

CLINICAL STUDY

Radical gastrectomy with D2 lymph node dissection after neoadjuvant therapy

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ABSTRACT

OBJECTIVES: This study focuses on the evaluation of the effectiveness of radical gastrectomy with D2 node dissection after neoadjuvant therapy in the patients with gastric cancer. Gastric cancer is a widespread type of cancer, and it is the third leading cause of death in the cancer patients. Metastases most often occur in the lymph nodes and therefore, in addition to gastrectomy, lymph node dissection is often performed in the patients. We are distinguishing between D1, 2 and 3 dissections. As with other cancers, the effectiveness of neoadjuvant therapy is being considered, which aims to improve the patient's prognosis and thus the 5-year survival rate.

METHODS: Within the study, we evaluated a group of the patients diagnosed with gastric cancer (n=41). The average age of the patients was 62.3 years (20–72 years). 68.3 % (n=28) patients underwent neoadjuvant therapy before surgery, the remaining 31.7 % (n=13) underwent only radical gastrectomy with D2 lymphadenectomy. In all the cases, an open operational approach was implemented.

CONCLUSION: Lymphadenopathy was found in 85.4 % of the patients. Complications occurred in both groups, but in the group with neoadjuvant therapy their share was lower (14.3 % vs 23.1 %), while in the group without neoadjuvant treatment the proportion of duodenal leaks was higher, as well as the number of reoperations. In total, an average of 30 ± 8 lymph nodes were harvested. A lower number of T3–4 cases was found in the neoadjuvant group (17.9 % vs 61.6 %), confirming that the tumour size was significantly smaller in the neoadjuvant group than in the group, who did not undergo it and underwent only surgical treatment. Relapse was found in 29.3 % of the patients after neoadjuvant treatment and in 38.5 % of the patients without neoadjuvant treatment. Also, mortality due to relapse was higher in the group without neoadjuvant treatment (30.8 % vs 21.7 %). The average survival was 25 months (Tab. 3, Fig. 3, Ref. 60). Text in PDF www.elis.sk

KEY WORDS: radical gastrectomy, D2 lymph node dissection, neoadjuvant therapy.

Introduction

Gastric cancer is the third most common type of cancer and the third most common cause of cancer deaths (1, 34). This aggressive cancer has very poor prognostic factors (45). Gastric Cancer society reported that every year more than 800 000 people are affected by this type of cancer (38, 43). Gastric cancer occurrence is by 70% in developing countries (44). Compared to the colorectal cancer, it is a more aggressive tumour with a heterogeneous origin (2). This type of cancer has in recent years a declining tendency; however, it is a disease which is the fourth leading cause of cancer death in Europe (31). Declining tendency is the result of improved early

surgical interventions and chemo/radiotherapy regimens (34). The cancer does not metastasize to distant organs in the earlier stages, but often metastasizes to the lymph nodes (1). However, in addition to the lymph nodes, it often metastasizes to the liver (2). About 2/3 of the patients have the disease diagnosed at a locally advanced stage (3). Gastric cancer has a low 5-year survival rate, ranging from 5–15 % (4). In the presence of distant metastases, the overall survival of the patient decreases (2) (Tab. 1).

Surgical and endoscopic resection are the only curative methods in the treatment of gastric cancer (32, 33, 35). The area of resection and the extent of lymphadenectomy should be considered during surgical treatment. The extent of resection depends

Tab. 1. Monitored group of the patients.

n=41	
Age of patients	20–72 years
Average age	62.3 years
Gender	
– male	65.9 % (n=27)
– female	34.1 % (n=14)
Average surgery time for SG	254 min (145–460 min)
Average monitoring time	53 months (range 7–24 months)

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on the extent of the tumour. In radical surgery, the goal is to achieve a clear resection edge (5). Radical gastrectomy for gastric cancer is the basic treatment in the patients with advanced disease (6). Risk factors for postoperative morbidity and mortality after gastrectomy are: patient age, comorbidities, haemoglobin and albumin levels (7). It is recommended to perform if a 5 cm margin can be secured (8).

