiveness of the Course, and to improve the content of the Educational Programme. This questionnaire covers: the content of provided information, the quality of presentations and the effectiveness of the teaching style. The above categories are graded from 1-5, from very good to very poor. The results from this evaluation system are mailed to the Speakers and kept in our archives. In addition, a multiple-choice examination is completed by the Participants, without the obligation to sign their names.

In the First Series sixteen courses were offered and covered the following topics: **GYN, BONE/SOFT TISSUES, PEDIATRIC, SKIN, LIVER, LUNG, BREAST, PROSTATE, SALIVARY GLANDS, THYROID, OESOPHAGUS-STOMACH-DUODENUM-BILIARY TRACT-PANCREAS, SMALL-LARGE INTESTINE, KIDNEYS and URINARY BLADDER PATHOLOGY/ONCOLOGY.**

In the Second Series twelve courses were offered and covered the following topics: **VULVA-VAGINA-CERVIX, ENDOMETRIUM-OVARIES-ACCESSORIES, PROSTATE, BREAST, SKIN, BONE& SOFT TISSUE (25<sup>th</sup> SILVER COURSE), LUNG-PLEURA-MEDIASTINUM, KIDNEYS & ADRENALS, LIVER PATHOLOGY/ONCOLOGY.**

In 2010, consistent with our commitment for interactive participation of all (Organizing Committee, Tutors and Students) in the realization of IUCPs, a questionnaire was distributed at the end of the course asking for the preferred subject of IUCP 2011. The topic **GYN PATHOLOGY/ONCOLOGY** was voted by the vast majority for 2011. This topic was offered for the third time, thus, the third series of IUCP commenced. In the following years the topics were **LIVER PATHOLOGY/ONCOLOGY** (2012), **BREAST PATHOLOGY/ONCOLOGY** (2013), **SKIN PATHOLOGY/ONCOLOGY** (2014) and **HEAD & NECK PATHOLOGY/ONCOLOGY**. In 2016 the 33<sup>rd</sup> IUCP with the topic of **NEURO PATHOLOGY/ONCOLOGY** was offered.

During my long career in organizing the IUCP, I have faced several challenges and I have learned a lot from hands-on experience. For a successful organization the active involvement of a University Medical School is necessary. Publicity should also be provided by the official Societies of Pathology (Hellenic, European Society of Pathology and IAP). Furthermore, personal communication with the directors of large National and International Hospitals is always helpful. For this reason, an attractive poster is always circulated through e-mail with all the available information. Participation is always encouraged if the registration fees are the lowest possible. This cannot be achieved without sponsoring by the Societies of Pathology. Since the aim of the Course is educational we always encourage the participation of residents and young Pathologists from our neighboring Balkan countries, by waiving their registration fee.

We believe that with the organization of the IUCP our Institution, along with ESCOP and Euro Cell Path, has significantly contributed to the field of Continuing Medical Education in Europe

## GASTRIC POLYPS-GASTRIC CARCINOMA - NEW CLASSIFICATION

### C. Barbatis

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**Gastric Polyps:** Gastric polyps are lesions sporadic or in relationship to polyposis syndromes. The main categories are: Non-neoplastic, hamartomatous/polyps of polyposis syndromes, neoplastic, reactive and heterotopic tissue. >90% are asymptomatic but anemia, bleeding, pain, obstruction occur and they are polyps with malignant potential.

The commonest type (47% of all polyps) is the **Fundic Gastric polyp (FGP) sporadic, the result of PPIs** (Proton Pump Inhibitors) or **syndromic** associated with FAP syndrome. They are small size lesions (1-8 mm), related to activating mutations of  $\beta$ -catenin gene with <1% chance of malignancy but numerous carpet-like lesions are associated with FAP and with epithelial dysplasia in 25-41%. The clinical approach to management of FGPs is biopsy to exclude dysplasia or malignancy, resection if >10mm. and colonoscopy if they are numerous and in <40 years old. Surveillance is not recommended.

**Hyperplastic Polyps:** Sessile, pedunculated, antral (usually) composed of proliferating foveolar epithelium extending to the deep lamina propria and they may contain parietal cells, chief cells or pyloric glands hence the overlapping with hamartomas and inflammatory lesions. There is strong association with chronic gastritis, Helicobacter-Pylori and chemical gastritis. The incidence of dysplasia is low (1.9-19%) but there is association with increased risk of synchronous carcinoma in other site of the stomach. Resection is suggested without obligatory surveillance but multiple biopsies of the uninvolved gastric mucosa around the polyp should be taken. Only 0.6-2,1% are reported to develop gastric adenocarcinoma (GA).

**Adenomatous polyps:** 6-10% of all gastric polyps in Western populations. They are associated with atrophic gastritis and intestinal metaplasia (IM) and with increased risk of adenocarcinoma in the polyp and in other sites of the stomach. Management recommendations: Complete resection, thorough examination of the entire gastric mucosa for other lesions. Repeat endoscopy in 6 months if removal is incomplete or there is High Grade dysplasia. There is no optional surveillance protocol but annual surveillance for all other types.

**Pyloric Gland Adenoma:** Rare polypoid lesion composed of closely packed pyloric gland-type tubules but they may undergo malignant transformation. It is usually associated with autoimmune gastritis and IM.

**Hamartomatous polyps:** This type of GPs are important as they are gastric syndromic polyps and they may be indistinguishable from usual hyperplastic polyps. For the diagnosis clinical information and knowledge of endoscopic findings are essential. Main types: **Peutz-Jeghers and Juvenile polyps.**

**IFP (Inflammatory Fibrous Polyp) or Vanek polyp:** It is a neoplastic lesion CD 34+ related to PDGFR $\alpha$  activating mutations. Rare lesion without malignant potential.

**Gastric Carcinoma:** Current Classification.

Classification of GC is essential for therapeutic management, prognosis and prevention and as GC is a complex heterogeneous malignancy classification systems have been proposed, updated, debated and open to change according to the new knowledge on gastric carcinogenesis.

The **new classification** is based on **histological types, genotypes and molecular phenotypes** but I will refer to the Distal GC which is defined as tumor with "the epicenter is >5 cm distal to GEJ or within 5 cm of GEJ but does not extend into it or to the oesophagus". Two main types of prognostic importance are recognized. **Early GC** as invasive tumor confined to mucosa/and or submucosa with or without lymph node metastasis (5 years survival till 90%). **Differential diagnosis** (DF) from **High Grade** dysplasia and **Regenerative atypia.**

**Advanced GC:** Invasive lesion to the muscularis propria and beyond (5 years survival < 60%).

GC is **Sporadic** (90%), **Hereditary** 1% (e-cadherin mutations) and **Familial** (10%). A newly described entity is the Autosomal dominant Syndrome of Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (**GAPPS**)

Table 1. Current 2010 WHO Histological Classification of GC.

