Critical review in the surgical pathology of carcinoma of the stomach

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Abstract

Further to a thorough analysis of the management of the surgical specimen for gastric carcinomas, guidelines were defined following several recommendations including informative gross and microscopic descriptions associated to a final correct staging of the tumour, according to the TNM classification and must at least include tumour penetration, nodal or distant metastases.
The Belgian working party for GI cancer debate on these data and present a check-list that would help pathologists. (Acta gastroenterol. belg., **2004**, 67, **34-39**).

Key words : gastric cancer, staging, histology.

Introduction

Despite an overall rise in the incidence of gastrointestinal malignancies in the United States, there has been a significant decrease in the incidence of distal gastric adenocarcinoma in the past few decades (1).

Nevertheless, gastric carcinoma remains the height leading cause of cancer in the United States. Approximately 14700 patients will die of this disease. Only a small fraction of patients present with localised disease and the five-year survival rate is less than 2O% and has not changed significantly during the past 30 to 40 years.

Incidence of gastric carcinoma varies widely throughout the world, countries like Chile and Japan have the highest incidences. Studies among migrants have shown that emigrants from high-incidence countries to low-incidence countries are characterised by a decrease risk of developing gastric carcinoma, strongly suggest important role of environmental factors.

More than 95% of malignant gastric cancers are adenocarcinomas ; the remaining 5% consist in lymphomas, mesenchymatous malignant tumours and infrequently carcinoid tumours (1).

As consequence of its high variability with respect to epidemiology, genetic, morphology and biologic behaviour, many different classification systems have been proposed for the histologic classification and grading of gastric cancer. The fact that so many systems are in use simultaneously indicates that none are satisfactory. For clinical use, a classification system should ideally be easy to use, reliable, reproducible, biologically meaningful and clinically relevant.

In addition, the prognosis of surgical resected gastric carcinoma is influenced significantly by the presence of lymph node metastases and the extent of surgical resection remains area of controversy. A new system designates gastric resection as D0, D1 or D2, depending on the extent of nodal resection.

D0 refers to gastrectomy with incomplete resection of N1 nodes ; D1 and D2 resection refers with resection of nodes in and outside the perigastric region ; in addition D2 resection may also involved resections of other organs.

In Western countries D1 resection is the most common operation performed, in Japan a systematic approach has been developed to guide the extent of lymph-node dissection (1,2,3,4,6,7).

Already actually, most of western surgeons tend to use the D2 gastrectomy as a standard procedure ; despite more postoperative complications, reoperations and a greater hospital stay.

Gross and endoscopic features

On basis of clinical presentation and prognosis gastric cancer are subdivided into two major subtypes : early gastric cancer and advanced gastric cancer. In 1962 the Japanese Society of Gastroenterological Endoscopy defined early gastric cancer as a lesion confined to the gastric mucosa or submucosa, regardless of the presence of lymph node metastases.

Most of them are asymptomatic, occur about twice as frequently in males and in patients over 50 years.

They have been primarily described in Japan where they represent about 50% of gastric cancers.

There are some controversies if early gastric carcinoma and the advanced gastric carcinoma are similar tumour at different stages of development.

Some studies suggest that most early carcinomas progress with time to typical advanced type. The time interval for early gastric carcinoma to transform into advanced carcinoma is variable ranging from 6 to 21 years, the time period for transformation depends in part on the stage of the early cancer, invading of the submucosa accelerates this transformation.

Advanced gastric cancers are defined as cancers that have invaded into or beyond the muscularis propria, irrespective of whether lymph node metastases are present.

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These tumours occur in middle-aged and elderly with predilection for male patients.

In most countries except Japan, gastric carcinomas are advanced at time of presentation and only 40% of patients who undergo exploratory laparotomy may have a curative resection (1).

Surgical resection is only feasible for tumours below stage T4 and useful only in patients with stage T1-2N0M0 tumours.

