TOPIC HIGHLIGHT

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Pathohistological classification systems in gastric cancer: Diagnostic relevance and prognostic value

Felix Berlth, Elfriede Bollschweiler, Uta Drebber, Arnulf H Hoelscher, Stefan Moenig

Felix Berlth, Elfriede Bollschweiler, Arnulf H Hoelscher, Stefan Moenig, Department of General, Visceral and Cancer Surgery, University of Cologne, 50937 Cologne, Germany
Uta Drebber, Department of Pathology, University of Cologne, 50937 Cologne, Germany
Author contributions: Moenig S, Bollschweiler E and Hoelscher AH contributed ideas from previous publications regarding different classification systems of gastric cancer and also pointed out the position of the German S3 guideline; As an expert pathologist, Drebber U reviewed the manuscript from a pathological point of view and described the clinical routine concerning the diagnosis and classification of gastric cancer; Berlth F generated the topic of the article and wrote the manuscript.
Correspondence to: Stefan Moenig, Professor, Department of General, Visceral and Cancer Surgery, University of Cologne, Kerpener Str. 62, 50937 Cologne, Germany. stefan.moenig@uk-koeln.de
Telephone: +49-221-4786273 **Fax:** +49-221-4787440
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Abstract

Several pathohistological classification systems exist for the diagnosis of gastric cancer. Many studies have investigated the correlation between the pathohistological characteristics in gastric cancer and patient characteristics, disease specific criteria and overall outcome. It is still controversial as to which classification system imparts the most reliable information, and therefore, the choice of system may vary in clinical routine. In addition to the most common classification systems, such as the Laurén and the World Health Organization (WHO) classifications, other authors have tried to characterize and classify gastric cancer based on the microscopic morphology and in reference to the clinical outcome of the patients. In more than 50 years of systematic classification of the pathohistological characteristics of gastric cancer, there is no sole classification system that is consistently used worldwide in diagnostics and research. However, several national guidelines for the treatment of gastric cancer refer to the Laurén or the WHO classifications regarding therapeutic decision-making, which underlines the importance of a reliable classification system for gastric cancer. The latest results from gastric cancer studies indicate that it might be useful to integrate DNA- and RNA-based features of gastric cancer into the classification systems to establish prognostic relevance. This article reviews the diagnostic relevance and the prognostic value of different pathohistological classification systems in gastric cancer.

Core tip: The establishment of a pathohistological classification system for gastric cancer with significant prognostic relevance is highly desirable. Numerous classification systems have been introduced by different authors. Although none of them could reach a consensus, the Laurén classification and the World Health Organization classification are widely used. The characteristics of each classification system as well as the prospect for future developments are presented in this article.

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INTRODUCTION

Gastric cancer is responsible for approximately 10% of cancer-related deaths worldwide; it is the second most common cause of cancer-related deaths and the fourth most commonly diagnosed cancer worldwide[1,2]. Although the incidence is persistently declining due to changes in nutrition and better prevention and treatment, gastric cancer is still associated with a poor prognosis. In the age of microscopic pathology, it has been of greater interest not only to classify the heterogeneous, histological appearance of the tumor cells but also to find a classification scheme with an independent prognostic relevance. To make patient-specific decisions regarding diagnosis and treatment, it is crucial to establish a solid pathohistological classification system. Numerous pathohistological classification systems have been established for gastric cancer thus far, but there is still controversy as to which classifications unify a prognostic correlation with a high validity and practicability in diagnosis and clinical routine.

LAURÉN CLASSIFICATION

Since its establishment in 1965, the Laurén classification of gastric cancer has been the most commonly used and the most studied classification for gastric adenocarcinoma among all of the classification systems. Laurén divided the histology of gastric cancer into two groups, *i.e.*, the intestinal type and the diffuse type (Table 1); later, the indeterminate type was included to describe an uncommon histology[3,4]. Signet ring cell carcinoma is included in the diffuse type. Most studies showed the intestinal type to be the most common, followed by the diffuse and then indeterminate type[5-7]. There is evidence that the intestinal type is associated with intestinal metaplasia of the gastric mucosa and with the presence of *Helicobacter pylori*. In some studies, the incidence of the diffuse type was found to be higher in younger, female patients[8], which may indicate distinct tumor development pathways for intestinal and diffuse adenocarcinoma of the stomach.