In addition to resection, lymph node dissection is performed during surgical treatment (5). In D1 dissection of lymph nodes, perigastric nodes are removed (9). D2 lymphadenectomy should consist of resection of the perigastric lymph nodes, the lymph nodes along the left side of the stomach, the liver and spleen artery, and the hepatoduodenal ligament (10). D3 dissection of lymph nodes is also performed, which consists of a complete removal of lymph nodes from the coeliac axis and para-aortic between the truncus coeliacus and the upper mesenteric. With an adequate lymph node dissection, a minimum of 15 nodes must be removed (9).

D2 lymph node dissection is currently the standard surgical procedure for the treatment of gastric cancer in cT1N+ and T2–4 (1, 7, 39), although some authors recommend this procedure only at the T2–4 and N+ stages. At these stages, D2 lymph node dissection is more efficient than D1 or D1+, as it achieves a higher survival rate. At present, D2 lymphadenectomy is performed with a preservation of the pancreas and spleen. However, D2 is a more demanding type of surgery compared to D1 (10). Recurrence after D2 lymph node dissection is lower compared to recurrence after limited surgery (1). The addition of perioperative and adjuvant chemotherapy has been shown to increase the long-term survival rate of the patients with this disease (6). A combination of neoadjuvant and adjuvant chemotherapy is also a benefit for the patient, but not every patient can receive adjuvant therapy (3). In our work, we focused on evaluating the effectiveness of neoadjuvant chemotherapy in the patients with gastric cancer, who underwent radical gastrectomy with D2 lymph node dissection.

Materials and methods

In the last decade, a multidisciplinary approach has been proposed in the treatment of gastric cancer with the adoption of neoadjuvant (preoperative or perioperative) treatment – chemotherapy.

In the period from 2017–2021, we performed a 5-year monitoring of the patients after radical gastrectomy with D2 lymph node dissection after neoadjuvant therapy at the Surgical department in

Tab. 2. Observed results.

	Sum (n=41)	NT (n=28)	Without NT (n=13)
Postoperative complications	17.1 % (n=7)	14.3 % (n=4)	23.1 % (n=3)
Duodenal leak	9.8 % (n=4)	7.1 % (n=2)	15.4 % (n=2)
Reoperation (lapar.)	2.4 % (n=1)	0 7.7 % (n=1)	
Postoperative deaths	4.9 % (n=2)	3.6 % (n=1)	7.7 % (n=1)
Postoperative liver failure	2.4 % (n=1)	3.6 % (n=1)	0
Reoperation–postoperative embolization into AP	2.4 % (n=1)	0	7.7 % (n=1)
Pathology			
1. Adenocarcinoma	85.4 % (n=35)		
– papillary	39.1 % (n=19)		
– tubular	24.4 % (n=10)		
– mucinous	14.6 % (n=6)		
– from the cells of the liver	7.3 % (n=3)		
2. Adenosquamous or squamous carcinoma	9.7 % (n=4)		
3. Undifferentiated carcinoma	4.9 % (n=2)		
Average tumour length	48 mm (5–160 mm)	45 mm (5–120 mm)	53 mm (10–160 mm)
Average tumour width	42 mm (0–110 mm)	40 mm (5–140 mm)	47 mm (10–160 mm)
Tumor classification			
T1	4.9 % (n=2)	7.1 % (n=2)	0
T2	63.4 % (n=26)	75 % (n=21)	38.5 % (n=5)
T3	24.4 % (n=10)	14.3 % (n=4)	46.2 % (n=6)
T4	7.3 % (n=3)	3.6 % (n=1)	15.4 % (n=2)
Average number of l. nodules	30±8	27	35
Lymph node classification			
N0	43.9 % (n=18)	53.6 % (n=15)	23.1 % (n=3)
N1	46.3 % (n=19)	42.9 % (n=12)	52.6 % (n=7)
N2	7.3 % (n=3)	3.6 % (n=1)	15.4 % (n=2)
N3	2.4 % (n=1)	0	7.7 % (n=1)
Distant metastases			
M0	61 % (n=25)	75 % (n=21)	30.8 % (n=4)
M1	14.6 % (n=6)	10.7 % (n=3)	23.1 % (n=3)
Mx	24.4 % (n=10)	14.3 % (n=4)	46.2 % (n=6)

Nitra. Surgical treatment was performed by 6 certified attestants. In selected period, 41 patients underwent radical gastrectomy with D2 lymph node dissection. Neoadjuvant therapy (NT) was indicated in 68.3 % (n = 28) patients. The median monitoring of the patients was 33 months. The average age of the patients was 62.3 years (20–72 years), with 65.9 % (n = 27) being men.