Histologic and microscopic features

Histologic types of gastric carcinomas

Gastric carcinomas are also characterised by histopathologic patterns that have demonstrated values in terms of epidemiologic parameters of demographic distribution and survival. These histological types related to the Lauren's, Ming, WHO and Goseki's classification, no one is ideal, in part because many tumours are not uniform and show considerable overlap of histologic patterns.

Lauren proposed classifying gastric carcinomas into two types : intestinal and diffuse.

The most common variant in population at high risk is the so-called intestinal type, in which malignant cell form glandular structures. The overriding etiologic factors in this type are of an environmental nature and are related to diet and infection. Diffuse carcinomas are relatively more common in populations at low risk developing gastric cancer. They are defined as a poorly differentiated adenocarcinoma, often with signet-ring cell and features of Linitis Plastica. Environmental factors appear to be of less etiologic significance than genetic influences (8).

The Ming classification is based on the nature of the advancing margins of the tumour and subdivided into expending or infiltrative carcinomas. In general, Ming's expansive and infiltrative tumours correspond to Lauren's intestinal and diffuse tumour type with similar overlapping patterns (+/- 15% of the cases, who are impossible to classify) (8).

These classifications have important surgical management implications and prognostic values ; a subtotal gastrectomy might be sufficient for the Lauren intestinal type, whereas a total gastrectomy is recommended for diffuse type tumour.

Differentiating between expanding and infiltrative growth patterns has also prognostic implication ; patients with well-circumscribed tumour have survival periods almost twice as long as those with infiltrating tumour.

It is anyway essential to clearly indicate the histologic type.

The Goseki classification combines two tumour features, tubular differentiation and amount of intracytoplasmic mucus, in four categories, and seems to have some prognostic information additional to the TNM stage, in term of overall survival.

Table 1. — **WHO classification of carcinoma of the stomach**

Adenocarcinoma
Papillary adenocarcinoma
Tubular adenocarcinomma
Mucinous adernocarcinoma (> 50% mucinous)
Signet ring cell carcinoma (> 50% signet ring cells)
Adenosquamous carcinoma
Squamous carcinoma
Small cell carcinoma
Undifferentiated carcinoma
Other (specify)

This grading system identifies subgroups of patients who have a poorer prognosis than predicted by TNM staging alone (9).

Other system such as those of Mulligan has also been introduced as well as lymphocytic and eosinophilic infiltrate.

Finally, the WHO histologic classification is the simplest and most reproducible, she is the most widely used but it is not proven if the histological grading affect prognosis of gastric cancer (table 1).

Degree of tumour differentiation

Gastric carcinomas are also subdivided into three types based on the degree of glandular formation and cytological abnormalities (table 2).

Tubular carcinomas are assigned Grade 1, signet-ring cell carcinomas are assigned Grade 3 and small cell carcinomas and undifferentiated carcinomas as Grade 4.

The rare squamous cell carcinomas has his own classification agree to WHO International Histological Classification of Tumour.

It is still unclear whether the variations in behaviour of gastric tumour are due to stage and grade independently.

Already undifferentiated tumours are more likely associated with more advanced stage and poor outcome (10,11).

Staging

Nevertheless, stage classification remains the most important prospective prognosis as well as for precise analysis of the results of treatment.

The overall prognosis of gastric cancer varies widely from country to country.

The best results appear in Japan with survival rate around 70%, in Europe this rate falls to 35% and in the USA to 20%. These differences result in more frequent diagnosis of early gastric cancer and more aggressive surgical approaches in Japan.

The prognosis of early gastric cancer is excellent with a 5-year survival rate about 85 to 95% both in Western countries and Japan.

The prognosis of advanced gastric cancer is worldwide poor with an overall 5-year survival rate about 10%.

Table 2. — **Histologic grade**

For adenocarcinomas, a histologic grade is based on the extent of glandular differentiation is suggested as shown below	
Grade X	Grade cannot be assessed
Grade 1	Well differentiated (> 95% of tumour composed of glands)
Grade 2	Moderately differentiated (50%-95% of tumour composed of glands)
Grade 3	Poorly differentiated (5-49% of tumour composed of glands)
Grade 4	Undifferentiated (< 5% of tumour composed of glands)

TNM classification of malignant tumours, sixth edition.