The prognostic relevance of Laurén's classification is still controversial. In some studies, Laurén's pathohistological subtypes of gastric cancer did not show a correlation with the patient's outcome[9-11], whereas other studies demonstrated a prognostic significance for the classification system[12]; some investigators even demonstrated that Laurén's classification can be used as an independent prognostic factor[13,14]. In those studies, the presence of a diffuse adenocarcinoma was correlated with a worse outcome. As this correlation has not been verified in other patient cohorts, the prognostic significance of Laurén's classification cannot be viewed as a generally established, but rather as a circumstance of one group's results.

Due to its high clinical relevance, the reliability of the Laurén classification has also been tested. The concordance of intra- and inter-observer agreement was tested using a percentage and kappa statistics that ranged from 77%-95%, indicating a good overall agreement, although a certain rate of mismatches was found. In studies investigating the concordance of biopsy- and specimen-based histological diagnosis in gastric cancer, a mismatch for the Laurén classification was found in 16%-26%. This mismatch was primarily explained as a focal manifestation of diffuse adenocarcinoma in specimens that the biopsy indicated as an intestinal adenocarcinoma[15,16]. With respect to the influence the histology might have in terms of treatment, a control biopsy was recommended in cases of uncertain histology.

Concerning the accuracy of esophagogastroduodenoscopy and endoscopic ultrasound in the diagnosis of gastric cancer, the diffuse type was described as a factor leading to underestimation of tumor infiltration, or T-category[17]. Therefore, in endoscopic treatment of gastric adenocarcinoma, an intestinal type indicated by the Laurén classification is favored in the national guidelines of Japan and Germany and in European Society for Medical Oncology guidelines[18-20]. The German S3 Guidelines also refer to Laurén's classification when recommending a resection margin of 8 cm for the diffuse type and a 5 cm margin for the intestinal type[18]. The rationale for this recommendation is given in several studies by Hornig *et al*[21] who found a sometimes discontinuous proliferation of diffuse gastric cancers[22,23]. These recommendations in national guidelines and the histological findings underline the significance of the Laurén classification and clarify why it is favored over other pathohistological classification systems.

WORLD HEALTH ORGANIZATION CLASSIFICATION

The World Health Organization (WHO) classification issued in 2010 appears to be the most detailed among all pathohistological classification systems. It is remarkable that the WHO classification includes not only adenocarcinoma of the stomach but also all other types of gastric tumors of lower frequency (Table 1)[24]. The gastric adenocarcinoma type is divided into several subgroups including papillary, tubular, mucinous and mixed carcinoma, which can be compared to the indeterminate type in the Laurén classification. The poorly cohesive carcinoma type includes the signet ring cell carcinoma. All other classified gastric adenocarcinomas can be designated as uncommon because of their minor clinical relevance. In the WHO classification, the most common type of gastric cancer is the tubular adenocarcinoma, followed by the papillary and mucinous types. The signet ring cell carcinoma accounts for approximately 10% of gastric cancers and is defined by the presence of signet ring cells in over 50% of the tumor[24-27]. The prognosis of the signet ring cell carcinoma is controversial. Most authors have described a worse prognosis for the signet ring cell carcinoma compared to other subtypes of gastric cancer[28,29]. Recent studies indicate that, on the contrary, signet ring cell carcinoma of the stomach does not differ in prognosis from the other types of gastric

Table 1	Laurén and World Health Organization classification
Laurén classification	World Health Organization classification
Intestinal type	Papillary adenocarcinoma
	Tubular adenocarcinoma
	Mucinous adenocarcinoma
Diffuse type	Signet-ring cell carcinoma and other poorly cohesive carcinomas
Indeterminate type	Mixed carcinoma
	Adenosquamous Carcinoma
	Squamous cell carcinoma
	Hepatoid adenocarcinoma
	Carcinoma with lymphoid stroma
	Choriocarcinoma
	Carcinosarcoma
	Parietal cell carcinoma
	Malignant rhabdoid tumor
	Mucoepidermoid carcinoma
	Paneth cell carcinoma
	Undifferentiated carcinoma
	Mixed adeno-neuroendocrine carcinoma
	Endodermal sinus tumor
	Embryonal carcinoma
	Pure gastric yolk sac tumor
	Oncocytic adenocarcinoma

