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Modern approaches to the treatment of esophageal cancer (literature review)

Relevance. *Esophageal carcinoma (EC) ranks 8th place in the structure of cancer morbidity and 6th - in the structure of mortality worldwide. 400,000 deaths are registered annually (4.9% of the total number of cases). EC is the most lethal among all solid tumors due to its aggressive course and poor survival. Despite the improvement of surgical treatment methods, the EC treatment outcomes remain unsatisfactory. About 70-80% of patients are admitted to specialized clinics at the advanced stages of the disease. It limits the operability, and the 5-year survival in many clinics does not exceed 20-25%. These facts actualize the search for more efficient EC treatment methods. Multimodal therapy with a conformal component stands out as the most promising.*

Purpose of the study – *a comparative evaluation of modern methods of EC treatment.*

Results. *4-year overall survival of patients who received multimodal treatment was statistically significantly higher compared to those who received only surgery in the extent of esophageal resection (33.3±2.4% vs. 18.9±3.5%, t = 3.22, p <0.05). Recurrence-free survival of patients with EC stage II-III after multimodal therapy was also higher than after only surgical treatment (27.3±2.7% vs. 16.2±3.6%). Regression of EC after multimodal therapy: complete – in 18.1%, partial – in 45.5% of patients, stabilization of the process – in the rest of patients.*

Conclusion. *Advanced EC remain an acute healthcare problem in the world, including the Republic of Kazakhstan. Only surgical treatment does not give satisfactory results in advanced EC. Multimodal approach to treatment ensures the best survival rates in locally advanced EC. Chemoradiation treatment of inoperable EC gives significantly better results compared to only independent (radical) radiotherapy as the only method of special treatment.*

Keywords: *esophageal cancer, epidemiology of esophageal cancer, multimodal therapy, surgical treatment of esophageal cancer.*

Introduction. Esophageal carcinoma (EC) ranks 8th place in the structure of cancer morbidity and 6th - in the structure of mortality worldwide. 400,000 deaths are registered annually (4.9% of the total number of cases) [1]. EC is the most lethal among all solid tumors due to its aggressive course and poor survival.

Epidemiology. According to GLOBOCAN 2012 (IARC, 456,000 new EC cases were registered in 2012 (3.2% of the total number of cases), with an expected increase up to 2 110 000 new cases by 2025. EC ranks 6th place in the mortality structure, with approximately 400,000 deaths each year (4.9% of the total number of cases) [1]. In the so-called endemic foci of EC which are the northern regions of China EC incidence reaches 250 cases per 100 thousand male population and about 160 cases per 100 thousand female population. A high incidence (over 150 cases per 100 000) is also registered in Iran and Caspian countries, namely in some areas of Turkmenistan, Kazakhstan, and Karakalpakstan adjoining the Caspian Sea.

In the US and Western Europe, the annual EC incidence varies from 5 to 8 cases per 100 000 with a 5% annual growth [2]. The incidence pattern in Africa requires a special attention: most part of Africa has the lowest incidence of EC. For instance, Ethiopia is the only country with no cases of EC. At the same time, southern Africa hosts the high incidence center for EC [3].

In Kazakhstan in 2016 EC ranked 10th in the structure of cancer morbidity, accounting for 3.5% of all cancer cases. The oncological service of Kazakhstan has reported 1,300 new cases and about 900 fatal cases during the year. The highest EC rate was recorded in West-Kazakhstan (12.8%), Kyzylorda (12.0%), and Atyrau (11.1%) regions. The average EC incidence was 7.2 per 100 000, the mortality – 4.9 per 100 000 [4].

The proportion of histological forms of EC has changed recently. *Bosetti et al.* demonstrated an evident increase in EC frequency in the past 20 years in northern Europe and the US [24]. It was caused by an increasing incidence of Barrett syndrome, primarily due to a high incidence of obesity and reflux esophagitis. As a result, squamous cell tumors were mainly observed in the upper and middle thirds of esophagus, and adenocarcinoma was mainly detected in the lower third of esophagus [5]. At that, according to *Arnold et al.* esophageal squamous cell cancer (ESCC) prevailed worldwide accounting for 87% of cases [6].