Tubular  
Papillary  
Mucinous  
Poorly Cohesive (including signet ring carcinoma)  
Mixed  
Adenosquamous  
Hepatoid  
Medullary (carcinoma with lymphoid stroma)

Undifferentiated

For histological typing a pattern should be expressed in > 50% of tumor

Lauren's classification of Intestinal, Diffuse, Mixed types is still in use

### TNM STAGING SYSTEM

TX	Primary tumor cannot be assessed
To	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of lamina propria
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria of muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum of adjacent structures. T3 tumors also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures such as spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum
N	Category definitions, gastric cancer
NX	Regional lymph node(s) cannot be assessed
NO	No regional lymph node metastasis
N1	Metastasis in 1 to 2 regional lymph nodes
N2	Metastasis in 3 to 6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
	<ul style="list-style-type: none"> <li>Positive peritoneal cytology is classified as metastatic disease (M1)</li> <li>Anatomic stage/prognostic groupings have been changed</li> </ul>
M	Metastatic disease

Classification of GC according to mucin phenotype

1. Gastric (MUC5AC, TFF1+)
2. Intestinal (MUC2, CDX2, CD10)
3. Mixed (gastric-intestinal)
4. Null phenotype

### Unusual types of GC

**Clear cell variant:** 8,5% of GCs show clear change and this component indicates worse prognosis.

**Micropapillary type:** It should be noted in surgical pathology reports even if it is <5% in a GC of other types and it carries worse prognosis.

**Medullary Ca:** >80% are associated with E-B Virus. It has the best prognosis of all

**Molecular subtypes of GC:** EBV-positive

MSI

GS (genomically stable)

CIS (chromosomal instability)

### Molecular phenotype and its significance in GC

1. Her-2 amplification (20% of intestinal type GC) is considered as "single molecular alteration with predictive value to therapy response.
  2. CDH1 LOH 10% of all types - poor prognosis
  3. MSI 15-20% of all cases (h MLH1 promoter hypermethylation) a marker of good prognosis but poor response to conventional chemotherapy.
  4. KRAS amplifications are associated with adverse prognosis
  5. EBV GC
- EBV -CIMP expression  
PDL1/2 overexpression

**In conclusion:** GC is a heterogeneous malignancy and current classification exists but it always in the process of changing, adapting to the new knowledge based on the genetics and pathways of gastric carcinogenesis.

## REFERENCES

1. G. Obenhuber et al. *Virch Arch* 2000; 437(6): 581-90
2. Islam Bs Et al. *Gastroenterol Hepatol (NY)*. 2013; 9 (10): 640-651
3. *An. Surg Oncol* 2010; 17 (12): 3077-3079 (7<sup>th</sup> edition AJCC)
4. Hamilton R, Aatonen LA *IARC ; 2000:39-52*
5. *Gastrointest Endosc* 2003; 58: S3-43
6. Oliveira C et al. *Gastroenterol* 2009; 136: 2137-48
7. Ahn S, Park DY. *Arch Pathol Lab Med* 2016; 140: 397-405
8. Kushima R et al. *Cancer* 2006; 9: 177-182
9. Worthley et al *Gut* 2012: 774-779

## GASTROINTESTINAL LYMPHOMAS

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The gastrointestinal tract is a major component of the immune system and the diversity of different lymphoid elements such as organized lymphoid tissues (Waldeyer ring, Peyer patches, and appendix), isolated lymphoid aggregates, intraepithelial lymphocytes and lamina propria lymphoid cells is reflected in the wide spectrum of lymphoproliferative disorders that can involve the gastrointestinal organs. A large variety of lymphoma types may develop as primary gastrointestinal neoplasms (Table 1) and about 20-25% of primary extranodal lymphomas occur in the gastrointestinal tract.

**Table 1**

Classification of Gastrointestinal Lymphomas
<i>B-cell lymphomas</i>
<ul style="list-style-type: none"> <li>• Extranodal marginal zone lymphoma of mucosal associated lymphoid tissue (MALT lymphoma)               <ul style="list-style-type: none"> <li>▪ Immunoproliferative small intestinal disease (IPSID)</li> </ul> </li> <li>• Primary intestinal follicular lymphoma               <ul style="list-style-type: none"> <li>▪ Duodenal-type follicular lymphoma</li> </ul> </li> <li>• Mantle cell lymphoma</li> <li>• Diffuse large B-cell lymphoma, not otherwise specified (Germinal center B-cell type, Activated B-cell type)               <ul style="list-style-type: none"> <li>▪ DLBCL with a MALT lymphoma component</li> </ul> </li> <li>• Burkitt lymphoma</li> <li>• Plasmablastic lymphoma</li> <li>• Rare subtypes (Lymphomatoid granulomatosis, ALK+ large B-cell lymphoma, B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt lymphoma)</li> </ul>
<i>T-cell lymphomas</i>
<ul style="list-style-type: none"> <li>• Enteropathy-associated T-cell lymphoma</li> <li>• Monomorphic epitheliotropic intestinal T-cell lymphoma</li> <li>• Peripheral T-cell lymphoma, not otherwise specified</li> <li>• Extranodal NK/T-cell lymphoma, nasal type</li> <li>• Indolent T-cell lymphoproliferative disorder of the GI tract (provisional entity, WHO 2017)</li> <li>• Rare subtypes (Angioimmunoblastic T-cell lymphoma, ALK+ and ALK- Anaplastic large cell lymphoma)</li> </ul>
<i>Immunodeficiency-associated lymphoproliferative disorders</i>
<i>Classical Hodgkin lymphoma (extremely rare)</i>

Stomach is the most commonly involved part and B-cell lymphomas are much more frequent than T-cell lymphomas, with high-grade subtypes overall outnumbering indolent lymphomas. Although a few entities such as enteropathy-associated T-cell lymphoma or immunoproliferative small intestinal disease essentially do not arise elsewhere than in the gastrointestinal tract, in most instances the primary gastrointestinal lymphomas belong to entities that also occur in lymph nodes or other mucosal sites.

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), Enteropathy-associated T-cell lymphoma and Monomorphic epitheliotropic intestinal T-cell lymphoma are the prototypic primary gastrointestinal B-cell and T-cell lymphomas, respectively.

*Gastric MALT lymphoma (gMALT)* is one of the most frequent primary gastrointestinal lymphoma. Around 90% of gMALT are associated with chronic *H.pylori* (H.P.) infection and many cases will regress with eradication of the microorganism. The neoplastic infiltrate comprises small to medium-sized lymphoid cells, with monocytoid or centrocytic-like appearance, which expand the marginal zones of reactive secondary lymphoid follicles, spread diffusely and frequently colonize the reactive germinal centers. Subsets of the cases show monotypic plasmacytoid differentiation whereas lymphoepithelial lesions (infiltration of epithelial structures by groups of  $\geq 3$  small lymphocytes) are a common although not completely specific finding. The t(11;18)(q21;q21)/API2-MALT1 translocation has been detected overall in approximately 25% of gastric and 18% of primary intestinal MALT lymphomas, and its presence predicts for failure of regression with H.P. eradication.

As there is no single sensitive and specific biomarker for MALT lymphoma, the differential diagnosis with other small B-cell lymphomas relies on a combination of morphological, immunophenotypical and molecular genetic features. Establishing a diagnosis of lymphomas on small biopsies may be difficult, especially when an abnormal phenotype (CD5+ or CD43+) or a clonal plasma cell population is not revealed by the immunostains. In these cases, demonstration of a monoclonal immunoglobulin gene rearrangement is supportive of a diagnosis of lymphoma.

