SCHOLASTIC:
Journal of Natural and Medical Education
Volume 2 Issue 5, Year 2023 ISSN: 2835-303X
https://univerpubl.com/index.php/scholastic

Neoadjuvant Chemotherapy Followed by Surgery Versus Surgery Alone in Patiens with Esophageal Cancer: Results of Surgical Treatment

Yusupbekov A. (Akhmedjanovich) Abrorjon
MD, DSc, Professor, Deputy director of Republic specialized scientific-practical medical center of oncology and radiology (National Cancer Center of Uzbekistan), Tashkent, Uzbekistan

Tuychiev D. (Dilshodovich) Otabek
MD, senior researcher in thoracic surgical oncology department of Republic specialized scientific-practical medical center of oncology and radiology (National Cancer Center of Uzbekistan), Tashkent, Uzbekistan

Usmanov B. (Baymatovich) Bekzod
MD, PhD, senior researcher in Oncology and Hematology department of Tashkent State Pediatric Institute, Tashkent, Uzbekistan

Kamishev V. (Viktorovich) Sergey
MD, DSc, chairman of 2-nd Chemotherapy department of Republic specialized scientific-practical medical center of oncology and radiology (National Cancer Center of Uzbekistan), Tashkent, Uzbekistan

Article Information

Received: March 29, 2023
Accepted: April 29, 2023
Published: May 31, 2023

Keywords: *esophageal cancer, neoadjuvant chemotherapy, curative surgergy, short-term results, complications.*

ABSTRACT

Objective: This research was intended to demonstrate the short-term results of the surgical treatment of patients with operable esophageal scuamouse cell cancer by comparing the group treated with neoadjuvant chemotherapy with the group treated with surgery alone.

Method: 52 patients, who were documented in archives of the National Cancer Center of Uzbekistan from 2011 to 2022, treated with neoadjuvant chamotherapy following curative intend esophagectomy were included to our study. For control group, patients with comparable gender and age parameters, the degree of concomitant diseases and the volume of operations who underwent only surgical intervention during the specified period were randomized.

Result: Postoperative complications were recorded in 21/52 (40.38%) patients in the study group and in 18/55 (32.72%) patients in the control group. Two patients (3.84%) in the study group and three patients (5.44%) in the control group died within 30 days of surgery. Frequency of non-fatal therapeutic postoperative complications was almost the same in both groups. However, pulmonary complications were more common in the nCTS group

Conclusion: Thus, it can be concluded that preoperative CRT does not affect a significant increase in the incidence of surgical and therapeutic complications in patients with resectable cancer of the thoracic esophagus, while it has been proven to prolong the disease-free survival and overall survival. However, individualization of the combined treatment regimen in this group of patients is necessary.

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

Background

Esophageal squamous cell carcinoma (ESCC) accounts for the majority of esophageal malignancies worldwide and reaches up to 90% in the Eastern Hemisphere. Despite the full volume of radical intervention, prognosis in patients with ESCC is unfavorable, with a 5-year survival rate of 20 to 30%. Factors influencing this poor prognosis include the presence of an early locally advanced process and undetected metastatic cancer at initial diagnosis. Due to the high frequency of locoregional recurrence and long - term progress, the combination of surgical treatment with systemic chemotherapy is of great interest [1-7].

Advantages of preoperative chemotherapy include an increased likelihood of R0 resection by lowering the stage of the tumor and improvement in symptoms caused by the tumor itself [1,8,9]. It is also believed that systemic chemotherapy can help eliminate micrometastases and circulating tumor cells. More recently, the importance of controlling systemic diseases has been highlighted through new understanding of the process of cancer metastasis. For decades, distant tumor metastasis was considered as the axis of the last stage of the disease. Currently, evidence is accumulating that dissemination can occur already at an early stage of the disease. Theoretically, the use of preoperative chemotherapy may have a positive effect on the survival of patients with esophageal cancer [2,3,10,11]. In this paper, we present the short-term results of the surgical treatment of patients with operable ESCC by comparing the group treated with neoadjuvant chemotherapy (nCTS) with the group treated with surgery alone (S).

