UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA
FACULTY OF GENERAL MEDICINE

CONTRIBUTIONS TO
THE IMAGING AND IMMUNOHISTOCHEMISTRY STUDY
OF
GASTRIC CARCINOMA

ABSTRACT OF
PHD THESIS

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INTRODUCTION
The world's annual deaths from cancer is 12% of all deaths and in industrialized countries the percentage rises to 25%. Although lung and breast cancers are most common in men, respectively, in women, cancers of the gastrointestinal tract, including those of the oesophagus, stomach, colon, liver and pancreas determine the occurrence of about 3 million new cases and over 2 million deaths annually, making them the most common cancers worldwide [Carl-McGrath et al. 2007, Hamilton and Aaltonen 2000]. Gastric cancer staging is essential to identify patients who may benefit from curative treatment and those who can benefit only palliative treatment, so any diagnostic method that helps in assessing tumour invasion in the depth of gastric mucosa is, in turn, essential [Puli et al. 2008].

CURRENT KNOWLEDGE
Gastric carcinogenesis is the progressive pathological process by which normal gastric mucosa undergoes multiple transformations that may lead to cancer. The process is under the influence of numerous risk factors that act early or late [Correa 1992, Correa 2004]. Risk factors can be grouped into genetic and family factors, environmental factors, precursor lesions and precancerous lesions [Christian et al. 1999]. Genetic and familial factors are family history of gastric cancer, genetic predisposition, blood group A, nonpolipos hereditary colon cancer syndrome. Environmental factors involved in the development of the carcinogenic process are the low economic status and poverty, hipersodic diet rich in tinned and smoked foods, lack of refrigeration, diet low in protective factors, antioxidants, dietary fibres [Cocco and colab.1996]. Precursor lesions are histological changes developed at the level of gastric mucosa that are considered to present a risk of developing gastric adenocarcinoma, which are represented by chronic atrophic gastritis with intestinal metaplasia, Helicobacter pylori chronic gastritis, gastric polyposis, pernicious anaemia, Menetrier hyperplastic gastritis, stomach resected for other disease, Barrett oesophagus, stomach acid reduction to achlorhydria [Antonioli 1994; Filipe 1994; Sipponen and Marshall 2000]. The precancerous lesions are tissue changes that may progress to malignancy and are involved in gastric carcinogenesis [De la Riva et al. 2004]. Imaging explorations are essential in evaluating gastric cancer both in early stages and in advanced ones; they contribute to the diagnosis, staging and prognosis as well as to specifying therapeutic behaviour and lesion topography. In this respect X-ray with contrast, upper gastrointestinal endoscopy, EUS, magnification endoscopy, endoscopic chromoscopy, CT are used. Stomach radiography using barium sulphate as a contrast substance is, currently, the most common method of diagnosis of gastric cancer, which highlights the niche-gap- infiltration triad. Correct examination needs proper compression,
emphasizing mucosal relief, the technique of double contrast examination of the filler [Maruyama and Baha 1994].
Double contrast technique allows to obtain good-resolution radiographic images and the examination of stomach areas that are harder to reveal-great tuberosity, card, front and rear subtuberositary faces, the method is carried out in four steps represented by a mucosography in thin layer under compression, a mucosography with hypotonia and air distension, a parietography of repletion and insufflation [Levine et al. 1988].
Upper gastrointestinal endoscopy is the most important exploration in the diagnosis of early gastric cancer. This method has the following advantages: it visualises early gastric cancer, allows sampling gastric mucosa biopsies, to determine whether malignant or benign gastric ulceration and allows the diagnosis and monitoring of the dynamics of precancerous stages: atrophic gastritis with intestinal metaplasia, pernicious anaemia, gastric polyps, stomach resected, gastric dysplasia [Lambert 2002, Graham and colab. 2008, Ciurea et al. 2009].
EUS combines upper gastrointestinal endoscopy with ultrasound by attaching the tip of an ultrasound transducer with variable frequency of 5-20 MHz, a method that allows visualization of the gastric wall and adjacent structures. Gastric endoscopy with magnification associates classic endoscopic examination with a process of magnification of up to 150 times by using a complex optical system that behaves like a high resolution microscope.
When examined by computer tomography (CT), gastric wall is usually presented as a structure in three layers 1 cm thick, composed of: the inner layer with high attenuation, represented by the mucous membrane, the intermediate layer with low attenuation, representing submucosa and outer layer with high attenuation, formed of muscle and serous components [Hori et al. 1992; Megibow 1994].

