SENSITIVITY OF DIAGNOSTIC METHODS AND TNM CLASSIFICATION IN STAGING OF GASTRIC CARCINOMA

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Preoperative staging in patients with malign gastric disease is of crucial importance for its multimodal treatment. The research included a group of 65 patients with gastric carcinoma. Targeted preoperative diagnostic procedures were performed as a basis for determining the preoperative and postoperative (TNM) degree. The diagnostic techniques used for the clinical and statistical examinations included ultrasonography (US), multi-slice computerized tomography (MSCT) and endoscopic ultrasound (EUS). The sensitivity of MSCT used for preoperative T status, compared to the postoperative findings, amounted to 39%, while the EUS sensitivity used for an assessment of the depth of tumour infiltration for T status amounted to 83%. The ultrasound examination could not detect enlarged lymph nodes in 58 out of 65 subjects with gastric carcinoma who had intra-operatively detected enlarged nodes, while a realistic positive finding of spreading malign process was detected in lymph nodes N1 in three patients and N2 in four patients. Ultrasound examination proved to be the least sensitive, with the detection rate of the affected lymph nodes in gastric carcinoma patients of only 11%. The MSCT proved as a reliable diagnostic technique in 43% of the preoperative assessments of malign process spreading into lymph nodes. Preoperatively, M0 status was found in 67.21% of the patients, while it was intraoperatively confirmed in 62.29%. The M0 status was preoperatively underestimated in 8.1% (M0 into M1) of patients.

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Key words: staging, gastric carcinoma, diagnostic methods

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Introduction

The frequency of gastric carcinoma is in gradual decline in many countries, including Serbia. However, gastric carcinoma is still the most frequent cause of death in all digestive tract carcinoma cases, which points to the practical relevance of the research. Numerous difficulties have been linked with timely diagnosis of the disease, while the success of surgical treatment depends primarily on its early detection. A long clinical period is one of the basic gastric carcinoma characteristics (up to several months) (1). For this reason, a number of patients (according to some statistics, as many as 50%) seek surgical help too late, at an incurable stage of the disease. The prognosis of the course of the disease thus de-

pends on early diagnosis but also on the type of the applied surgical intervention. A preoperative diagnosis is important for determining all elements indicating the extent of how radical a surgical intervention should be in order to guarantee a longer survival rate (2).

For that purpose, all patients should be examined by contrast radiography, by applying high-sensitivity barium and gastric gas distention fibre gastroscopy, ultrasonography (US), multi-slice computerized tomography (MSCT) and endoscopic ultrasonography (EUS)(3,4).

In addition to these most significant diagnostic procedures, there is a range of auxiliary diagnostic techniques which can contribute to early gastric carcinoma diagnosis. These include, primarily, NMR in a strictly indicated framework, assessment of gastric juice acidity level, determining the carcino-embryonal antigen concentration (tumour markers), cytological examination of gastric juice, routine laboratory analyses, etc (7,8).

Patients and methods

The research included a group of 65 patients with gastric carcinoma (35 male and 30 female, aged 37-83 years) (Table 1), treated at the General

Surgery Clinic of the City of Niš, in the period January 1, 2011 – November 1, 2012. The patients were subjected to targeted preoperative diagnostic procedures, used as a basis for defining a preoperative,

intraoperative and final staging (pTNM). Targeted diagnostic procedures, clinical examinations and statistical data processing were performed in all patients.

Table 1. Age structure of the patients with gastric carcinoma by gender

Gender	Number	Average age	Age (Range)
Men	35	65 ± 9	37-83
Women	30	59 ± 13°	37-78
Total	65	62 ± 11	37-83

^ap < 0,05

Ultrasonography (US) of abdomen and gastroduodenal region was used for the detection of metastases and involvement of regional lymph nodes. SIMENS ACUSON X 300 was used in this research.

TOSHIBA AQULION MS Computerized tomography (MSCT) was used for determining the extent to which the lymph nodes were affected and in order to verify metastases.

Endoscopic ultrasound (EUS) was applied for determining intramuscular expansion of carcinoma and identification of metastases in regional lymph nodes. The examinations were performed using a 12MHz probe.