Table 2	Goseki and Ming classification
Goseki classification	
Group I	
Tubular differentiation-well	
Mucus in cytoplasm-poor	
Group II	
Tubular differentiation-well	
Mucus in cytoplasm-poor	
Group III	
Tubular differentiation-poor	
Mucus in cytoplasm-poor	
Group IV	
Tubular differentiation-poor	
Mucus in Cytoplasm-rich	
Ming classification	
Expanding type	
Infiltrating type	

cancer[30]. Furthermore, signet ring cell carcinoma was shown to have an irregular uptake of ^{18}F-fluorodeoxyglucose during positron emission tomography radionuclide imaging; consequently, this tumor as well as any metastases cannot be detected reliably[31]. Patients with a papillary adenocarcinoma experience a poor prognosis, a tendency for metastatic disease, a higher age at diagnosis and location in the upper third of the stomach[32]. Another study that employed the previous WHO classification found that poorly differentiated and mucinous adenocarcinomas have a worse prognosis than the papillary and tubular subtypes. In the same study, the WHO classification appeared to be an independent prognostic factor[33]. Kawamura et al[34] also found a poor prognosis associated with mucinous adenocarcinoma, which suggests a link with advanced stage and metastatic disease. However, unlike most common types of gastric malignancies, the WHO classification is more widely used for studies of infrequent types of gastric cancer. For adenosquamous carcinomas of the stomach, a poor prognosis and a case of simultaneous gastric adenocarcinoma are described[35,36]. In a recent review of the hepatoid adenocarcinoma type, the median survival of 182 patients with a gastric primary lesion was 13 mo, and 63.9% showed lymph node metastasis[37]. Most of the infrequent types of gastric malignancies are described in case reports, so a systematic investigation of their prognoses is not readily available. As the previous WHO classification was renewed in 2010, it is expected that more gastric cancer studies that refer to the most recent WHO classification will be conducted in the near future.

An indication for the significance of the WHO classification can be seen in a similar Japanese classification system. Although the Japanese classification divides the common types of gastric adenocarcinoma into addi-

tional subtypes, (e.g., tubular adenocarcinoma is divided into well-differentiated and moderately differentiated adenocarcinoma), a dependence on the WHO classification system is evident[38]. This particular subdivision of tubular adenocarcinoma was based on differences in the submucosal invasion rate, lymph node metastasis and size of the lesions[39].

GOSEKI CLASSIFICATION

In 1992, Goseki et al[40] described a new histopathological classification that divides gastric cancer into four groups, as presented in Table 2. In the article, a correlation of the subtypes with the patterns of metastasis and local growth was present in 200 autopsy cases. Other groups showed a correlation of the Goseki classification with the Laurén and the WHO classifications, but there was only a moderate level of inter-observer agreement. A high level of agreement among observers could be achieved concerning the mucus production, and in later studies, the presence of mucus was highly associated with the prognosis[41,42]. An independent prognostic significance of the Goseki classification was subsequently debated. Despite some evidence[43], most studies that focused on this question could not confirm a prognostic independence of the Goseki classification, but did confirm a correlation with the preexisting histopathological characteristics such as those in the union international contre le cancer (UICC) system, grade, and Laurén and WHO classifications[11,44,45].

MING CLASSIFICATION

The Ming classification system is based on the growth pattern of the lesion and recognizes two main growth patterns: the expanding growth pattern and the infiltrating growth pattern (Table 2), which was found to be the less frequent type[46]. In his original work, Ming connected the two growth patterns to specific characteristics, positing that the expanding type originates as an intestinal metaplasia, whereas the infiltrating type emerges from individual cells. The Ming classification system may be

simple and clinically useful, but several subsequent studies could not identify this classification as an independent prognostic factor; a correlation was found with the pre-existing classification systems[9,47,48].

OTHER CLASSIFICATIONS

In addition to the aforementioned histopathological classification systems for gastric cancer, some other authors have tried to establish systems based on the preexisting classifications or on histological findings. In 1982, Grundmann *et al*[49] proposed a classification system for gastric cancer with a focus on the depth of invasion. Caneiro *et al*[50] published a classification system for gastric cancer based on morphological appearance and showed an independent prognostic significance for the four subtypes. The Japanese Histological Classification of Gastric Cancer is based on the WHO classification and includes several subtypes in addition to the common histologic types[38]. However, none of these classification systems is used worldwide for research purposes, as no advantages of any one particular classification over the others have been confirmed.

