GASTRIC CANCER: THE IMPORTANCE OF PATHOLOGY IN SURVIVAL AFTER RESECTION

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Keywords: *lymph node metastasis, gastric carcinoma, histology*

Abstract: *Background: Lymph node ratio and lymph node status are the most important prognostic factors in the patients with gastric carcinoma, and the depth of wall invasion, and the prognostic significance of the histological type is unclear. The extent of stomach resection in gastric cancer depends on tumour size, tumour location, depth of invasion, and the histological allocation to intestinal or diffuse type according to Laurén. The aim of this study was to determine the prognostic value of the intestinal and diffuse histological types of gastric carcinoma, and of the well and poorly differentiated types. Material and method: In this study, we histopathologically assessed 252 patients with gastric cancer, by well and poorly differentiated type. Well differentiated carcinoma of the stomach included tubular and papillary adenocarcinomas, poorly differentiated medullary carcinoma, and well differentiated mucinous carcinoma (WDGC). For poorly differentiated carcinoma, we included the scirrhous carcinoma, signet ring cell carcinoma, and poorly differentiated mucinous gastric carcinoma (PDGC). Results: In the patients with PDGC, the tumour was located in the middle third of the stomach, with lymph node metastasis, serosal invasion (T3-T4), and peritoneal carcinomatosis (rarely). The patients with WDGC were with the tumour located in the lower third of the stomach, small tumour size and liver metastasis. The 5-year survival rate with serosa positive tumours, but with lymph node negative, was in WDGC of 32% vs. 28% in PDGC. p=0,086. The 5-year survival rate in the patients with serosa negative, but lymph node positive cancer, was of 28% in WDSC, vs. 29% in PDGC, p=0.008. The overall 5-year survival rate for the patients with WDGC was of 29% vs. 21% in PDGC. p=0,058, situation visible in tumours ≥ 10 cm, (21% vs. 14%, p=0,017). Multivariate analysis indicated that from the pathological point of view, tumour satus, histological type (WDGC vs. PDGC) were independent prognostic factors. Conclusions. Histological type is on indicator for tumour progression in gastric carcinoma. In the management of the gastric carcinoma, the histological type of tumour, (well and poorly differentiated), the depth of wall infiltration, and the status of the lymph node (N+,N-), as well as the size of the tumour (≥5cm, ≥10cm) should be evaluated.*

Cuvinte cheie: *metastaze limfatice, carcinom gastric, histologie*

Rezumat: *Introducere: Raţia nodulilor limfatici şi starea nodulilor limfatici reprezintă cel mai important factor prognostic la pacienţii cu cancer gastric, semnificaţia prognostică a gradului de profunzime a invaziei peretelui gastric, precum şi a tipului histopatologic este neclară. Extensia rezecţiei gastrice în cancerul gastric depinde de mărimea tumorii, de topografia tumorii, de profunzimea invaziei parietale şi de încadrarea în tipul histologic intestinal sau difuz al clasificării Laurén. Scopul acestui studiu a fost de a determina valoarea prognostică al tipului histologic intestinal şi difuz în cancerul gastric, precum şi a tipurilor bine şi slab diferenţiate. Material şi metodă: În acest studiu au fost evaluaţi histopatologic 252 de pacienţi cu cancer gastric, prin încadrare în tipul bine şi slab diferenţiat. Adenocarcinomul gastric bine diferenţiat a inclus cele tubulare şi papilare, în cel slab diferenţiat a fost încadrat carcinomul medular şi carcinomul mucipar bine diferenţiat (CGBD). În categoria carcinomului slab diferenţiat a fost inclus carcinomul schiros, carcinomul în inel cu pecetă şi carcinomul mucipar slab diferenţiat.(CGSD). Rezultate: La pacienţii cu CGSD, tumorile au fost localizate în 1/3 medie a stomacului, fiind în prezenţa metastazelor din nodulii limfatici (N+), cu invazia seroasei (T3-T4) şi cu prezenţa carcinomatozei peritoneale (rar). Pacienţii cu CGBD, au prezentat tumori localizate în 1/3 inferioară a stomacului, tumorile fiind de dimensiuni mai mici, şi cu metastaze hepatice. Procentul de supravieţuire la 5 ani la pacienţii cu prezenţa invaziei seroasei, însă cu (N-),a fost de 32% în CGBD, faţă de 28% din CGSD, p=0,086. Procentul de supravieţuire la 5 ani la pacienţii fără invazia seroasei, dar cu N+, a fost de 28% în CGBD şi de 29% în cancerele slab diferenţiate, p=0,008. Supravieţuirea generală la 5 ani pentru pacienţii cu CGBD a fost de 29% faţă de 21% din CGSD, p=0,058, situaţie vizibilă în tumorile ≥ de 10 cm (21% faţă de 14%), p=0,017. Analiza multivariată indică faptul că din punct de vedere histopatologic, starea tumorii, tipul histologic (CGBD faţă de CGSD) au fost factori de prognostic independenţi. Concluzii: Tipul histologic reprezintă un indicator pentru prognosticul evoluţiei tumorii în cancerul gastric. În terapia cancerului gastric, este necesară evaluarea tipului histologic al tumorii (bine sau slab diferenţiat), al profunzimii invaziei peretelui gastric şi starea nodulilor limfatici (N+ faţă de N-).*

