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ORIGINAL ARTICLE

The role of laparoscopic staging in the management of gastric cancer

Znaczenie laparoskopowej oceny zaawansowania w leczeniu raka żołądka

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ABSTRACT:

Aim: Staging laparoscopy enables us to carry out palliative treatment, neo-adjuvant therapy for curative resection or direct curative resection and to make a decision on appropriate strategy leading to minimal morbidity by avoiding unnecessary laparotomies. In the present study, the importance of staging laparoscopy was retrospectively investigated by studying clinical and pathological data.

Material and methods: Data of 70 out of 350 patients who underwent diagnostic laparoscopy due to gastric cancer at Surgical Oncology Department between August 2013 and January 2020 were retrospectively analyzed.

Results: Peritoneal biopsy was positive for malignancy in 41 (58.5%) and negative in 29 (41.5%) of the patients who underwent SL. Peritoneal cytology (PC) results were negative in 32 (45.7%) patients and positive in 38 (54.3%) patients. Peritoneal biopsy and cytology results were concurrently positive in 35 patients and concurrently negative in 26 patients.

Conclusions: In conclusion, even the most developed imaging methods cannot provide for 100% correct staging, therefore SL plays an important role in the treatment of gastric cancer and laparoscopic staging is considered a simple, inexpensive, safe and well tolerated method in patients suspected of peritoneal disease who cannot be adequately evaluated with pre-operative methods.

KEYWORDS: cytology, gastrectomy, peritoneal biopsy, staging laparoscopy

STRESZCZENIE:

Cel: Laparoskopia z oceną zaawansowania (ang. *staging laparoscopy*; SL) pozwala na wdrożenie leczenia paliatywnego, terapii neoadjuwantowej przed leczeniem operacyjnym lub na bezpośrednią resekcję radykalną oraz na ustalenie strategii postępowania, co pozwala ograniczyć śmiertelność poprzez uniknięcie niepotrzebnych laparotomii. W naszym badaniu retrospektywnie oceniliśmy znaczenie laparoskopii z oceną zaawansowania w oparciu o dane kliniczne i histopatologiczne.

Materiał i metody: Analizie retrospektywnej poddano dane 70 z 350 pacjentów poddawanych diagnostycznej laparoskopii z powodu raka żołądka w Klinice Chirurgii Onkologicznej od sierpnia 2013 do stycznia 2020 roku.

Wyniki: Biopsja otrzewnej była dodatnia na obecność komórek nowotworowych u 41 (58,5%) pacjentów i ujemna u 29 (41,5%) pacjentów poddawanych SL. Cytologia płynu z otrzewnej była ujemna u 32 (45,7%) pacjentów i dodatnia u 38 (54,3%) pacjentów. Wyniki biopsji i cytologii były równocześnie dodatnie u 35 pacjentów i jednocześnie ujemne u 26 pacjentów.

Wnioski: Podsumowując, nawet najbardziej zaawansowane metody obrazowania nie pozawalają w 100% ocenić zaawansowania procesu nowotworowego, tym samym SL odgrywa istotną rolę w leczeniu pacjentów z rakiem żołądka. Laparoskopowa ocena zaawansowania, jako zabieg prosty, tani, bezpieczny i dobrze tolerowany, powinna stanowić podstawę postępowania u pacjentów z podejrzeniem zajęcia otrzewnej, u których nie udaje się w pełni ocenić zaawansowania choroby badaniami przedoperacyjnymi.

SŁOWA KLUCZOWE: biopsja otrzewnej, cytologia, gastrektomia, laparoskopowa ocena zaawansowania

ABBREVIATIONS

CEA – Carcinoembryonic Antigen
HIPEC – Hyperthermic İntra-peritoneal Chemotherapy
JCOG – Japanese Clinical Oncology Group
P – Periton
PC – Peritoneal Cytology
SL – Staging Laparoscopy
UICC – International Union Against Cancer

INTRODUCTION

Gastric cancer is the fourth leading cancer type worldwide and the second leading cause of cancer-related deaths [1]. Peritoneum is one the most common recurrence sites and mean survival is approximately one year following recurrence [2]. Peritoneal spread is 4% in early stage gastric cancer and about 25% in local advanced stage tumors [3]. Computed tomography, endoscopic ultrasonography and positron emission tomography may be used for detecting