The prognosis of gastric cancer has been widely surveyed in Japan where the Japanese Research Society for Gastric Cancer (JRSGC) has conducted this survey and their General Rules for Gastric Study (GRGCS) has been extensively used to classify the stages of gastric cancer (12).

However the GRGCS was modified in 1985 to accommodate contemporary therapeutic approaches. In 1987 the Union International contre le cancer (UICC) proposed a new stage classification, to accommodate the development in surgical procedures according to the surveys in Japan and the USA.

In the autor's opinion, the TNM classification (UICC) is the most valuable classification system, with prognostic value for survival, and the most commonly used system.

Tumour penetration, nodal metastases, location in the stomach, multicentricity, and distant metastases are the most important guides to prognosis.

Curative resection, depth of invasion, and lymph node metastases are the most significant prognostic factors, and the presence of lymph node metastases influences significantly the prognosis (12).

The lymph node status, expressed in terms of the pN categories proposed by the TNM classification or the n categories of the Japanese Classification (JCGC), have been essential components of the widely used stage classification for gastric carcinoma.

In the most recent edition of the TNM classification (fifth edition), however, the anatomic extent of lymph node metastasis was replaced by the number of metastatic lymph nodes, another known prognostic factor to define new pN categories.

Some studies compared these new TNM and the JCGC modes of lymph node status assessment, nevertheless direct comparison was sometimes difficult according to the different lymph node dissection procedure.

These studies reveal that the new TNM classification, in subjects with the same n number by the Japanese classification indicates that the prognosis of gastric cancer is more closely associated with the number of metastatic regional nodes than with the anatomical position of lymph node metastasis.

It has however demonstrated that the TNM system is less accurate if less than the minimum number of 15 nodes is available (13,14,15,16).

There was no significant difference between the prognosis of patients with M1 and pN3 disease. However, there were significant differences in the long-term outcome related to the number of involved lymph nodes, suggesting that the pN category can be extended to include patients with M1 lesions.

A numeric staging system is easier than a sophisticated localization of lymph nodes around the stomach and reduces the problems involved in the pathologic assessment of lymph node metastasis. One of the disadvantages is the possibility of increase in the number of unclassified patients. Some studies report 13 to 76% patients with less than 15 lymph nodes examined. These unclassified patients result in part from the difference in surgical procedure and in part in the effort required by the pathologist to retrieve and section the required number of lymph nodes (14,17).

According the sixth edition of the TNM classification, a pN0 determination may be assessed even though fewer than the recommended number of nodes have been analysed. However the Belgian Working group advises to keep on using the previous TNM classification on assessing lymph nodes and to use pNx when insufficient lymph nodes have been assessed (< 15).

Practice

Following some guidelines according the New International Union Against Cancer TNM staging and the New Joint Committee on Cancer.

The sixth edition of the TNM classification is now available and mentions some staging modification.

A final standard report should mention a clear patient identification, including name, age and gender associated to some relevant clinical information, for example previous diagnoses and treatment for gastric cancer, previous Billroth procedure, macroscopic and microscopic examination and finally, a correct staging of the tumour, according the TNM classification.

Macroscopic examination

Macroscopic examination must describe if the specimen is fixed or unfixed, open or unopened, the number of pieces, dimensions and orientation of the specimen, the length of attached oesophagus and/or duodenum and the type of surgical resection.

Tumoral location, configuration and dimensions (three dimensions) must be noted, even when tumour configuration and size have been shown adverse prognostic value in many studies, the prognostic value is controversial since a large number of smaller studies have failed to demonstrate independent prognostic significance for these pathologic features (18).