Precise and complete pathological examination is the basis for positive and differential diagnosis of gastric cancer and directs the therapeutic approach. The stomach develops many different types of gastric cancer. Adenocarcinoma originating in glandular cells, the most common form of cancer of the digestive tract, represents 90-95% of all malignant tumours, the rest up to 5% are gastrointestinal stromal tumours, squamous cell carcinomas, gastric lymphomas and carcinoid. In order to classify gastric cancer multiple systems are used (Borrmann, Lauren, WHO, Goseki) but none is entirely satisfactory [Shang and Peña, 2005].
Early gastric cancer (CGP) is a carcinoma limited to mucosa or mucosa and submucosa regardless of lymph node status.
Gastric cancer staging in the TNM system is achieved through three parameters and is based on clinical examination, imaging and / or surgical exploration [Hermanek et al. 1999] T parameter: defines the depth of primary tumour invasion, the parameter N: defines the effect on regional lymph and parameter M: defines distant metastases. Topography of the primary tumour is coded by the terms A, M, C respectively corresponding to antrum, stomach and central...
Immunohistochemical techniques complete the histo-pathological investigation especially in affirming the positive diagnosis, differentiation of gastric cancer from metastases arising from adenocarcinoma and prognosis evaluation [Lee et al. 2003].

PERSONAL CONTRIBUTION

STUDY OBJECTIVES

Gastric cancer, a major health problem worldwide, is most often diagnosed late and associated with high mortality. The topic presented is of great topical interest, both due to the need to identify both an algorithm of diagnostic and prognostic factors necessary to specify the most effective treatment strategies. Research is based on comprehensive evaluation of a significant group of 119 patients, and the goals to be pursued during the study were:
- imaging evaluation of patients with gastric cancer through upper gastrointestinal endoscopy, EUS and computer tomography
- anatomopathological/imunohistochemical exploration and evaluation of patients with gastric cancer: assessment with conventional staining techniques, secretory profile evaluation using special staining techniques and immunohistochemical investigation of the potential for proliferation and secretory profile.
- Assessment of the survival of patients with gastric cancer
- Establishment of correlations between different methods of morphological investigation proposed and the survival of patients with gastric cancer.

MATERIAL AND METHODS

Criteria for inclusion of patients in the study group and subgroups were endoscopic imaging and biopsy accompanied by the histopathological diagnosis of gastric carcinoma
Exclusion criteria for patients from the group and subgroups of the study were: patient refusal to undergo investigation and contraindication to implementing the various stages of the investigation algorithm
The study was prospective including selected cases of patients with gastric carcinoma diagnosed in the clinic in the period 2003 - 2006 and was divided into four chapters: general clinical research context, imaging study, morphological study and the study of correlations between methods of morphological investigation.

Preliminary data on the morphological and clinical parameters measured were entered into computer database tables in the Microsoft Access module of the software package Microsoft Office XP Professional.
Upper gastrointestinal endoscopy was performed with endoscopes with front view.
Upper gastrointestinal EUS was performed with linear EUS attached to the video-endoscopy lines.
Computer tomography examination was not performed as a routine in all patients, but in a limited number of cases, carefully selected, aiming at a correct
staging of gastric cancer and correlation of computed tomography data with the results of upper gastrointestinal endoscopy, endoscopic ultrasonography, histological and immunohistochemical investigation.

In this study the presence of Helicobacter pylori infection was monitored in all patients and so was its correlation with the morphological changes revealed by macroscopic and imaging investigation. To assess the microscopic parameters two types of gastric tissue were used. In the endoscopic examination 4-8 tumour fragments were taken in each case

Tumour fragments were subjected to conventional histological processing techniques after which serial sections were made from each block. The first three sections were stained using conventional staining methods. Conventional stains used were hematoxylin-eosin staining, Alcian blue staining and staining with Mucicarmin.

The next two sections were used for immunohistochemical labelling. For immunohistochemical labelling IHC method was used indirect three-stage avidin-biotin-peroxidase (ABC) following a protocol used in the Laboratory of Pathology of the Institute of Pathology, University of Turin.

GENERAL CLINICAL DATA

Gastric carcinomas studied were far more common in men, and their number is almost two times higher than that of women - a ratio M / F of 1

Patients included in the study group were mostly adults and mostly elderly. Of the 119 cases included in the study only 14 were alive at its conclusion at the end of 2008

Comparison between periods by age distribution of women and men in the study shows that while, in men, the presence of cancer is almost equal to the elderly and mature adult, in women, almost three quarters of cases were aged over 65 years.