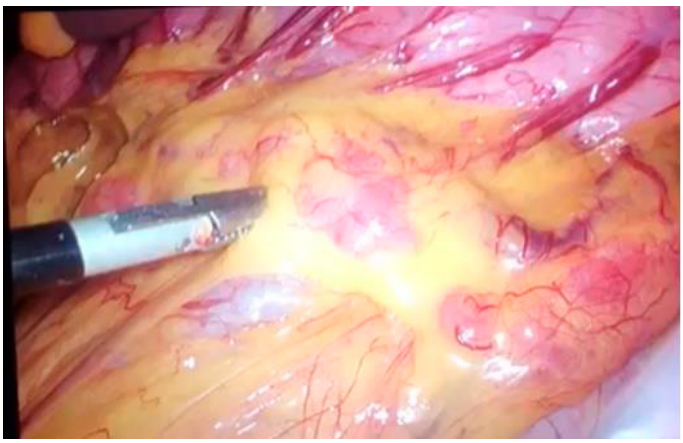

Fig. 1. Bulky lymph nodes.

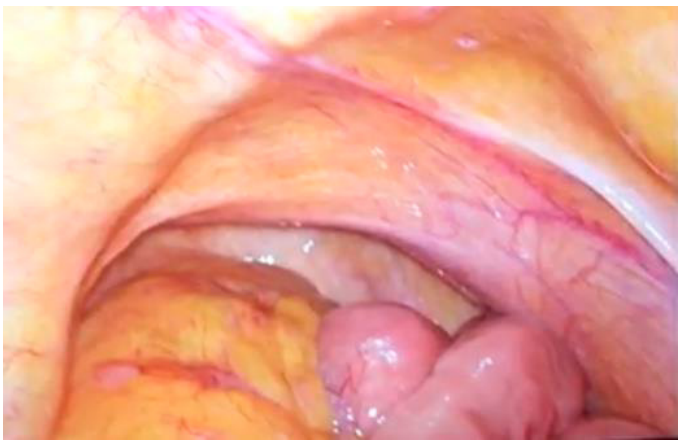

Fig. 2. Peritoneal implant.

distant metastasis, tumor size and spread in preoperative staging of gastric cancer. however peritoneal spreads, superficial liver metastases and tumor implants in mesenteric root may not be visualized with imaging methods [4]. Staging laparoscopy (SL) is a minimally invasive method used for detection of peritoneal spread and occult metastases that cannot be evaluated with imaging methods, and for cytologic evaluation, and it should be performed in all patients who are planned to undergo curative surgery. According to the American Joint Committee on Cancer Seventh and Eighth Edition on Staging System (M1), detection of tumor cells with cytologic examination is an accepted diagnostic method in metastasis, even in the absence of peritoneal or distant metastases On the other hand, patients who do not have visceral or peritoneal metastasis and whose cytology result is negative, are qualified to curative surgery [5]. Popova et al. first showed the importance of SL in 1980s and suggested that almost half of the patients would avoid unnecessary laparotomy [6]. The question is which patients should undergo SL. There is no clear information on this issue in literature [7]. However, according to the Japanese Clinical Oncology Group (JCOG), patients with T4–T4 and/or node positive, large Bormann type 3 (> 8 cm) or type 4 cancer, suspicion of peritoneal spread and serosal spread undergo SL [8, 9]. SL may detect distant metastases and occult peritoneal spread more clearly [10]. Laparoscopy with staging enables us to carry out palliative treatment, neo-adjuvant therapy for curative resection or direct curative resection and to decide on appropriate strategy minimizing morbidity by avoiding unnecessary laparotomies [11]. In the present study, the importance of SL was retrospectively investigated using clinical and pathologic data.

MATERIAL AND METHODS

Patient Selection

Data of 70 out of 350 patients who underwent diagnostic laparoscopy due to gastric cancer at Surgical Oncology Department between August 2013 and January 2020 were retrospectively analyzed. Exclusion criteria: distant metastasis with pre-operative imaging methods, no possibility for R0 resection, previous operations, T1 tumor, synchronous tumor, co-morbidities that could complicate surgery, urgent surgeries (due to bleeding, stenosis or perforation) and less than 18 years of age. Indications for SL included diagnosis of adenocarcinoma with biopsy, T3-4 N0-3 M0, suspected peritoneal disease, Bormann type 3 (> 8 cm) and bulky and/or para-aortic lymph node [8].

