

THE ROLE OF PREOPERATIVE STAGING OF GASTRIC CANCER IN PLANNING RADICAL SURGICAL TREATMENT

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Summary. *Although gastric cancer incidence is gradually decreasing, it is still the most common cause of death of all digestive system cancers. The aim of preoperative staging is to estimate the possibility of complete resectability of the tumor and the metastatic involvement of lymph nodes. Only if preoperative staging is indicative of R0, the prognosis of the disease can be ameliorated using surgical procedures. This study is based on the analysis of the clinical data of 65 gastric cancer patients (35 males, 30 females, aged 37-83), treated at Surgical Clinic, Niš Clinical Center, during the period 2000-2001, who underwent targeted preoperative diagnostic actions in order for preoperative and intra-operative staging to be determined. Clinical, morphological (macroscopic, microscopic, histochemical) and statistic research was done in all patients. In 38% of them, preoperative and intra-operative findings coincided, and in 60% patients a higher level of gastric cancer was identified, while in 2% it was lower. A significant correlation between the preoperative estimate of gastric cancer and the intra-operative finding was determined ($r = 0.630$; $p < 0.001$). The preoperative staging coincided with the definite one in 45% cases. In equal percent it was overestimated, mostly at stage II, when the percent of coincidence was only 33%. Only in 5% cases the preoperative staging was underestimated in relation to the postoperative one. The highest coincidence was at stadium IV, which is expected, as the last stadium is the easiest to detect but, unfortunately, the chances for survival are minimal. These results show that not even the modern diagnostic methods can give satisfactory results in the preoperative estimate of the disease and that a macroscopic appearance of lymph nodes is not sufficient for the estimation of the presence of metastatic deposits. For these reasons, modern TNM classification is not only based on preoperative and operative findings, but also on the pathohistological finding of the relevant specimen (pTNM).*

Key words: *Gastric cancer, preoperative staging, radical treatment*

Introduction

Gastric cancer is the second most frequent malignant disease of the digestive system, right after colorectal cancer. However, it is still the most common cause of death. Gastric cancer prognosis is extremely bad, with a five-year survival in only 5-15% of all patients. Early symptomatology of gastric cancer is highly poor and unspecific and, consequently, very hard to detect in the early stages, when the possibilities for treatment are the best. For this reason, a great number of patients (even 50% according to many statistics) go to the surgeon's when the disease reaches a non-curative stage. The prognosis of the disease depends not only on early diagnosis, but also on the method used in surgical treatment. According to preoperative staging, all elements relevant for radical surgery which would guarantee a longer survival should be verified. The treatment of gastric cancer is primarily surgical. Only an adequate surgical procedure, in an early stage of the disease, gives better results. Disagreements about the optimal approach to surgical treatment of gastric cancer are the consequence of the non-existence of uniquely adopted criteria, not only

on determination of the disease stadium, but also on the choice of optimal surgical procedure and the exact definition of curative resection.

Aim of the Study

Given the above facts, as well as differences in the available number of diagnostic procedures in health institution, we define the aim of our research:

1. Making TNM classification of gastric cancer based on preoperative diagnostic procedures;
2. Defining the preoperative stage of gastric cancer based on TNM classification;
3. Determining the type of therapy, the type of surgical procedure according to preoperative staging; and
4. Comparing preoperative to postoperative (definite) stage.

Patients and Methods

The study was done at Surgical Clinic and the Clinic for Gastroenterology and Hepatology, Niš Clinical

Center, partly retrospectively and partly prospectively. Retrospectively, we obtained the data from clinical protocols of the Clinic for Gastroenterology and Hepatology and disease histories of the patients operated on at Surgical Clinic in the period 1997-1999 with no previous targeted preoperative staging. The prospective study included 65 gastric cancer patients (35 male, 30 female, aged 37-83) treated at Surgical Clinic from January 1, 2000 to November 1, 2001. They underwent targeted preoperative diagnostic procedures on which preoperative and intra-operative staging was defined. Clinical, morphological (macroscopic, microscopic and histochemical) and statistical examinations were performed in all patients.