DISCUSSION

There have been many attempts to classify gastric cancer according to its pathohistological characteristics. The very early attempt by Laurén still appears to be the classification system with the highest prevalence in research and clinical practice among all of the classification systems. Many studies illustrate a prognostic independence for the Laurén classification, yet other studies have not validated this relationship. In summary, all of the discussed classifications have demonstrated clinical practicality and relevance as well as providing pertinent data for comparison with Laurén's classification system. Interestingly, all attempts to produce a superior classification system have failed, although all are based on the apparent histopathological characteristics of gastric cancer. The only classification with a comparable significance is the WHO classification, which is the only system that classifies all malignancies with a primary lesion in the stomach irrespective of the cellular origins. The WHO classification system is widely used for the diagnosis and description of infrequent gastric neoplasms and is mentioned in many studies investigating the pathohistological characteristics of gastric cancer. Although the Goseki and Ming classifications can be understood on a cellular level, both classifications have not been proven to be superior to the preexisting systems, with the Laurén classification scheme as the gold standard. That no other attempt has surpassed the classification system of Laurén, established in 1965, is a testament to the complexity of the pathohistological characteristics of gastric cancer. Recent studies recommend that gastric cancer no longer be classified according to histology alone, but with the help of molecular markers or DNA- and RNA-based characteristics[25,51]. Although no reliable concept has been established, with the help of new technologies it is possible to construct a classification of gastric cancer with an independent prognostic relevance. Therefore, it is not necessary to create a completely new classification system; instead, it is easier to complement a preexisting classification with molecular and genetic findings.

Regarding the clinical practice of diagnosis and treatment, the classification systems of Laurén and the WHO predominate in published studies as well as in several national guidelines, such as the German S3 guideline for gastric cancer and the Japanese Classification of Gastric Cancer. As long as there is no widely accepted classification system with prognostic independence, both the Laurén and the WHO classification systems should continue to be used so that data presented in different studies can be compared. Such comparisons are important in order to segregate subgroups of patients with certain clinical features or different outcomes.

This is especially relevant for treatment decisions in clinical practice, where a pathohistological classification system that has an association with the prognosis is highly desirable. Such a classification could lead the way to a more personalized decision-making process for treatment of gastric cancer.

REFERENCES

1   **Parkin DM**. International variation. *Oncogene* 2004; **23**: 6329-6340 [PMID: 15322508 DOI: 10.1038/sj.onc.1207726]
2   **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBO-CAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]
3   **Lauren P**. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. an attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49 [PMID: 14320675]
4   **Leocata P**, Ventura L, Giunta M, Guadagni S, Fortunato C, Discepoli S, Ventura T. [Gastric carcinoma: a histopathological study of 705 cases]. *Ann Ital Chir* 1998; **69**: 331-337 [PMID: 9835105]
5   **López-Carrillo L**, Vega-Ramos B, Costa-Dias R, Rascón-Pacheco RA. Histological types of gastric cancer in Mexico. *Int J Epidemiol* 1997; **26**: 1166-1171 [PMID: 9447395 DOI: 10.1093/ije/26.6.1166]
6   **Dobru D**, Pascu O, Tantau M, Gheorghe C, Goldis A, Balan G, Coman F, Fraticiu A, Dumitru E, Mutescu E, Saftoiu A, Bacarea V. An epidemiological study of gastric cancer in the adult population referred to gastroenterology medical services in Romania -- a multicentric study. *Rom J Gastroenterol* 2004; **13**: 275-279 [PMID: 15624023]
7   **Parsonnet J**, Vandersteen D, Goates J, Sibley RK, Pritikin J, Chang Y. Helicobacter pylori infection in intestinal- and diffuse-type gastric adenocarcinomas. *J Natl Cancer Inst* 1991; **83**: 640-643 [PMID: 2023282 DOI: 10.1093/jnci/83.9.640]
8   **Kaneko S**, Yoshimura T. Time trend analysis of gastric cancer incidence in Japan by histological types, 1975-1989. *Br J Cancer* 2001; **84**: 400-405 [PMID: 11161407 DOI: 10.1054/bjoc.2000.1602]
9   **Garnier P**, Vielh P, Asselain B, Durand JC, Girodet J, Pilleron JP, Salmon RJ. [Prognostic value of the Lauren and Ming classifications in gastric adenocarcinoma. Multidimensional analysis]. *Gastroenterol Clin Biol* 1988; **12**: 553-558 [PMID: 3417082]
10   **Calli Demirkan N**, Tunçyürek M, Ugur Ertan E, Bülent Al-

kanat M, İçöz G. [Correlation of histological classifications of gastric carcinomas with location and prognosis]. *Gastroenterol Clin Biol* 2002; **26**: 610-615 [PMID: 12193861]