Materials and methods

The number of patients included in the study was 52 patients in the nCTS group and 55 patients in the S group . All eligible patients had histologically confirmed esophageal squamous cell carcinoma and surgery was performed at the National Cancer Center from 2011 to 2022. Patients were considered operable if the disease was clinically limited to the local region (tumor stage 1, 2, 3, or 4a; any nodal stage and no distant metastases). Patients with distal esophageal carcinoma and suspected celiac lymph node involvement (M1a) were also considered eligible for surgery. Exclusion criteria: unresectable cases identified during surgery. Patients scheduled for preoperative chemotherapy were treated with two cycles followed by assessment of clinical response. Response was assessed two to three weeks after the last cycle of chemotherapy. The clinical response after chemotherapy was assessed using esophagogastroscopy and MSCT of the chest and abdomen with *per os* contrast. Tumor responses were assessed according to World Health Organization (WHO) criteria. The complete absence of any signs of malignant disease, including negative results of a biopsy from the area of the former tumor, was regarded as a complete regression (CR). Partial regression (PR) was defined as > 50% reduction in tumor volume without the appearance of new lesions. Stable process (SP) was defined as tumor progression up to 25% or the appearance of a new lymph node. Patients with a complete or partial response received two additional courses of chemotherapy, while patients who did not respond to treatment (stable disease or progressive disease) were referred for immediate surgery. Patients with progressive disease (T4b or M1b disease) were treated palliatively and were followed up. Patients, who were randomized to surgery alone, were operated as soon as possible. Patients receiving chemotherapy went to surgery on 4-6 weeks after the last cycle of treatment.

Neoadjuvant chemotherapy

For neoadjuvant chemotherapy of operated patients, were used chemotherapy regimens with Cisplatin + 5-fluorouracil (5FU) and Cisplatin (carboplatin) + Pacletaxel. Cisplatin at a dose of 80 mg/m^2 was administered intravenously over 4 hours on the first day of each cycle before and after adequate hydration. 5-FU at a dose of 750 mg/m^2/day on days 1-4 was administered intravenously as a 96 hour infusion. In the second regimen, Cisplatin at a dose of 80 mg/m^2 was

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

also administered intravenously for 4 hours on the first day of each cycle before and after adequate hydration (with concomitant diseases of the cardiovascular system of moderate severity, with subcompensated impaired liver and kidney function, Carboplatin was used [AUC 5]). Pacletaxel at a dose of 175 mg/m^2 was administered intravenously over 2 hours on the first day of each cycle, preceded by promedication, dexomethasone at a dose of 8 mg was administered intravenously, up to 12, 6 and 1 hours before the chemotherapy infusion. These cycles were repeated at week 4. In the case of a clinical response, two subsequent courses of chemotherapy were performed at the 7th and 10th weeks. All patients received prophylactic anti-nausea treatment with 5-HT3 receptor antagonists during chemotherapy. Treatment-related toxicity was measured according to WHO guidelines. Retreatment with the next cycle was allowed only with an absolute neutrophil count of at least 3500/mm^3 and a platelet count of at least 100,000/mm^3. Treatment can be delayed up to 2 weeks.

Surgery and Histological examination

For tumors of the upper third of the intrathoracic esophagus, a three-zone esophagectomy (MacKeown operation), for tumors of the middle and lower third of the intrathoracic esophagus, the Ivor -Lewis operation was performed. The tumor and adjacent lymph nodes are excised as a single block. The left gastric artery was transected at the site of its origin with resection of the local lymph nodes. The continuity of the digestive tract was restored by the formation of the gastric tube. Tumor stage after resection was classified according to the TNM classification of the International Cancer Committee. Resections were classified as radical when all margins were free of tumor cells on microscopic examination (R0). Resections were considered non-radical if microscopic examination revealed tumor cells on the resection line (R1) or the presence of non-removed macroscopically tumor tissues (R2).

Results

Between January 2011 and December 2022, 52 patients, documented in the archives of the National Cancer Center were treated with neoadjuvant chemotherapy followed by surgery (nCTS group, N=52). For the control group, patients with comparable gender and age parameters, the degree of concomitant diseases and the volume of operations who underwent only surgical intervention during the specified period were randomized (S group, N=55). Exclusion criteria was any simultaneous and combined surgery.