The applied TNM classification was the one presented by the International Union against Cancer (UICC) in the seventh edition of American Joint Committee on Cancer (AJCC/UICC TNM classification, 7th ed. 2010, XV, 649 p), which is the most frequently used one, by most tertiary health institutions worldwide.

The statistical processing was performed by descriptive, parametrical and non-parametrical statistics. One-Way ANOVA program was used for com-

parison of parametrical variables, while the frequency was tested by Spearman's $\chi 2$ test. The correlations was tested by the Spearman's correlation coefficient $\rho > 0.01$ as a non-parametrical version of the Pearson's correlation coefficient. Error risk discrepancies of not more than 5% were considered as statistically significant for discarding the zero hypothesis. Method sensitivity level was determined as the ratio of truly positive findings with the sum of truly positive and falsely negative findings.

Results

A comparative overview of preoperative and post-operative findings by TNM classification is provided in this section.

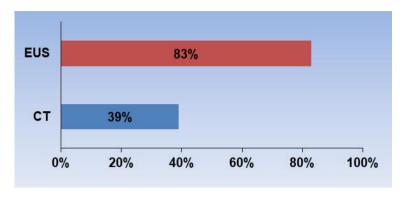
A comparison between the preoperative and postoperative (final findings) tumour staging of gastric carcinoma showed a significant, mid-level coincidence with the Spearman's rank correlation coefficient $\rho=0.638\ (p<0.001)$ (Table 2).

Table 2. Postoperative tumour staging compared to the preoperative finding

Preoperative tumour staging	Postoperative tumour staging				
	T1	T2	Т3	T4	Total
Т1	1	1	-	-	2
T2	-	1	4	1	6
Т3	ı	7	10	6	23
T4	-	-	-	34	34
Total	1	9	14	41	65

The postoperative staging coincided with the preoperative one in 83% of the patients examined by endoscopic ultrasonography (EUS). Preoperative

T findings by multi-slice computerized tomography (MSCT) performed in 40 subjects, coincided with the pT status in 39% of the subjects (Graph 1).



Graph 1. EUS and CT sensitivity in preoperative diagnosis of tumour expansion into the gastric wall, compared to the postoperative PT finding

Table 3 shows a comparison of the preoperative staging with the postoperative findings in enlarged lymph nodes. Although the findings significantly correspond with each other, the value of

Spearman's rank correlation coefficient of $\rho=0.360$ (p < 0.05) indicates a low correlation of pre - and postoperative finding of tumor expansion to lymph nodes.

Table 3. Preoperative staging of lymph node involvement in gastric carcinoma patients, compared to the postoperative finding

Preoperative staging of lymph nodes	Postoperative staging of lymph nodes			
	NO	N1	N2	Total
NO	2	14	7	23
N1	2	7	9	18
N2	-	-	24	24
Total	4	21	40	65

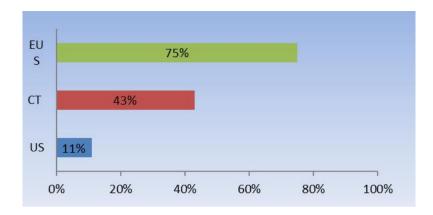
Ultrasonography could not detect enlarged lymph nodes in 58 out of 65 subjects, in which the enlarged lymph nodes were confirmed intraoperatively, whereas malign process expansion to lymph nodes was evident in 8 subjects (N1 in 4 and N2 in 4, respectively). Ultrasonography showed the lowest sensitivity in determining the stage of lymph node involvement in gastric carcinoma patients (11%). The MSCT proved as a reliable diagnostic technique in 43% of the preoperative assessments of malign process spreading into the lymph nodes. Out of the 65 gastric carcinoma patients examined by EUS, the finding was truly positive in 49, while in 16 patients the NO finding was falsely negative. Thus, EUS proved to be sensitive in the detection of malign process expansion into the lymph nodes in 75% of the cases.

The CT sensitivity rate in preoperative lymph node staging was 43%. This method confirmed a truly positive finding of the presence of malignant process in lymph nodes in 27 out of 65 subjects,

while it was truly negative in 5 patients (7.7%) and falsely negative in 33 patients (50.8%), compared to the postoperative finding.

