UDC: 616.329-089.844-006.66+612.087 DOI: 10.52532/2663-4864-2020-3-57-20-27

I.A. ILYIN[1], V.T. MALKEVICH[1]

[1]N.N. Alexandrov National Cancer Center of Belarus, Minsk, the Republic of Belarus

The impact of fatal complications on surgical esophagocoloplasty outcome in cancer patients

Relevance: *The impact of esophageal cancer surgery complications on survival rate remains a challenge due to the complications and mortality associated with surgical esophagocoloplasty.*

The purpose of this study *was to assess the impact of fatal complications (colonic graft necrosis and pneumonia) on surgical esophagocoloplasty outcomes in cancer patients.*

Results: *The analysis included 110 patients treated by colonic esophagoplasty for esophageal carcinomas and gastroesophageal junction carcinomas. The frequency of postoperative complications of degree III-IV according to Clavien-Dindo was 36.4% (40/110). Pneumonia developed in 15% (16/110), colonic graft necrosis – in 5% (6/110). Out of all causes of death (pneumonia, graft necrosis, bleeding, pulmonary thromboembolism), only graft necrosis (odds ratio (OR) 21.112 [95% CI 2.751-162.013] p=0.003) and pneumonia (OR 15.141 [95% CI 3.225-71.089] p=0.001) were the predictors for 90-days' mortality. Mortality from pneumonia amounted to 37.5% (6/16), from necrosis – 50% (3/6). Median overall survival without pneumonia (n=94) and with pneumonia (n=16) was 26.6 and 8.0 months, respectively ($p_{logrank}$=0.030; p_{cox}=0.034). Median overall survival without graft necrosis (n=104) and with necrosis (n=6) was 26.6 and 3.7 months, respectively ($p_{logrank}$=0.0001; p_{cox}=0.001). The patients subjected to colonic esophagoplasty with planning (n=55) had fewer postoperative complications (56.4% [31/55] vs. 16.4% [9/55], p<0.0001), lower risk of their development (OR 0.151, 95% CI 0.0620.369, p<0.0001), higher overall 10-year survival (26.0% vs. 17.7%) and median survival (49.8 vs. 17.4 months, $p_{logrank}$=0.038, p_{cox}=0.041).*

Conclusions: *Postoperative development of* pneumonia or colonic graft necrosis is associated with a significant deterioration in treatment outcomes. Improving the surgical management of cancer patients who require esophagocoloplasty has the potential to improve long-term survival.

Keywords: *esophageal cancer, esophagogastric junction cancer, surgical treatment, combined surgical procedures, esophagocoloplasty, selective angiography, vascularization.*

Introduction: Surgery of malignant tumors of the esophagus and esophagogastric junction is one of the most invasive methods to treat carcinomas of the upper digestive tract. Several authors shared the opinion that surgical complications can impair long-term treatment outcomes. Krarup et al. showed that a failure of anastomosis after therapeutic colon cancer resection could deteriorate the survival rate [1]. Tokunaga et al. also found that intra-abdominal infectious complications after gastrectomy for gastric cancer worsened the patients' overall and relapse-free survival [2]. The impact of esophageal cancer surgery complications on survival remains an acute issue discussed in a few publications. Some studies have shown a significant effect of postoperative complications on a decrease in survival [3-6], while others have not proven this pattern [7, 8].

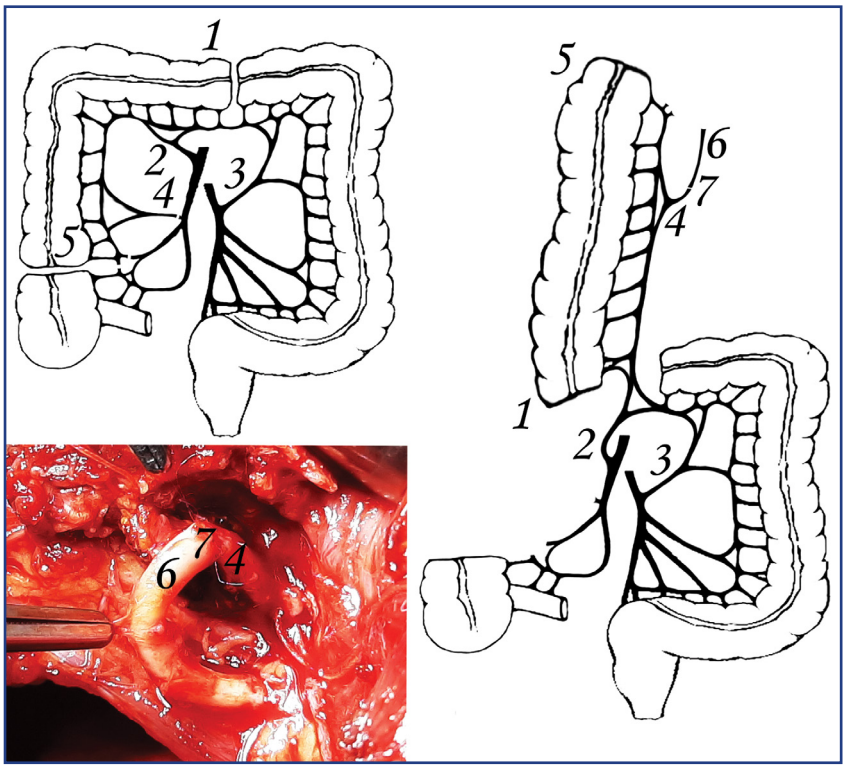
Esophagoplasty, its specific complications, and associated mortality remain a challenge.

In the analyzed publications, certain factors that influence survival were studied in the groups of patients after various variants of esophagectomy where a gastric transplant was used as a plastic material. However, we could find no published observations regarding surgeries where a segment of the patient's colon was used as a transplant for esophagoplasty.