Table 1 show that the two groups were similar in age, gender, location of the tumor process, and comorbidities that can affect the postoperative results of surgery.

Table 1. Clinical and age-gender characteristics

Characteristics	nCTS		S		Total		*p-value*
Age	**n**	**%**	**n**	**%**	**n**	**%**	***0.039***
≤49	**11**	**(21,15%)**	**10**	**(18,18%)**	**21**	**(19,62%)**	
50-69	**35**	**(67,3%)**	**37**	**(67,27%)**	**72**	**(67,28%)**	
≥70	**6**	**(11,5%)**	**8**	**(14,54%)**	**14**	**(13,08%)**	
Sex	**n**	**%**	**n**	**%**	**n**	**%**	***0.041***
Male	**34**	**(65,38%)**	**35**	**(63,63%)**	**69**	**(64,48%)**	
Female	**18**	**(34,6%)**	**20**	**(36,36%)**	**38**	**(35,51%)**	
Tumor location	**n**	**%**	**n**	**%**	**n**	**%**	***0.064***
Upper	**1**	**(1,92%)**	**2**	**(3,63%)**	**3**	**(2,8%)**	
Middle	**14**	**(26,92%)**	**15**	**(27,27%)**	**29**	**(27,1%)**	
Lower	**13**	**(25,0%)**	**18**	**(32,72%)**	**31**	**(28,97%)**	
Upper-middle	**3**	**(5,76%)**	**2**	**(3,63%)**	**5**	**(4,67%)**	

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

Middle-lower	**21**	**(40,38%)**	**18**	**(32,72%)**	**39**	**(36,44%)**	
Concomitant disease	**n**	**%**	**n**	**%**	**n**	**%**	***0.05***
Ischemic heart disease	**28 (53,84%)**		**33 (60,0%)**		**61 (57,0%)**		***0.038***
FC1	**4 (7,7%)**		**4 (7,27%)**		**8 (7,47%)**		
FC2	**24 (46,15%)**		**29 (52,72%)**		**53 (49,53%)**		
Ischemic heart disease (arrhythmia)	**6 (11,53%)**		**6 (10,9%)**		**12 (11,2%)**		***0.76***
Paroxysm	**2 (3,84%)**		**3 (5,76%)**		**5 (4,67%)**		
Extrasystole	**4 (7,7%)**		**3 (5,76%)**		**7 (6,54%)**		
Hypertonic disease	**35 (67,3%)**		**34 (61,81%)**		**69 (64,48%)**		***0.041***
1 degree	**5 (9,6%)**		**4 (7,27%)**		**9 (8,4%)**		
2 degree	**25 (48,0%)**		**23 (41,81%)**		**48 (44,85%)**		
3 degree	**5 (9,6%)**		**7 (12,72%)**		**12 (11,2%)**		
Diabetes mellitus	**7 (13,46%)**		**11 (20,0%)**		**18 (16,8%)**		***0.061***
Compensated	**3 (5,76%)**		**4 (7,27%)**		**7 (6,54%)**		
Subcompensated	**4 (7,7%)**		**6 (10,9%)**		**10 (9,34%)**		
Decompensated	**0 (0%)**		**1 (1,81%)**		**1 (0,93%)**		
COPD	**6 (11,53%)**		**7 (12,72%)**		**13 (12,14%)**		***0.91***
Hepatitis	**13 (25,0%)**		**14 (25,45%)**		**27 (25,23%)**		***0.057***
Remission	**9 (17,3%)**		**12 (21,81%)**		**21 (19,62%)**		
Small activity	**3 (5,76%)**		**1 (1,81%)**		**4 (3,73%)**		
Moderate activity	**1 (1,92%)**		**1 (1,81%)**		**2 (1,86%)**		
CRF	**1 (1,92%)**		**1 (1,81%)**		**2 (1,86%)**		***1.0***

FC – functional class, COPD – Chronic obstructive pulmonary disease, CRF – chronic renal failure

Chemotherapy

Of the 52 patients who received preoperative chemotherapy, 49 (94.2%) patients received two or more cycles, and 3 patients (5.8%) received one cycle. The reason why only one cycle was performed has not been established. Evaluation of the clinical response after two courses of chemotherapy showed partial regression in 25 patients who subsequently underwent esophagectomy. 27 patients required more cycles of nCT due to the insufficient effect of chemotherapy. 11 patients received 4 courses of nCT, there were also cases of nCT up to 9 courses, the cause of which was not documented. Evaluation of the clinical response after additional cycles of chemotherapy showed a complete response in three patients. Detailed data on toxicity associated with chemotherapy are not available. All patients in the current study received standard anti-nausea prophylaxis with 5-HT3 receptor antagonists during chemotherapy.