Patients with neoplastic pathology of the head and neck had a higher frequency of EC vs the general population. The literature described the phenomenon of carcinogenic impact on the epithelium of upper aero-digestive paths (nose and oropharynx, larynx, upper respiratory tract, and esophagus). That impact was responsible for a higher incidence of subsequent tumor lesions of the esophagus after the head and neck cancer development [7].

EC had the highest one-year mortality among all cancers. Up to 65% of patients died within one year after diagnosis [8]. The main cause of high mortality was late detection of advanced forms of EC. *Davydov et al.* reported that 65-75% of patients had stages III-IV of EC at diagnosis [5].

EC treatment has remained one of the most challenging segments of oncology. Surgery was the main meth-

od of treatment of EC while chemoradiation therapy was used only as palliative care. 70-80% of patients were admitted to specialized clinics with advanced stages of the disease what limited the operability. In many clinics, the 5-year survival did not exceed 20-25%.

EC treatment. Transhiatal and transthoracic approaches were widely used for surgical treatment of EC though the operative approaches and stoma formation techniques were still under discussion.

M. Orringer (2007) who had the widest experience in transhiatal esophagectomy associated such approach with much less postoperative complications and nosocomial mortality vs transthoracic approach (postoperative mortality - 3%) [9]. Nevertheless, many authors criticized the limited possibilities for mediastinal lymphadenectomy with that approach. *I. Stilidi* had analyzed the findings of large randomized studies to conclude that the long-term outcome in patients with the invasion of submucosal layer were twice higher after transthoracic vs transhiatal approaches (54.2% vs. 25.5%) [10].

Another large randomized study conducted by *J. Hulsher et al.* has shown the advantage of transthoracic vs. transhiatal esophagectomy (5-year survival – 39% vs. 29%, relapse-free 5-year survival – 39% vs. 27%, respectively; CI 95 %) [11].

Based on the above, many clinics of the world stick to a subtotal esophagus resection with extended lymphadenectomy combined with esophagoplasty with the whole stomach or a stalk from the greater gastric curvature, and the formation of esophagogastric anastomosis of the right pleural cavity (Ivor Lewis procedure) or cervical anastomosis (McKeown procedure) as the standard for EC surgery. Some experts preferred cervical anastomosis (CA) because of the high mortality due to the failure of intrapleural anastomosis (IPA). *A. Kavaykin* has reported the failure of IPA in 8.7±5.6% of cases. Different authors have reported different postoperative mortality with IPA (1.8% to 26.2%) [12]. The CA failures were reported in 12% of cases, with a much lower postoperative mortality [9]. In spite of a significant prevalence of CA failures over IPA failures (RR – 3.43, CI 95%: 1.09-10.78, p = 0.03), a large-scale comparative meta-analysis conducted by *Bierre et al.* has not shown a significant difference in nosocomial mortality between the two groups (RR – 1.24, CI 95%: 0.35-4.41, p = 0.74) [13].

S. Dvoretsky has noted that CA was associated with 2-2.5 times more cases of failure and damage to the recurrent nerve leading to a higher risk of postoperative pulmonary complications [14]. *I. Stilidi* has justified the formation of cervical anastomosis only at tumor localization in the tracheal segment when the esophagus was *extirpated,* and not *resected,* and the transplant had to be connected with the pharynx. Transthoracic subtotal esophagectomy has provided a satisfactory oncological outcome in case of thoracic esophagus cancer located below the aortic segment [10].

Tumor staging was the most important *prognostic factor* determining the outcome of any treatment method, including surgery. According to *B. Miroshnikov et al.*, the total 5-year survival at the tumor length below 5 cm was equal to 37.7%, at the tumor length of 5 to 10 cm – 15.3%, and at the tumor length of 10 cm or more – 0% [15].

Tumor metastasis in regional lymph nodes was another important factor. *N. Sato* has shown that an extended abdominal and mediastinal lymph nodes' dissection allowed achieving high 5-year survival in patients at the initial stage of cancer. The survival was declining with the stage progression: stage I – 87%, stage II – 57%, stage III – 31% [16]. *T. Matsubara et al.* have reported the 5-year survival rate of 89% at N_0, and 54% at N_1 [17].

Japanese surgeons from the Tokyo Institute of Gastroenterology have presented the review of treatment outcome of 333 patients with invasive EC after radical (R0) surgery. Combined 5-year survival after extensive two- and three-zone surgical interventions was equal to 47.5% what was much higher than after standard surgical procedures (20.0%) [18].