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Article received on 20.07.2012 and accepted for publication on 03.09.2012
ACTA MEDICA TRANSILVANICA December 2012;2(4):227-232

INTRODUCTION

The prognosis in the patients with gastric carcinoma is determined by a series of tumour and patient associated factors.(1-3) Ideally, as many prognostic factors as possible should be known before starting the therapy, so that therapy can be tailored to each patient. The gastric carcinoma can be divided into two major categories.(4)

The intestinal or differentiated type is characterized by expansive growth and liver metastasis. The diffuse or infiltrative, undifferentiated type is characterized by peritoneal metastasis (carcinomatosis) and infiltrative growth. The aggressive tumours are the poorly differentiated type tumours, and include signet ring cell carcinoma, mucinous adenocarcinoma, but some of these tumours show biological behaviour similar to the differentiated type tumours.(5,6)

Therefore, the histological classification of gastric cancer is a complex and difficult task, primarily because different histological features often coexist in the same tumour, and the morphology of gastric carcinoma shows substantial variation of histopathological differentiation.(7,8,9) Among the various classification systems, the most widely used are those proposed by Lauren and the World Health Organization (WHO).

The WHO classification is based on morphological features. Gastric carcinoma is divided into five categories: adenocarcinoma, adenosquamous cell carcinoma, squamous cell carcinoma, undifferentiated and unclassified carcinoma. Adenocarcinoma is subdivided into four types: papillary, mucinous, tubular and signet ring cell carcinoma.(11)

The histological type of resected specimens is reflected by the Laurén classification, and the extension of resection depends on tumour location, tumour size, depth of invasion and histology.(11)

In the diffuse type of the tumour, a total gastrectomy with systematic lymphadenectomy would be performed, with a possible exception for the early gastric cancer of the antrum.(13,14). In the antrum tumours of the intestinal type, especially CT_1 and CT_2, a subtotal gastrectomy with standardized lymphadenectomy may be preferred.(15)

The new staging system of the American Joint Committee on Cancer (AJCC) and International Union against Cancer (UICC) and the AJCC/UICC classification based on the number of lymph node metastasis is superior to the Japanese classification system based on the level of the lymph node metastasis.(16,17) In colorectal carcinoma, the Dukes classification is used, because it is simple and accurate in estimating prognosis.(18) The Dukes classification system could be applied to gastric carcinoma and a subdivision of Dukes C cases according to the depth of wall invasion is useful.(19,20)

PURPOSE

The aim of this study was to determine the prognostic value of the intestinal and diffuse histological types of gastric carcinoma and of the well and poorly differentiated types.

METHODS

A consecutives series of 252 patients with gastric carcinoma was studied. All patients were treated by gastrectomy and lymph node dissection between 1980 and 2005. All resected specimens were fixed in 10% formalin, included in paraffin, stained by hematoxylin and eosin, and examined routinely by the pathologists of our hospital, immediately after surgery.

From histopathology papers and surgical reports, we have the type of surgery, depth of wall infiltration, status of lymph node invasion, the neural and vascular permeation, the liver metastasis, the size and tumour location, age of patient, peritoneal carcinomatosis.

The biopsies from the gastric tumour were stained with hematoxylin-eosin (HE).

In 100 patients from 252 patients, we have the Laurén histological classification based on preoperative gastric endoscopic biopsies and comparison with resection specimen.

Both, endoscopically and surgically gained specimens were subtyped and reclassified by histopathological appearance according to the classification of Laurén.

In this study, we divided poorly differentiated adenocarcinoma, and the mucinous adenocarcinoma was divided into well and poorly differentiated type.

In the category of well differentiated gastric carcinoma, there have been identified 25 papillary adenocarcinoma, 55 well differentiated tubular adenocarcinomas, 43 moderately differentiated tubular adenocarcinomas, 15 poorly differentiated medullary adenocarcinomas and 2 mucinous adenocarcinomas, n=140.