The **clinical study** included:

1. anamnesis;
2. biochemical analysis of the patients' blood samples;
3. contrast radiography done on the conventional device Siemens Undistat with TV chain, and used method was the method of application of contrast means-BaSO₄, as positive contrast;

4. gastroduodenoscopy, along with the estimate of macroscopic appearance and localization of gastric cancer, as well as sample-taking for histopathological and histochemical examination. The macroscopic appearance was estimated and classified into one of the Borrmann (1) types. Localization of tumor was determined by splitting the gaster into three anatomical parts: the upper third (C), the medium third (M) and the lower third (A). The device used for oesophagogastroduodenoscopy was Olympus GTI Q-30;

5. Gastric and gastroduodenal echosonography, the aim of which was verification of the presence of metastases and regional lymph node involvement. Siemens Siena and Acuson 128 hp devices were used;

6. Computerized tomography for the estimation of nodal involvement and verification of metastases was conducted using a Siemens HiQ scanner from 1991;

7. Endoscopic ultrasound was used for verification of intramural spreading of the cancer and metastatic identification in regional lymphatic nodules. The examinations were done with a 12 MHz probe, property of Gastroenterology Institute of the Clinical Center of Serbia;

8. TNM classification was used, proposed by UICC 1987, which is nowadays applied in a majority of medical institutions.

Morphological study:

Staining methods used for pathohistological diagnosis:

1. standard HE-staining;
2. methods of histochemical determination of mucinous cancers (gelatinous adenocancer and "signet ring cell" cancer): PAS, for neutral mucin secretion and HID-AB PH=2.5 for verification of sialo- and sulphomycin synthesis.

Gastric cancer was classified according to Lauren (2): intestinal, diffuse and mixed type. MALT (mucosa-associated lymphonoid tissue) gastric lymphoma was classified by Ann Arbor (3).

Statistical data processing was done using SPSS 12.0 for Windows for descriptive, parametric and non-parametric statistic. The one-way ANOVA program was used in order to compare the parametric variables, while the frequency was tested using the Spearman X² test. In order to test the correlation Spearman the coefficient of correlation "r" was used. The significant difference was considered the ones on the level risk if mistaking up to 5% for rejection of zero hypothesis. The sensitivity of the method was defined as a relation between truly positive results with the sum of truly positive and fake negative results.

Results

A total of 65 patients suffering from gastric cancer were treated at Surgical Clinic, Niš Clinical Center. The incidence of gastric cancer in the region of Niš with the population of 500,000 was 7/6 of 100,000 citizens in the period 2000/2001.

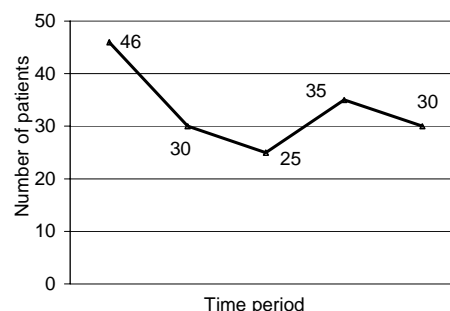


Fig. 1. Gastric cancer incidence in Niš region during the period 1997-2000

Table 1. Mean age and sex ratio of patients

Gender	Number	Mean age	Age (range)
Men	35	65 ± 9	37-83
Women	30	59 ± 13 ^a	37-78
All	65	62 ± 11	37-73

^a p<0.05

Figure 2 shows the blood group findings in patients with gastric cancer. The greatest number of gastric cancer patients (21/65) had A+ blood group ($\chi^2=31.6$; p<0.001).