Data Collection

Operation and pathology reports, pre-operative hematological and biochemical parameters, tumor markers, demographic features, peritoneal cytology and biopsy, distant metastasis, stage and decreasing tumor size were analyzed. The results of radiological examinations (chest X-ray, computed tomography, endoscopy, endo-ultrasonography, and positron emission tomography) were retrospectively obtained from electronic records.

The aim of the study was to reveal the changes in treatment strategies caused by SL. Staging was done based on the 14th edition of the Japanese Classification of Gastric Carcinoma by the Japanese Gastric Cancer Association and TNM classification (17). Bormann type 3 was defined as ulcerative and infiltrative, type 4 was defined as diffuse gastric cancer. Bulky lymph nodes were defined as lymph nodes larger than 3 cm (Fig. 1.) or lymph nodes larger than 1.5 cm in the central region [12]. Tumor size was evaluated with endoscopy and tomography and the largest size was recorded.

Laparoscopic Staging Technique

Colonic clearance was provided by using laxatives and bowel prep one night before the operation and the operation was performed following 8-hour fasting. A single dose of prophylactic antibiotic (cefazolin 1 g) was administered pre-operatively. All patients were put in reverse Trendelenburg and French position with both arms closed. A 12-mm camera trochar (PT00015248, Medtronic, Dublin, Ireland) was inserted over the umbilicus, a 5-mm trochar was inserted from the left upper quadrant and a 12-mm trochar was inserted from the right upper quadrant. The abdomen was washed with 350–400 cc of saline solution at this site in case of the presence of ascites, while the subphrenic, subhepatic, omentum and both paracolic regions were washed with 350–400 cc of saline solution. If there was no ascites, the patient was put in Trendelenburg position and 50 cc of fluid were aspirated from the Douglas pouch. After this procedure, the abdominal cavity was examined for the presence of distant metastasis, invasion of the tumor into the serosa and adjacent tissue, peritoneal disease, bulky lymph node, implants in the liver, stomach, omentum and mesenterium (Fig. 2.). Exploration was started at the right quadrant and continued in clockwise direction. Specimens were obtained in the presence of atypical lymph nodes and biopsies were obtained in case of no

Tab. I. Descriptive characteristics.

VARIABLES		
Age	Mean ± SD	59.50 ± 13.69
	Median (Min–Max)	63.00 (22.00–80.00)
Gender, n (%)	Female	21 (30.0)
	Male	49 (70.0)
Location, n (%)	Cardia	14 (20.0)
	Corpus	37 (52.9)
	Antrum	16 (22.9)
	Linitis Plastica	3 (4.2)
Pathological T Stage, n (%)	Non-operated	42 (60.0)
	T3	12 (17.2)
	T4a	15 (21.4)
	T1	1 (1.4)
Pathological N Stage, n (%)	0	6 (8.6)
	1	4 (5.7)
	2	9 (12.9)
	3a	8 (11.4)
	3b	1 (1.4)
	Non-operated	42 (60.0)
Treatment approach, n (%)	Palliative	42 (60.0)
	Surgery after neo-adjuvant therapy	15 (21.4)
	The same session	13 (18.6)
Survival, n (%)	Died	46 (65.7)
	Survived	24 (34.3)
Peritoneal Metastasis, n (%)	Negative	29 (41.4)
	Positive	41 (58.6)
Peritoneal Cytology, n (%)	Negative	32 (45.7)
	Positive	38 (54.3)
CA19–9, n (%)	Normal	46 (65.7)
	High	24 (34.3)
CEA, n (%)	Normal	53 (75.7)
	High	17 (24.3)
Tumor size	Mean ± SD	6.80 ±2.30
	Median (Min–Max)	7.00 (1.50–11.00)
Survival time	Mean ± SD	17.37 ±15.73
	Median (Min–Max)	13.25 (1.00–75.00)
Lessening of tumor size	Mean ± SD	36.00 ±9.67
	Median (Min–Max)	40.00 (20.00–50.00)
Lessening of node size	Mean ± SD	33.67 ±6.67
	Median (Min–Max)	30.00 (20.00–40.00)
Time until the operation	Mean ± SD	23.86 ±47.50
	Median (Min–Max)	0.00 (0.00–180.00)