The comparison between the distribution of origin in women and men in the study shows a significant aspect, namely that for men the number of patients coming from rural areas is almost equal to that of those from urban areas, whereas for women, the number of those from rural areas is almost two times larger than those from urban areas. Analysis of the correlation between survival and the environment of origin of patients showed that in the study group, patients from rural areas had a higher survival rate than those in urban areas. Analysis of the correlation between survival and the presence of H. pylori infection has shown a somewhat paradoxical aspect, namely a higher average survival in patients carrying H. pylori infection compared to those without.
**Imaging studies**

Endoscopic study. Apart from the fact that it represented the major criterion for inclusion of cases in the study group, endoscopic examination allowed assessment of two important morphological features, namely the macroscopic appearance of gastric mucosal lesions and their location.

All gastric lesions examined, with one exception, were classified in one of four main macroscopic aspects of advanced forms of gastric carcinoma. The most frequently observed macroscopic aspect in the patients investigated was the exophytic formation, protruding from the gastric mucosal surface, with an irregular appearance, like cauliflower which presented either a central ulcer or multiple ulcers of different depths to the external surface, an aspect encountered in two thirds of cases at the macroscopic investigation. They followed with a frequency five and six times smaller, plant and infiltrative types.

EUS study. EUS examination allowed assessment of the three important morphological features that are part of the staging of malignant neoplastic processes, namely the degree of gastric wall invasion (T), regional lymph nodes affected (N) and the remote invasion (M).

Almost two thirds of the cases investigated EUS had issues falling in phase III of the invasion of the staging system "T", in other words, tumours that have invaded the gastric wall in its entirety, without exceeding the serous peritoneal area.

Evaluation of gastric satellite node groups showed that for over one third of cases between 1 and 6 lymph perigastric nodes were recorded in each case located at under 3 cm from the parietal tumour formation. and have completed at least one of the criteria for malignancy.

Computed tomography study

For CT investigation, nearly two thirds of the cases met the inclusion criteria for imaging tumour proliferation of T4 invasion, i.e. the tumour had spread beyond the stomach wall, in the tissue structures in the immediate vicinity.

**MORPHOPATHOLOGICAL STUDY**

Macroscopic evaluation

Location. Most tumours developed on a stomach that has not previously had any surgery. The location of tumours operated in various segments of the stomach corresponds to the distribution identified in the entire group of patients.

The degree of extension in the stomach.

The percentage of tumours extended beyond the boundaries of a single segment was lower in the group of operated tumours than in the entire group (19% vs. 28%).

Macroscopic appearance. In the group of operated tumours the distribution of various macroscopic aspects was more uniform and frequency hierarchy was different than in the whole group. Thus, in this group were predominantly infiltrative tumours, but they represented only one third of cases, followed by
vegetative and ulcerated tumours, ulcerated tumours and, finally, vegetative tumours.

Microscopic aspects

Microscopic aspects of endoscopic biopsy fragments. Starting again from the small size and superficial location of the tissue taken it was considered that the most appropriate system for evaluating the microscopic appearance of tumours for gastric endoscopic biopsy samples is the classification system based on morphological appearance required by the World Health Organization (WHO).

According to this classification system, three-quarters of the microscopic aspects of the biopsy fragment patterns were tubular adenocarcinoma. The second system of classification system used was Lauren (1965), according to which less than half of the tumours were classified as "diffuse" while the "intestine" type was identified in only 35% of cases. The third system of classification used was Goseki (1992), where the majority of tumours studied - 85% - were composed of tumour cells with secretory properties.

Correlations between histopathological classifications.

The correlation between the WHO and Lauren classifications showed a nearly complete overlap between the types of glandular differentiation of the WHO classification and the "intestine" type of Lauren classification as well as between types with weak or no differentiation in the WHO classification and the types of "diffuse", "mixed" and intermediate in Lauren classification. Therefore, considering the extent of agreement between the two assessment systems but taking into account the degree of simplicity and especially the correlation with the epidemiological factor and the clinical one in Lauren classification, it would be preferable for the practitioners to renounce to the morphological classification recommended by WHO in favour of the Lauren classification system. Correlation of the WHO classification system and Goseki system was difficult to assess given that 84% of the tumours operated revealed in immunomarking the presence of different types of mucin in the cytoplasm of tumour cells, whether drafted or not glandular lumen. Due to the large number of tumours that demonstrated a secretory feature, as in the case of the correlation with the WHO classification, a correlation between Lauren and Goseki classifications proposed could not be established.