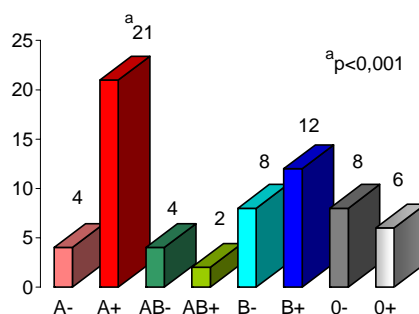


Fig. 2. Distribution of blood groups in patients

Table 2 shows the digestive system symptoms in gastric cancer patients. Pain in the epigastrium and anorexia are, individually, the most frequent symptoms. Loss of weight and vomiting were most frequently observed, while dysphagia was noticed in only 11% of the patients.

Table 2. Digestive system symptoms in patients

Symptoms	Positive	Negative
Epigastric pain	62 (95%)	3 (5%)
Anorexia	62 (95%)	3 (5%)
Body weight loss	57 (88%)	8 (12%)
Vomiting	36 (55%)	29 (45%)
Dysphagia	14 (21%)	51 (79%)

The symptoms by organ and system are shown in Table 3. A total of 65% patients had paleness of skin and visible mucosis, while icterus and ascites were noticed at a lower percentage.

Table 3. Other symptoms in patients

Symptoms	Positive	Negative
Skin and mucosal paleness	42 (65%)	23 (35%)
Icterus	6 (9%)	59 (91%)
Ascites	11 (25%)	49 (75%)

Macroscopic modalities of gastric cancer are given in Figure 3. The greatest number of patients (46/65) had the ulcerous form of gastric cancer ($\chi^2 = 75.6$; $p < 0.001$), the polypoid form (12) was detected at a lower percent, while the superficially spreading cancer (3) and linitis plastica maligna (4) form were least frequent.

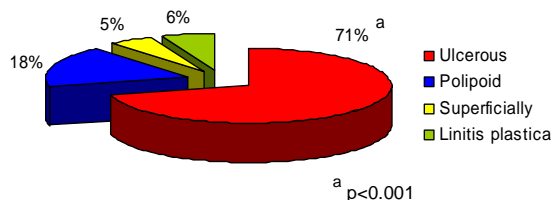


Fig. 3. Macroscopic forms of gastric cancer

A US was done in 61 patients, CT and EUS in 40, and chest radiography in all patients. Because of the unavailability of adequate diagnostic methods, determination of T-stage was done in only 40 patients. We were not able to determine T-staging with certainty in 25 patients, so complete determination of preoperative staging was impossible.

After classification of the results into proper stadiums (I-IV), the following data were obtained: in 38% cases, a match between the preoperative and intra-operative finding was present; in 60% patients a higher level of gastric cancer spread was established intra-operatively rather than preoperatively; and in 2% patients this stadium was lower. By testing the correlation, a significant correlation was determined between the preoperative estimate of gastric cancer spread and the intra-operative finding. The coefficient of correlation

$r = 0.630$ ($P < 0.001$), however, indicates a moderate strength of correlation between the two findings (Table 4).

Table 4. Comparison of preoperative staging and the intra-operative finding in patients

Preoperative finding	Intraoperative finding						Overall
	IA	IB	II	IIIA	IIIB	IV	
IA	—	—	1	—	—	—	1
IB	—	—	—	1	2	—	3
II	—	1	2	6	5	2	16
IIIA	—	—	—	1	3	2	6
IIIB	—	—	—	—	1	2	3
IV	—	—	—	—	—	11	11
Overall		1	3	8	11	17	40

The preoperative staging matched the definite one in 45% of cases. In equal percent of patients, it was overestimated, in particular at stadium II, when the percent of correspondence was only 33%. In only 5% patients, the preoperative staging was underestimated compared to the postoperative finding. The highest percent of coincidence was at stadium IV, which is expected, as the last stadium is easiest to detect but, unfortunately, with minimum chance for curing (Table 5).