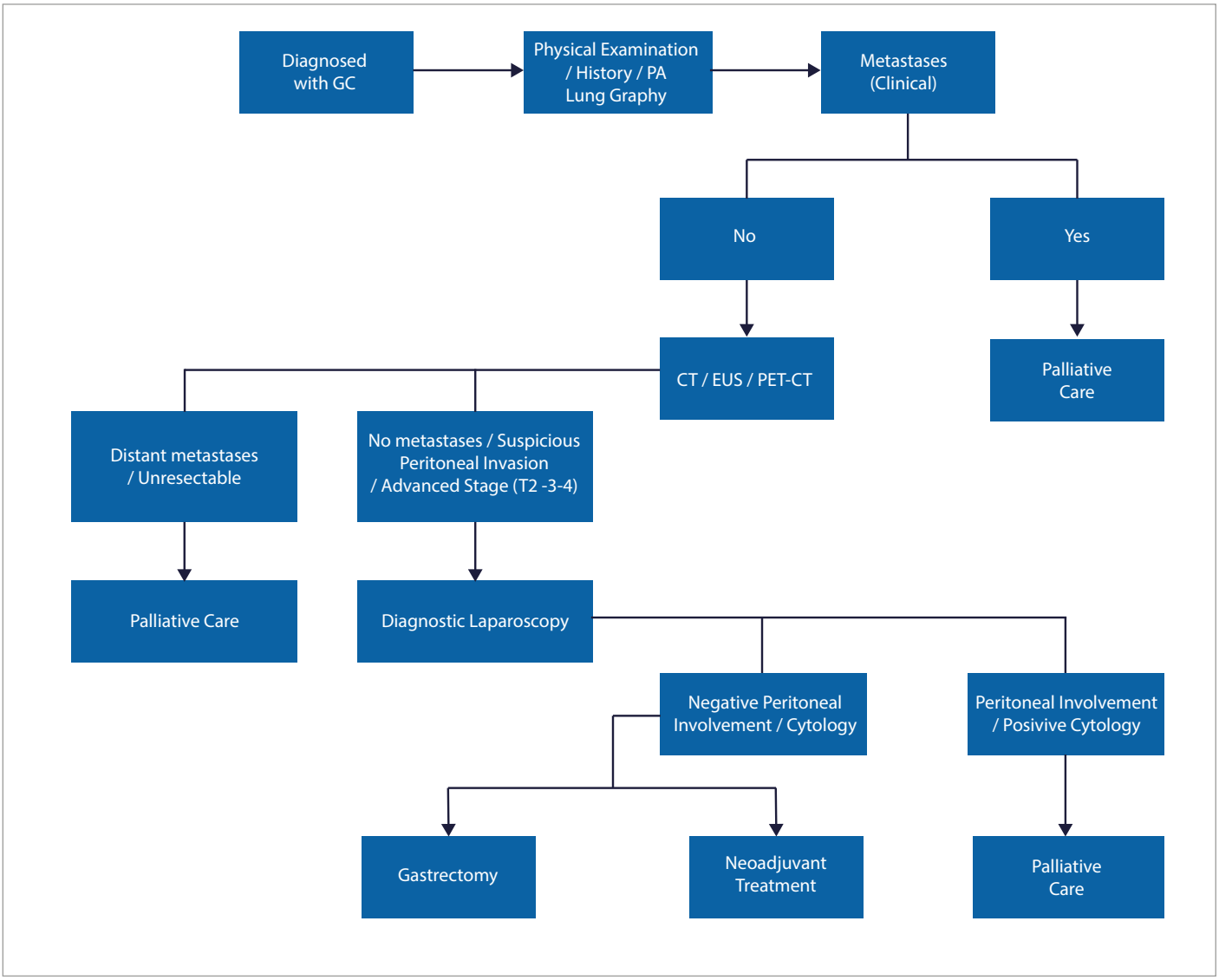

Fig. 3. The algorithm.

possible complete excision. The peritoneal biopsy specimen was sent to frozen section analysis to determine treatment type. The use of electro-cautery was minimized when obtaining biopsies because thermal effect influences the quality of the tissue sampled for frozen section. Laparoscopic gastrectomy was continued if the frozen section result was negative and the R0 resection could be performed; neo-adjuvant therapy was performed if R0 could not be performed. Palliative treatment was chosen if peritoneal spread and cytology results were positive. The algorithm of our clinic is depicted in Fig. 3.

