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REVIEW

MODERN APPROACHES TO ESOPHAGEAL SQUAMOUS CELL CARCINOMA THERAPY: PARADIGM SHIFT?

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ABSTRACT

Esophageal cancer (EC) is one of the most aggressive malignant neoplasms, ranking sixth among oncological causes of death. According to GLOBOCAN, more than half a million people die from this disease every year, and by 2040 this indicator is expected to increase almost twice. In most patients, esophageal cancer is diagnosed at stages III–IV of the disease. Currently, the standard of treatment for inoperable patients with EC is simultaneous chemoradiotherapy.

One of the main methods of treatment of patients with non-metastatic esophageal lesion remains surgical intervention in the volume of esophagectomy with radical lymph dissection, accompanied by quite frequent serious postoperative complications. However, the results of surgical treatment of locally advanced esophageal cancer alone remain unsatisfactory, and the five-year survival rate is less than 20 %. In order to improve the oncological results of treatment, various combinations of drug and radiation therapy are used (preoperative chemotherapy or chemoradiotherapy, independent chemoradiotherapy). To date, recommendations for the treatment of locally advanced esophageal cancer vary from country to country. Trimodal therapy (preoperative chemoradiotherapy up to TFD – 46 Gy with 5 cycles of weekly chemotherapy according to the carboplatin + paclitaxel scheme followed by surgical treatment) is the standard in operable patients with non-metastatic squamous cell carcinoma of the esophagus in our and European countries. In Asian countries, preference is given to neoadjuvant chemotherapy, based on the data of the JCOG1109 (NExT) study, in which it was shown that the addition of docetaxel to neoadjuvant therapy with cisplatin and fluorouracil is accompanied by an improvement in overall survival and acceptable toxicity, compared with the CF regimen and chemoradiotherapy.

A separate issue is the place of lifesaving esophagectomy in patients who have received a course of radical chemoradiotherapy. Unfortunately, according to several researchers, recurrent or persistent esophageal cancer remains an urgent problem with a risk of relapse of the disease in up to 60 % of cases.

We have studied the data of the Russian and global literature concerning the treatment of squamous cell carcinoma of the esophagus.

Keywords: squamous cell carcinoma, esophageal cancer, combined treatment, neoadjuvant treatment, chemotherapy, immunotherapy, chemoradiotherapy, esophagectomy

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ОБЗОР

СОВРЕМЕННЫЕ ВОЗМОЖНОСТИ ТЕРАПИИ ПЛОСКОКЛЕТОЧНОГО РАКА ПИЩЕВОДА: СМЕНА ПАРАДИГМ?

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РЕЗЮМЕ

Рак пищевода (РП) является одним из самых агрессивных злокачественных новообразований, занимая шестое место среди онкологических причин смертности. По данным GLOBOCAN, более полумиллиона человек ежегодно умирает от данного заболевания, а к 2040 г. ожидается увеличение данного показателя практически в 2 раза. У большинства больных рак пищевода диагностируется на III–IV стадиях заболевания. В настоящее время, стандартом лечения неоперабельных больных РП является одновременная химиолучевая терапия.

Одним из основных методов лечения пациентов с неметастатическим поражением пищевода остается оперативное вмешательство в объеме эзофагэктомии с радикальной лимфодиссекцией, сопровождающееся довольно частыми серьезными послеоперационными осложнениями. Однако, результаты только хирургического лечения местно-распространенного рака пищевода остаются неудовлетворительными, и показатель пятилетней выживаемости составляет менее 20 %. В целях улучшения онкологических результатов лечения используются различные комбинации лекарственной и лучевой терапии (предоперационная химиотерапия или химиолучевая терапия, самостоятельная химиолучевая терапия). На сегодняшний день, рекомендации по лечению местно-распространенного рака пищевода различаются в разных странах. Тримодальная терапия (предоперационная химиолучевая до СОД – 46 Гр с 5 циклами еженедельной ПХТ по схеме карбоплатин + паклитаксел с последующим хирургическим лечением) является стандартом у операбельных пациентов с неметастатическим плоскоклеточным раком пищевода в нашей и европейских странах. В азиатских странах предпочтение отдается неоадъювантной химиотерапии, базируясь на данных исследования JCOG1109 (NExT), в котором было показано, что добавление доцетаксела к неоадъювантной терапии цисплатином и фторурацилом сопровождается улучшением показателей общей выживаемости и приемлемой токсичностью, по сравнению со схемой CF и химиолучевой терапией.

Отдельным вопросом стоит место спасительной эзофагэктомии у больных, получивших курс радикального химиолучевого лечения. К сожалению, по данным ряда исследователей, рецидивирующий или персистирующий рак пищевода остается актуальной проблемой с риском развития рецидива заболевания до 60 % случаев.

Мы изучили данные российской и общемировой литературы, касающиеся вопроса лечения плоскоклеточного рака пищевода.

Ключевые слова: плоскоклеточный рак, рак пищевода, комбинированное лечение, неоадъювантное лечение, химиотерапия, иммунотерапия, химиолучевая терапия, эзофагэктомия

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INTRODUCTION

Esophageal cancer ranks 9th in terms of the number of new cases detected and 6th in terms of cancer mortality. Currently, neoadjuvant polychemotherapy and chemoradiotherapy are the standard treatment for locally advanced esophageal cancer in combination with subsequent surgical intervention. However, to date, the optimal regimen and radiation dose have not been developed, as well as the time period between the end of neoadjuvant treatment and surgical intervention, and the frequency of relapses remains high. Currently, immunotherapy is being actively introduced into general clinical practice. Many authors suggest that the inclusion of this component in the neoadjuvant treatment regimen may increase survival rates and increase the frequency of pathomorphological response in patients with locally advanced esophageal cancer.