11   **Mönig S**, Baldus SE, Collet PH, Zirbes TK, Bollschweiler E, Thiele J, Dienes HP, Hölscher AH. Histological grading in gastric cancer by Goseki classification: correlation with histopathological subtypes and prognosis. *Anticancer Res* 2001; **21**: 617-620 [PMID: 11299815]

12   **Yu CC**, Levison DA, Dunn JA, Ward LC, Demonakou M, Allum WH, Hallisey MT. Pathological prognostic factors in the second British Stomach Cancer Group trial of adjuvant therapy in resectable gastric cancer. *Br J Cancer* 1995; **71**: 1106-1110 [PMID: 7734309]

13   **Guglielmi A**, de Manzoni G, Tomezzoli A, Ricci F, Pelosi G, Laterza E, Di Leo A, Bonfiglio M. [Prognostic value of histologic classifications of advanced stomach cancer: comparative study of Lauren's and Goseki's classifications]. *Chir Ital* 1997; **49**: 45-49 [PMID: 9612652]

14   **Qiu MZ**, Cai MY, Zhang DS, Wang ZQ, Wang DS, Li YH, Xu RH. Clinicopathological characteristics and prognostic analysis of Lauren classification in gastric adenocarcinoma in China. *J Transl Med* 2013; **11**: 58 [PMID: 23497313 DOI: 10.1186/1479-5876-11-58]

15   **Hansson LE**, Lindgren A, Nyrén O. Can endoscopic biopsy specimens be used for reliable Laurén classification of gastric cancer? *Scand J Gastroenterol* 1996; **31**: 711-715 [PMID: 8819223 DOI: 10.3109/00365529609009155]

16   **Flucke U**, Mönig SP, Baldus SE, Zirbes TK, Bollschweiler E, Thiele J, Dienes HP, Hölscher AH. Differences between biopsy- or specimen-related Laurén and World Health Organization classification in gastric cancer. *World J Surg* 2002; **26**: 137-140 [PMID: 11865338 DOI: 10.1007/s00268-001-0195-0]

17   **Ahn HS**, Lee HJ, Yoo MW, Kim SG, Im JP, Kim SH, Kim WH, Lee KU, Yang HK. Diagnostic accuracy of T and N stages with endoscopy, stomach protocol CT, and endoscopic ultrasonography in early gastric cancer. *J Surg Oncol* 2009; **99**: 20-27 [PMID: 18937032 DOI: 10.1002/jso.21170]

18   **Meyer HJ**, Hölscher AH, Lordick F, Messmann H, Mönig S, Schumacher C, Stahl M, Wilke H, Möhler M. [Current S3 guidelines on surgical treatment of gastric carcinoma]. *Chirurg* 2012; **83**: 31-37 [PMID: 22127381 DOI: 10.1007/s00104-011-2149-x]

19   **Gotoda T**, Iwasaki M, Kusano C, Seewald S, Oda I. Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria. *Br J Surg* 2010; **97**: 868-871 [PMID: 20301163 DOI: 10.1002/bjs.7033]

20   **Okines A**, Verheij M, Allum W, Cunningham D, Cervantes A. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** Suppl 5: v50-v54 [PMID: 20555102 DOI: 10.1093/annonc/mdq164]

21   **Hornig D**, Hermanek P, Gall FP. The Significance of the Extent of Proximal Margins of Clearance in Gastric Cancer Surgery. *Scnad J Gastroenterol* 1987; **22**: 69-71

22   **Hermanek P**. pTNM and residual tumor classifications: problems of assessment and prognostic significance. *World J Surg* 1995; **19**: 184-190 [PMID: 7754621 DOI: 10.1007/BF00308624]