Table 5. Comparison of preoperative staging and the postoperative (definite) finding in patients

Preoperative finding	Postoperative finding						Overall
	IA	IB	II	IIIA	IIIB	IV	
IA	1	—	1	—	—	—	2
IB	—	—	2	1	—	—	3
II	—	1	6	5	4	2	18
IIIA	—	—	—	1	3	1	5
IIIB	—	—	—	—	2	—	2
IV	—	—	—	—	1	9	10
Overall	1	1	9	7	10	12	40

Discussion

A successful surgical treatment has always depended on the stadium of a disease. More optimism is provided by the new understanding of the lymphatic gastric drainage, as well as by the attempts of removing the metastatically changed lymphatic nodules. The condition for estimation of this new approach would be a unique TNM classification and identification of metastases in the lymphatic gastric system (4).

Until 1985, the three rival TNM systems existed, UICC, AJCC and JJC (4), which introduced too much confusion and did not make it possible for comparative analyses to be done. The meeting held in Hawaii, 1985, adopted a modified system which helped overcome the problems of comparing the results of various authors, obtained in the preoperative determination of the gastric cancer stadium (5). This system has been changed two more times.

In 1987, the UICC-TNM system replaced the category of tumor size with the parameter of depth of pene-

tration – T-status – due to new diagnostic methods (CT, endoscopic ultrasound, etc.) (6). N (N0, N1 and N2) status in this classification was determined according to the location of metastases in lymph nodes (7,8).

In 1997, the fifth edition of TNM classification was recommended which introduced N3 lymph nodes state into staging, based on their number intruding as a conclusion that localization and number of positive nodes are two independent prognostic factors (9,10,11,12,13).

The choice of the operative procedure depends on the stadium of a disease, the size and localization of the primary tumor, lymph node involvement and the general patient's condition. Tumor is proclaimed inoperable if metastases or diffused peritoneal involvement by metastatic process are found (14). Radical gastrectomy was a method of choice for all cases of gastric cancer from 1940 to 1950 (15). Since then, the operative gastric cancer treatment has undergone many changes, but the agreement about the optimal procedure is still not achieved, in particular about the extensiveness of resection and the necessity of lymphadenectomy and resection of the surrounding organs. This estimate is based on preoperative research, but the final decision is made during the operation.

Modern practice in the USA considering typical gastric resection because of cancer includes subtotal or total gastrectomy for medium third lesions (depending of the size and proximal tumor spreading), as well as total gastrectomy with oesophagojejunostomy in proximal third lesions, gastro-oesophageal junction or at extensive lesions of medium third. Apart from this, perigastric lymph nodes along the minor or great curvature, and lymph nodes along the left gastric artery are typically removed. The minor and major omenta are resected. However, as a rule, coeliac, hepatic, peripancreatic and splenic lymph nodes are left (16).

The American College of Surgeons (1993) published in its study that less than half of resected samples included gastric and perigastric lymph nodes. The usual hepatic, coeliac and splenic lymph nodes were included in only 6%, 14% and 18%, respectively. Only 5% patients with gastrectomy with clear margins underwent D2 dissection as previously described. The total level of survival which shows only the mortality of cancer was 26% (17).

Japanese experience with surgical resection of progressive gastric cancer is quite different. According to the systematic approach, a standard operation in Japan for progressive gastric cancer is D2 resection, during which N1 and N2 group of lymph nodes are removed. After extensive experience with this operation, Maruyama et al. (1989) from National Central Hospital for Cancer in Tokyo reported that the postoperative level of mortality was 0.4% at D2 and D3 resection. Apart from it, the levels of survival have increased by 71-76% in phase II, 39-63% in phase III a, 28-39% phase III b, and 2-10% in the last 30 years (18).