The purpose of this study was to assess the impact of fatal complications (graft necrosis and pneumonia) on the outcomes of surgical esophagocoloplasty in cancer patients.

Materials and methods: The study included 110 patients who underwent colonic esophagoplasty for esophageal carcinoma or esophagogastric junction carcinoma. By the moment of reconstruction, interventions were divided into primary (39.1%, 43/110), repeated (39.1%, 43/110), and delayed (21.8%, 24/110). The patients' average age was: median – 56.50, interquartile range – 49.25-62.50 years; body mass index: median – 20.10, interquartile range – 19.96-24.31. Men prevailed in the cohort (85%, 93/110).

In 50% (55/110) patients, the colon esophagoplasty planning method was applied to increase surgery efficiency. The method's essence is that a selective angiography (upper and lower mesentericographies) is conducted pre-op to study the vascular peculiarities of the blood supply to the colon to form a viable and functional transplant. The data obtained is used for a test clamping of supply vessels during surgery to assess the viability of the formed intestinal segment. Any signs of ischemia and ineffective blood supply to the graft require a transition to another reconstruction option. In the absence of such a possibility, the graft is vascularized by anastomosing the colon-intestinal and internal thoracic arteries (Figure 1).



Legend: 1 – aboral end of the graft, 2 – middle colic artery, 3 – left colic artery, 4 – crossed right colic artery, 5 – oral end of the graft, 6 – Internal thoracic artery, 7 – inter-arterial vascular anastomosis
Figure 1 – Graft formation and vascularization scheme

The total and adjusted survival rates were calculated by Kaplan-Meier. The survival in the analyzed cohorts was compared by the Mantel-Cox Log Rank test ($p_{logrank}$). The influence of variables on the occurrence of the studied events was assessed by logistic regression with the determination of the odds ratio (OR). The factors influencing the relative risk (RR) of death were determined by Cox regression analysis (p_{cox}).

Results and Discussion: The overall frequency of postoperative complications after esophagectomy varies widely (20 to 80%) [9, 10]. In this study, the frequency of the degree III-IV complications after esophagocoloplasty by Clavien-Dindo classification was 36.4% (40/110), including pneumonia – 15% (16/110), anastomosis failure – 7% (8/110), graft necrosis – 5% (6/110), bleeding – 4% (4/110), peritonitis – 3% (3/110), intestinal obstruction – 1% (2/110), pulmonary embolism – 1% (2/110).

90-day postoperative mortality was 10% (11/110). Of the fatal cases, 5.5% (6/110) were caused by pneumonia, 1.8% (2/110) – by graft necrosis, another 1.8% (2/110) – by bleeding, and 0.9% (1/110) – by pulmonary thromboembolism. The predictors of 90-day mortality from all causes of death (pneumonia, graft necrosis, bleeding, pulmonary thromboembolism) included necrosis (OR 21.112 [95% CI 2.751-162.013] p=0.003) and pneumonia (OR 15.141 [95% CI 3.225-71.089] p=0.001).

Pneumonia was one of the life-threatening complications in patients after surgery with esophagocoloplasty. Pneumonia developed in 14.4% (16/110) patients and caused death in 5.5% (6/110) cases. Moreover, pneumonia-caused mortality amounted to 37.5% (6/16). The presence of pneumonia increased the risk of 90-day mortality (OR 10.68 [95% CI 2.755-41.401], p=0.001) and worsened the long-term survival prognosis (RR 1.953 [95% CI 1.052-3.625], p_{cox}=0.034). Thus, the overall survival without pneumonia (n=94) and with pneumonia (n=16) after esophagocoloplasty was equal to: 1-year survival – 77.5% vs. 40.9%, 3-year survival – 44.9% vs. 27.3%, 5-year survival – 35.9% vs. 27.3%, 7-year survival – 30.5% vs. 13.6%, and 10-year survival – 26.4% vs. 13.6%; median survival was 26.6 months vs. 8.0 months, respectively (Figure 2).

The development of pneumonia in 8 out of 56 treated patients with stages I-II cancer did not affect their overall survival ($p_{logrank}$=0.090; p_{cox}=0.099). However, it impaired the specific survival due to a 2.6-times' higher risk of death from cancer (p_{cox}=0.039). The 10-year survival decreased from 36.6% to 25.0%; the median survival rate – from 63.0 to 5.0 months ($p_{logrank}$=0.031) (Figure 3, Table 1).

The pneumonia-dependent survival and death risk analysis in 8 out of 54 patients with cancer stages III-IV showed no negative impact of pneumonia on the overall ($p_{logrank}$=0.199; p_{cox}=0.205) or specific survival ($p_{logrank}$=0.105); p_{cox}=0.113) (Figure 3, Table 1).

Multifactorial regression analysis revealed, with a predictive accuracy of 90.9%, which independent variables were to be included in the final equation to calculate the risk of developing postoperative pneumonia. The planning method (OR 0.037 [95% CI 0.003-0.394], p=0.006) and intraoperative antibiotic prophylaxis (OR 0.206 [95% CI 0.043-0.985], p=0.048) had a protective role. Neoadjuvant

chemoradiotherapy (OR 22.794 [95% CI 1.053-493.418], p=0.046), previous surgery with gastrectomy (before surgery with esophagocoloplasty) (OR 17.387 [95% CI 2.673-113.1], p=0.003), and concomitant type II diabetes mellitus (OR 19.827 [95% CI 1.276-308.151], p=0.003) were the negative factors.