Results

On average, the surgery lasted 254 minutes (range = 145–460 min). The estimated average blood loss was 146 ml (range = 45–250 ml). Lymphadenopathy occurred in 85.4 % (n = 35) of the patients but was absent in the remaining 14.6 % (6). We reported postoperative complications in 17.1 % (n = 7) of the patients, with 14.3 % (n = 4) in the neoadjuvant group compared to 23.1 % (n = 3) in the treatment. Overall, duodenal leakage was found in 9.8 % (n = 4), (NT 7.1 % vs without NT 23.1 %) and reoperation was necessary in 2.4 % (n = 1) (without NT 7.7 %). In the group with neoadjuvant therapy, 3.6 % (n = 1) of patients died due to postoperative liver failure and in the group without neoadjuvant treatment 7.7 % (n = 1) after reoperation by embolization into AP, a total of

Tab. 3. Monitoring results.

Average length of hospital stay	10 days (range 7–24 days)		
Average viewing length	53 months (range 7–24 months)		
Number of patients with relapse	29.3 % (n=12)	25 % (n=7)	38.5 % (n=5)
Number of deaths after relapse	24.4 % (n=10)	21.4 % (n=6)	30.8 % (n=4)
Total 3-year survival-gastrectomy	85.4 % (n=35)	89.3 % (n=25)	76.9 % (n=10)
Overall. 5-year survival	75.6 % (n=31)	78.6 % (n=22)	69.2 % (n=9)
Overall. 5-year survival after adenocarcinoma	83.8 % (n=31)		
Overall. 5-year survival after mucinous type	75 % (n=3)		

17.1 % of the patients died. An average of 30 ± 8 lymph nodes was harvested. The average length of hospital stay of all the patients was 10 days (range = 7–24) and the average monitoring was 53 months (range = 3–12). The disease relapsed in 29.3 % (n = 12) patients (NT 25 % vs without NT 38.5 %), of which 24.4 % (10) (NT 21.4 % vs. without NT 30.8 %) died from the disease and their average survival was 25 months (range = 12–38) (Tabs 2 and 3).

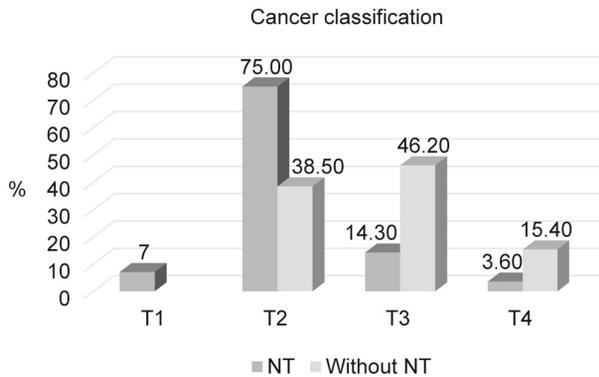


Fig. 1. Cancer classification.

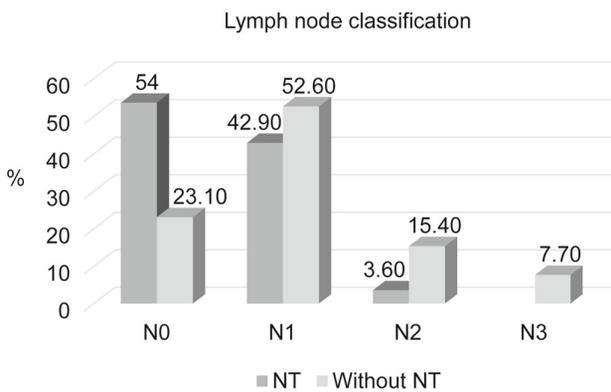


Fig. 2. Lymph node classification.