23   **Gall FP**, Hermanek P. New aspects in the surgical treatment of gastric carcinoma--a comparative study of 1636 patients operated on between 1969 and 1982. *Eur J Surg Oncol* 1985; **11**: 219-225 [PMID: 2411603]

24   **Fléjou JF**. [WHO Classification of digestive tumors: the fourth edition]. *Ann Pathol* 2011; **31**: S27-S31 [PMID: 22054452 DOI: 10.1016/j.annpat.2011.08.001]

25   **Hu B**, El Hajj N, Sittler S, Lammert N, Barnes R, Meloni-Ehrig A. Gastric cancer: Classification, histology and application of molecular pathology. *J Gastrointest Oncol* 2012; **3**: 251-261 [PMID: 22943016 DOI: 10.3978/j.issn.2078-6891.2012.021]

26   **Sarbia M**, Becker KF, Höfler H. Pathology of upper gastrointestinal malignancies. *Semin Oncol* 2004; **31**: 465-475 [PMID: 15297939 DOI: 10.1053/j.seminoncol.2004.04.020]

27   **Werner M**, Becker KF, Keller G, Höfler H. Gastric adenocarcinoma: pathomorphology and molecular pathology. *J Cancer Res Clin Oncol* 2001; **127**: 207-216 [PMID: 11315254 DOI: 10.1007/s004320000195]

28   **Ribeiro MM**, Sarmento JA, Sobrinho Simões MA, Bastos J. Prognostic significance of Lauren and Ming classifications and other pathologic parameters in gastric carcinoma. *Cancer* 1981; **47**: 780-784 [PMID: 7226025]

29   **Hass HG**, Smith U, Jäger C, Schäffer M, Wellhäuber U, Hehr T, Markmann HU, Nehls O, Denzlinger C. Signet ring cell carcinoma of the stomach is significantly associated with poor prognosis and diffuse gastric cancer (Lauren's): single-center experience of 160 cases. *Onkologie* 2011; **34**: 682-686 [PMID: 22156447 DOI: 10.1159/000334545]

30   **Taghavi S**, Jayarajan SN, Davey A, Willis AI. Prognostic significance of signet ring gastric cancer. *J Clin Oncol* 2012; **30**: 3493-3498 [PMID: 22927530 DOI: 10.1200/jco.2012.42.6635]

31   **Alakus H**, Batur M, Schmidt M, Drebber U, Baldus SE, Vallböhmer D, Prenzel KL, Metzger R, Bollschweiler E, Hölscher AH, Mönig SP. Variable 18F-fluorodeoxyglucose uptake in gastric cancer is associated with different levels of GLUT-1 expression. *Nucl Med Commun* 2010; **31**: 532-538 [PMID: 20220543 DOI: 10.1097/MNM.0b013e32833823ac]

32   **Yasuda K**, Adachi Y, Shiraishi N, Maeo S, Kitano S. Papillary adenocarcinoma of the stomach. *Gastric Cancer* 2000; **3**: 33-38 [PMID: 11984707 DOI: 10.1007/PL00011687]

33   **Zheng HC**, Zheng YS, Xia P, Xu XY, Xing YN, Takahashi H, Guan YF, Takano Y. The pathobiological behaviors and prognosis associated with Japanese gastric adenocarcinomas of pure WHO histological subtypes. *Histol Histopathol* 2010; **25**: 445-452 [PMID: 20183797]

34   **Kawamura H**, Kondo Y, Osawa S, Nisida Y, Okada K, Isizu H, Uebayasi T, Takahasi M, Hata T. A clinicopathologic study of mucinous adenocarcinoma of the stomach. *Gastric Cancer* 2001; **4**: 83-86 [PMID: 11706765 DOI: 10.1007/s101200100032]

35   **Toyota N**, Minagi S, Takeuchi T, Sadamitsu N. Adenosquamous carcinoma of the stomach associated with separate early gastric cancer (type IIc). *J Gastroenterol* 1996; **31**: 105-108 [PMID: 8808437 DOI: 10.1007/BF01211195]

36   **Faria GR**, Eloy C, Preto JR, Costa EL, Almeida T, Barbosa J, Paiva ME, Sousa-Rodrigues J, Pimenta A. Primary gastric adenosquamous carcinoma in a Caucasian woman: a case report. *J Med Case Rep* 2010; **4**: 351 [PMID: 21034475 DOI: 10.1186/1752-1947-4-351]