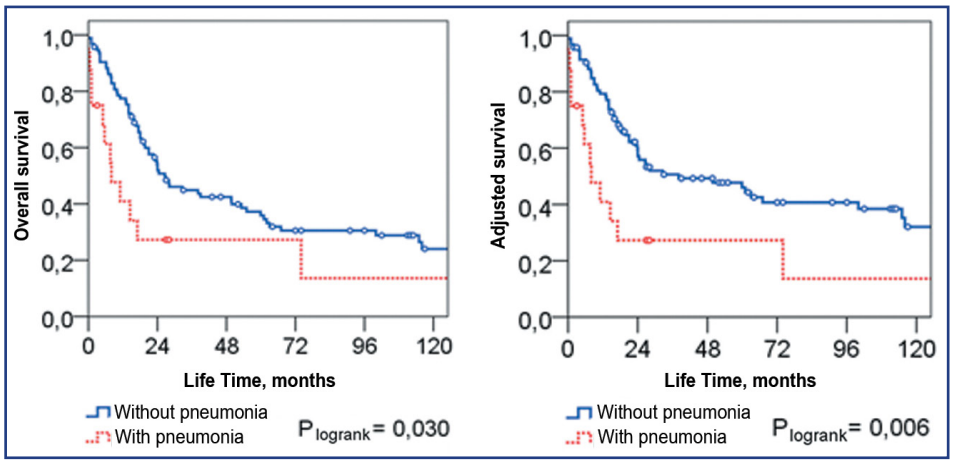


Figure 2 – Pneumonia-dependent survival (n=16/110) after surgery with esophagocoloplasty for esophageal carcinoma or esophagogastric junction carcinoma

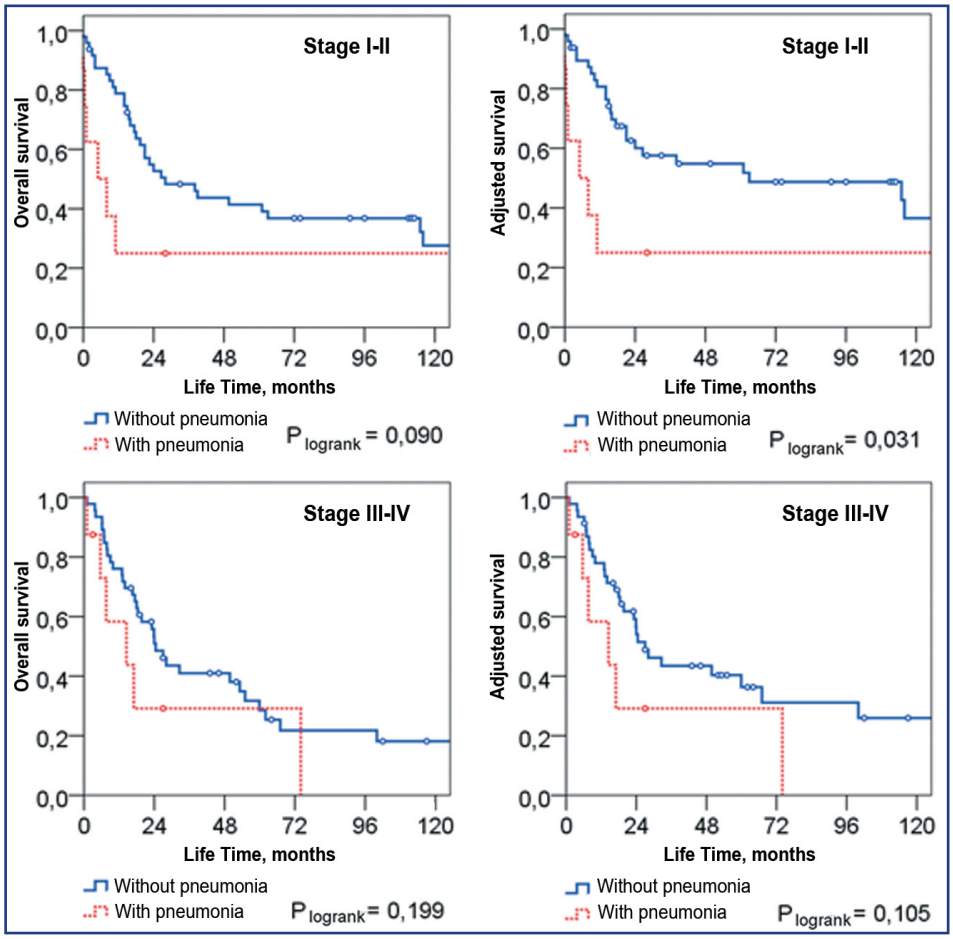


Figure 3 – Pneumonia-dependent survival in patients after surgery with esophagocoloplasty for esophagus carcinoma or esophagogastric junction carcinoma, at cancer stages I-II or III-IV

Table 1 – Cancer stage-dependent effect of pneumonia on the survival of patients after surgery with esophagocoloplasty for esophagus carcinoma or esophagogastric junction carcinoma

Cancer stage	Pneumonia	Overall survival	p_{cox}	Adjusted survival	p_{cox}
I-II	8/56	RR 2.097 [95% CI 0.869-5.056]	0.099	RR 2.584 [95% CI 1.050-6.362]	0.039
III-IV	8/54	RR 1.762 [95% CI 0.734-4.232]	0.205	RR 2.054 [95% CI 0.844-4.999]	0.113
I-IV	16/110	RR 1.953 [95% CI 1.052-3.625]	0.034	RR 2.365 [95% CI 1.259-4.442]	0.007

The success of esophagus surgery largely depends on the plastic phase of the operation. The necrosis of the large intestine transplant, which was diagnosed in 5.4% (6/110) cases, is a specific complication of surgery for esophagus carcinoma or esophagogastric junction carcinoma. Multivariate analysis revealed the independent predictors with a negative effect on the risk of graft necrosis. The predictors included in the equation were: cardiac events in the form of rhythm disturbances (OR 137.213 [95% CI 3.313-5,683.49], p=0.010), lung resections preceding esophagocoloplasty (OR 57.797 [95% CI 2.382-1,402.399] p=0.013), liver cirrhosis (OR 24.72 [95% CI 1.141-535.616] p=0.041), and massive adhesions in the abdominal cavity (OR 66.46 [95% CI 4.295-1,028.483] p=0.003). The formation of graft from the right flank is required to straighten the hepatic bend of the colon. In a pronounced adhesive process, the middle colic artery right branch ligation increased the risk of graft necrosis by 10.5 times (OR 10.556 [95% CI 1.852-60.15] p=0.008) due to a decreased efficiency of blood supply to the marginal vessel feeding the intestinal segment. In turn, the ineffective blood supply to the oral end of the graft from the colon right flank could be due to the narrowing or rupture of the marginal vessel between the right and middle colic arteries and increased the risk of necrosis by 6.3 times (OR 6.29 [95% CI 1.076-44.626] p=0.039).