Graph 2 shows the sensitivity rate of abdominal ultrasonography, EUS and CT in detecting the affected lymph nodes in gastric carcinoma patients.

Table 4 shows the preoperative findings of distant metastases in gastric carcinoma subjects, compared to the postoperative findings. The absence of distant metastases was postoperatively confirmed in 42 patients (67.21%), whereas distant metastases were found in 23 of the subjects (32.79%). However, in two out of the 65 subjects, distant metastases were determined only postoperatively, so it was intraoperatively confirmed in 62.29%. The applied diagnostic procedures (abdomen echosonography, CT, lung radiography) for preoperative distant metastasis staging in gastric carcinoma patients proved to be sensitive in 91.9% of the cases, compared to the final finding and diagnosis.



Graph 2. Sensitivity of abdominal ultrasound, endoscopic ultrasound and CT in preoperative detection of the degree of malign process expansion to lymph nodes in gastric carcinoma patients, compared to the postoperative finding

Table 4. Preoperative finding of distant metastases in gastric carcinoma patients, compared to the postoperative finding

Preoperative finding of	Postoperative finding of distant metastases			
distant metastases	МО	M1	Total	
Not defined	1	-	1	
МО	41	2	43	
M1	-	21	21	
Total	42	23	65	

Discussion

Preoperative staging in patients with malignant gastric disease is of crucial importance for its multi-modal treatment. Today, it tends to go beyond a simple staging of the depth of tumour infiltration into the gastric wall (T), staging of the degree of regional lymph node involvement (N), and presence or absence of distant metastases (M). A contemporary approach to this problem includes an assessment of the prognostic factors, such as Ras protein, p53 tumour suppressor gene, growth factor receptors, tumour proliferation-related antigens, as well as protolithic factors. Recent techniques include both radiographic processing - routine ultrasonography (US), endoscopy and endoscopic ultrasound (EUS), multi-slice computerized tomography (MSCT) and surgical laparoscopy and laparoscopic ultrasonography (1).

T staging and method sensitivity

A comparison of preoperative staging with the postoperative finding of gastric carcinoma expansion has shown a significant but medium degree of matching with the Spearman's correlation coefficient ρ = 0.638 (p < 0.001) (Table 2).

In line with improved experience, multi-slice computerized tomography (MSCT) is increasingly used for detecting gastric carcinoma. Coburn et al.

(2010) have reported that the use of CT scanning for gastric carcinoma detection has increased from 28% of the subjects in 1982 to 84% in 2007. Approximately 2/3 of the scanning in both groups have indicated carcinoma. In cases of gastric carcinoma, MSCT most frequently shows thickening of the gastric wall. Gastric wall thickness varies from 0.5 to 4 cm and correlates with tumor penetration (2). MSCT use for accurate gastric carcinoma T staging is still controversial. MSCT is obviously a less precise method than exploration and can be misleading in staging. Chen et al. (2007) have reported a comparative study of 75 patients in which T status staging was performed by MSCT, and consequently by surgery. The findings of this study indicate that as many as 31% of the subjects were graded lower than the actual status, while the MSCT overestimated it in 16% (3). In our research, MSCT sensitivity use for preoperative T staging was 39%, compared to the postoperative finding.

Our research has shown 83% of the EUS sensitivity regarding T staging of tumor infiltration depth (Graph 1). Shill et al. (2015) have concluded that EUS T staging was 78%. The accuracy rate for T1 amounted to 80% (in 20% of the cases it was overestimated), which is a high staging sensitivity, according to these authors. T staging proved to be reliable in 63% of the cases for T2 stage, while it amounted to 95% and 83% for T3 and T4 stage, respectively (4). Fairweather et al. (2015) have