In spite of the popularity of three-zone lymphadenectomy in Japan, *H. Ma et al.* have reported the average number of metastatic lymph nodes equal to 59.5-82 at extensive three-zone lymphadenectomy. As far as the esophagus lymphatic system contained 118-234 lymph nodes and taking into account the elevated risk of postoperative complications after three-zone lymphadenectomy, that kind of surgery could be used only in individual cases [19]. Based on that data, *M. Orringer* has made an assumption about the systemic nature of EC and the impossibility to remove all metastatic lymph nodes. So, the author of the largest study on transhiatal esophagectomy did not see tangible benefits of extended lymphadenectomy and offered his own method of surgery as the safest one [9].

M. Davydov recommended three-zone lymphadenectomy for EC in the following cases: medium and upper thoracic esophagus tumor localization, for patients aged below 70 y.o., for T1-3 tumors, and in the case of absence of distant hematogenous metastases, at metastases in no more than 4 lymph nodes, especially with the metastases in upper mediastinum and cervical-supraclavicular nodes, and in the case of feasibility of radical surgery [20].

Prospects for surgical treatment of esophageal carcinoma (EC). The advances in hardware, anesthesiology and critical care medicine, as well as mass screening programs for early EC detection, have created conditions for wide use of minimally invasive esophagectomy (MIE) worldwide in the recent years. Today, 15 to 30% of all esophagectomies are performed in the form of MIE.

Luketich et al. have shared the widest (over 1000 cases) experience of video-assisted thoracoscopic esophagectomy. Only 4.5% (45/1011) patients required the transition to open surgery. The reasons for conversion at the thoracoscopic stage included: pleural fusions (n = 4), steady bleeding (n = 6), adhesion of tumor to surrounding organs, or the need to evaluate the tumor boundaries (n = 8). 21 lymph nodes on average were removed at the thoracoscopic stage. RO resection amounted to 98% with negative boundaries at the final pathological examination. The obtained experience has proven the safety and low postoperative mortality of the procedure. Average stay in the ICU was 2 days; average hospital stay was 8 days. Overall 1-year survival broken down by stages was: stage 0 – 86%, stage I – 89%, stage IIa – 80%, stage IIb – 76%, stage III – 63%, and stage IV – 44%. MIE procedure was significantly longer than the open esophagectomy (OE) but was associated with a less blood loss [21].

In the meta-analysis conducted by *Dantoc et al.* (1586 patients), 16 control cases have proven the feasibility of MIE-lymphadenectomy and good visualization of the surgical field. The 5-year survival in different arms did not differ significantly (MIE – 31.1%; OE – 26%). MIE has allowed meeting the current oncological requirements for EC sur-

gery to achieve comparable 3- and 5-year survival vs radical OE [22].

According to the first findings of the only large-scale prospective multicenter randomized controlled clinical trial enrolling 115 patients which was conducted in 2012 and was devoted to the comparison of MIE and OE (Traditionally Invasive vs Minimally Invasive Esophagectomy, TIME), the share of pulmonary complications during the first fortnight after surgery was significantly lower in the MIE group vs. the OE group (9% vs 29%), with no statistically significant differences in the rate of other complications. The number of lymph nodes removed and the rate of "positive" resection boundary were the same as after traditional interventions [23].

Radiotherapy (RT) as an independent method of EC treatment. RT was implemented as an independent method of EC treatment in case of impossibility of surgical treatment at tumor localization in cervical esophagus, relevant functional contraindications to surgery, or the patient refusal to undergo the surgery. In patients with inoperable tumors (T1-2) (due to aforesaid reasons) without regional lymph nodes lesion, independent RT allowed achieving 5-year survival in 30-70% of cases. Depending on the tumor staging, RT was used as radical or palliative treatment aimed to relieve dysphagia, pain, and etc. However, only 45–60% of patients showed a complete or partial tumor regression after a radical course of remote RT with the total boost dose of 60–70 Gy. The 3-year survival varied from 15 to 27%, according to different authors [24].

Combined treatment of EC. In more advanced forms of EC (> T3N0), when 5-year survival was observed in less than 30% of patients, *chemoradiation therapy* (CRT) prevailed as special treatment and allowed obtaining the most efficient outcome [25].