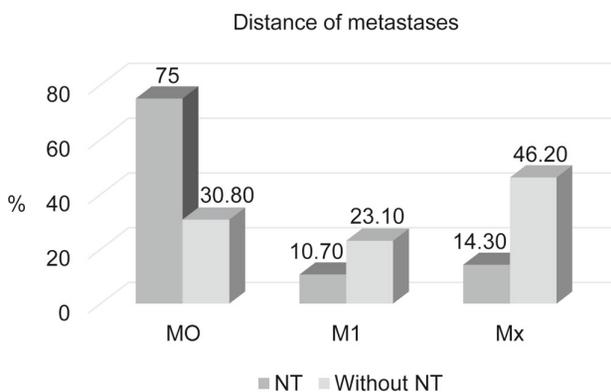


Fig. 3. Distance of metastases.

Withing the monitoring time, we observed differences in cancer size between the groups. The average tumour length in the group NT was 45 mm (range = 5–120 mm) and without NT 53 mm (range = 10–160 mm) and the average width in NT was 40 mm (range = 5–140 mm) and in the group with only surgical treatment 47 mm (range = 10–160 mm). We also noticed a difference in the representation of the T classification in the groups. In the neoadjuvant group, stage T1 was found in 7.1 % (n = 2) of the patients. T2 was found in 75 % (n = 21) in the NT group and in the group without NT in 38.5 % (n = 5). In the neoadjuvant group, T3 was found in 14.3 % (n = 4) of the patients and T4 in 3.6 % (n = 1) of the patients. In the group without neoadjuvant therapy, the incidence of T3 and T4 tumours was higher (46.2 % (n = 6) and 15.4 % (n = 2)) (Figs 1, 2, 3).

Preoperative data were available for 41 patients in the group with preoperative chemotherapy N = 28 and without neoadjuvant CHT N = 13. Five patients did not undertake chemotherapy for the following reasons: patient request (one patient), reassessment as inoperable (one patient), deterioration before chemotherapy (one patient), need for immediate surgery (one patient), and problems with the Hickman catheter (one patient). Of the 28 patients who started neoadjuvant treatment, 25 patients completed three cycles. The reasons for not completing the three preoperative cycles were as follows: toxic effects (1 patient – 2 cycles), patient request (1 patient – 2 cycles), Hickman catheter problems (one patient – 2 cycles).

Out of a total of 41 patients, 35 patients (85 %) subsequently underwent a postoperative chemotherapy. The reasons for not starting postoperative chemotherapy after the first three cycles in 6 patients were as follows- disease progression and early death (1 patient), postoperative complications (1 patient), problems with a Hickman catheter (1 patient), previous toxic effects (1 patient), insufficient response to preoperative treatment (1 patient), and worsening of coexisting disease (1 patient). Out of a total of 41 patients, 35 patients (85 %) completed three postoperative cycles.

The patients were indicated for either neoadjuvant chemotherapy and surgical resection (perioperative-chemotherapeutic group) or surgical resection alone (surgical group). Treatment was allocated using a minimization method according to the following stratification factors: age, tumour location (e.g., stomach or distal esophagus), CT finding.

Chemotherapy was administered in three cycles preoperatively and in three postoperative cycles. Each 3-week cycle consisted of epirubicin by intravenous bolus on day 1, cisplatin intravenously

with hydration on day 1, and fluorouracil for 21 days by continuous intravenous infusion using a two-lumen Hickman catheter and a portable infusion pump. One mg of warfarin daily was recommended for thrombosis prophylaxis. A complete blood count was taken before each chemotherapy cycle and the levels of nitrogen, blood urea, electrolytes, serum creatinine and liver function were determined.

The results showed that neoadjuvant chemotherapy significantly increased the rate of R0 resection (79 % vs 68 %) and reduced tumour size (T1 / T2 52 % vs 35 %) and metastases in regional nodes (N0 / N1 84 % vs 68 %) as the surgery itself preoperatively.