The evaluation of the invasion. Examination of surgical excision parts allows accurate assessment of the degree of extension of tumour proliferation in gastric wall depth... Assessment of the severity of gastric tumour is conditioned not only by the depth to which it penetrates the gastric wall layers, but also the interception of structure components of the gastric wall. Parietal structures that were most frequently invaded were blood vessels, a third of cases operated, whereas, perineural invasion was present only in five patients, meaning almost 20% of cases. Another element supporting tumour aggressiveness was the extension of malignant proliferation, by lymph to regional lymph nodes. Sometimes the tumour cell phenotype was aggressive enough to destroy nodal capsule and...
expand tumour invasion front to conjunctive peri nodal tissue. This extension may account for the increased size of lymph nodes affected, and this phenomenon can be observed both on EUS or CT images and directly intraoperative.

The degree of aggressiveness. There is still no standardized scale for assessment of Ki67 Index. In our study, we conducted an objective analysis of the percentage of tumour cells in active phases of the cell cycle using a dedicated program of microscopic morphometry which allowed us to calculate precisely the index of cell proliferation. For more nuanced layering of cases we fixed the jump interval from one score to another as "10%". Ki67 index values calculated at the 26 operated cases were recorded in a range between 6% and 47% with an average of 20% +/- 10%.

P53 index. As for investigating nuclear antigen Ki67, p53 protein expression analysis was performed using the same dedicated microscopic morphometry program that has allowed us to calculate precisely the p53 index. p53 index values calculated were enrolled in a range between 11% and 56% with an average of 27% +/- 14%. Most carcinomas p53 + were tumour-infiltrating, with type pathologic diffuse mixed or intermediate (Unclassifiable) and all p53 + tumors were of secretor phenotype.

On the other hand, most p53 + tumors had a high degree of local invasion, more than half of them exceeding peritoneal serous and metastases in regional lymph.

Histopathological diagnosis on gastric biopsy samples is still one of guidance, but useful for patients for whom it establishes the impossibility to use surgery as a treatment option.

Histopathological examination of endoscopic biopsy sample staining battery consisting of two special stains for mucin and the two immunomarkers revealed in all cases, the presence of a secretion produced in the cytoplasm of tumor cells, the major criterion for diagnosing of the presence of intracellular secretion being positivity for at least one of the immunohistochemical markers employed.

CORRELATIONS BETWEEN METHODS OF MORPHOLOGICAL INVESTIGATION

Comparisons between macroscopic endoscopic and pathological evaluations

Assessment of tumor location

Overall, the degree of consistency in the assessment of tumor location is significant - 91.7% - but the percentage of almost 42% relative consistency urges to a more thorough endoscopic evaluation of the location where the tumors are of sensible dimensions.

Evaluation of macroscopic appearance. Overall, the degree of consistency in the assessment of macroscopic appearance of tumor proliferation was only 73.1%. The relatively high degree of mismatch of approximately 27% consisting of mislabeling forms showing infiltrative lesions and ulcers as large vegetative
ulceration, should lead to a careful evaluation of these infiltrative forms as it
would seem that they have a better survival rate than those vegetative and
ulcerated.

Computed tomography evaluation vs. histopathological evaluation of the
surgical samples. Overall, as for the comparison of wall invasion with CT and
endoscopic ultrasonography, it is noted that in a significant number of cases, CT
has tended to overestimate the degree of invasion of the tumor process in the
depth of the gastric wall compared with histopathological investigation, which
demonstrates that histopathological examination has a higher degree of accuracy
than CT in the evaluation of gastric wall invasion by tumor formation
Overall, it appears that there was a significant degree of concordance between
the two methods in assessing the morphological evaluation of lymph node
invasion by primitive malignant proliferation and when the results were
discordant, it was usually due to overstatement of regional lymph invasion by
CT.
Overall, CT is very useful investigation to detect any secondary tumors, its
reliability being completed by histopathological confirmation on the fragments
of tissue taken from areas indicated by imaging investigation.

Global assessment of tumor invasion by establishing aggregation stages of
development from scores obtained at the three evaluation criteria (T, N and M)
was consistent between the two ways of morphological investigation in just
46.7% of the cases studied.
Overall, in a significant percentage of cases the CT scan overestimated the stage
of the tumors studied compared with the histopathological findings,
overvaluation being primarily due to excessive inaccurate assessment of gastric
wall invasion and, to a lesser extent, to an inaccurate appreciation of a more
extensive lymph node invasion.