Large-scale randomized clinical trials (RTOG 85-01) on the use of independent (radical) RT as the only special treatment of inoperable EC patients vs the use of CRT have shown an overwhelming advantage of CRT compared to independent RT. During radical RT, the total boost dose was 64 Gy in 32 fractions, and during CRT – 50 Gy in 25 fractions. At that, the total 5-year survival after independent RT was 0% compared to 27% after CRT. Distant metastases and local recurrences were also lower after CRT vs RT (16% vs. 30% and 46% vs. 65%, respectively) [26].

It is evident that CRT with a conformal component is much more efficient in treating inoperable EC than independent RT.

Multimodal therapy of EC. Despite the advances in surgical treatment techniques, the EC treatment outcome remains unsatisfactory. The reasons for that are: late detection, an extremely aggressive course of the disease, early dissemination, and lymphatic metastasing. About 70-80% of patients are admitted to specialized clinics at the advanced stages of the disease. It limits the operability, and the 5-year survival in many clinics does not exceed 20-25%. These facts actualize the search for more efficient EC treatment methods. Multimodal therapy with a conformal component stands out as the most promising. Preoperative CRT of malignant tumors is aimed at: the reduction of tumor biological activity, the reduction of tumor size, the impact on invisible metastases, the creation of ablastic conditions during surgery, and the reduction of recurrence and metastasing rates. It is important to note that such approach often turns non-resectable tumors into resectable ones.

B. Burmeister et al. have published the results of a study covering 256 patients who received CRT including cisplatin, 5-fluorouracil, and RT at a dose of 35 Gy in 15 fractions, followed by surgery (Group 1), or only surgical treatment (Group 2). The complete response was achieved in 15.1% of patients after CRT, of them, 26.3% had squamous cell carcinoma, and 9% – adenocarcinoma. R0 resections were more often in Group 1 than in Group 2 (103 out of 128 [80%] vs 76 out of 128 [59%], respectively, p = 0 · 0002). Group 1 patients also had less positive lymph nodes (44 out of 103 [43%] vs 69 out of 103 [67%], p = 0·003). Nevertheless, postoperative complications, mortality and median survival did not differ significantly in both groups (the survival was 21.7 and 18.5 months, respectively) [27].

E. Abzalbek has presented own results of the study covering 138 patients with EC stage II-III receiving multimodal treatment (Group 1) and only surgical treatment in the form of esophagectomy (Group 2). The overall 4-year survival in Group 1 (33.3±2.4%) was statistically higher than in Group 2 (18.9±3.5%, t = 3.22, p <0.05). The recurrence-free survival in Group 1 was also higher than in Group 2 (27.3±2.7% vs. 16.2±3.6%, respectively). The developed method of multimodal EC treatment has contributed to the achievement of the following outcomes: complete regression – in 18.1%, partial regression – in 45.5% of patients, stabilization of the process – in the rest of the patients [28].

The meta-analysis published by *Pasquali et al.* is also worth mentioning. It covers the results of 33 randomized studies conducted worldwide (6072 patients). According to the authors, the immediate and long-term outcomes of neoadjuvant CRT with subsequent surgical treatment were higher compared to surgical treatment only (RR – 0.77, CI 95% [0.67-0.87]. At the same time, the combination of surgical treatment with adjuvant therapy did not show significantly better results in terms of survival (RR – 0.87; CI 95% [0.67-1.14] [29].

The meta-analysis made by *H. Ma et al.* has shown that multimodal therapy allowed to reach better overall and relapse-free survival rates vs. only surgical treatment (RR – 0.60, CI - 95% [0.40-0.91], P = 0.02). The 3-year and 5-year survival rates in both groups have showed no significant statistical difference (P>0.05). The authors also noted that the adjuvant chemotherapy had not provided a significant improvement in overall and relapse-free survival [30].

Thus, neoadjuvant CRT reduces the tumor advancement, increases its resectability, eliminates potential systemic metastases, and, ultimately, improves the relapse-free and overall survival rates.

Conclusion. Advanced EC remains an acute healthcare problem in the world, including the Republic of Kazakhstan. Only surgical treatment does not give satisfactory results in advanced EC. The multimodal approach provides the best survival results in locally advanced EC. Chemoradiation treatment of inoperable EC gives significantly better results compared to only independent (radical) radiotherapy as the only method of special treatment.

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