Statistical Analysis

Data were analyzed by using SPSS 11.5 program. In descriptive statistics, mean ± standard deviation and median (minimum--maximum) values were used for quantitative variables and patient number (percent) was used for qualitative variables. Logistic regression analysis was used for detection of the risk factors that influence dependent qualitative variables. Survival analyses on qualitative and quantitative variables were done with the Kaplan-Meier method and the significant differences between groups were detected by using the log-rank test. A P-value of < 0.05 was accepted as statistically significant.

RESULTS

Seventy patients underwent diagnostic laparoscopy due to gastric cancer. Of the patients, 21 (30%) were females and 49 (70%) were males. Mean operative time was 52.8 min including frozen time. Post-operative mortality and complications did not develop and overall survival was 34.3%. All descriptive characteristics are shown in Tab. I.

Peritoneal biopsy was positive for malignancy in 41 (58.5%) and negative in 29 (41.5%) patients who underwent SL. Peritoneal cytology (PC) results were negative in 32 (45.7%) patients and positive in 38 (54.3%) patients. Peritoneal biopsy and cytology results were concurrently positive in 35 patients and concurrently negative in 26 patients. While peritoneal biopsy results were positive and cytology results were negative in only 6 patients, peritoneal biopsy was negative and cytology was positive in 3 patients.

In the study, a total of 28 patients underwent gastrectomy. Gastrectomy was continued as peritoneal cytology and biopsy results were negative in 13 patients, while 15 patients had a locally advanced disease and they underwent neo-adjuvant therapy. Only one patient underwent R1 resection following neo-adjuvant therapy and

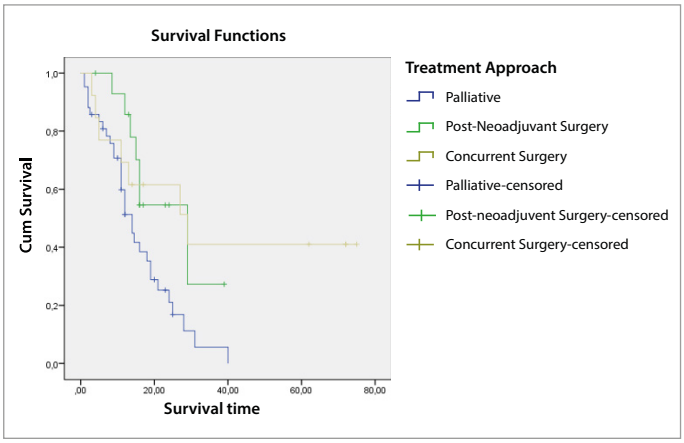

Fig. 4. The Kaplan-Meier survival curve according to treatment approaches.

the other patients had R0 resection. In the patients receiving neo-adjuvant therapy, a mean decrease in tumor size was 36 ± 9.67% and the median was 40% (20–50%). For node size reduction this was 33.67 ± 6.67% and 30% (20–40%), respectively. The mean duration between diagnosis and surgery after neo-adjuvant therapy was 3.6 months. Forty-two patients did not undergo surgery and they received palliative therapy. A statistically significant relationship was found between treatment approaches and survival (P = 0.011) (Fig. 4.).

Almost all of our patients had clinically T3/T4 tumor and the post-operative pathology result was T1 following neo-adjuvant therapy in only one patient. A nearly significant relationship was found with peritoneal metastasis, particularly in T4a tumors (P = 0.051). This relationship was not significant in the other stages due to the small number of patients and the fact that all cases were T3–T4. Bulky lymph node was present in 45 patients and there was a statistically significant relationship with peritoneal metastasis (P = 0.021). While 20 patients were N(-), 50 patients were N(+). Of tumor markers, only CEA was high and there was a statistically significant relationship with peritoneal cytology positivity (P = 0.042). Peritoneal, serosal, omental implant or distant metastasis were not visualized with pre-operative imaging methods but they were further detected with diagnostic laparoscopy in 33 (47.14%) patients.