For tumours involving the gastroesophageal junction, specific observations should be recorded in an attempt to

establish the exact site of origin of the tumour. The gastroesophageal junction is defined as the junction of the tubular oesophagus and the stomach irrespective of the type of epithelial lining of the oesophagus. The pathologist should record the proportion of tumour mass located in the oesophagus and stomach, the greatest dimensions of oesophageal and gastric portion of the tumour, and, the anatomic location of the centre of the tumour.

If more than 50% of the tumour involves the esophagus, the tumour is classified as esophageal, if more than 50% involves the stomach, she is classified as gastric and if she is equally located above and below the gastro-oesophageal junction, she is designated as a junction tumour.

Moreover, squamous, small cell and undifferentiated types are classified as oesophageal tumour, whereas adenocarcinomas and signet ring cell carcinomas are classified as gastric tumour (19).

Most important, is to notice the estimated depth of invasion and the distance from margin : proximal, distal and radial, represented by the nonperitoneal soft tissue margin closest to the deepest tumour penetration. In the stomach, the mesenteric margin is the only radial margin. It also may be helpful to mark the margins closest to the tumour with ink and to designate them in the macroscopic description.

Lesions in non-cancerous stomach must also be mentioned, like the regional lymph nodes, including, perigastric nodes along the lesser and greater curvature and the nodes located along the left gastric, common hepatic, hepatoduodenal, splenic and celiac arteries, and the metastasis to other organ(s) or structure(s).

Involvement of other intra-abdominal lymph nodes, such as hepatoduodenal, retropancreatic, mesenteric, and para-aortic are classified as distant metastasis.

Tissue submitted for microscopic evaluation

Tissue submitted for microscopic evaluation must a least include, the point of deepest tumoural penetration, interface tumour- adjacent stomach, visceral serosa overlaying tumour, the margins, all the lymph nodes and the other lesions seen in the stomach or other tissue and organs.

It is recommended to keep at least 3 tumoral fragments.

Frozen section tissue fragments will be useful for special studies like DNA or cytogenetic analysis.

Microscopic evaluation

The report must mention the tumoral histologic type, according the World Health Organisation but other classifications such as the Lauren classification may be used in addition (18). The term “carcinoma, NOS (not otherwise specified) is not part of the World Health Organisation classification.

It is to note that some pathologists classify *in situ* carcinoma under the term “severe or high-grade, dysplasia”.

The histologic grade, based on the extent of glandular differentiation must also be mentioned, as the extent of invasion, according the sixth edition of the TNM classification (10,11).

Some staging modifications involve the separation of T2 into T2a when tumour invades muscularis propria and T2b when tumour invades subserosa.

This separation is justified because post-surgical survival following resection for cure has been shown to be significantly different with 2 and 5-year survival rate of 74 and 62% for T2a and respectively 57 and 40% for T2b (19).

In addition, a tumour may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments or into the greater or lesser omentum without perforation of the visceral peritonuem covering these structures and will be classified as T2. If there is perforation of the visceral peritoneum covering the gastric ligaments or omenta, the tumour is classified as T3 (21,22).

The report will also mention the extension into oesophagus or/and duodenum.

Moreover the intramural extension into the duodenum or oesophagus is classified by the depth of greatest invasion in any of these sites, including the stomach (21,22).

Blood, lymphatic and perineural invasion may also be related, but

actually, if both have been shown to be adverse prognostic factors, however, their microscopic presence does not qualify as local extension as defined by the T classification (18,19,20,21,22).

Additional pathologic findings, including, chronic gastritis, intestinal metaplasia, dysplasia, atrophy or Helicobacter pylori, if present must also be specified.

Finally, margins, number of regional lymph nodes, number of metastatic regional lymph nodes and distant metastasis must be mentioned (25).

We purpose a standard report including the most relevant macroscopic and microscopic data associated to a final staging to uniform the results and use them for more accurate comparison between treatments and follow up in different centres (Cf. annexe : checklist gastric cancer, pathological report).