found 81% of EUS in T1 staging, while it was 71%, 87% and 79% for T2, T3 and T4 staging, respectively (5). The obtained percentage of EUS sensitivity in our research is in accordance with such findings of other authors, regardless of the relatively low number of subjects in the series (Graph 1). T staging EUS sensitivity range from 71% to 95% (4) can be, perhaps, explained by a difficulty in discerning between T2 (subserous infiltration) from T3 stage. These two stages are clear indicators of a distinction between localized and progressed tumors. The EUS findings can sometimes be both falsely positive and falsely negative. Sometimes, it is difficult to make a distinction among tumorous tissue, inflammationinduced changes of the surrounding connecting tissue or the surrounding fibrous alterations (1). A comparison of MSCT, EUS and intraoperative finding with the final pTNM staging of the depth of gastric tumor invasion, performed by Pech et al. (2006), indicates that T staging was done correctly in 42% of the cases by MSCT, while the results were correct in 71% and 55% by EUS and intraoperative surgical finding, respectively (6). Similarly, Mehmedović et al. (2014) reported that EUS finding coincided with the surgical finding in as many as 92% compared to significantly lower matching rate of MSCT finding (only 42%) (7). With regard to T3, i.e., T4 stating, Hallinan and Venkatesh (2013), have emphasized the fact that 88% of the T3 and T4-staged tumors have metastases in lymph nodes, indicating that the concomitant T stage can be an important criterion for detecting the nature of endoscopically examined lymph nodes (8).

N staging and method sensitivity

A comparison of preoperative staging results by abdominal ultrasonography, computerized tomography and endoscopic ultrasonography with the final pN status has led us to the following findings:

The ultrasound examination could not detect enlarged lymph nodes in 58 out of 65 subjects with gastric carcinoma who had intraoperatively detected enlarged nodes, while a realistic positive finding of spreading malign process was detected in lymph nodes N1 in 3 patients and N2 in 4 patients (Table 3.). Ultrasound examination proved to be the least sensitive, with the detection rate of the affected lymph nodes in gastric carcinoma patients of only 11%.

In our research, the MSCT proved as a reliable diagnostic technique in 43% of the preoperative assessments of malign process spreading into lymph nodes (Graph 2). Van Vliet et al. (2007) compared the MSCT sensitivity for preoperative staging with the sensitivity of preoperative abdominal ultrasonography in detecting tumor invasion to the surrounding lymph nodes. In a series of 95 subjects the sensitivity of affected lymph node detection for preoperative MSCT was 26.6%, whereas for abdominal ultrasound it was 20% (9). A comparison between these results and our findings suggests that neither MSCT nor US can be considered as reliable methods for detecting potential tumor invasion to the surrounding, primarily, perigastric lymph nodes. We also suggest that MSCT is a slightly more superior method of verification of advanced tumor in N2 stage and detection of distant metastases. Our research has indicated particularly poor performance of abdominal ultrasound as a method of detection of nodal metastases.

Endoscopic ultrasound (EUS) sensitivity to detecting an invasion of the malign process into the surrounding lymph nodes is 75% in total. Shil et al. (2015) suggest that when it comes to N staging, EUS is significantly sensitive in 78-87% (4). However, this method can only detect the lymph nodes in immediate proximity to the gastric wall. N2 stage, i.e. lymph nodes farther than 3cm from the primary tumor can hardly be diagnosed by EUS. Griniatsos et al. (2011) found a correlation of T stage with the number and focalization of lymph nodes (10). Similarly to Javaid et al. (2004), this group of authors concludes that in T3 stage 88% of the lymph nodes are positive (14). Hallinan and Venkatesh (2013) preoperative endoscopic ultrasonography (EUS) on 254 consecutive patients with gastric carcinoma and compared the findings with the final pathohistological results. EUS yielded correct N sta-ging in 66%, while the accuracy in N0 stage was as high as 93%. However, in N1 and N2 staging (64% and 52%, respectively), EUS proved to be less reliable (8).

M staging and method sensitivity

The M status was determined by RŐ (rentgen) US and MSCT. Preoperatively, M0 status was found in 67.21% of the patients, while it was intraoperatively confirmed in 62.29%. The M0 status was preoperatively underestimated in 8.1% (M0 into M1). The M1 status was confirmed intraoperatively in the patients with secondary invasion of the disease (Table 4).