*Immunoproliferative small intestinal disease (IPSID)* is a rare variant of intestinal MALT lymphoma with extensive plasmacytic differentiation, usually involving the duodenum or jejunum, characterized by a geographic restriction to the eastern Mediterranean area, Middle and Far East and Africa. IPSID usually affects young adults, who present with malabsorption, diarrhea, abdominal pain and weight loss. By immunohistochemistry, the deep-seated lymphoid infiltrate comprises CD20+ B cells, and the plasma cells express the alpha heavy chain, and no light chains. This peculiar feature is related to deletions in the variable (VH) and the first constant domain (CH1) of the alpha heavy chain gene, resulting in expression of a truncated heavy chain, preventing from assembly with a light chain. Some reports have documented isolation of *Campylobacter jejuni* and *Campylobacter coli* from the stools and diseased tissues of IPSID patients who were successfully treated by antibiotics, suggesting that an ongoing immune response to a chronic infection with *Campylobacter* species drives the clonal B-cell proliferation.

*Enteropathy-associated T cell lymphoma (EATL)* is defined as a lymphoma derived from intraepithelial T lymphocytes and is more prevalent in Western populations especially in Northern Europe where celiac disease is more prevalent. In the previous WHO edition (2008) this lymphoma subtype was designated as EATL type I, whereas EATL type II is now (WHO revised 4<sup>th</sup> edition, 2017) considered a distinct entity, renamed *monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)*. MEITL is rare in western populations and represents the more prevalent type in Asian-Pacific studies and shows no association with celiac disease. Both may present with acute symptoms due to intestinal perforation, obstruction or bleeding and both carry a poor prognosis, with < 20% five-year survival. Some patients having benefited from surgical resection followed by chemotherapy plus autologous stem cell transplantation have achieved long-term survival. EATL and MEITL have different morphology and immunophenotypic profiles. Both types share common recurrent chromosomal imbalances and also distinct genetic alterations.

EATL is composed of pleomorphic, medium to large, occasionally anaplastic lymphoid cells. Extensive necrosis and a high mitotic rate are common features. A polymorphic inflammatory infiltrate rich in histiocytes and eosinophils is frequently present, sometimes obscuring the lymphoma cells. The neoplastic cells are usually cCD3+, CD5-, CD4-, CD8-, CD56-, and diffusely express cytotoxic markers with an activated profile (TIA1, Granzyme B and/or perforin). Most cases are CD30+, and interestingly complete remission was reported recently in a patient with CD30+ EATL, after brentuximab vedotin administration. The neoplastic cells are EBV-negative and usually express TCR $\alpha\beta$  and the intraepithelial homing integrin CD103.

MEITL typically comprises a monomorphic proliferation of medium-sized cells, without necrosis and inflammation that spread to the adjacent mucosa by featuring marked epitheliotropism. The neoplastic cells are usually CD3+ CD5- CD7+ CD4-/CD8+ CD30- CD56+, with an activated cytotoxic immunophenotype. EBV is negative. Aberrant expression of CD20 and/or other B-cell markers may be seen in up to 25% of the cases. The megakaryocyte-associated tyrosine kinase (MATEK) has been documented as a novel marker of MEITL. Most cases express TCR $\gamma\delta$ .

### Conclusion

The variety of intestinal lymphomas and lymphoproliferations renders their diagnosis commonly challenging, not only because of the difficulties to acquire an appropriate sample of the tumor and the adjacent mucosa for the evaluation of the important features of the entities but also because as a lymphoid organ, reactive conditions are common, either in the context of the transient activation of the immune system by an immunogen or in the context of a chronic inflammatory disease. The diagnostic algorithm should include: 1) a good knowledge of the clinical history of the patient, 2) immunophenotypic analysis, with lineage specific and clonality ( $\kappa$  and  $\lambda$  light chains) markers, activation markers such as CD30 and viral specific markers, for the detection of EBV or other viral infections, 3) FISH analysis for recurrent chromosomal imbalances, 4) molecular analysis with B- or T-cell clonality assays and 5) recognition of the indolent NK and T-cell lymphoproliferative disorders of the GI tract. The correct diagnosis supplemented by the new imaging techniques like capsule endoscopy, endoscopic ultrasound and PET-CT, the recent insights into the pathobiology of lymphomas and the deeper knowledge of the organization and function of GI immune system will form the basis for the comprehensive study of this type of neoplasms and the development and validation of new treatment modalities.

### REFERENCES

1. Sheridan BS, Lefrancois L. Regional and mucosal memory T cells. *Nature Immunology* 2011;12:485-491
2. Swerdlow S. ed. *WHO classification of tumours of haematopoietic and lymphoid tissues*. Lyon, 2017
3. Zhang S et al. The t(14;18)(q32;q21)/IGH-MALT1 translocation in gastrointestinal extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). *Histopathology* 2014;64:791-798
4. Foukas PG, de Leval L. Recent advances in intestinal lymphomas. *Histopathology* 2015;66:112-136
5. Roberti A. Type II enteropathy-associated T-cell lymphoma features a unique genomic profile with highly recurrent SETD2 alterations. *Nat Commun*. 2016 Sep 7;7:12602. doi: 10.1038/ncomms12602

## COLITIS – A PATTERN-BASED APPROACH

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Chronic inflammatory bowel disease includes, strictly spoken, two diseases, that is, ulcerative colitis and Crohn's disease. Both represent a steadily growing burden for the European health care system. The pathologist's role in the management of the disease includes assistance in initial diagnosis, assessment of activity, differential diagnosis and diagnosis of dysplasia and/or cancer.

Analysis of multiple biopsies allows a correct diagnosis of inflammatory bowel disease in 66-75% of newly diagnosed patients. Providing additional endoscopic and clinical data to the pathologist increases the diagnostic accuracy, allowing a final diagnosis in more than 90% of cases, respectively.

### The histological features useful for a diagnosis of inflammatory bowel disease may be grouped into four categories:

- Mucosal (crypt) architecture
- Lamina propria cellularity
- Infiltration by neutrophils
- Epithelial changes

Abnormalities in mucosal (crypt) architecture include crypt distortion, branching, atrophy (shortening), reduced crypt density and surface epithelium irregularities (pseudovillous change). These changes are particularly pronounced in ulcerative colitis (57-100% of cases), but may also occur in Crohn's disease (27-71% of cases). Within the stroma, there is a transmucosal increase of inflammatory cells with basal plasmacytosis. Neutrophils (cryptitis / crypt abscess formation) are markers of disease activity. Epithelial changes include epithelial damage and mucin depletion (at active sites), metaplastic changes (markers of chronicity).