In patients with stage I gastric cancer, gastrectomy with lymphadenectomy is a method of choice. For non-

cardial lesions and those that are non-diffuse on the stomach, subtotal gastrectomy is chosen, as it is confirmed that it leads to survival rates similar to those obtained at total gastrectomy. When lesion includes cardia, proximal subtotal gastrectomy or total gastrectomy (with removal of the necessary part of the oesophagus) can have a curative effect. If lesion diffusely includes the stomach, total gastrectomy is necessary. Minimal demand is removal of the perigastric lymph, as in stadium I perigastric nodes can contain malignant cells (19). Surgical resection with regional lymphadenectomy is a method of choice in patients with stadium II gastric cancer (20). If the lesion is not in the cardia and does not diffusely include the stomach, subtotal gastrectomy is a method of choice. If the lesion includes the cardia, proximal subtotal or total gastrectomy is done for curative purposes. If the stomach is diffusely included, total gastrectomy with removal of the relevant lymph nodes is demanded. The role of extensive resection of lymph nodes (D2) is not reliable (21), and in some studies it is shown to result in an increased level of mortality (22, 23). As a matter of fact, extended D2 lymphadenectomy is performed in Japan where in the studies was shown that provides higher level of survival in relation to limited D1 lymphadenectomy. The evidence for this attitude was first provided in 1991 by Kodama et al., who reported a five-year survival in 39% of patients submitted to D2 lymphadenectomy, compared to 18% patients submitted to D1 lymphadenectomy (24). Numerous other Japanese studies have confirmed this finding. However, randomized controlled studies in the West have not demonstrated a positive contribution to the higher level of survival at D2 compared to D1 lymphadenectomy (25). For example, the "British study" reported the increased level of postoperative morbidity (28% at D1 and 46% at D2) and mortality (6.5% at D1 and 13% at D2) during the performance of D2 lymphadenectomy with no significant difference in five-year survival (35% at D1 and 32% at D2) (26). Similar to this, the "Netherlands' study" showed the increase in morbidity (25% at D1 and 43% at D2) and mortality (6.5% at D1 and 13% at D2) with no useful effect on survival during the performance of more radical, extended D2 lymphadenectomies (27). Also, the multivariate comparative analysis of D1 and D2 lymphadenectomy done in this study shows that the performance of adjuvant splenectomy carries an increased risk of a direct postoperative lethal result and an increase in the total level of postoperative complications. For this reason, splenectomy is not recommended as a routine adjuvant procedure (as part of extensive D2 lymphadenectomy) while performing gastrectomy for gastric cancer, with the exception of cases of local extension of a basic pathological process. All patients in stage III in whom the possibility of tumor resection is evident are surgically treated. Up to 15% patients in stage III can only be treated surgically, especially if lymph nodes are minimally affected (<7 of lymph nodes according to the 1997 classification). Radical

operation is a standard treatment option: curative resection is done only in patients in whom the lymph nodules are not extensively affected at the time of surgical procedure. All patients in stage IV (M0) in whom resection is possible are surgically treated following chemotherapy. However, a great number of patients in stage IV of the disease have non-resectable tumors (which is confirmed by a surgical exploration or preoperatively by CT, EUS, videolaparoscopic method or some other way) (28). Since at stadium IV the level of survival is very low, multiple other therapeutic modalities are to be considered and applied according to the disease status.

Employing the previously listed research methods on a group of 40 patients, we performed TNM classification and defined the staging and the method of surgical treatment. Intra-operative and definite staging demand clearly labeled borders of a resected sample and a group of lymph nodes. Based on the employed diagnostic procedures and confirmed preoperative and intra-operative staging, we performed two types of surgical resections, R1 and R2, with total and subtotal gastrectomy wherever possible. Where these interventions were not possible due to an advanced process, condition of the patient, emergency or inoperability, we did palliative surgery, explorative laporotomy, or treated the patients conservatively. In 11 patients a total gastrectomy was planned, in 14 subtotal, six patients demanded palliative operation, and eight explorative laporotomy as an attempt of palliation and confirmation of the preoperative staging. Out of all planned total gastrectomies, 45.5% were done with different types of lymphadenectomy, and 54.5% were subtotal gastrectomies. Of all preoperatively planned subtotal gastrectomies, only 36% were performed, while in 64%, the surgical procedure was substituted intra-operatively for total gastrec-

tomies, palliative and explorative procedures. Palliative operations and explorative laparotomies were performed in 50% cases. Planned radical treatments were performed in 45% cases, while in 55% there came to an intra-operative change of surgical "tactics". The percentage of planned and completed operations coincides to a high extent with the preoperative and postoperative (definite) pTNM staging in the group of patients in whom it was performed at all states. This transparently shows the role of preoperative staging of gastric cancer while planning a radical surgical treatment.