Surgical intervention

The mean time from hospitalization to surgery was 6 days in the S group. Two patients (3.84%) in the nCTS group and three patients (5.44%) in the S group died within 30 days of surgery. Postoperative complications were recorded in 21/52 (40.38%) patients in the nCTS group and in 18/55 (32.72%) patients in the S group. Frequency of non-fatal therapeutic postoperative complications was almost the same in both groups (Table 2). However, pulmonary complications were more common in the nCTS group (P =0.62).

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

Table 2. Therapeutic postoperative complications

Complications	nCTS (n=52)	S (n=55)	*P-value*
Respiratory complications	**7 (13,46%)**	**5 (9,1%)**	***P=0.62***
Pneumonia	**2 (3,84%)**	**1 (1,81%)**	
COVID pneumonia	**0 (0%)**	**1 (1,81%)**	
RDS	**1 (1,92%)**	**0 (0%)**	
Plevritis	**4 (7,7%)**	**3 (5,45%)**	
Cardiovascular complications	**6 (11,53%)**	**7 (12,72%)**	***P=0.58***
Arrhythmia	**2 (3,84%)**	**4 (7,27%)**	
Acute coronary syndrome	**0 (0%)**	**1 (1,81%)**	
Cardiac failure	**3 (5,76%)**	**1 (1,81%)**	
TELA	**1 (1,92%)**	**1 (1,81%)**	
Mortality	**1 (1,92%)**	**2 (3,63%)**	***P=0.87***

RDS – respiratory distress syndrome, TELA – thromboembolism of lung arteries

Of the 52 patients in the nCTS group who underwent surgical resection, 80.7% had a R0 resection, 11.53% had a R1 resection, and 7.7% had a R2 resection. Of the 55 patients in the S group who underwent surgical resection, 75.7% had a R0 resection, 15.8% had a R1 resection, and 8.6% had a R2 resection. Although more patients in the nCTS group had more R0 and R1 resections compared with the S group, no significant differences were observed (*P*=0.049). Also, there was not major difference between the number of R2 resections in both treatment groups (P=0.71) (Table 3).

Table 3. Marginal research results

Resection margin	nCTS	S	Total	*P-value*
R0	**42 (80,76%)**	**39 (70,9%)**	**81 (75,7%)**	***0.049***
R1	**6 (11,53%)**	**11 (20,0%)**	**17 (15,88%)**	***0.53***
R2	**4 (7,7%)**	**5 (9,1%)**	**9 (8,65%)**	***0.99***

As surgical complications after esophagectomy in our study groups, we took those complications that required active management. According to the incident of surgical complications, 8 (15.38%) complications were observed in the nCTS group, 6 (10.9%) cases in the S group (*P*=0.43). Table 4 shows that the most common complication in the main group was anastomotic leakage (5.76%), while in the control group chylotrax met more than the rest (5.45%).

Table 4. Surgical postoperative complications

Complications	nCTS (n=8)	S (n=6)	*p-value 0.43*
Bleeding	**1 (1,92%)**	**0 (0%)**	***1.0***
Anastomotic leakage	**3 (5,76%)**	**2 (3,63%)**	***0.87***
Transplant necrosis	**2 (3,84%)**	**1 (1,81%)**	***0.91***
Chylothorax	**1 (1,92%)**	**3 (5,45%)**	***0.73***
Reoperation	**1 (1,92%)**	**0 (0%)**	***1.0***
Mortality	**1 (1,92%)**	**1 (1,81%)**	***0.62***

Despite the greater number of complications in the first group, the severity of these complications according to the Clavien - Dindo gradation turned out to be almost the same (Table 5).