In poorly differentiated gastric carcinoma, we have 64 poorly differentiated scirrhous adenocarcinomas, 7 mucinous adenocarcinomas, 41 signet ring cell carcinomas, n=112.

For the classification of gastric carcinoma, we use the criteria of Laurén system and the Dukes classification system. In the Dukes classification, stage A included tumours limited to the mucosa, submucosa or muscularis propria, of the wall of the stomach. Dukes B included all tumours extending into the subserosa or serosa of the gastric wall; Dukes C included all tumours with N+ (lymph node metastasis).

In this study, Dukes C cases were subdivided according to the depth of wall invasion: C_a in which tumour invasion was not beyond the muscularis propria, C_b where tumour invasion was beyond the muscularis propria. Follow-up continued until death, of far more than four years for the surviving patients. The cumulative survival rates were calculated using the Kaplan-Meier method, and the survival curves were tested by the Mantel-Cox method. Statistically significant differences were analyzed by the chi-square test for categorical variables and by the Student test for compared data for continuous variables.

The histological classification in 100 patients was compared with the WHO classification and the Laurén system.

RESULTS

Tables no. 1 and 2 show the comparison between the preoperative and postoperative classification according to Laurén. This study was accomplished on 100 cases, from all 252 cases from this study.

Table no. 1. Laurén histopathological classification (preoperative gastric biopsy and resection specimens) in 100 gastric carcinoma

	Biopsy diagnosis n=%	**Specimen diagnosis n=%**
Intestinal	48	43
Diffuse	36	34
Mixed	7	16
Unclassified	9	7

Table no. 2. Comparison between Laurén's classification based on endoscopic biopsies and surgical specimens.

	Surgical specimens				
Endoscopic biopsy	Intestinal	Diffuse	Mixed	Unclassified	Total
Intestinal	36	2	7	1	46

Diffuse	0	30	4	1	35
Mixed	2	1	5	1	9
Unclassified	5	1	2	2	10
Total	43	34	18	5	
Sensibility	88.30%	91,1	27,9%	40%	
Specificity	81,5	92,4	95%	90,7%	

In 46 intestinal type of tumours, only 36 (79%) showed a pure intestinal growth pattern in the resected tumours, 7 cases were reorganized as mixed type, 2 cases as diffuse type, and 1 as unclassifiable. Therefore, in 10 patients, an adequate histological diagnosis according to Laurén, was not established taking into account the evolution of the preoperative biopsy (table no. 2).

In endoscopic biopsy, the diffuse type was present in 35 cases, and in surgical specimen, the diagnosis was confirmed in only 30 cases. Regarding the WHO classification, 83% of cases showed concordance between the preoperative endoscopic biopsy and resection specimen. Of these, 44% were tubular adenocarcinoma, 2% mucinous carcinoma, 27% signet ring cell carcinoma (table no. 3).

Table no. 3. Comparison between WHO classification based on biopsy and surgical specimens.

	Biopsy diagnosis %	**Surgical specimen diagnosis %**
Adenocarcinoma		
Mucinous	2	1
Signet ring cell carcinoma	16	16
Mixed	1	0
Tubular papillary carcinoma	29	26
Undifferentiated carcinoma	2	7
Total	50	50

Well differentiated gastric carcinomas (WDGC) were frequently found in the lower third of the stomach (52% vs. 30%). These tumours were treated by distal gastrectomy (71% vs. 58%), having a reduced size (4,7cm vs. 6.3cm) (table no. 4).

Table no. 4. Clinicopathological characteristics

Variables		**Well differentiated n=141 %**	**Poorly differentiated n=111 %**	**P value**
Location	Upper	32 (23%)	16 (15%)	<0.01
	Middle	36 (25%)	60 (55%)	
	Lower	73 (52%)	35 (30%)	
Gastrectomy	Total	41 (29%)	46 (42%)	<0,01
	Partial	100 (71%)	65 (58%)	
Serosal invasion	Absent	81 (57%)	52 (47%)	<0,05
	Present	60 (43%)	59 (53%)	
Lymph node metastasis	Absent	57 (40%)	49 (45%)	<0,01
	Present	84 (60%)	62 (55%)	
Liver metastasis	Absent	133 (94%)	111 (100%)	<0.01
	Present	8 (6%)	0 (0%)	
Vascular permeation	Absent	7 (5%)	3 (2%)	N.S.
	Present	134 (95%)	108 (98%)	
Stage of disease	I, II	41 (29%)	17 (16%)	<0,01
	III; IV	100 (71%)	94 (84%)	
Dukes	A	13 (9%)	8 (8%)	<0,05
	B	71 (51%)	41 (37%)	
	C_a	9 (7%)	11 (10%)	
	C_b	48 (34%)	51 (45%)	

The frequency of serosal invasion (43% vs. 53,3%), N+ (40% vs. 54%), stage III and IV cases (29% vs 44%) was also different between the WDGC and PDGC. In WDGC, liver metastasis was frequent in 6%, in PDGC, the presence of peritoneal carcinomatosis was found in 6% of the patients.