### The key histological features of ulcerative colitis are the following:

- Diffuse (continuous) mucosal disease that begins in the rectum and spreads variably to the proximal colon (it is usually worse distally)
- Severe diffuse mucosal architectural abnormalities (crypt shortening and distortion, decreased crypt density)
- Severe diffuse transmucosal increase of (predominantly mononuclear) inflammatory cells with basal plasmacytosis
- Epithelial abnormalities, such as surface epithelial damage and mucin depletion as well as Paneth cell metaplasia (in biopsies obtained distal to the hepatic flexure)
- Tissue fragments both within the same biopsy and within separately submitted specimens tend to show the same degree of inflammation

### The key histological features of Crohn's disease are the following:

- Segmental (discontinuous) transmural disease ("skip lesions" with fissures, fistulae) with variable rectal involvement and variable disease severity (usually worse proximally)
- Focal (discontinuous) crypt architectural abnormalities (focal crypt atrophy and distortion)
- Focal (discontinuous) inflammation (focal mononuclear expansion of the lamina propria, focal cryptitis). Focal or patchy inflammation may be observed in biopsies submitted from different parts of the bowel or may be present within tissue fragments of the same biopsy, not rarely within a single biopsy specimen
- Aphthous erosions/ulcers and deep fissures, any location
- Epithelioid cell granulomas (not crypt related) in approximately 20% of mucosal biopsies (up to 50% in resections) - they need to be differentiated from so-called cryptolytic granulomas (unspecific foreign body reaction to ruptured crypts, may occur in several types of colitis)

While ulcerative colitis is usually restricted to the large bowel (apart from so-called backwash ileitis and rare upper tract involvement in children and adolescents), Crohn's disease may affect the whole gastrointestinal tract: Crohn's disease affecting both small and large bowel is seen in about 40-50% of cases, isolated small bowel or isolated large bowel disease in 30-35% and 15-25% of cases respectively. Upper tract involvement is common in Crohn's disease and may be detected in 50-75% of cases, usually in the form of focally enhanced gastritis (with and without granulomatous reaction).

The differential diagnosis between ulcerative colitis and Crohn's disease may be difficult, since overlapping morphological features are seen in 10-15% of cases. In unclear cases diagnosis of indeterminate colitis (for resection specimens) or IBD unclassified, IBDU (for biopsies) should be made. It has to be acknowledged that there is no single pathognomonic histological feature, and the diagnosis typically rests on a combination of clinical, laboratory, endoscopic, and histological observations, with ulcerative colitis showing more severe architectural and inflammatory abnormalities than Crohn's disease.

Please note: Differential diagnosis may be particularly challenging under therapy, since mucosal healing in ulcerative colitis may cause discontinuous inflammation (and "rectal sparing").

	Infectious colitis	UC active phase	UC in remission	Crohn's disease
<b>Crypt architectural abnormalities</b>	- / (+)	+++	+ / ++	(+)
<b>Metaplastic Paneth cells / mucin depletion</b>	-	++	++ / (+)	(+)
<b>Mononuclear cells ↑</b>	(+)	+++	-	(+)
<b>Neutrophils</b>	+++	+++	-	++
<b>Granulomas / giant cells</b>	(+)	(+)	-	++
<b>Continous morphologic changes</b>	(+)	+++	++ / (+)	-
<b>Discontinous morphologic changes</b>	+	-	- / (+)	++

The pathologist's report should include information on the grade of disease activity. This mainly holds true for ulcerative colitis (and is less important for Crohn's disease due to its discontinuous nature). Different scoring systems have been developed. Please note: Endoscopic mucosal healing does not automatically mean histology healing. The latter, however, is important for prediction of the disease course, that is, patient management.

Ulcerative colitis and Crohn's disease need to be differentiated from **other types of colitis**, such as infectious colitis (mainly active inflammation, no basal plasmacytosis, preserved crypt architecture), different types of drug-induced colitis (NSAIDs, antibiotics, chemotherapy, mycophenolate mofetil or MMF, biologicals), segmental colitis associated with diverticulosis (SCAD, syn. diverticular colitis) and also the so-called microscopic colitides. The latter include lymphocytic and collagenous colitis. Both show an increased transmucosal inflammatory infiltrate and preserved crypt architecture. The hallmark of lymphocytic colitis is increased intraepithelial lymphocytosis (>20 intraepithelial lymphocytes per 100 epithelial cells), the hallmark of collagenous colitis is a thickened collagen band underneath the surface epithelium (>10µ).

Finally, patients with inflammatory bowel disease are at increased risk for cancer. Long disease duration, extensive bowel involvement, young age at onset and severity of microscopic inflammation have been identified as the main risk factors. On the histological level, dysplasia (intraepithelial neoplasia) represents the best and most reliable marker of malignancy risk. It develops only in areas with chronic inflammation and can be divided into four diagnostic categories: negative (regenerating epithelium), indefinite and positive for low-grade and high-grade dysplasia.

	Colitis-associated dysplasia	Regenerating epithelium
<b>Crypt architecture</b>	Altered (budding, branching, cribriforming, crowding or back-to-back growth)	Preserved
<b>Cytologic atypia</b> <b>N/C ratio</b> <b>Nuclei</b> <b>Nucleoli</b> <b>Mitoses</b>	Moderate (to marked) Increased Hyperchromatic, stratification Prominent, enlarged (or multiple) Frequent, pathological mitoses	Mild (to moderate) Normal No stratification May be prominent, usually not enlarged Frequent, normal looking
<b>Surface maturation</b>	No	Yes
<b>Increased lamina propria inflammation</b>	Variable	Usually present

Immunohistochemistry using antibody preparations directed against p53 may be of help in selected cases. Pathological staining patterns include p53 overexpression (due to impaired protein degradation) or total lack of staining (due to protein truncation; internal positive control of active non-mutated p53 necessary). According to international guidelines, confirmation of dysplasia by an independent expert gastrointestinal pathologist is recommended.

Patients may also develop dysplasia independent from the disease, that is, sporadic adenomas. The distinction is easy, when the neoplastic lesion is removed from uninvolved mucosa. However, if the neoplastic polyp originates from inflamed mucosa, the pathologist should at least try to differentiate colitis-dependent (raised) dysplasia (syn. dysplasia associated lesion or mass, DALM) from colitis-independent dysplasia (sporadic adenoma, syn. adenoma-like mass, ALM). The following table may help to guide the differential diagnosis.

	Colitis-associated elevated (raised) non-adenoma-like lesion	Adenoma-like lesion (sporadic adenoma)
<b>Age</b>	< 50 years	> 60 years
<b>Extent of disease</b>	Usually total	Usually subtotal
<b>Activity of disease</b>	Usually active	Usually inactive
<b>Disease duration</b>	Long (>10 years)	Short (<10 years)
<b>Macroscopy</b>	Large, velvety patches or irregular (asymmetric) plaques	Small, well circumscribed, regular (symmetric) polypoid lesions
<b>Associated flat dysplasia</b>	Common (no sharp delineation)	Absent (sharp delineation)
<b>Histology of lesion</b>	Irregular neoplastic glands (varying configuration, size and diameter) with varying amounts of stroma	Regular neoplastic glands (similar configuration, size and diameter) with low amounts of stroma
<b>Increased (mononuclear) lamina propria inflammation</b>	Usually present	Usually absent
<b>Mixture of benign / dysplastic crypts at surface</b>	Usually present	Usually absent