Anatomical imaging, including computed tomography (CT), magnetic resonance, endoscopy, and ultrasound, was one of the main methods in our cohort of the patients to determine the effectiveness of neoadjuvant therapy. In general, CT-based solid tumour response assessment (RECIST) criteria are used to calculate the length of the lesion before and after treatment to assess the degree of response. However, with tumour shrinkage and fibrosis, the accuracy of TNM staging by CT decreases. The accuracy of T staging decreased to 52 % and N staging to 84 %. With the development of endoscopic technology, endoscopic ultrasound (EUS) is receiving an increasing attention. EUS has advantages over CT and positron emission tomography, especially in the T1–T2 stage.

Indication of neoadjuvant chemotherapy should be consulted with a multidisciplinary team in case of advanced tumour. Several aspects need to be considered before determining treatment: determining the preoperative stage of the tumour as accurately as possible and symptoms associated with advanced stages of the disease.

Contraindications are the presence of obstruction and bleeding. However, the age of the patient should also be considered.

Neoadjuvant treatment can be performed in the patients with metastases – this is cN +. It is also indicated for the TNM3 stage and higher, but is also possible for the earlier stages. The indication in our group was the presence of a serous infiltrating tumour, carcinomas with large and metastatic nodes, Bormann's carcinomas type 4 and localized adenocarcinomas.

The patients of any age were eligible for neoadjuvant chemotherapy if they had histologically proven gastric or lower esophageal adenocarcinoma, which was considered stage II (via submucosa) or higher, without the evidence of distant metastases or locally advanced inoperable disease, as assessed by computed tomography or endoUSG.

The condition of the patients receiving neoadjuvant chemotherapy was not associated with tumour invasion (stage T, $p = 0.195$), lymph node spread (stage N, $p = 0.679$) or clinical disease ($p = 0.195$).

Tumours were stratified according to the depth of lymph node invasion and involvement in the patients undergoing neoadjuvant CHT and follow-up surgery and in the patients undergoing surgery only – for patients with pT1-2-pT4 and for pT1-2-pT4 with the patients with positive nodes. In these two subgroups of patients, the 5-year survival periods were 78.6 % and 69.2 %, respectively.

The surgery took place within six weeks after randomization in the surgical group and three to six weeks after the end of the third

cycle of chemotherapy in the preoperative chemotherapy group. Postoperative chemotherapy started 6 to 12 weeks after surgery.

The two groups did not differ significantly in terms of operative time, blood loss, surgical diseases, or postoperative length of stay (both $p > 0.05$).

Discussion

Gastric cancer is one of the most common cancers and is associated with a high mortality. Especially in advanced patients, the prognosis of the disease is poor despite recent advances in treatment (11). Gastric cancer is classified by two types, which is intestinal and the diffuse. The intestinal type has malignant cells, which can make a form of gastric carcinogenesis (36). Radical gastrectomy with regional lymph node dissection has proven to be the most effective. In the patients with advanced disease, radical gastrectomy is recommended worldwide along with D2 lymph node dissection. Radical gastrectomy is indicated, for example, in the patients with cancer of the upper third of the stomach (11). This procedure is currently considered the gold standard in the treatment of gastric cancer (7). The study results of Duchon et al. showed that in between patient's prognosis and the anatomic localization of the affected lymph nodes in case of gastric cancer patient's survival was the strongest correlation, however this correlation was not statistically significant (30).

Also, in our department of surgery, the given surgical procedure is chosen as the primary procedure in the treatment of patients with advanced disease. Radical gastrectomy with D2 lymphadenectomy is a complex surgical procedure that requires a multidisciplinary approach in intraoperative and postoperative management (7). Preoperative staging significantly affects the patient's decision to use multimodal treatment and also affects the patient's prognosis. Staging is also specified on the basis of examination of the resected sample together with the assessment of the depth of tumour invasion. It is also important to assess the extent of lymph node involvement, which is the key prognostic factor, along with the rate of lymphatic and blood vessel invasion (12).