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

Table 5. Surgical complication grades according to the Clavien-Dindo classification

Complication grade	nCTS (n=8)	S (n=6)
I grade	0 (0%)	0 (0%)
II grade	1 (1,92%)	1 (1,81%)
IIIa grade	4 (7,7%)	2 (3,63%)
IIIb grade	3 (5,76%)	2 (3,63%)
IVa grade	0 (0%)	1 (1,81%)
IVb grade	0 (0%)	0 (0%)
V grade	1 (1,92%)	1 (1,81%)

Discussion

The impact of neoadjuvant chemotherapy on the survival of patients with esophageal squamous cell carcinoma is no longer in doubt. Despite this, in the latest world scientific literature there are more and more ambivalent opinions regarding the effect of this toxic treatment method on postoperative complications [12,13]. Among recent researches, publications devoted to the study of neoadjuvant chemotherapy on the short-term results of extended operations in patients with ESCC are quite rare. Very often, neoadjuvant chemotherapy is combined with radiation therapy, which significantly affects the somatic status of patients [1,10]. Based on this, we studied only the effect of chemotherapy on the 30-days results of subsequent surgery.

Shogenov M.M. et al., published the results of combined treatment of patients with ESCC compared with surgery alone. The patients were divided into two groups: the main group (n=26), which underwent combined treatment, and the control group (n=30), where only surgical treatment was performed. Preoperative chemotherapy included two courses of chemotherapy. Surgical intervention was performed in the volume of subtotal resection of the esophagus with intrapleural anastomosis with a wide gastric transplant. R0 resections were performed in 24 (92.3%) patients of the main group and 26 (86.7%) in the control group. When evaluating postoperative complications, it was found that in the group of patients who received preoperative chemoradiotherapy, therapeutic complications were observed in 17 (65%) patients, in the control group - in 18 (60%). The frequency of surgical complications was slightly higher in the complex treatment group and amounted to 26.92% versus 20% in the surgical treatment group. A lethal outcome in the postoperative period was observed in one patient in the combined treatment group, which was 3.84% [7].

In a study by J. Boonstra et al., an analysis was made of the effect of preoperative chemotherapy on immediate outcomes in patients with esophageal squamous cell carcinoma. 169 patients were divided into two groups (CTS - 85, S - 84 patients). Of the 85 patients in the main group, 66 (77.6%) patients received esophagectomy after neoadvant chemotherapy. Of the control group, 70 (83.3%) patients out of 84 underwent resection of the esophagus. All patients were operated on in the volume of transthoracic resection of the esophagus with simultaneous plasty, if necessary, the formation of an anastomosis on the neck. Although the frequency of R0 resections in the CTS group was higher than in the S group, no significant differences were observed in the overall structure of resection radicalism. The incidence of anastomotic leakage in both groups was the same and was observed in 8 patients in the CTS group (11%) and 9 (11%) in the monotherapy group. 30-day mortality was 5% in the CTS group and 8.3% in the S group, respectively [10].

Analysis of results of the chemotherapy effect on the subsequent operation of patients with ESCC in the world literature is quite rare. Meta-analysis conducted by Kidane V. and colleagues in the study of the role of neoadjuvant chemotherapy in the multimodal treatment of patients

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

with resectable esophageal cancer included 13 randomized trials with a total of 2362 patients. All patients were also divided into two groups: I group - patients with preoperative CT + surgery, group II - patients after surgical treatment. According to the authors' review, R0 resection in the main group was 58%, and in the control group 52%. The incidence of postoperative complications in the main and control groups was 33% and 36%, respectively. Anastomotic leakage occurred in 5.8% of patients in the muldimodal treatment group, 6.3% in the group of surgical treatment alone. Postoperative death, on average, was 6.3% and 6.8% for the main and control groups, respectively. The data presented in this review indicate no significant differences in the incidence of postoperative complications in the two compared groups [9].

In a retrospective cohort study conducted by Hurmuzlu M. with co-authors to study the effect of high-dose chemoradiotherapy followed by surgery or only surgical treatment for esophageal cancer, 107 patients were selected (the first group included patients who were treated with only surgical intervention (n=45); in the second group, treatment started with preoperative CRT followed by surgery (n=62)). It was shown that postoperative complications occurred within 30 days after surgery in 73.3% patients of first group and in 80.6% patients of second group. The frequency of respiratory complications was 44.4% and 45.2% respectively. At the same time, anastomotic leakage occurred in 11.1% patients of the first group and in 6.4% patients of the second group. It should be noted that the authors also found no significant differences in the incidence of complications in the two compared groups [14].