The overall survival after esophagocoloplasty in patients without graft necrosis (n=104) was: 74.6% after one year, 44.9% after three years, 36.4% after five years, 30.0% after seven years, and 26.2% after ten years (Figure 4).

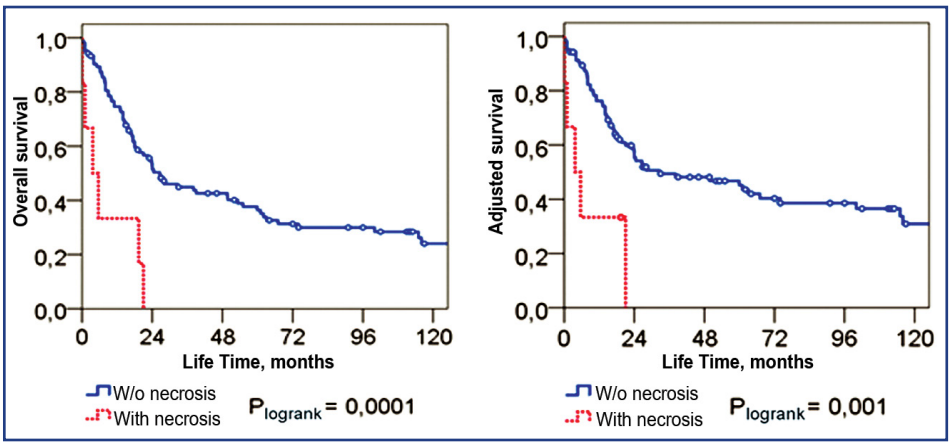


Figure 4 – Necrosis-dependent survival (n=6/110) after surgery with esophagocoloplasty for esophagus carcinoma or esophagogastric junction carcinoma

The median survival with and without graft necrosis was 3.7 and 26.6 months, respectively. With graft necrosis (n=6), the 1-year survival rate was 33.3%; no patients survived three years. The maximum life expectancy was 21 months.

In stage I-II carcinomas, graft necrosis after surgery with esophagocoloplasty (n=4/56) decreased the overall 1-year survival decreased from 72.7% to 50.0%, and the median overall survival – from 28.0 to 1.0 month ($p_{logrank}$=0.016) (Figure 5).

No patients with necrosis survived two years; the maximum life expectancy was 21 months. Without necrosis, the 2-year overall survival was 52.6% (Figure 5).

Graft necrosis after surgery with esophagocoloplasty increased the risk of death from all causes by 3.4 times (p_{cox}=0.025). The adjusted specific survival and the risk of death from cancer were not affected ($p_{logrank}$=0.077, p_{cox}=0.093) (Table 2).

In patients with cancer stage III-IV (n = 54), the graft necrosis that developed in 2 cases decreased the median overall survival from 24.0 to 3.7 months ($p_{logrank}$=0.0001) and the median adjusted survival – from 27.0 to 3.7 months ($p_{logrank}$=0.001). The maximum life expectancy was 5.6 months (Figure 5).

The colon graft necrosis increased the risk of death from that complication and worsened the prognosis. It was evidenced by the negative impact of the studied parameter on the overall (p_{cox}=0.001) and adjusted (p_{cox}=0.003) survival in the entire cohort of 110 patients (Table 2).

30-day mortality in necrosis was 33.3% (2/6) vs. 6.7% (7/104) in cases without necrosis (p=0.015). Both 60- and 90-day mortality was 50% (3/6) with necrosis vs. 7.7% (8/104) without necrosis (p=0.027). The causes of deaths also varied (p=0.028). 33.3% (2/6) of patients with necrosis died due to that complication vs. 16.7% (1/6) who died from arrosive hemorrhage. In contrast, in patients without necrosis, the main cause of postoperative mortality was pneumonia (5.8%, 6/104); pulmonary thromboembolism and bleeding (each 1.0%, 1/104) were less common.

The use of esophagocoloplasty planning reduced the frequency of ischemic complications (graft necrosis and a failure of esophagus anastomosis) from 30.9% (17/55) to 7.3% (4/55) (p=0.002) and the risk of their development (OR 0.175 [95% CI 0.055-0.563], p=0.003). At that, the frequency of failure of esophagocolic anastomosis decreased from 21.8% (12/55) to 5.5% (3/55) cases (p=0.013). The planning method allowed considering the anatomical features when forming the graft to choose the best variant of esophagocoloplasty. When forming the graft, the right colic artery ligation at the junction with the superior mesenteric artery (Figure 6) reduced the risk of ischemic complications by 2.9 times (OR 0.342 [95% CI 0.121-0.961], p=0.042).