D2 lymphadenectomy is the standard procedure mostly in eastern countries (46, 47, 48). As part of D2 lymph node dissection, we removed 30 ± 8 lymph nodes. This was a significantly higher average number than recommended in literature, where dissection is adequate when removing more than 15 nodes (9, 13). As well as our experience, the results of various studies point to the fact, that radical gastrectomy is often associated with the occurrence of non-surgical postoperative complications. Anastomotic leakage is most common (7). There were 4 cases of duodenal leakage in our group of patients. According to Zizzo et al (14), duodenal leakage after subtotal or radial gastrectomy is one of the most serious life-threatening complications. According to the authors, the incidence of duodenal leakage is 1.6–5 % (14). In our case, it was 8.7 % of the patients, but in none of the cases did we record leak as the cause of death of the patient. Duodenal leakage mortality is reported at 16–20 % and morbidity at 75 %. However, as Zikko et al (14) state that it is difficult to unambiguously determine the degree of leakage due to the heterogeneity of the data. In our case,

the duodenal leak prolonged the hospital stay after radical gastrectomy with D2 lymphadenectomy, and the reason for this fact is, according to the authors, infection, the presence of intra-abdominal abscess or bleeding, or acute pancreatitis.

5-year survival rates after radical gastrectomy vary across continents (8). The reason for these differences is currently unclear, but the volume of resection, less aggressive surgical approach, poorer staging and different biology are thought to contribute to this fact (8). Survival may be affected not only by tumour resection, but also by the extent of lymphadenectomy. For D2, the level of survival in Asia and Europe is higher than for D1, which is often performed mainly in North America (8). It was also shown that surgeons can safely perform D2 gastrectomy when spleen and pancreas are preserved (59,60), which leads to lower morbidity. In terms of survival, for the patients which are diagnosed with early gastric cancer (cT1N0), D1+ is recommended (40). However, there are several guidelines, which recommends curative resection with D2 lymphadenectomy. Particularly: Japanese gastric cancer treatment guidelines (49), Clinical practice guidelines for gastric cancer in Korea: an evidence-based approach. *J Gastric Cancer* (50), The Italian Research Group for Gastric Cancer (GIRCG) guidelines for gastric cancer staging and treatment (51), Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology (52), Guidelines for the management of oesophageal and gastric cancer, current S3 guidelines on surgical treatment of gastric carcinoma from Germany (53), ESMO (European Society of Surgical Oncology) Guidelines Working Group (54), European Society of Radiotherapy and Oncology (ESTRO) Gastric cancer guidelines (55) and NCCN Guidelines (56).

Hosoda et al (15) evaluated the results of long-term survival, with a minimum follow-up of 3 years. The monitoring included 40 patients, who underwent neoadjuvant chemotherapy and subsequent gastrectomy with D2 lymphadenectomy in the period from 2010 to 2017 due to the presence of large ulceroinvasive carcinoma, linitis plastica or N2 lymphadenopathy. The patients subsequently underwent adjuvant treatment. Adjuvant therapy was completed by 80 % of the patients within 1 year. The authors found an overall 3-year survival rate of 77.5 %, but a 3-year survival rate of 62.5 %. The results of the study support our findings that neoadjuvant as well as adjuvant therapy is of great importance in high-risk gastric cancers and increases the survival rate of the patients after radical gastrectomy with D2 lymphadenectomy.

The principle of treatment by resection is similar in many countries, but differences can be observed in preoperative and postoperative adjuvant treatment (16). Perioperative chemotherapy or postoperative chemotherapy is to be recommended especially in the patients with less than D1 resection, as well as in the patients with high-risk relapse, i. j. T3, T4 or N + M0. Current studies are examining the activity of new chemotherapeutic regimens (including neoadjuvant strategies) and their benefits in adequately treated patients (41). In Europe, neoadjuvant therapy is preferred for locally advanced cancers. This procedure was also confirmed to be effective by the MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) study, which confirmed a

higher survival rate of the patients on neoadjuvant therapy compared to the patients in whom perioperative chemotherapy was not performed. In contrast, postoperative adjuvant chemoradiotherapy is preferred in America and postoperative adjuvant chemotherapy is preferred in Asia. In Asia, neoadjuvant chemotherapy is given only to selected patients (16). Thus, different standards in chemotherapy have a significant impact on the survival of the patients with gastric cancer (17).