A statistically significant relationship was found between T and N stage and survival, with P-values being 0.007 and 0.039, respectively. A statistically significant relationship was found with regard to survival in P/PS-negative and P/PS-positive patients (P = 0.008) (Fig. 5.).

DISCUSSION

Laparoscopy is a technique that yields 90% accurate results for the assessment of resectability [13]. Treatment modalities of the patients may change based on the results of SL and unnecessary operations increasing morbidity and mortality can be avoided [14]. Treatment modality was changed in 55.7% of the patients following SL. Pre-operative resection was planned in 33 (47.14%) patients but SL revealed peritoneal spread and, as a result, palliative treatment was chosen. The results are similar to those from literature [15, 16]. In most of the studies in literature the indications as well as the inclusion and exclusion criteria are not clear. We performed SL in those patients who had T3-4N0-3M0 tumor, suspected peritoneal disease, Bormann type 3 (> 8 cm) – type 4, bulky and/or para-aortic lymph node. We performed SL for large tumors as the peritoneal spread risk is higher and the prognosis is poorer in these patients, and we considered SL to be more beneficial [8, 17]. On the other hand, bulky and para-aortic lymph nodes do not correlate with the likelihood of peritoneal disease as strongly as the tumor size. There are also studies available in literature showing the opposite [18]. The rate of peritoneal metastases was found to be high in patients with bulky lymph nodes and the difference was statistically significant (P = 0.021).

Unnecessary operations are avoided in some patients thanks to SL. In our study, 42 patients were referred to palliative therapy and unnecessary surgical interventions connected with potential morbidity and mortality were avoided. In literature, palliative resection was reported not to yield better results than chemotherapy and the present study also shows that the patients with serosal and adjacent tissue invasion should be referred to neo-adjuvant therapy which may allow for R0 resection, even if the absence of peritoneal disease [19].

The chance for R0 resection increases through stage reduction following neo-adjuvant therapy for tumors in which peritoneal involvement and cytology are negative. However, the borders cannot be clearly distinguished from the liver, pancreas and adjacent soft tissues, which leads to adhesions or requires more extensive resections. Tanizawa et al. reported that the R0 resection was performed in 20 out of 30 advanced-stage gastric cancer patients following neo-adjuvant chemotherapy [20]. In our study, we conducted neo-adjuvant therapy following SL in 15 patients. The R0 resection was performed in 14 (93.3%) patients and R1 in 1 (6.7%) patient following neo-adjuvant therapy. The number of R0 resections increases together with fewer post-operative complications following neo-adjuvant therapy after SL.

In literature, metastases are divided into two groups: those with positive peritoneal cytology and with positive peritoneal biopsy [21]. Therefore, local advancement is divided into 4 groups: PC(+) P(+), PC(-) P(-), PC(+) P(-), PC(-) P(+). The P(+) patients undergo palliative treatment and unnecessary operations are avoided [22], P(-)PC(+) patients are still under debate. This status is accepted as distant metastasis according to the International Union Against Cancer (UICC) staging system [23]. Some authors do not recommend curative surgery in patients who do not have a significant metastatic disease but are PC(+) [22]. Prognosis of the P(-) PC(+) patients was shown to be better than in P(+) PC(+) patients in the study of Lee et al. [24]. In another study, some of the P(-) PC(+) patients converted to P(-) PC(-) following neo-adjuvant therapy and showed better survival as compared to the PC(+) patients that did not convert [25]. Badgwell et al. reported that P(-) PC(+) patients became P(-) PC(-) following neo-adjuvant chemotherapy and this had an oncologic benefit [26]. In another study, no difference was found between neo-adjuvant therapy and post-operative adjuvant therapy in P(-) PC(+) patients [27]. In literature, the incidence of cytology positivity varies between 4% and 40%, while the ratio of peritoneal spread varies between 26% and 70% in peritoneal cytology positivity, with specificity between 70% and 100% [22, 28]. The incidence of PC(+) was found to be 54.3% in our study. This high variability of cytology has naturally led to it being criticized. We performed curative surgery in 3 P(-) PC(+) patients among the ones who underwent SL in our clinic. Post-operative