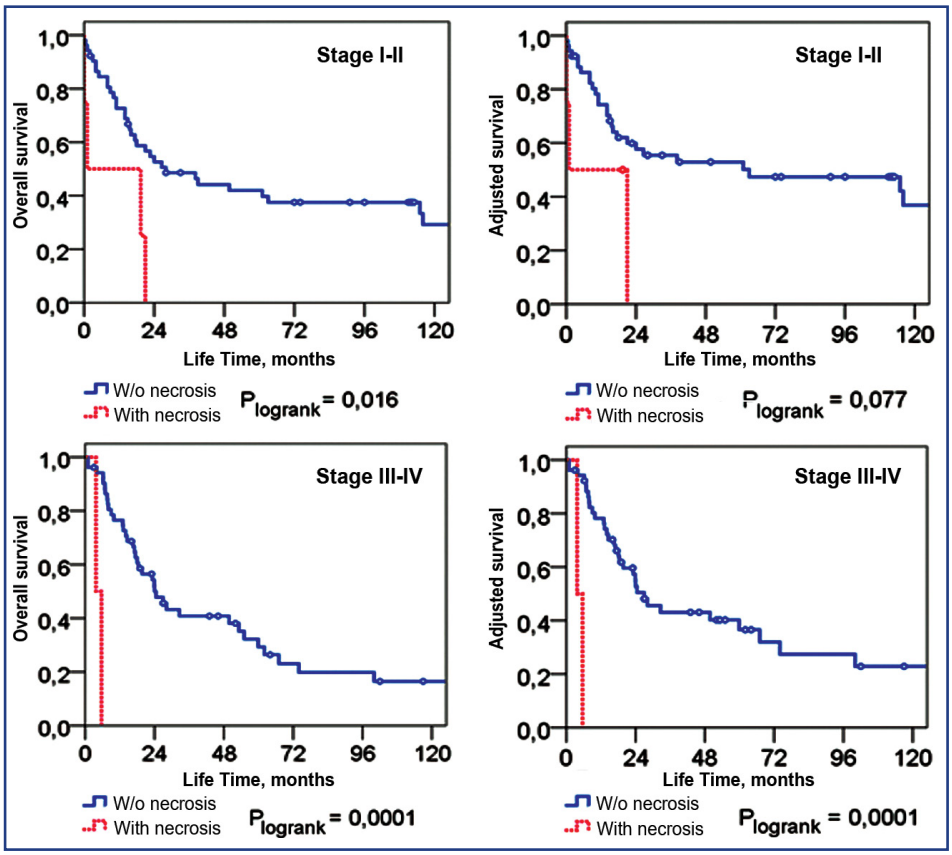
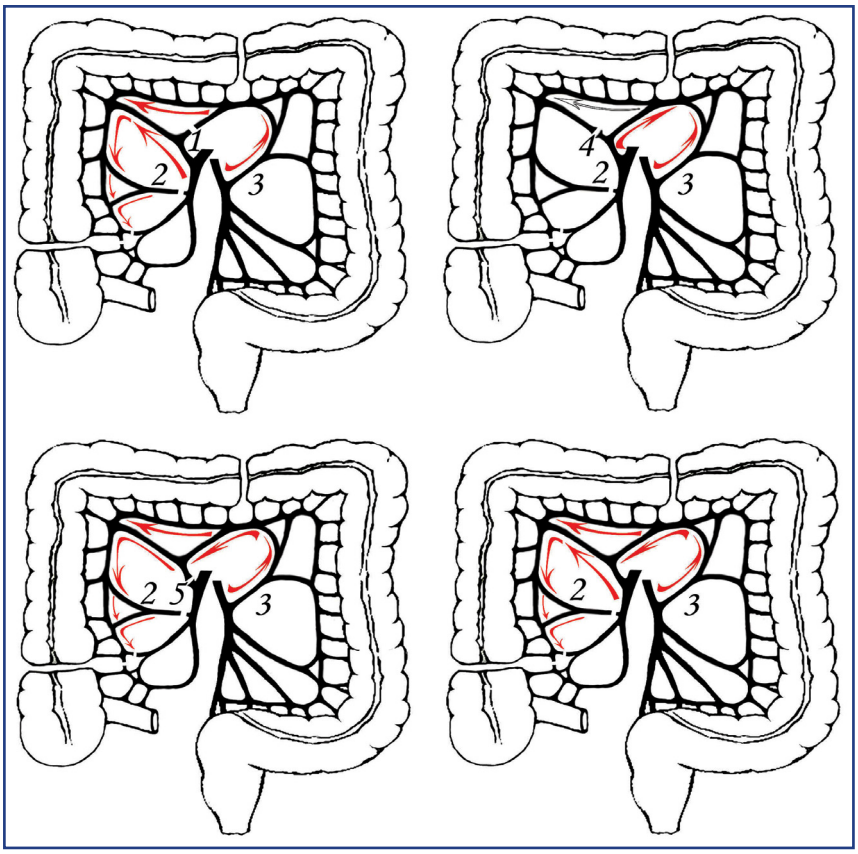


Figure 5 – Necrosis-dependent survival in patients after surgery with esophagocoloplasty for esophagus carcinoma or esophagogastric junction carcinoma, at cancer stages I-II or III-IV



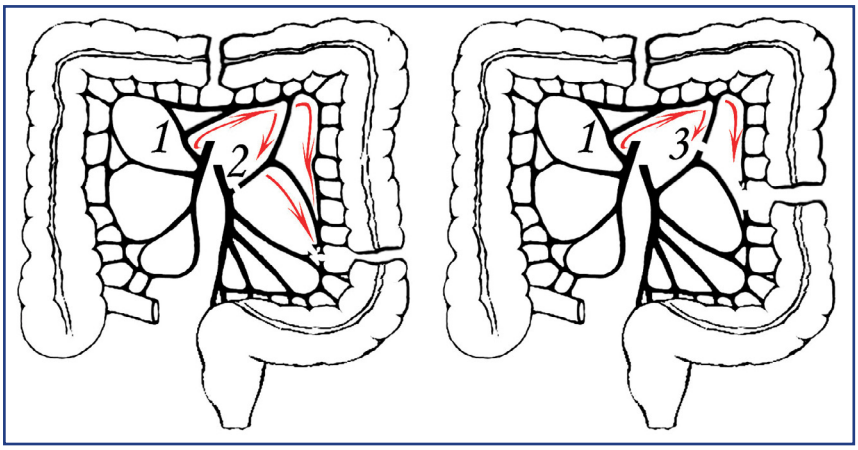
Legend: 1 – the intersection of the left branch of the middle colic artery,
2 – the intersection of the right colic artery, 3 – the left colic artery,
4 – the intersection of the right branch of the middle colic artery (should be avoided),
5 – the intersection of the main trunk of the middle colic artery
Figure 6 – Middle colic vessels' intersection scheme