## REFERENCES

1. Magro F, Langner C, Driessen A, Ensari A, Geboes K, Mantzaris GJ, Villanacci V, Becheanu G, Borralho Nunes P, Cathomas G, Fries W, Jouret-Mourin A, Mescoli C, de Petris G, Rubio CA, Shepherd NA, Vieth M, Eliakim R; European Society of Pathology (ESP); European Crohn's and Colitis Organisation (ECCO). European consensus on the histopathology of inflammatory bowel disease. *J Crohns Colitis*. 2013; 7: 827-51
2. Langner C, Magro F, Driessen A, Ensari A, Mantzaris GJ, Villanacci V, Becheanu G, Borralho Nunes P, Cathomas G, Fries W, Jouret-Mourin A, Mescoli C, de Petris G, Rubio CA, Shepherd NA, Vieth M, Eliakim R, Geboes K; European Society of Pathology; European Crohn's and Colitis Foundation. The histopathological approach to inflammatory bowel disease: a practice guide. *Virchows Arch*. 2014; 464: 511-27
3. Langner C, Aust D, Ensari A, Villanacci V, Becheanu G, Miehleke S, Geboes K, Münch A; Working Group of Digestive Diseases of the European Society of Pathology (ESP) and the European Microscopic Colitis Group (EMCG). Histology of microscopic colitis-review with a practical approach for pathologists. *Histopathology*. 2015; 66: 613-26

## DRUG INDUCED COLITIS

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Drug induced lesions of the gastrointestinal (GI)-tract comprise 7% of drug related side effects whereas over 700 drugs cause diarrhea. Pathogenesis includes direct toxicity, immune mediated mechanisms and infection involvement. Increased eosinophils and crypt epithelial cells apoptosis are suggestive of drugs. The diversity of microscopic patterns of drug induced intestinal damage simulates the spectrum of primary colonic diseases and is shown in table 1.

**Table 1:** Microscopic patterns of drug-induced damage in the large intestine.

- Acute colitis
- Ischemic-type colitis
- Pseudomembranous colitis
- Focal active colitis
- Eosinophilic colitis
- Microscopic colitis
  - Collagenous colitis
  - Lymphocytic colitis
- Inflammatory bowel disease-like colitis
  - Crohn-like
  - Ulcerative colitis-like
- Graft-versus-host-like disease
- Non-specific ulceration

#### Specific patterns

- Diaphragm disease (NSAIDs)
- Melanosis (pseudomelanosis) coli
- Necrosis (Kayexalate)
- Fibrosis (pancreatic enzyme supplements)

### Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Nearly 10 % of newly diagnosed colonic inflammation results from NSAIDs. Several mechanisms have been suggested, such as increased mucosa permeability due to direct toxicity, formation of drug-enterocyte adducts, induction of intracellular ATP deficiency, increased cytokine release and disruption of microcirculation, while the most discussed mechanism is their inhibitory effect on prostaglandin synthesis. Histology exhibits analogous diversity including mucosa ulceration, microscopic colitis, ischemic colitis, Crohn's disease-like and ulcerative colitis-like lesions. Thinned mucosa with edema, mucosa hemorrhages, irregularity of the crypts which may be increased in height, and ulcers are frequently encountered. Most NSAIDs lesions are located in the right colon due to a higher concentration of the drug at this site. NSAIDs may initiate IBD or cause reactivation of quiescent disease. They have also been associated with complications of diverticular disease, such as hemorrhage, perforation and fistulous tract formation.

### Chemotherapeutic Agents

Colitis related to chemotherapeutic drugs varies in severity while crypt damage is a predominant finding. Prominent epithelial cell apoptosis, crypt denudation as well as nuclear pyknosis, karyorrhexis and polymorphism constitute diagnostic features. Other findings are oedema, inflammatory infiltrates with neutrophils and eosinophils and in severe cases extensive necrosis and ulcerations.

### Immunosuppressants and Checkpoint Inhibitors (CPIs)

Several gastrointestinal, particularly colonic complications emerge due to increasing administration of immunosuppressants and CPIs (MMF, anti-CTLA4, anti-PD-L1, anti-TNF) in the management of inflammatory or malignant disorders. One should be aware not only of the clinical side effects, but also of the histological patterns, since they often imitate IBD-colitis. Genetic predisposition, immune dysregulation and the involvement of the microbiome are under investigation.

### Mycophenolate mofetil (MMF)

MMF is widely used as one of the most effective immunosuppressants. It is the 2-morpholinoethyl-ester of mycophenolic acid (MPA) initially known as an antibiotic compound. MPA is an inhibitor of inosine 5-monophosphate dehydrogenase (IMPDH). By preventing the synthesis of guanosine nucleotides, MPA has a potent anti-proliferative effect on these cell types which are dependent on de novo purine synthesis pathway. B and T lymphocytes are selectively affected due to their almost complete dependence on the latter mechanism in contrast to other cells having advantage of

a second salvage pathway. The most common adverse effect of MMF in transplant patients is watery afebrile diarrhea with an incidence reaching 36% in renal transplant recipients which resides after drug withdrawal.

MMF-related colitis has been described under different histological patterns exhibiting morphological similarities to inflammatory bowel disease (IBD). Histologically, the diagnostic hallmark of MMF-induced colitis is an IBD-like histological pattern with mucosa atrophy and crypt distortion in association with increased apoptosis of crypt epithelial cells. Increased number of apoptotic cells in the crypt epithelium, crypt angulation, crypt dilation with flattened epithelium or denudation and crypt abscesses containing apoptotic bodies in the lumen, aid in differentiation from IBD, while significant crypt distortion, dense inflammation, absence of endocrine cell aggregates, the prominence of the lesions in the right colon and no clinical history of bone marrow transplantation, help in the differential diagnosis from GVHD. Direct toxicity, immune mediated mechanisms (MMF-induced immune dysregulation or autoimmunity to putative autoantigens, such as adducts formed by MMF acyl-glucuronides metabolites and cellular proteins) as well as changes in resident gut flora or bacterial infections eliciting an ongoing immune response, have been implicated in pathogenesis.

### Ipilimumab

Ipilimumab is a human monoclonal antibody (IgG1) which blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4), a key negative regulator of T cell activation playing a crucial role in maintaining immune self-tolerance. It is also constitutively expressed by CD25, CD4 regulatory T cells (Tregs) which down-regulate immune reaction.

Immunotherapy with antiCTLA-4 mAbs (Ipilimumab) as a second-line treatment for patients with metastatic melanoma and other malignancies leads to colitis with watery-bloody diarrhea manifestation.

Histology ranges from normal mucosa to severe inflammation with erosions and ulcerations. Lesions are diffuse and less frequently patchy, characterized by predominantly neutrophilic, lymphocytic or mixed mucosa infiltrates of variable density commonly observed in association with neutrophilic, lymphocytic and rarely eosinophilic cryptitis. Crypt abscesses, crypt destruction and crypts with thinned, mucin depleted epithelium constitute additional findings. Lymphoid hyperplasia is frequently encountered. Pathologic findings exhibit similarities to those of IBD. The diffuse nature of inflammation is shared with ulcerative colitis, but architectural distortion and preferential involvement of distal colon and rectum are missing. The differential diagnosis from Crohn's disease relies on the absence of distinctive features, such as granulomas, aphthous or fissuring ulcers, bowel wall thickening, proximal colon and terminal ileum involvement. The only feature which may be proven to be of diagnostic significance are the atrophic crypts with mucin depleted thinned epithelium. Diagnosis should be based on appropriate clinical information.