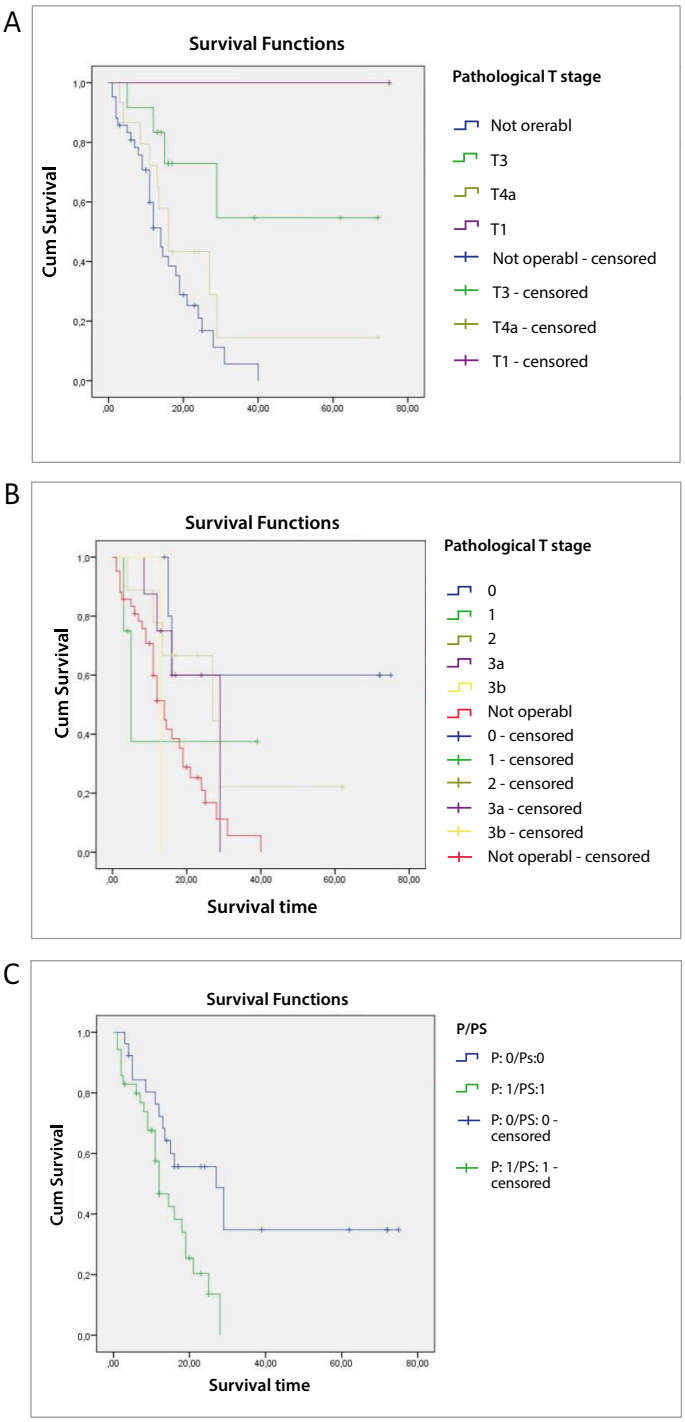

Fig. 5. The Kaplan-Meier survival curve according to pathological stages and P/PS-negative and P/PS-positive patients.

follow-ups of the patients continue and recurrence has not developed. We believe that this allows for a better comparison between curative surgery and subsequent chemotherapy, and palliative approach in cytology-positive patients, with an increase in of the number of such studies.