Table 2 – Cancer stage-dependent effect of graft necrosis on the survival of patients after surgery with esophagocoloplasty for esophagus carcinoma or esophagogastric junction carcinoma

Cancer stage	Necrosis	Overall Survival	p_{cox}	Adjusted Survival	p_{cox}
I-II	4/56	RR 3.399 [95% CI 1.168-9.893]	0.025	RR 2.839 [95% CI 0.841-9.581]	0.093
III-IV	2/54	RR 21.74 [95% CI 3.558-132.845]	0.001	RR 21.74 [95% CI 3.558-132.845]	0.001
I-IV	6/110	RR 4.41 [95% CI 1.871-10.392]	0.001	RR 4.061 [95% CI 1.596-10.338]	0.003

When straightening the hepatic bend of the colon during the isolation of the middle colic vessels, the ligation of the right branch of the middle colic artery was to be avoided (Figure 6) since it increased the risk of ischemic complications by 3.6 times (OR 3.661 [95% CI 1.032-12.99], p=0.045). Ischemia developed due to the opposite blood flow along the ascending branch of the left colic artery and the left branch of the middle colic artery, which decreased blood supply efficiency to the marginal vessel. On the contrary, the ligation of the left branch of the middle colic artery (Figure 6) had a positive effect since it doubled the blood supply to the graft from the ascending branch of the left colic artery and the right branch of the middle colic artery and reduced the risk of ischemic complications (necrosis and insolvency) by 5.6 times (OR 0.179 [95% CI 0.039-0.816] p=0.026). In case the above graft formation variant is not suitable, the middle colic artery was intersected at the joint of the main trunk with the superior mesenteric artery (Figure 6) to create an additional arterial arch consisting of the right and left branches of the middle colic artery.

In the formation of a graft from the left flank, the level of the intersection of the left colic artery was important. The intersection at the level of its ascending branch (Figure 7) increased the risk of ischemic complications by 13.6 times (OR 13.594 [95% CI 2.424-76.243] p=0.003). For this reason, the artery should be intersected at a safe level of the main trunk of the left colic artery to create an additional arterial arch consisting of the ascending and descending branches of the left colic artery (OR 1.324 [95% CI 0.426-4.117] p=0.628) (Figure 7).



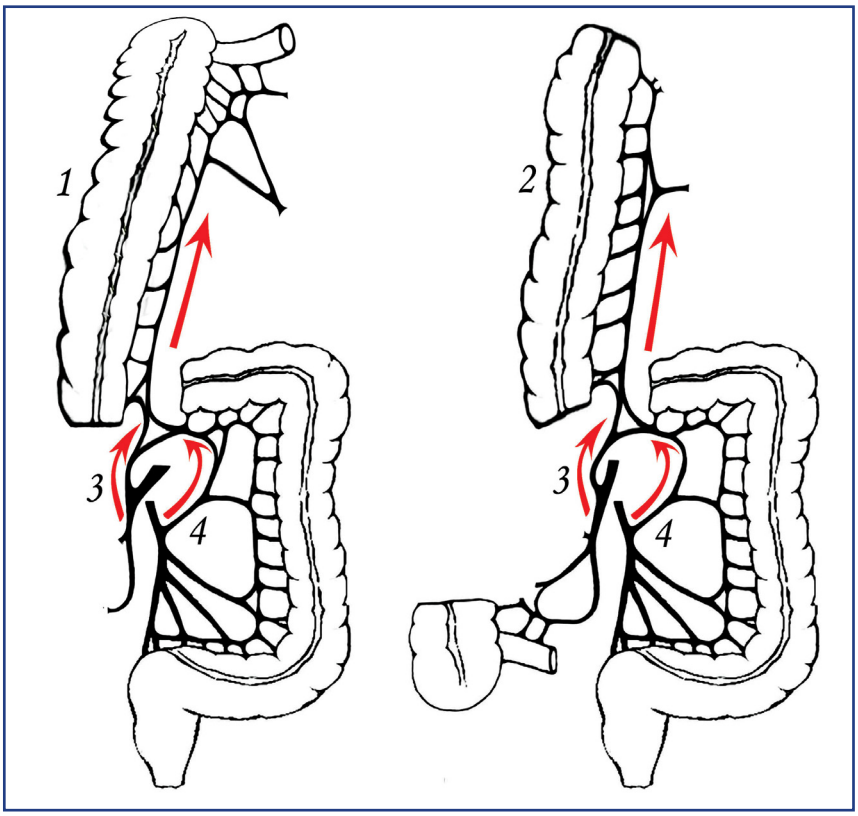
Legend: 1 – middle colic artery, 2 – the intersection of the main trunk of the left colic artery (correct), 3 – the intersection of the ascending branch of the left colic artery (should be avoided)
Figure 7 – Left colic arteries' intersection scheme

In 9 cases, the colonic segment from the right flank was formed without crossing the middle colic vessels (Figure 8). It created an enhanced blood supply to the graft from the left and middle colic vessels (Figure 8).