The strong association of Ipilimumab administration with colitis development is indicative of disruption of immune regulation. It is possible that T-cells recognize intestinal autoantigens or foreign antigens (from food or enteric microbes) unless down-regulated by mechanisms requiring CTLA-4. It has also been suggested that Ipilimumab may interfere with T-cell differentiation upon activation or by selectively enriching pre-existing T-cells with an antigen-specificity. The fact that only a subset of patients develops colitis or that colitis may be refractory to treatment, indicate differences regarding diet, intestinal microbiota and genetic background. Finally, a treatment-induced functional defect of T-reg cannot be excluded, since no depletion of the latter cells has been observed.

The histological findings are not specific and mostly resemble IBD, thus rendering appropriate clinical information crucial for diagnosis.

### Anti-TNFa (Tumor Necrosis Factor alpha) antibodies

TNFa (Tumor Necrosis Factor alpha) is a pleiotropic cytokine with proinflammatory and immunoregulatory properties, produced mainly by activated macrophages and T lymphocytes. Production of several other proinflammatory cytokines (e.g. IL-1 and IL-6) and cell adhesion molecules is induced, and leukocytes migration is triggered. Anti-tumor necrosis factor (anti-TNFa) agents have been adapted in treatment of immune diseases including IBD. Paradoxical appearance of IBD - type colitis (de novo onset or manifestation of a subclinical IBD) can occur during treatment with anti-TNFa antibodies due to disruption of cytokine balance and regulation. Anti-TNFa antibodies induced colitis may affect duodenum, terminal ileum and colon or it may present itself as a pancolitis. Clinical manifestations may include abdominal pain, weight loss, diarrhea (watery-bloody), oral aphthous ulcers, fissures or anal fistulas can be observed. Histopathological findings are that of Crohn's disease or Crohn-like colitis at 93.7%, while 6.25% of the cases present with an ulcerative colitis histological pattern.

## REFERENCES

1. *Gastrointestinal Pathology: An Atlas and Text Third Edition.* Cecilia M. Fenoglio-Preiser, Amy E. Noffsinger, Grant N. Stemmermann, Patrick E. Lantz M. Freeman H.J. Colitis associated with biological agents. *World J Gastroenterol*, 2012; 18(16): 1871-1874
2. Assarzaghan N, Montgomery E, Anders RA. Immune checkpoint inhibitor colitis: the flip side of the wonder drugs. *Virchows Arch*. 2017. [Epub ahead of print]
3. Liapis G, Boletis J, Skalioti C, Bamias G, Delladetsima I. Histological spectrum of mycophenolate mofetil-related colitis: association with apoptosis. *Histopathology*, 2013; 63:649-58.
4. Star KV, Ho VT, Wang HH, Odze RD. Histologic features in colon biopsies can discriminate mycophenolate from GVHD-induced colitis. *Am J Surg Pathol*, 2013
5. Bamias G, Delladetsima I, Perdiki M, Siakavellas SI, Goukos D et al. Immunological Characteristics of Colitis Associated with Anti-CTLA-4 Antibody Therapy. *Cancer Invest*, 2017;35:443-455

## NEW INSIGHTS IN COLORECTAL CARCINOGENESIS

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Colorectal carcinoma (CRC) is among the five most frequent cancers worldwide. Only second to breast cancer in women and third after prostate and lung cancer in men. According to GLOBOCAN online analysis tool [1] the CRC mortality rate in 2018 is estimated around 215000 persons in Europe and approximately 2500 of them only in Greece. It seems that western developed countries have much more higher rates of colorectal cancer incidence while parts of Asia, Africa and India have lower incidence rates [2].

Diet and lifestyle play an essential role regarding the etiology in colorectal carcinogenesis. Higher amounts of animal fat intake with less vegetable fiber consumption and reduced physical activity appear to be very important contributors to colorectal carcinogenesis. Tobacco and alcohol users appear to be more affected [3]. Moreover there is increasing evidence that imbalances in gut microbiota can damage indirectly the colorectal epithelium DNA by producing high levels of reactive oxygen species (ROS) or by transforming the tumor inflammatory microenvironment. Bacterial flora dysregulation can damage directly the colonic mucosa cell DNA by producing certain bacterial toxins. In addition patients with inflammatory bowel disease have higher risk of CRC a fact that indicates a direct interconnection between cancer and inflammation [4]. On the other hand, important multiprotein complexes like inflammasomes seem to have an ambiguous role in inflammatory carcinogenesis that need to be elucidated [5]. Finally inhibitors of important enzymes of the arachidonic acid metabolism such as NSAIDs have shown that the pharmacologic chemoprevention has an important protective role against CRC [3].

Up to three pathogenetic mechanisms from which CRC can arise have been described. Chromosomal instability mechanisms (CIN), the microsatellite instability pathway (MSI) and the CpG island methylator mechanism (CIMP). These three mechanisms comprise both genetic and epigenetic molecular events [6]. Each of them is characterized by a series of accumulated molecular events that lead to dysregulation of oncosuppressor genes or chromosomal integrity, sufficient to initiate carcinogenesis at the colonic epithelium [7].

The basic genetic models of CRC are: the sporadic CRC which comprise almost 80% of all adenocarcinomas of the large intestine named as adenoma-carcinoma sequence model or APC/b-catenin pathway model. Part of this group is the Familial adenomatous polyposis (FAP) colon cancer which is also characterized by CIN. A small percentage of this group is developed by serrated adenomas, a group of neoplastic polyps that can progress versus CRC with a different mechanism named CIMP [11]. In the same group of inherited familial polyposis syndromes a small group of adenomatous polyposis without APC mutations named MYH-associated polyposis also with CIMP pathogenetic mechanisms of base excision repair (BER) gene mutations has similar clinical appearance as the attenuated form of FAP [8]. Finally Hereditary Non polyposis Colon Cancer or Lynch syndrome accounts for 4-5% of all the other groups of colon adenocarcinoma and it is correlated with epigenetic events of methylation of the CpG island of the MMR genes such as MSH2, MLH1, MSH6 and PMS1 and PMS2. On the other hand the MSI pathway comprises about 15% of all CRC. These adenocarcinomas have a distinct morphology clinical and prognostic behavior [7] [8].

In 2015 an international consortium of groups of experts came to an agreement to unite the diverse molecular subclassifications of colorectal genotyping into 4 basic molecular groups. The consensus molecular groups [10]. According to this consensus the first molecular consensus group (CMS1) is named MSI immune molecular group and consists of about 14% of colorectal adenocarcinomas. The second molecular consensus group (CMS2) is the Canonical molecular group characterized by the APC/b catenin pathway with 37% of colorectal adenocarcinomas. The third group (CMS3) is named Metabolic and 13% of adenocarcinomas are of this molecular group type. The fourth group is named the Mesenchymal molecular consensus group (CMS4) and 23% of all colorectal adenocarcinomas have the molecular signature of EMT phenotype. All 4 of the molecular consensus groups have specific biological behavior and some of them are characterized by distinct clinical course and morphology [9] [10].