Conclusion

Modern staging of gastric cancer should be accomplished not only employing contrast radiography and endoscopy, but also using the routine ultrasonography, computerized tomography, endoscopic ultrasonography, NMR, and nowadays increasingly used surgical laparoscopy, intra-abdominal ultrasonography and laparoscopic ultrasonography. Along with surgical laparoscopy, the abdominal lavage followed by precise cytological and immuno-histochemical determination of free tumor cells is always done.

Preoperative TNM staging coincides with intra-operative findings in 38% cases and with definite ones in 45% cases, which indicates that no modern diagnostic method can provide satisfying results in the preoperative estimation of the disease. The macroscopic visualization of lymph nodes, therefore, is not a valid index for the presence of metastatic deposits. For these reasons, modern TNM classification is based on the pathohistological finding of a resected specimen (pTNM), in addition to preoperative and intra-operative finding.

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ULOGA PREOPERATIVNOG STADIJUMA (STAGING) MALIGNOMA ŽELUCA U PLANIRANJU RADIKALNOSTI HIRURŠKOG LEČENJA

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Kratak sadržaj: *Iako je učestalost karcinoma želuca u postepenom opadanju, još uvek je najčešći uzrok smrti od svih karcinoma digestivnog trakta. Cilj određivanja preoperativnog stadijuma bolesti je utvrđivanje mogućnosti kompletne resektabilnosti tumora i metastatske zahvaćenosti limfatičnog drenažnog sistema. Jedino ako na osnovu preoperativnog stadijuma očekujemo R0, resekciju prognoza bolesti može biti poboljšana hirurškim zahvatom. Ispitivanje je obuhvatilo grupu od 65 pacijenata sa karcinomom želuca (35 muškaraca i 30 žena, starosne dobi od 37-83 godina), koji su lečeni na Hirurškoj klinici u Nišu u periodu od 1.1.2000. god. do 1.11.2001. god. i kod kojih su urađeni ciljani preoperativni dijagnostički postupci uz težnju određivanja kako preoperativnog, tako i intraoperativnog stadijuma. Kod svih pacijenata primenjivana su klinička, morfološka (makroskopska, mikroskopska i histohemijska) i statistička ispitivanja. U 38% se preoperativni i intraoperativni nalaz poklapao, u 60% ispitanika je intraoperativno utvrđen viši stepen proširenosti karcinoma želuca, dok je u 2% bio niži. Utvrđena je signifikantna korelacija nalaza preoperativne procene proširenosti karcinoma želuca u odnosu na intraoperativni nalaz ali sa korelacionim koeficijentom od $r = 0,630$ ($p < 0,001$). Preoperativni staging bio je saglasan sa definitivnim u 45% ispitivanih slučajeva. U jednakom procentu bio je precenjen, najviše kod II stadijuma gde je procenat saglasnosti samo 33%. Samo u 5% je preoperativni staging bio potcenjen u odnosu na postoperativni. Najveći procenat poklapanja bio je kod IV stadijuma što je razumljivo, jer se poslednji stadijum najlakše detektuje ali su na žalost kod ovih pacijenata šanse za preživljavanje minimalne. Ovakvi rezultati istraživanja ukazuju da ni savremene dijagnostičke metode još uvek ne mogu da daju zadovoljavajuće rezultate u preoperativnoj proceni bolesti kao i da makroskopski izgled limfnih nodusa nije dovoljan da se oceni prisustvo metastatskih depozita. Iz ovih razloga se savremena TNM klasifikacija bazira, kako na preoperativnom i operativnom nalazu, tako i na patohistološkom nalazu resekovanog preparata (pTNM).*

Ključne reči: *Karcinom želuca, preoperativni staging, radikalitet*