The use of esophagocoloplasty planning resulted in less frequent postoperative complications of stages III-IV (16.4%, 9/55 vs. 56.4%, 31/55, p<0.0001) and a lower risk of their development (OS 0.151 [95% CI 0.062-0.369], p<0.0001). The implementation of this method allows considering the possibility to ligate the left branch of the middle colic artery only (without ligation of its main trunk). This creates conditions for straightening the hepatic bend and providing the graft with additional blood supply from the upper mesenteric artery pool along the main trunk of the middle colic artery and its right branch and naturally reduces the risk of postoperative complications (OR 0.434 [95% CI 0.202–0.933], p=0.033).

The analysis of stage-dependent survival (cancer stages I-II vs. III-IV) showed that the choice of an optimal esophagus reconstruction option in accordance with the developed planning method and taking into account the angioarchitecture features provided the best results in a cohort of patients with cancer stage III-IV (n=54) (Figure 9).

Thus, the overall 10-year survival rate increased from 17.7% to 26.0% ($p_{logrank}$=0.038), the adjusted 10-year survival rate – from 21.3% to 36.1% ($p_{logrank}$=0.007). Moreover, in patients with a deliberately poor prognosis (stage III-IV), the risk of death from all causes decreased by 1.6 times (p_{cox}=0.041), the risk of death from cancer – by 2 times (p_{cox}=0.009) (Table 3).



Legend: 1 – combined small-colon transplant, 2 – a transplant from the right flank of the colon, 3 – middle colic artery, 4 – left colic artery
Figure 8 – Graft formation scheme with a double source of blood supply

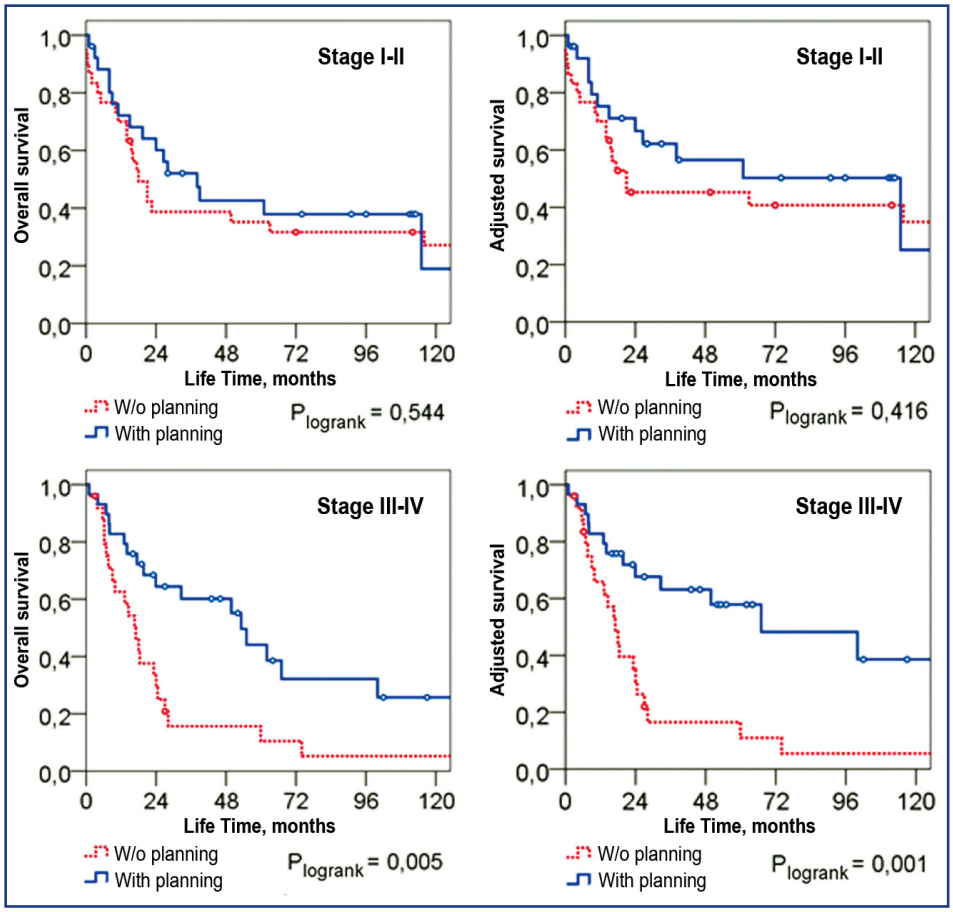


Figure 9 – Planning-dependent survival of patients after surgery with esophagocoloplasty for esophagus carcinoma or esophagogastric junction carcinoma, at cancer stages I-II and III-IV

Table 3 - The impact of the planning method on the survival of patients after surgery with esophagocoloplasty for esophagus carcinoma or esophagogastric junction carcinoma

Cancer stage	Application of the method	Overall Survival	p_{cox}	Adjusted Survival	p_{cox}
I-II	26/56	OP 0.817 [95% ДИ 0.425-1.574]	0,547	OP 0.739 [95% ДИ 0,354-1.542]	0.420
III-IV	29/54	OP 0.417 [95% ДИ 0.221-0.786]	0,007	OP 0.324 [95% ДИ 0,160-0.656]	0.002
I-IV	55/110	OP 0.624 [95% ДИ 0.397-0.980]	0,041	OP 0.510 [95% ДИ 0,308-0.844]	0.009

The use of planning in 29 out of 54 patients with cancer stage III-IV allowed reducing the risk of patients' death from all causes by 2.4 times (p_{cox}=0.007) and cancer deaths – by 3.1 times (p_{cox}=0.007). The overall 10-year survival increased from 5.2% to 25.7%, its median – from 17.0 to 53.2 months, the adjusted 10-year survival – from 5.5% to 38.6%, its median – from 17.0 to 67.0 months.