The recent developments in cancer chemotherapy have improved the treatment results of some patients with positive cytology, with the survival time reaching 5 years following radical surgery with chemotherapy. The use of various chemotherapy combinations together with surgery is a promising strategy even in patients with low density peritoneal metastasis [29]. Can hyperthermic intra-peritoneal chemotherapy (HIPEC) be applied to cytology-positive patients? The efficiency of HIPEC was shown in cytology-positive patients in the study of Ishigami et al. [30]. Cytology was shown to become negative in 24 out of 82 patients in phase 2 study by the same team [31]. These results were promising for us because HIPEC could be useful in cytology-positive patients.

In the study of Bentrem et al., R0 resection and cytology examination were performed in patients without a visible metastasis in pre-operative imaging and cytology positivity was shown to increase with T stage increase. Tumor location and nodal involvement were shown not to be related with cytology positivity [32]. Benevolo et al. reported that cytology could be positive in early T stage patients with nodal involvement [33]. In our study, a statistical significance was not found in peritoneal cytology positivity with regard to tumor location, nodal involvement and T stage. The reasons for not detecting a significant association with the T stage may the following: all our patients were T3–T4 because other stages were excluded and the population size was small. As a result of all these studies, the most important factors that influence cytology positivity were found to be T and clinical stage, with the importance of SL gradually increasing in advanced T stage gastric cancer patients, owing to which a correct treatment may be applied.

Studies are available in literature reveal the sensitivity of SL in detecting a peritoneal disease. Sometimes laparoscopy shows only distant metastases. Irino et al. showed the incidence of peritoneal disease to be 47% [34], while Hosogi et al. – 45% [35], and Ikoma [36], Miki [37], Ishigami [38] and Yamgata [39] – 36%, 53.4%, 42.7% and 46%, respectively. This rate was 45.7% in our study. One of the most important causes of such discrepancies is different indications, and thus we consider that these rates would increase when common indications are established. False negativity is one of the main problems in SL, with the rate reaching 17% in SLs performed for similar indications in literature [37]. The implants are usually overlooked because of small tumoral structures in the small intestine and colonic mucosa. False negativity was 3 (10.7%) in our study. This rate cannot be neglected and the importance of thorough exploration of organs (and particularly intestinal mesentery) during SL is emphasized in the studies. Cytologic samples should be taken from many sites after peritoneal washing (subphrenic, subhepatic, pelvic, paracolic, omentum) and not only from a single region, for reducing false negativities. We believe that the differences among countries follow from different indications and technical specifications.

Criticism, mainly about the indications, is also present in SL. Indications may be widened; however, this leads to unnecessary SLs so we consider that current indications are sufficient. We also consider that SL is less expensive as compared to unnecessary laparotomies if performed in proper patient populations; shorter hospital stay also supports this. Although trochar sites are reported to be risky for tumor implantation, we did not notice this in our clinic and studies are available in literature reporting that this risk does not increase [23]. The fact of its being an invasive procedure is an issue of concern by some researchers. However, we suggest not to worry as this is a short procedure that usually does not lead to complications.

We believe that clinical use of tumor markers should be extended because these markers were reported to be potentially related with peritoneal disease [40]. In our study, CEA > 3 ng/mL was considered high, and a significant correlation was found between CEA and peritoneal cytology positivity ($P = 0.042$).

No statistically significant correlation was found with CA 19–9 ($P > 0.05$). The association between tumor markers and peritoneal disease would be better explained with more study populations and studies on this issue, which would lead to fewer false negative results with SL.

The study has some limitations, such as small patient population, retrospective design, no reports on the neo-adjuvant treatment regimens and inclusion of only T3–T4 stage gastric cancer cases (According to NCCN, it is possible to treat the T1b stage or higher).

CONCLUSIONS

Even the most developed imaging methods cannot provide 100% correct staging, therefore SL plays an important role in the treatment of gastric cancer and laparoscopic staging is essential as a simple, inexpensive, safe and well tolerated method in patients with suspected peritoneal disease and who cannot be clearly evaluated with pre-operative methods. Although SL has been applied for years in gastric cancer patients, the total patient number is insufficient and the current studies do not support this approach [15, 16].

Its clear benefits were shown in multi-disciplinary treatment modalities and advanced stage gastric cancers. SL will potentially play a more important role in the studies on gastric cancer in future. Unnecessary laparotomies could be avoided with more accurate patient selection and the selected patients could be referred for chemotherapy, which would give better treatment results. The important point is the standardization of patient selection.

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