Conclusion

In this manner, it can be concluded that preoperative CT does not affect a significant increase in the incidence of early surgical and therapeutic complications in patients with resectable cancer of the thoracic esophagus. At the mean time, it has been proven to suggestively prolong the disease-free survival and overall survival. However, individualization of the combined treatment regimen in this group of patients is essential.

Reference

1. Franko J, McAvoy S, Timing of esophagectomy after neoadjuvant chemoradiation treatment in squamous cell carcinoma, Surgery, Volume 164, Issue 3, 2018, Pages 455-459.
2. Po-Kuei Hsu, Ling-I Chien, Lin-Chi Chuang, et al. Modified En Bloc Esophagectomy for Squamous Cell Carcinoma After Neoadjuvant Chemoradiotherapy, The Annals of Thoracic Surgery, 01/2023
3. Shah RD, Cassano AD, Neifeld JP. Neoadjuvant therapy for esophageal cancer. *World J Gastrointest Oncol* 2014; 6(10): 403-406
4. Sung H, Ferlay J, Siegel R. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA CANCER J CLIN 2021;71:209–249
5. Yusupbekov A.A., Khairuddinov R.V., Tuychiev O.D. et al. Modern Views In Diagnostics And Treatment Of Esophageal Cancer (Literature Review). European Science Review № 3–4 2019 March–April. P 57-62
6. Yusupbekov A.A., Kanda M, Tuychiev O.D., et al. Junichi Sakamoto et.al. Surveillance of esophageal cancer in the Republic of Uzbekistan from 2000 to 2018. Asian Pacific Journal of Cancer Preview. № 21(8) 2020. P 2281-2285
7. Shogenov MS, Davidov MM, Allakhverdyan AK, et al. Influence of preoperative chemo-radiotherapy to rate of postoperative complications on patients with Esophageal cancer. Malignant tumors/2018; 8(4):30-36

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

8. [Шогенов М. С., Давыдов М. М., Аллахвердиев А. К., и др. Влияние предоперационной химиолучевой терапии на частоту послеоперационных осложнений у больных раком грудного отдела пищевода // Злокачественные опухоли 2018; 8(4):30-36]
9. Kanda M, Shimizu D, Miyata K, et al. Neoadjuvant docetaxel, oxaliplatin plus S-1 for treating clinical stage III squamous cell carcinoma of the esophagus: Study protocol of an open-label phase II trial. Contemporary ClinicalTrialsCommunications24(2021)100853
10. Kidane_B, Coughlin_S, Vogt_K, et al. Preoperative chemotherapy for resectable thoracic esophageal cancer. *Cochrane Database of Systematic Reviews* 2015, Issue 5. Art. No.: CD001556.
11. Boonstra et al.: Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal squamous cell carcinoma: Long-term results of a randomized controlled trial. BMC Cancer 2011 11:181.
12. Drolaiz H.W.L, Nina S, Emmerson J, et al. Neoadjuvant chemotherapy improves survival in patients with oesophageal mucinous adenocarcinoma: Post-hocanalysis of the UK MRC OE02 and OE05 trials. European Journal of Cancer 170 (2022) 140e148
13. Kandilis A, Iniguez CB, Khalil N, et al. Residual lymph node disease and mortality following neoadjuvant chemoradiation and curative esophagectomy for distal esophageal adenocarcinoma. JTCVS Open c March 2021/ Volume 5, Number C
14. Okamura A.,1 Watanabe M.,1 Mine S.,1 et al. Failure of neoadjuvant chemotherapy for resectable esophageal squamous cell carcinoma. *Diseases of the Esophagus* (2017) 30, 1–8
15. Hurmuzlu M., Ovrebo K., Monge O.R., et al. High-dose chemoradiotherapy followed by surgery versus surgery alone in esophageal cancer: a retrospective cohort study. *World J. Surg. Oncol.* 2010. Vol. 8(46).

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).