Colorectal cancer constitute an example of specific multistep process of carcinogenesis. Despite the various programs of prevention and community screening, prevalence and incidence in developed countries have been increasing in recent years especially in ages under 50. Our knowledge in colorectal carcinogenesis has grown significantly with the use of new molecular techniques and next generation sequence methods. The bacterial flora and the role of inflammasomes, as well as PPAR $\gamma$  receptors and the exact mechanisms of COX-2 inhibitors are nowadays among the famous fields of research concerning the interconnection of colorectal carcinogenesis and inflammation. Understanding the role of epigenetic modification mechanisms such as micro RNAs and long non coding RNAs may be of vital importance in revealing regions considered as the "dark matter" of cancer mechanisms and could lead us to the era of personalized medicine [6].

### REFERENCES

1. "GLOBOCAN 2012," 2012. [Online]. Available: <http://globocan.iarc.fr/Default.aspx>. [Accessed 15 02 2018]
2. Dusek, "Epidemiology of colorectal cancer: international comparison," 2015. [Online]. Available: <http://www.kolorektum.cz/>. [Accessed 15 02 2018]
3. R. Hans, "Colorectal carcinogenesis-update and perspectives," *World Journal of Gastroenterology*, pp. 151-164, 28 December 2014

4. C. A. "Gut Microbiota, Inflammation, and Colorectal Cancer," *Annu Rev Microbiol*, pp. 395-411, 08 September 2016
5. L. C. a. Z. J. "Inflammasomes and inflammation-induced Cancer," *Frontiers in Immunology*, 15 March 2017
6. T. K. "Colorectal cancer carcinogenesis: a review of mechanisms," *Cancer Biology and Medicine*, pp. 120-135, 2016
7. M. M. "Molecular pathological classification of colon cancer," *Virchows Archiv*, pp. 125-134, 20 June 2016
8. R. S. Robbins and Cotran *Pathologic Basis of Disease Professional Edition*, Elsevier, 2015
9. G. J. "The Consensus Molecular Subtypes of Colorectal Cancer," *Nature Medicine*, pp. 1350-1356, 15 November 2015
10. T. K. "Consensus Molecular Subtypes of Colorectal Cancer and their Clinical Implications.," *International Biological and Biomedical Journal*, 13 June 2017
11. F. Ernst, "Molecular aspects of Colorectal Carcinogenesis: A review," *Journal of Cancer Biology and Research*, 06 February 2015

## COLORECTAL ADENOCARCINOMA

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#### 1. Tumor Site – Classification

The tumor is classified according to its site. Tumors located at the border between two subsites of the colon (eg, cecum and ascending colon) are registered as tumors of the subsite that is more involved.

A tumor is classified as rectal if its inferior margin lies less than 16 cm from the anal verge or if any part of the tumor is located at least partly within the supply of the superior rectal artery.

#### 2. Histologic Types

##### WHO Classification of Colorectal Carcinoma

Adenocarcinoma

Mucinous (colloid) adenocarcinoma (greater than 50% mucin)

Signet-ring cell carcinoma (greater than 50% signet-ring cells)

Medullary carcinoma

Micropapillary adenocarcinoma

Serrated adenocarcinoma

Squamous cell carcinoma

Adenosquamous carcinoma

Spindle cell carcinoma

Poorly differentiated neuroendocrine carcinoma

Large cell neuroendocrine carcinoma

Small cell neuroendocrine carcinoma

Mixed adenoneuroendocrine carcinoma

Undifferentiated carcinoma

#### 3. Histologic Grade

Grade 1: Well differentiated (>95% gland formation)

Grade 2: Moderately differentiated (50–95% gland formation)

Grade 3: Poorly differentiated (<50% gland formation)

Grade 4: Undifferentiated (no gland formation or mucin; no squamous or neuroendocrine differentiation)

#### 4. Carcinoma in an Adenomatous Polyp: Microscopic Tumor Extension and High-Risk Features

Colorectal adenomas containing invasive adenocarcinoma that extends through into the submucosa have been defined as malignant polyps.

Evaluation of histologic factors related to the risk of adverse outcome

- Histologic grade
- Status of the resection margin
- Lymphatic/venous vessel involvement
- Invasive front –tumor budding
- Depth or area of submucosal invasion

#### 5. Lymph-Vascular and Perineural Invasion

Small vessel (lymphatics, capillaries, and postcapillary venules) invasion is associated with lymph node metastasis and has been shown to be independent indicator of adverse outcome in several studies.

Venous invasion can be extramural or intramural. Extramural venous invasion has been demonstrated by multivariate analysis to be an independent adverse prognostic factor in multiple studies and is a risk factor for liver metastasis.<sup>25</sup> The significance of intramural venous invasion is less clear.

Perineural invasion has also been shown to be independent indicator of poor prognosis.

#### 6. Tumor Budding

The presence of single cells or small clusters of less than five cells at the advancing front of the tumor is considered as peritumoral tumor budding. High tumor budding in adenocarcinoma arising in polyp is a significant risk factor for nodal involvement, with tumor budding being the most significant factor in some studies.

#### 7. Polyps

The adenocarcinoma can arise in adenomatous (tubular, tubulovillous, or villous) or serrated (sessile serrated adenoma/polyp or traditional serrated adenoma) polyp. A sessile serrated adenoma may develop cytologic dysplasia resembling tubular adenoma during neoplastic progression. These are presumed to be the precursors of right-sided adenocarcinomas with high levels of microsatellite instability (MSI-H)

#### 8. Perforation

Tumor perforation is associated with a poor outcome, including high in-hospital mortality and morbidity.<sup>41</sup> Perforation of the uninvolved colon proximal to an obstructing tumor is also associated with high mortality because of generalized peritonitis and sepsis.

#### 9. Assessment of the mesorectal envelope

The nonperitonealized surface of the fresh specimen is examined circumferentially, and the completeness of the mesorectum is scored as described below. The entire specimen is scored according to the worst area.

##### Incomplete

- Little bulk to the mesorectum
- Defects in the mesorectum down to the muscularis propria
- After transverse sectioning, the circumferential margin appears very irregular

##### Nearly Complete

- Moderate bulk to the mesorectum
- Irregularity of the mesorectal surface with defects greater than 5 mm, but none extending to the muscularis propria
- No areas of visibility of the muscularis propria except at the insertion site of the levator ani muscles

##### Complete

- Intact bulky mesorectum with a smooth surface
- Only minor irregularities of the mesorectal surface
- No surface defects greater than 5 mm in depth
- No coning towards the distal margin of the specimen
- After transverse sectioning, the circumferential margin appears smooth

#### 10. Margins

Proximal and distal margins are dissection margins, accounting for all layers of the colon wall.

The radial margin represents the adventitial soft tissue margin closest to the deepest penetration of tumor and is created surgically by blunt or sharp dissection of the retroperitoneal or subperitoneal aspect, respectively

The serosal surface (visceral peritoneum) does not constitute a surgical margin.