Li et al (18) reported in their research on the detection of survival predictors of neoadjuvant chemotherapy in the patients, who underwent radical gastrectomy with D2 lymph node dissection. The authors found that haemoglobin levels after neoadjuvant chemotherapy and changes in lymphocyte to monocyte ratio were significant independent prognostic factors (18). The study report of Hoskovec et al reported a new treatment option, which can improve the results of treatment of advanced gastric carcinoma mostly in case of (T3–T4), which is aggressive surgical resection (35).

Kung et al (6) based on their study reported that the median overall survival in the patients after total gastrectomy was 33.6 months, with a 5-year survival rate of 38.7 % in the D1 + /D2 group compared to 30.8 months and 32.6 % in group D0 / D1. Based on our practical experience, we agree with the authors' opinion that D2 lymphadenectomy has a higher rate of long-term survival compared to D0 / D1. Overall, studies indicate that D2 dissection is safe and is associated with an acceptable level of complications (6).

Smid et al concluded in their study, that the only treatment modality of gastric cancer which could lead to patients' cure under optimal conditions was radical surgery (29). Better results in gastric cancer treatment are presented, when it is diagnosed in early stages, with an adequate treatment of R0 resection of stomach, D2 lymphadenectomy and suitable perioperative chemotherapy (37).

D2 is currently considered the standard curative treatment for gastric cancer patients in Europe (19). This procedure has been accepted also in Far East for early as well as advanced gastric cancer (57). The method was developed in the East, but was gradually adopted by European surgeons several decades ago. The quality of D2 dissection has also improved in recent years, but some differences in survival can still be observed in Europe and the East. In Europe, it is therefore necessary to focus on improving the achieved results (19), which is also the aim of our study.

The study of Roviello et al provided the evaluation of significance of the number of metastatic nodes in early gastric cancer. He arrived to the conclusion, that nodes had significant impact and when more than 15 nodes were retrieved and better staging was achieved, they considered the treatment of choice D2 lymphadenectomy (58).

Treatment of gastric cancer has improved in last decade, but it is still in question about best selection of therapy (42). The benefit of neoadjuvant therapy in the patients undergoing radical gastrectomy with D2 lymph node dissection was observed in our study in a reduction in tumour size. This effect has been confirmed in other studies (3), with the authors noting a complete clinical treatment for gastric cancer in 5.8% and partial treatment in 30.4 %. Also, in the group after neoadjuvant therapy, a smaller tumour size was found compared to the group, in which only surgical treatment was

performed. The disadvantage is the possibility of a pathological response to neoadjuvant therapy, which was investigated in Schumacher et al (3) and occurred in 7.1 % of the patients. Overall, however, neoadjuvant therapy was associated with a higher rate of complete resection, a smaller size of primary carcinoma, and a lower number of lymph node metastases (3). Likewise, Mihmanli et al (1) reported that neoadjuvant chemotherapy increased the overall survival.

De Manzoni stated, that neoadjuvant treatment contributed significantly to patient survival. According to the authors, it is recommended for the patients with a stage of cancer higher than T1 or N+. However, it is difficult to determine the preoperative stage of the cancer. Obstruction or bleeding may be present in advanced stages, but this is a contraindication to unadjusted treatment. It is also difficult to predict the neoplasm's response to neoadjuvant chemotherapy, but only an adequate response improves the patient's prognosis (20).

The importance of neoadjuvant therapy in total gastrectomy with D2 lymphadenectomy was also confirmed by the results of Wielen et al (21), who performed open gastrectomy in 49 patients in 2015–2018. All the patients underwent neoadjuvant chemotherapy. The annual survival rate was 90.4 % (21).

Claassen et al (22) in 2007–2015 treated 636 patients, complications were observed in 47 % and postoperative mortality was 2.2 %. Anastomosis leakage was observed in 5 patients. The authors state that we evaluated neoadjuvant chemotherapy as well as splenectomy and male gender were associated with a higher incidence of postoperative complications. Total gastrectomy has also been associated with a higher risk of morbidity (22).

In many surgical departments around the world, D2 lymphadenectomy is not performed frequently and therefore the new generation of surgeons has very little experience with this procedure (8), which in our experience may have a negative impact on the patient survival. It is also appropriate to consider neoadjuvant therapy in the patients in whom no contraindication was found, given that preoperative therapy results in a reduction in the size of the cancer, which has been confirmed in our work as well as in the work of other authors (3).