The overall 5-year survival rate for the patients with WDGC was higher than for the patients with PDGC (32% vs. 28%), and the difference was significant when WDGC and PDGC cases were compared among the patients with ≥10cm tumors (22% vs.14%), p=0,017.

The 5-year survival rate for the patients with serosa positive, but (N-) tumours (Dukes B) was significantly higher in WDGC than PDGC (41% vs. 28%) p=0,086, whereas the 5-year survival rate for the patients with serosa negative but (N+), (Dukes C_a) was significantly lower in WDGC than in PDGC (28% vs. 29%). p=0,008 (table no. 4).

In cases with or without serosal invasion and N+ (lymph node metastasis), Dukes A or Dukes C_b, 5-year survival rate was not different between WDGC and PDGC (figure no. 1), when only one of the serosal invasion or (N+) was present (Dukes B or Dukes C_a), 5-year survival rate was different between the two groups (figure no. 1)

Figure no. 1. The 5-year survival rate in WDGC, PDGC.

		Absent	Present
Serosal invasion	Absent	Dukes A Well 90% / Poor 88%	Dukes C_a Well 28% / Poor 29%
	Present	Dukes B Well 41% / Poor 28%	Dukes C_b Well 25% / Porr 21%

Prognostic factors: Multivariate analysis revealed that the prognostic factors were represented by the type of gastrectomy (partial vs. total, p<0,01, stage of disease (I, II vs. III, IV, p<0.01), size of tumour (<4cm vs.≥4cm, p<0,05).

Regarding the pathological variables of the tumour, the prognostic factors were the histological type (WDGC vs. PDGC, p<0,01) versus permeation (absent vs. present, p<0,05), Dukes classification (A vs. B vs. C, p<0,05), and the stage of disease (I, II vs. III, IV, p<0,01), with the size of the tumour (<4cm vs. ≥4cm, p<0,01).

In the tumours with curative intention resection in gastric carcinoma patients, the prognostic factors were: the histological type (WDGC vs. PDGC, p<0,05), stage of disease (I, II vs. III, IV, p<0,05), with the observation that there is a difference in prognosis after curative gastric resection for carcinoma between stage III_A and III_B about 5-year survival rate, and the presence of lymph node metastasis (absent vs. present, p<0,05).

DISCUSSIONS

Laurén identified two histological types in gastric carcinoma (10), intestinal and diffuse adenocarcinoma. Histological evaluation of the intestinal types defined this type as a glandular tumour resembling to colonic carcinoma, whereas the diffuse type was defined as a tumour with solitary or small clusters of tumour cells, without forming glands.(10,21,22) A substantial conflict of opinion still exist regarding the histopathological classification of gastric carcinoma, because of difficulties caused by different growth patterns or ratter undifferentiated tumour cells.(23,24,25) The accuracy of the preoperative Lauren classification is very important for the surgical strategy in order to assess the resection extension and lymphadenectomy.(14,26)

In 1997, Ming proposed a pathological classification of gastric carcinoma based on the pattern of tumour growth and invasiveness.(27) In this classification, the expanding type cancer grows en masse and by expansion showing a sharply delicate and circumscribed periphery, whereas the infiltrative type cancer grows deeply and widely by isolated individual tumour cells.(27) In 1982, Sugano (28) showed that gastric cancer could be classified into two types, which were correlated with the histogenesis of cancer. In this classification, the differentiated type included papillary and tubular adenocarcinoma, and the undifferentiated type included poorly differentiated adenocarcinoma, signet ring cell carcinoma and mucinous carcinoma. In the publication from Lauren (10) and from Baldus (24), the poorly differentiated adenocarcinomas, solid or medullary type, are characterized by closely patched tumour cells, well defined, boundary expansive tumour growth and hematogenous metastasis to the liver.