Considering the natural progression capacity of gastric cancer, there is a 27-37% probability that peritoneal implants can be detected during laparotomy (M1), although they have not been shown by the previously performed CT. Since the subjects with distant metastases are usually prone to intraoperative hemorrhage and obstruction by tumor mass is present in high percentage, which is most frequently lethal, we believe that this might be a strong argument to suggest that preoperative video laparoscopy is done in patients with advanced gastric carcinoma (11).

Due to embryological gastric rotation, gastric carcinoma gives metastases not only to the lymph nodes of the large and small omentum, but also into the truncus coeliacus nodes as well as retroperitoneal space along large blood vessels. A tumor can spread per continuitatem into the liver, pancreas, intestines, colon, and sometimes spleen. Rarely, in about 2% of the cases, gastric cancer can give metastases into bones. In women, metastases are frequent into ovaries (Krukenberg's tumor). According to Lauren, different histological tumor types give different metastases (13). The intestinal type, predominantly results in liver and lymph node metastases, while the diffuse type goes predominantly to peritoneum. Considering the pathways of invasion, abdominal MSCT seems to be necessary. An issue with MSCT is that it can detect peritoneal metastases

only in the presence of ascites (1). Our research has shown CT sensitivity of 57%, which is a considerable percentage. Metastases smaller than 10 mm in diameter pose a considerable problem. Since liver metastases detection depends on their size, they can be detected by ordinary MSCT in 50-60% of the cases. If MSCT is combined with arterial portography, the percentage of reliable metastases detection in liver increases and goes up to 81%, and if NMR is used, the sensitivity is up to 72% (12). However, intraoperative and laparoscopic ultrasound is still considered to be the most reliable method for the detection of liver metastases (1).

Conclusion

Preoperative T staging is confirmed by the intraperative one in about 57.5% and by the post-operative staging in about 52.5% of the cases. EUS sensitivity in the staging the depth of tumor infiltration is 83%, while the CT sensitivity is 39%,

which recommends EUS as a more sensitive T staging method.

Preoperative assessment of carcinoma invasion to lymph nodes is confirmed by intraoperative and postoperative staging (final pathological verification) in 34% and 32%, respectively. Transcutaneous ultrasonography is sensitive in assessing gastric cancer invasion into lymph nodes in 11%. T has verified the findings in lymph nodes in 43%, while EUS has verified the findings in the affected lymph nodes in 75% when it comes to perigastric lymph nodes not distant more than 3cm. EUS has proved to be a very reliable method for N0 and N1 status verification, while CT has shown superior results in N2 staging verification.

Detection of distant metastatic deposits (M staging) by US and MSCT is accurate in high percentage (97%), which decreases the possibility for intraoperative "surprises". These diagnostic procedures have a significant contribution to better planning of surgical treatment degree of radicality.

References

- Zlatić A, Radojković M, Ignjatović N, Stojanović M, Jeremić Lj. The role of preoperative staging of gastric cancer in planning radical surgical treat ment. Facta universitatis - series: Medicine and Biology 2006 vol. 13, iss. 1, pp. 19-24. [CrossRef] [PubMed]
- Coburn NG, Lourenco LG, Rossi SE, Gunraj N, Mahar AL, Helyer LK, et al. Management of gastric cancer in Ontario. J Surg Oncol 2010; 102(1):54-63. [CrossRef [PubMed]
- Chen CY, Hsu JS, Wu DC, Kang WY, Hsieh JS, Jaw TS, et al. Gastric cancer: preoperative local staging with 3D multi-detector row CT-correlation with surgical and histopathologic results. Radiology 2007; 242(2):472-82. [CrossRef] [PubMed]
- Shil BC, Banik RK, Saha SK, Faruque MO, Islam AS, Rahman MH. Initial experience with endoscopic ultrasound. Bangladesh Med Res Counc Bull 2015; 41(1):41-5. [CrossRef] [PubMed]
- Fairweather M, Jajoo K, Sainani N, Bertagnolli MM, Wang J. Accuracy of EUS and CT imaging in preoperative gastric cancer staging. J Surg Oncol 2015; 111(8):1016-20. [CrossRef] [PubMed]
- Pech O, May A, Günter E, Gossner L, Ell C. The impact of endoscopic ultrasound and computed tomography on the TNM staging of early cancer in Barrett's esophagus. Am J Gastroenterol 2006; 101(10):2223-9. [CrossRef] [PubMed]
- Mehmedovi? A, Mesihovi? R, Saray A, Vanis N. Gastric cancer staging: EUS and CT. Med Arch 2014; 68(1):34-6. [CrossRef] [PubMed]