EUS. Evaluation vs. histopathological evaluation of the samples
One can finally say that EUS examination has higher fidelity than CT in
assessing the degree of gastric wall invasion, but its fidelity is fairly limited by
the technical performance of the investigation equipment and that both
techniques of imaging investigation may, in certain circumstances, overstate the
degree of invasion of regional lymph nodes compared with the histopathological
examination.
CONCLUSIONS

Analysis of clinical, morphological and biological parameters evaluation, both individually in the three studies - clinical, imaging and pathological, and comparatively, led to the following conclusions:

1. Developed malignant proliferation of gastric mucosal epithelium associated with H. pylori infection mainly affected the men, without regard to age or socio-economic environment, while elderly women with low socioeconomic status were usually affected. H. pylori infection is a risk factor for gastric cancer, but does not influence prognosis.

2. Endoscopic examination combined with histological examination of endoscopically obtained gastric biopsy specimens have allowed the establishment of a morphological profile of the group of tumors included in the study:
   - the tumors studied were usually vegetative and ulcerated;
   - tumor location was mostly in the antro-pyloric region and adjacent regions - the lesser curvature and anterior and posterior faces of the stomach - where most extensive forms stuck;
   - the tumors located at the level of the great curve were only of exophyte type, with or without ulceration;
   - The architectural pattern of the tumor was mostly hollow, with a predominance of poorly and moderately differentiated forms

3. Gastric cancers studied were generally aggressive, which is supported both by the reduced survival and the indices of Ki67 and p53 positivity in all, respectively in 30% of cases subjected to surgery, these parameters being negative prognostic factors.

4. The Secretor nature of the tumor cells is indicated by the immunohistochemical markers MUC1 and MUC2 in the surgery samples, the evaluation of endoscopic biopsy material, often resulting in false negative results.

5. Most patients in the study were diagnosed in advanced stages of development and died within 48 months.

6. Tumors developed in adults and ulcerated forms had a better survival rate at 12 and 24 months compared with tumors in elderly patients, and other macroscopic forms respectively.

7. Cardial located tumors had a lower survival rate than noncardial ones both at 12 months and 24 months.

8. Histopathological examination performed on the gastric mucosa obtained by endoscopic biopsy has an indicative value since many of the malignant gastric epithelial proliferations develop mainly in the depth of gastric wall and a significant percentage of them contain several architectural patterns in different areas of the tumor, which determines limitations to the definition of the real
morphological profile and specification of the degree of tumor invasion of gastric wall.

9. The histopathological examination of the surgery sample is the most accurate method of assessing gastric wall invasion, followed in descending order of accuracy by EUS investigation – which has a tendency to underestimate and computer tomography - which has a tendency to overestimate the state of T.  
10. The histopathological examination provides the most accurate assessment of lymph perigastric invasion, EUS and computer-tomography techniques are equal, but with a tendency to overestimate the damage to ganglion.  
11. The computer tomography investigation is the examination of choice for the assessment of the tumor process remote dissemination 
12. The correct evaluation of gastric carcinomas involves:  
   - Establishing the diagnosis by endoscopic examination combined with histological examination of samples of gastric mucosa obtained by biopsy  
   - TNM staging system tumor by computer tomography and EUS.  
13. Diagnosis of advanced gastric cancer, the existence of very aggressive forms and infaust prognosis, revealed in this study is a warning on the moment of detection and the necessity for early disease diagnosis by developing an effective screening program. 
14. Improvements in imaging techniques, in particular, the increased ability to get a consistent fragment of the gastric wall and of the gastric mucosa by endoscopic biopsy, or endoscopic puncture allow a better preliminary assessment of gastric cancer. 
15. Difficulties in assessing the patient with gastric cancer can be reduced in the context of effective collaboration within a multidisciplinary team consisting of the internist / gastroenterologist, the radiologist and the pathologist, and by applying a clear and unbiased investigation algorithm.
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1996-1997-General Medicine Physician Urban Dispensary Caracal Olt
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1984-1990-Faculty of Medicine, Craiova
1978-1982-“Ioniă Asan” Highschool, Caracal, Olt
1970-1978-Primary School No.2, Caracal

3. Competences, member in societies, courses, congresses, papers
Competences:
- General Ultrasound

Member in societies:
- Romanian Society of Internal Medicine
- Romanian Society of Ultrasonography in Medicine and Biology

Courses:
- 2 long term courses of General Ultrasound
- 1 long term course-„Emergencies in General Medicine”
- 5 short term courses

Congresses:
- Congresses and Conferences organized by National Societies: 25 participations
- Other Medical Symposiums: 17 participations
Papers:
- Books: 2-(Principal author 1, Contributor 1)
- Extensive papers: First author-2
- Summary papers, posters: First author-8, Second author-6, Joint author-13