Mucinous adenocarcinoma can also be classified into two histological types according to the degree of glandular formation of tumour cells. Well differentiated type with highly differentiated tubular or papillary epithelium living mucin pools and poorly differentiated type with signet ring cells in mucin pools.(5) In the opinion of Adachi (5), mucinous adenocarcinoma of well differentiated type is characterized clinically by the old age of the patients, localized growth of the tumour and liver metastasis. The biological behaviour of poorly differentiated medullary adenocarcinoma and mucinous adenocarcinoma of well differentiated type is similar in WDGC and these two subtypes must be excluded from PDGC.(29,30)

The preoperative Laurén classification is very important because if a carcinoma biopsy is falsely interpreted as intestinal type, the extension of resection is limited. In this context, the safety margin represents the main issue, which should be of 4-5cm for the intestinal type, and 8-10 for the diffuse tumours.(13,14,31,32). If an intestinal type carcinoma diagnosed in the biopsy shows a diffuse growth pattern in the resected specimen, a subtotal and reduced safety margin would enhance the risk of a local recurrence, resulting in a worse prognosis.(32)

Therefore, the reliability of a preoperative Laurén classification of biopsied gastric cancer is a relevant problem in surgical oncology, and the results from literature present discrepancies between pre- and postoperative classification of gastric carcinomas in about 25% the cases. Johansson (cit.29) reported disagreement between histological diagnosis based on preoperative biopsies and resections in 65 of 382 patients (17%), Davessar (33) reported an overall histological diagnosis disagreement between the pre- and postoperative classification in 28%, and Amorosi (34) in 24%.

In the several clinicopathological studies on gastric cancer, the intestinal expanding, or the differentiated type cancer were associated with old male patients, with hematogenous metastasis to the liver, (35) whereas diffuse, infiltrative, of undifferentiated cancer were correlated with the young age and female predominance, ulcerative appearance and dissemination on the peritoneum.(28,36)

In the present study, we histologically classified gastric cancer into WDGC and PDCG, and confirmed that these two types showed differences in location, size of tumour, site of metastasis and local recurrence. According to Adachi (37), the differences between the pathological and morphological aspect in the WDGC and PDGC, can be attributed not only to the biological behaviour of the tumour cells, but also to the vascular architecture of tumour stroma. Noda et al. (cit. 32) evaluated 207 patients based of the Laurén classification system and classified that the 5-year survival rate was higher in the patients with intestinal type cancer than in those with diffuse type cancer (74% vs. 60%).

Ribeiro (38) et al., indicated that the 5-year survival in intestinal type was of 44% vs. 28% in diffuse tumours. It is not clear whether the histological type is important for estimating the evolution of the patients, and in prognostic evolution, irrespective of the tumour stage, the depth of the gastric wall infiltration, and the presence or not of lymph node metastasis.(39) In the present study, the results of the multivariate analysis showed that histological type (WDGC vs. PDGC) was one of the independent prognostic factors of the gastric adenocarcinoma.

In literature and in the present study, the 5-year survival was higher in the patients with WDGC than in those with PDGC, this difference was very apparent when comparing the tumour size (≥10cm tumours), or the Dukes type B tumours, (41% vs. 28%). The prognosis in PDGC is poor, even after curative radical gastrectomy and D_2 lymphadenectomy is performed.(13) In tumours with Dukes C_a (the tumour does not

invade the serosa, but presents N+), the survival rate was lower in WDGC (28%) that in PDGC (29%).

Moriguchi (40) et al. also found that intestinal type, or differentiated gastric adenocarcinoma was associated with a poorer prognosis than those diffuse or undifferentiated cancers, when the invasion was limited to mucosa or submucosa. Thus, we can explain the presence of hemotrophes metastasis of well differentiated cancers towards the liver and the degree of stomach wall tumour penetration.(5,40) Regarding this observation, the WDGC tumours are less favourable than those with PDGC when serosal invasion is absent, but lymph node metastasis is present. Depth of tumor invasion (5) and the lymph nodes are the most important prognostic factors and they are closely correlated.(22)

CONCLUSIONS

The histological type is important for assessing the cancer progression, and for the prognosis of the patients with gastric carcinoma. In the management of gastric carcinoma, it is important to evaluate the type of the histopathological results (WDGC and PDGC), with the depth of gastric wall infiltration and status of lymph node metastasis.

The diagnosis of a diffuse type carcinoma is a reliable result of the histopathological evaluation of biopsy specimen, whereas the diagnosis of an intestinal type has to be judged critically, especially if only a small number of biopsies could by investigated, or rebiopsies for diagnosis accuracy of the preoperative Lauren's classification of gastric adenocarcinoma, because the preoperative histopathological diagnosis may influence the surgical resection (subtotal/ total gastrectomy).

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