- Hallinan JT, Venkatesh SK. Gastric carcinoma: imaging diagnosis, staging and assessment of treatment response. Cancer Imaging 2013; 13:212-27.
 [CrossRef] [PubMed]
- Van Vliet EP, Steyerberg EW, Eijkemans MJ, Kuipers EJ, Siersema PD. Detection of distant metastases in patients with oesophageal or gastric cardia cancer: a diagnostic decision analysis. Br J Cancer 2007; 97(7):868-76. [CrossRef] [PubMed]
- Griniatsos J, Yiannakopoulou E, Gakiopoulou H, Alexandrou A, Dimitriou N, Karavokyros I, et al. Clinical implications of the histologically and immunehistochemically detected solitary lymph node metastases in gastric cancer. Scand J Surg 2011; 100(3):174-80. [CrossRef] [PubMed]
- Alatengbaolide, Lin D, Li Y, Xu H, Chen J, Wang B, et al. Lymph node ratio is an independent prognostic factor in gastric cancer after curative resection (R0) regardless of the examined number of lymph nodes. Am J Clin Oncol 2013; 36(4):325-30.
 [CrossRef] [PubMed]
- Kwee RM, Kwee TC. Modern imaging techniques for preoperative detection of distant metastases in gastric cancer. World J Gastroenterol 2015; 21 (37): 10502-9. [CrossRef] [PubMed]
- 13. Lauren P.The two histological main types of gastric carcinoma:diffuse an so-called intestinal-tzpe carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31-49.
- Javaid G, Shah OJ, Dar MA, Shah P, Wani NA, Zargar SA. Role of endoscopic ultrasonography in preoperative staging of gastric carcinoma. ANZ J Surg. 2004 Mar;74(3):108-11

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SENZITIVNOST DIJAGNOSTIČKIH METODA I TNM KLASIFIKACIJA U STAGING KARCINOMA ŽELUCA

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Preoperativni staging kod bolesnika sa malignim oboljenjem želuca je od presudnog značaja za njegov multimodalni tretman. Istraživanje je obuhvatilo grupu od 65 bolesnika sa karcinomom želuca. Ciljane preoperativne dijagnostičke procedure su obavljene kao osnova za određivanje preoperativnog i postoperativnog (TNM) stadijuma. Dijagnostičke tehnike koje su se koristile za klinička i statistička ispitivanja uključivale su ultra zvuk (UZ), multi-slajs kompjuterizovanu tomografiju (MSCT) i endoskopski ultrazvuk (EUZ). Senzitivnost MSCT-a u određivanju preoperativnog T statusa u poređenju sa postoperativnim nalazima iznosio je 39%, dok je osetljivost EUZ-a koji smo koristili za procenu dubine tumorske infiltracije za T stadijum iznosila 83%. Pregled ultrazvukom (UZ) ne može da detektuje uvećane limfne noduse kod 58 od 65 bolesnika sa karcinomom želuca i intraoperativno utvrđenim lifnim nodusima, dok je kod tri bolesnika dobijen realno pozitivan nalaz širenja malignog pocesa u limfne noduse N1 i kod četiri bolesnika u N2. Ultrazvuk je pokazao najnižu senzitivnost u detekciji zahvaćenih limfnih nodusa kod obolelih od karcinoma želuca koja je iznosila samo 11%. MSCT je kao pouzdana dijagnostička tehnika koja pokazuje tačnost u 43% kod preoperativnog određivanja stepena proširenosti malignog procesa na okolne limfne noduse. Preoperativno je M0 status utvrđen kod 67,21% bolesnika, a intraoperativno kod 62,29%. M0 status je preoperativno potcenjen kod 8,1% bolesnika (M0 u M1). Acta Medica Medianae 2018;57(1):5-11.

Ključne reči: staging, karcinom želuca, dijagnostičke metode