The USA Intergroup 0116 trial (23) demonstrated a strong persistent benefit from neoadjuvant radiochemotherapy. This trial was conducted on 556 patients. However, surgical standardization was lacking, because only 10 % of the patients underwent D2 resections, whereas over 50 % underwent D0 resection, which could have impact on the final results of the study. The National Cancer Data Base report on poor survival of US gastric carcinoma patients treated with gastrectomy (24) discussed the advantage of use of more extensive D2 lymphadenectomy and it came to the conclusion, that randomized trials of D1 versus D2 lymphadenectomy have failed to demonstrate a survival advantage of D2.

Neoadjuvant chemotherapy has become the standard treatment for gastric cancer in the United States and European countries. The main reason for the different treatment strategies is that gastric cancer is usually detected at an earlier stage in Asian countries such as Korea and Japan, due to national gastric cancer screening programs (26). In addition, many issues related to neo-

adjuvant treatment of gastric cancer should be addressed, such as indications for patients in various fields, chemotherapeutic regimens, treatment cycles, the extent of postoperative neoadjuvant chemotherapy, and the importance of postoperative radiotherapy.

Referring to the Chinese Society of Clinical Oncology's (CSCO) standard for the diagnosis and treatment of gastric cancer, neoadjuvant chemotherapy is recommended for T3–4N1–3M0 local gastric adenocarcinoma. Appropriate selection of the patients for neoadjuvant therapy can ensure maximum benefit for the patients based on accurate preoperative staging and reduce the significant morbidity of surgery in high-risk patient groups (25).

The National Comprehensive Cancer Network (NCCN) guidelines recommends neoadjuvant chemotherapy for the patients with resectable gastric cancer with clinical stage \geq T2N0–3M0. 9 Based on MAGIC and FNCLCC / FFCO studies, the guidelines of the European Society of Medical Oncology (ESMO) recommend neoadjuvant chemotherapy with cisplatin combined with fluorouracil for all the patients with resectable gastric cancer whose clinical stage is $>$ T2M0 (27).

The most accurate evaluation criterion for neoadjuvant chemotherapy is pathological evaluation, which is usually consistent with tumour regression grading (TRG). However, some studies have found that TRG has no predictive value for postoperative long-term survival, and the predictive effect of pCR rate is not as good as the effect of lymph node metastasis rate (28). Localized disease, limited to mucosa and submucosa, is best treated surgically, and has a five-year survival of 70 to 95 %. 1,2 As tumour cells spread through the submucosa, the risk of lymph node metastases increases and the likelihood of prolonged disease-free survival decreases. Western surgical and population series show that most patients have a tumour that has penetrated the submucosa and they have a five-year survival rate of 20 to 30 %.

Conclusion

Radical gastrectomy with D2 lymph node dissection is the gold standard for the treatment of T2–T4 gastric cancers. By adding neoadjuvant treatment, it is possible not only to shrink the tumour, which facilitates its resection, but also to improve the patient's prognosis and 5-year survival. Neoadjuvant CHT is safe and effective so for this reason, we recommend that neoadjuvant therapy to be performed in the patients in whom there is no contraindication before the actual treatment. In order to improve oncological outcomes, the resection rate must be improved, and neoadjuvant treatment must play a major role in conventional therapy. Pathological findings showed an improved tumour response and downstaging in the group of the patients after neoadjuvant CHT and radical gastrectomy with D2 lymphadenectomy as in the group with radical gastrectomy and D2 lymphadenectomy. The patients with neoadjuvant CHT had a favorable pathological response without an increase in postoperative complications. There is currently some consensus on the treatment regimen for gastric cancer, and postoperative adjuvant therapy combined with surgery is considered to be better than surgery alone. Neoadjuvant chemotherapy is better than surgery for stomach and distal esophageal cancer alone.

However, there is still a number of issues worth examining, such as evaluating the effectiveness of neoadjuvant chemotherapy and the role of targeted and immunological therapies.

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