Perspective

However controversy continues about the surgical and adjuvant treatment for gastric cancer, the aim of some recent studies is to develop a practical scoring system that is more detailed and reliable than staging in predicting prognosis for gastric cancer.

Some studies reveal that inclusion of more variables combining gross and microscopic features ; type of resection, and sometimes clinical features seems to be superior to standard staging.

These are some examples of the clinical use of these Prognostic Score for Gastric Cancer, but they have to be

evaluated in further prospective randomised studies and need further validation in different patient populations.

These Prognostic Score for Gastric Cancer will maybe help end the confusion of staging systems for gastric cancer (23).

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CHECKLIST GASTRIC CANCER

Pathological report

Patient's name :. …… Registration number : …….

Given name: …… Hospital/laboratory: ……..

Date of birth: ……./……./……. Preoperative treatment: ……..

TYPE OF INTERVENTION

❑ Total gastrectomy ❑ Polar superior gastrectomy
❑ Polar inferior gastrectomy

SURGICAL RESECTION

Proximal and distal longitudinal margins
❑ invaded ❑ free

Circumferential margin: ……mm remote from tumour

MACROSCOPIC EXAMINATION

❑ Specimen non fixed ❑ fixed
❑ Non open specimen ❑ open

-Tumour location:
❑ Cardia ❑ Fundus ❑ Corporeal ❑ Antrum
❑ esogastric junction ❑ pylor
❑ Lesser curvature ❑ greater curvature
❑ Antérieure wall ❑ Postérieure wall
❑ Multifocal ❑ Diffuse

- If 2nd location, please use separate sheet

Lengt of the lesser curvature : ……cm
Lengt of the greater curvature :… ……...cm
Lengt of the esophagus portion :…….. ……..cm
Lengt of the duodenal portion :….. ……cm
Tumour size (maximum diameter) : ..……cm
Distance tumour-resection margins :
proximal :……. cm distal : ……cm
Or between tumour and closest resection margin:…….cm
Distance between tumour and circumferential margin :……..cm

- Features :

❑ Exophytic ❑ protruded ❑ elevated
❑ Flat ❑ Diffuse flat (Linite plastique)
❑ Ulcerated ❑ Annular ❑ depressed ❑ excaveted

-Tumour perforation:……..
- Associated lesions : ❑ Ulceration
❑ Polyp(s)
❑ Loss of gastric folds
❑ Barrett

EXTENSION

- Number of lymph nodes examined :……..
- Number of invade lymph nodes :……..

- Métastases :
❑ Distant lymph nodes ❑ viscéral ❑ no précisable

Conclusions

Stage pTNM

❑ Tis ❑ T1 ❑ T2a ❑ T2b ❑ T3 ❑ T4
❑ Nx ❑ N1 ❑ N2 ❑ N3
❑ Mx ❑ M0 ❑ M1

Signature :

……

Date : ……

N.B Samples of tumour frozen :

HISTOLOGIC EXAMINATION

- Histologic type : WHO classification

❑ Adénocarcinoma ❑ papillary adenocarcinoma
❑ Tubular adenocarcinoma ❑ mucinous adenocarcinoma (colloïd)
❑ Signet ring cell carcinoma
❑ Adenosquamous carcinoma ❑ squamous cell carcinoma
❑ Small cell carcinoma ❑ undifferentiated carcinoma
❑ Other (specify)……

-Histologic grade:
❑x : Grade cannot be assessed
❑1 : Well differentiated
❑2 : Moderately differentiated
❑3 : Poorly differentiated
❑4 : Undifferentiated

- Depth of invasion :
❑ Carcinoma in situ : intraepithelial tumour without invasion of the lamina propria
❑ Tumour invades lamina propria (mucosa)
❑ Tumour invades submucosa
❑ Tumour invades muscularis propria
❑ Tumour invades subserosa
❑ Tumour penetrates serosa (visceral peritoneum) without invasion of adjacent structures
❑ Tumour directly invades adjacent structures
❑ Esophagus intramural extention : ……
❑ Duodenal intramural extention : ……..