37   **Su JS**, Chen YT, Wang RC, Wu CY, Lee SW, Lee TY. Clinicopathological characteristics in the differential diagnosis of hepatoid adenocarcinoma: a literature review. *World J Gastroenterol* 2013; **19**: 321-327 [PMID: 23372352 DOI: 10.3748/wjg.v19.i3.321]

38   **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]

39   **Fujii T**, Yoshida S, Abe K, Saito D, Yamaguchi H, Oguro Y, Maruyama K, Ochiai A, Hirota T. "Very well differentiated tubular adenocarcinoma" of the stomach: its endoscopic and histopathological characteristics. *Jpn J Clin Oncol* 1994; **24**: 128-134 [PMID: 8007422]

40   **Goseki N**, Takizawa T, Koike M. Differences in the mode of the extension of gastric cancer classified by histological type: new histological classification of gastric carcinoma. *Gut* 1992; **33**: 606-612 [PMID: 1377153]

41   **Dixon MF**, Martin IG, Sue-Ling HM, Wyatt JI, Quirke P, Johnston D. Goseki grading in gastric cancer: comparison with existing systems of grading and its reproducibility. *Histopathology* 1994; **25**: 309-316 [PMID: 7835835 DOI: 10.1111/j.1365-2559.1994.tb01348.x]

42   **Scilletta B**, Lanteri R, Rapisarda C, Greco L, Lanzafame S,

Torrisi A, Puleo S, Licata A. Gastric cancer: prognostic significance of the Goseki histological classification. *Chir Ital* 2002; **54**: 307-310 [PMID: 12192924]

43   **Songun I**, van de Velde CJ, Arends JW, Blok P, Grond AJ, Offerhaus GJ, Hermans J, van Krieken JH. Classification of gastric carcinoma using the Goseki system provides prognostic information additional to TNM staging. *Cancer* 1999; **85**: 2114-2118 [PMID: 10326687 DOI: 10.1002/(SICI)1097-0142(19990515)85]

44   **De Manzoni G**, Pedrazzani C, Di Leo A, Bonfiglio M, Zerman G, Tasselli S, Borzellino G. [Goseki classification in adenocarcinoma of the cardia]. *Minerva Chir* 2002; **57**: 449-455 [PMID: 12145574]

45   **Ventura L**, Chiominto A, Discepoli S, Ventura T, Di Giacomo C, Leocata P. Lack of prognostic significance in Goseki grading of gastric carcinoma. *J Exp Clin Cancer Res* 2002; **21**: 225-227 [PMID: 12148582]

46   **Ming SC**. Gastric carcinoma. A pathobiological classification. *Cancer* 1977; **39**: 2475-2485 [PMID: 872047 DOI: 10.1002/1097-0142(197706)39]

47   **Luebke T**, Baldus SE, Grass G, Bollschweiler E, Thiele J, Dienes HP, Hoelscher AH, Moenig SP. Histological grading in gastric cancer by Ming classification: correlation with histopathological subtypes, metastasis, and prognosis. *World J Surg* 2005; **29**: 1422-1427; discussion 1428 [PMID: 16222448 DOI: 10.1007/s00268-005-7795-z]

48   **Piard F**, Hillon P, Levillain P, Boutron MC, Milan C, Michiels R, Faivre J. [Does Ming's classification of gastric carcinomas have epidemiologic or prognostic value?]. *Ann Pathol* 1986; **6**: 329-334 [PMID: 3814273]

49   **Grundmann E**, Schlake W. Histological classification of gastric cancer from initial to advanced stages. *Pathol Res Pract* 1982; **173**: 260-274 [PMID: 6289288 DOI: 10.1016/s0344-0338(82)80088-5]

50   **Carneiro F**, Seixas M, Sobrinho-Simões M. New elements for an updated classification of the carcinomas of the stomach. *Pathol Res Pract* 1995; **191**: 571-584 [PMID: 7479380 DOI: 10.1016/s0344-0338(11)80878-2]

51   **Vauhkonen M**, Vauhkonen H, Sipponen P. Pathology and molecular biology of gastric cancer. *Best Pract Res Clin Gastroenterol* 2006; **20**: 651-674 [PMID: 16997151 DOI: 10.1016/j.bpg.2006.03.016]

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