#### 11. Treatment Effect

Neoadjuvant chemoradiation therapy in rectal cancer is associated with significant tumor response and downstaging.

Minimal residual disease has been shown to have a better prognosis than gross residual disease. A modified Ryan scheme is suggested for scoring of tumor response, and has been shown to provide good interobserver reproducibility and prognostic significance.

Description	Tumor Regression Score
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

#### 12. Tumor Deposits

Tumor deposits are tumor foci in the pericolic/perirectal fat or in adjacent mesentery (mesocolic or rectal fat), within the lymph drainage area of the primary tumor, but without identifiable lymph node tissue or vascular structure.

In the setting of preoperative or neoadjuvant therapy, the designation of tumor deposit should be used with caution as the tumor foci may represent residual primary tumor with incomplete response.

## TNM and Anatomic Stage/Prognostic Groupings (8th edition/2017)

## Primary tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ: invasion of lamina propria

T1 Tumor invades submucosa

T2 Tumor invades muscularis propria

T3 Tumor invades subserosa or into non-peritonealized pericolic or perirectal tissues

T4 Tumor directly invades other organs or structures and/or perforates visceral peritoneum

T4a Tumor perforates visceral peritoneum

T4b Tumor directly invades other organs or structures.

## Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node(s) metastasis

N1 Metastases in 1 to 3 regional lymph nodes

N1a Metastasis in 1 regional lymph node

N1b Metastasis in 2 to 3 regional lymph nodes

N1c Tumor deposits in the serosa or in non-peritonealized pericolic or perirectal soft tissue without regional lymph node metastasis

N2 Metastases in 4 or more regional lymph nodes

N2a Metastasis in 4–6 regional lymph nodes

N2b Metastasis in 7 or more regional lymph nodes

## Distant metastasis (M)

M0 No distant metastasis (no pathologic M0; use clinical M to complete stage group)

M1 Distant metastasis

M1a Metastasis confined to one organ (liver, lung, ovary, non-regional lymph nodes) without peritoneal metastasis

M1b Metastasis in more than one organ

M1c Metastasis to the peritoneum with or without other organ involvement

## 13. Biomarkers

1. Testing for microsatellite instability and/or status DNA mismatch repair enzymes by immunohistochemistry
2. PCR for MSI testing
3. Other mutation testing in colorectal cancer (such as KRAS, BRAF)

## REFERENCES

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017
2. Bosman FT, et al, eds. *WHO classification of tumors of the digestive system*. 4th ed. Lyon, France: IARC Press; 2010
3. Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. *Gastroenterology*. 2004 ;127(2):385–394
4. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. *Am J Gastroenterol*. 2012;107(9):1315–1330
5. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genet Med*. 2009;11(1):35–41

## GASTROINTESTINAL NEUROENDOCRINE NEOPLASMS

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Neuroendocrine neoplasms of the gastrointestinal system (GI-NENs) are a relatively uncommon, heterogeneous group, with diverse clinical behaviors and an increasing incidence and prevalence. They originate from neuroendocrine cells, distributed mainly in the mucosa and submucosa of the GI tract, part of the diffuse neuroendocrine system. In the GI, there are at least 15 neuroendocrine cell types producing either a peptide hormone or biogenic amine but all expressing the general neuroendocrine markers.

The biology of NENs depends on the primary tumor localization, their histopathological features and clinically they may be silent or manifest expression of hormone secretion.

Well-differentiated neuroendocrine tumors (NETs) occur more commonly than NECs. As the therapeutic options continue to expand, it is increasingly important to define robust prognostic markers to inform clinical decision making and the most challenging tasks in pathology are achieving the correct prognostic evaluation by recognizing their metastatic/ aggressive potential and the identification of NECs.

One of the major problems is the lack of universally accepted standards, both for nomenclature of NETs and for staging of disease. Since their first description with the name "carcinoid", several different classifications and staging have been published from expert communities in the field, causing confusions to both clinicians and pathologists.

**In the WHO 2010 classification**, there was a successful attempt to create a widely, universally accepted grade scheme and stage of GEP NENs.

It is adopted the name neuroendocrine (*to indicate the expression of neural + endocrine markers in neoplastic cells*) neoplasms (*to confirm that all NENs are considered to be malignant and potentially metastatic, with different biological aggressiveness*).

**According to morphological criteria**, NENs are categorized in two main completely different categories with different immune-morphological, molecular and clinical features and completely different therapy:

- a. *Well-differentiated neuroendocrine tumors* (NETs), broadly corresponding to "carcinoid tumors" or "well-differentiated (neuro)endocrine tumors/carcinomas" of previous classifications and
- b. *neuroendocrine carcinomas* (NECs) of small and large cell subtypes, corresponding to poorly differentiated (neuro) endocrine carcinomas of the previous classification.

**According to grade**, NENs are further divided in three groups, using the Ki-67 proliferation index and/or the mitotic count, G1 and G2 – NETs (<2 mitosis per 10HPF or 2–20 per 10HPF, respectively) and/or Ki67 index (<2% or 3–20%, respectively) and G3 NECs (>20 per 10 HPF) and Ki67 index (>20%). Grading requires mitotic count in at least 50 HPFs and ki-67 index as a % of 500–2000 cells in hot spot areas, the highest grade be assumed. In biopsy material it is sometimes difficult to determinate the accurate diagnosis and multiple biopsies may be needed.

**TNM staging**, depends on the site of origin. Two TNM systems still exist, from UICC and ENETS, with differences in the T-stage for appendiceal and pancreatic NETs.

**In the new 2017 WHO classification**, changes for pancreatic NENs, and these will most probably apply in the future WHO classification of GI-NETs, are:

- a. the Ki67 cutoff to separate G1 from G2 NETs has been moved from 2 to 3%
- b. a third, new tumor category added in NET subtype, characterized by a well-differentiated morphology with a high proliferation rate (Ki67 index>20% and mostly up to 55%), named **NET-G3** is added. NET-G3 has morphological features similar to NET, mitotic rate mostly in the G2 range, often evolving from a lower grade component and carrying MEN1, DAXX and ATRX mutations. *However, because, in some cases, it is difficult to distinguish G3 NET from NEC morphologically, additional immunohistochemistry may be used: abnormal p53 expression for NEC and if available loss of Rb for NEC and loss of DAXX or ATRX expression for well-differentiated NETs*
- c. the new term "mixed neuroendocrine/nonneuroendocrine neoplasms (MiNENs/MENENs)" replaces the term "mixed adenoneuroendocrine carcinomas (MANECs)" for neoplasms that are composed of both nonendocrine and neuroendocrine component, each of which represented at least 30% of the lesion and each of which having variable morphology, differentiation and malignant potential.
- d. Both UICC and ENETS use the same TNM staging for PanNENs.

*It is worth noting that:*

- a Ki67 cut-off of 5% has been proposed by some authors as the best one to differentiate G1 from G2 pancreatic NETs, but at the moment it is not accepted.
- for predicting treatment response, there are concerns for better dividing the G2 group into low G2 (Ki67<10%) effectively treated with SSA treatment and high G2 (Ki67>10%) with better response to everolimus.







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