Thus, the planning method (n=55/110) had a positive effect on patients with all cancer stages (I-IV) (Figure 10).

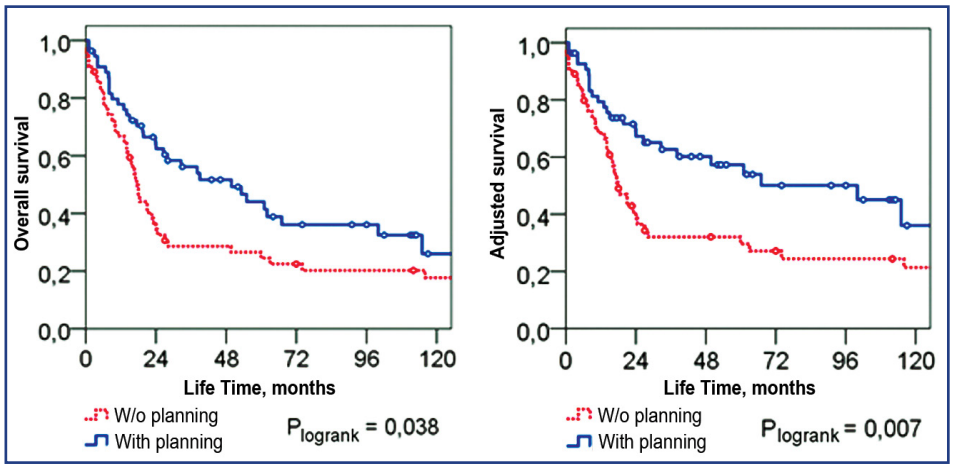


Figure 10 - Planning-dependent survival of the whole cohort of patients after surgery with esophagocoloplasty for esophagus carcinoma or esophagogastric junction carcinoma

A positive effect in survival rates was achieved through the use of the esophagocoloplasty planning method. This method reduced the mortality from 14.5% (8/55) to 1.8% (1/55) (p=0.015) after 30 days and from 16.4% (9/55) to 3.6% (2/55) (p=0.027) after 60 and 90 days. It also changed the structure and reduced the frequency of deaths due to pneumonia – from 7.3% (4/55) to 3.6% (2/55), necrosis – from 3.6% (2/55) to 0%, bleeding – from 3.6% (2/55) to 0%, and pulmonary thromboembolism – from 1.8% (1/55) to 0% (p=0.028).

Conclusions: Postoperative development of pneumonia or colonic graft necrosis after surgery with esophagocoloplasty is associated with a significant deterioration in immediate and long-term treatment results. Planning of the best option for esophagus reconstruction improves the surgical management of cancer patients who require esophagocoloplasty for esophagus carcinomas or esophagogastric junction carcinoma and has the potential to improve long-term survival of patients with a deliberately poor prognosis (cancer stage III-IV).

References:

1. Bashir Mohamed K., Hansen C.H., Krarup P.M., Fransgård T., Madsen M.T., Gögenur I. The impact of anastomotic leakage on recurrence and long-term survival in patients with colonic cancer: a systematic review and meta-analysis // Eur J Surg Oncol. – 2020. – Vol. 46, №3. – P. 439-447.

2. Tokunaga M., Tanizawa Y., Bando E., Kawamura T., Terashima M. Poor survival rate in patients with postoperative intra-abdominal infectious complications following curative gastrectomy for gastric cancer // Ann Surg Oncol. – 2013. – Vol. 20, №5. – P. 1575-83.

3. Hayami M., Watanabe M., Ishizuka N., Mine S., Imamura Y., Okamura A., Kurogochi T., Yamashita K. Prognostic impact of postoperative pulmonary complications following salvage esophagectomy after definitive chemoradiotherapy // J Surg Oncol. – 2018. – Vol. 117, №6. – P. 1251-1259.

4. Fransen L., Berkelmans G., Asti E., Van Berge Henegouwen M., Berlth F., Bonavina L. [et al.] FA01.02: the effect of postoperative complications after MIE on long-term survival: a retrospective, multi-center cohort study // Dis Esophagus. – 2018. – Vol. 31, №13. – P. 1.

5. Rasmussen S.R., Nielsen R.V., Fenger A.S., Siemsen M., Ravn H.B. Postoperative complications and survival after surgical resection of esophageal squamous cell carcinoma // J Thorac Dis. – 2018. – Vol. 10, №7. – P. 4052-4060.

6. Takeuchi M., Kawakubo H., Mayanagi S., Yoshida K., Fukuda K., Nakamura R., Suda K., Wada N., Takeuchi H., Kitagawa Y. Postoperative pneumonia is associated with long-term oncologic outcomes of definitive chemoradiotherapy followed by salvage esophagectomy for esophageal cancer // J Gastrointest Surg. – 2018. – Vol. 22, №11. – P. 1881-1889.

7. Li K.K., Wang Y.J., Liu X.H., Tan Q.Y., Jiang Y.G., Guo W. The effect of postoperative complications on survival of patients after minimally invasive esophagectomy for esophageal cancer // Surg Endosc. – 2017. – Vol. 31, №9. – P. 3475-3482.

8. Xia B.T., Rosato E.L., Chojnacki K.A., Crawford A.G., Weksler B., Berger A.C. Major perioperative morbidity does not affect long-term survival in patients undergoing esophagectomy for cancer of the esophagus or gastroesophageal junction // World J Surg. – 2013. – Vol. 37, №2. – P. 408-415.

9. Ott K., Sisic L., Büchler M. Squamous cell carcinoma of the esophagus // Chirurg. – 2011. – Vol. 82, № 11. – P. 974-980.

10. Miroshnikov B.I., Gorbunov G.N., Ivanov A.P. Plastica pishchevoda. [Plastic surgery of the esophagus]. – SPb: ELBI-SPb, 2012. – 368 p. [in Russian].