The most common histological subtypes of esophageal cancer are squamous cell carcinoma and adenocarcinoma. The incidence of esophageal adenocarcinoma has doubled in recent decades and prevails in the structure of the incidence of this localization in North America and European countries. In Asian countries and the Russian Federation, squamous cell carcinoma is currently the leading histological type.

The purpose of the study was to study the modern possibilities of therapy of localized and locally advanced squamous cell carcinoma of the esophagus, based on the analysis of publications in the Russian (e-library) and worldwide (PubMed; Cochrane) databases of literature.

Standards for the treatment of localized and locally advanced squamous cell carcinoma of the esophagus.

Today, according to the international classification of diseases, it is customary to divide esophageal cancer into a disease of the cervical and intra-thoracic. The term "cancer of the cervical esophagus" refers to the location of the tumor within 5 cm from m. cricopharyngeus. However, this definition has been expanded to any tumor of the esophagus located above the upper upper part of the chest. Cervical cancer accounts for 2 to 10 % of cases of esophageal cancer, with a predominant histological picture of squamous cell type [1].

In the combined treatment of cervical esophageal cancer, historically, remote radiation therapy or surgical intervention have been local methods of exposure. However, a number of studies have demonstrated equivalent results between chemoradiotherapy and surgery, which has changed the treatment paradigm [2]. The three-year survival rate of patients with cervical esophageal cancer ranges from 50 to 65 % [3]. To date, the surgical stage of treatment for cancer of the cervical esophagus is considered as a life-saving operation in the development of relapse after radical chemoradiotherapy. Additional problems with surgical treatment of cervical esophageal cancer are associated with the spread of the tumor to nearby structures, which may require an extension of the operation, for example, to pharyngolaryngectomy [4].

There are still no optimal regimens and regimens of chemotherapy as a component of chemoradiotherapy for tumors of the cervical esophagus. The best results, apparently, are obtained by a doublet based on platinum preparations with simultaneous radiation therapy [5]. Extrapolation of literature data on head and neck tumors demonstrated that radiation doses up to 60–70 Gy can be used, however, when using higher doses of radiation, there was no increase in survival rates [6; 7].

In patients with early forms of squamous cell carcinoma of the esophagus (intra-thoracic), including in-situ carcinoma (Tis) and tumors that grow into their own plate of the mucous and muscular membranes (T1a), without lymph node damage, endoscopic resection of the mucous membrane (EMR) or endoscopic dissection of the submucosal layer (ESD) is recommended [8].

ESD allows resection of the mucous and submucosal layers as a single unit, which allows for a higher resection frequency of R0, which is reflected in satisfactory long-term survival rates [8]. Adjuvant chemoradiotherapy is advisable in patients with poor prognostic factors, such as low-grade tumors, positive resection margins [9]. In patients after endoscopic resection of the mucous and submucosal layers of the esophagus, with morphological verification of invasion to the submucosal layer (T1b), further additional treatment is indicated, such as esophagectomy or chemoradiotherapy [10].

Patients with the absence of lymphatic collector damage, without the tumor spreading to the muscle

membrane proper (≤ T2N0) and a low risk of progression may be offered surgical treatment at the first stage in the volume of esophagectomy with lymph dissection [11]. However, it is worth noting that according to the literature, esophageal tumors with invasion into the deep mucous membrane (endosonographically corresponds to the lesion of M3) have an approximately 10 % risk of metastasis to regional lymph nodes. Squamous cell tumors penetrating beyond the upper third of the submucosa have a frequency of metastasis to the lymph nodes from 36 to 55 % [12].

When the tumor spreads to the muscle membrane itself and deeper (≥ T2), or when the lymphatic collectors are affected (N+), patients are shown multimodal therapy. In 2012, the results of the CROSS study (chemoradiotherapy of esophageal cancer followed by surgical intervention) were published, which showed an improvement in overall survival and the frequency of complete pathomorphological response in patients with both adenocarcinoma and squamous cell carcinoma of the esophagus, compared only with the surgical treatment option. This was a step towards the introduction of neoadjuvant chemoradiotherapy with the subsequent surgical stage of treatment in the clinical recommendations for the treatment of locally advanced esophageal cancer. In the CROSS cohort of patients, the frequency of complete pathomorphological response after induction 2 cycles of chemotherapy was 23 % for adenocarcinoma and 49 % for squamous cell carcinoma. It should be noted that 75 % of the patients in this study had adenocarcinoma. It is also worth noting that patients with tumor spread to the T4 level were not included in the trial [13]. After completion of neoadjuvant treatment and in the absence of progression, according to the results of a control examination, patients may be offered a surgical stage of treatment, in the volume of esophagectomy (McKewon operation or IvorLewis operation) with standard two- or three-zone lymph dissection [14].

Several authors conducted a comparative analysis of the results of treatment of patients who received a radical course of chemoradiotherapy with patients who underwent combined treatment together with the surgical stage of treatment. Thus, in the French study FFCD 9102, which included 259 patients with locally advanced cancer of the intra-thoracic esophagus, there was no significant difference in overall survival between these two groups. It should be noted that in 88.8 % of cases, a squamous histological variant of esophageal cancer was registered. However, the authors noted that esophagectomy after induction chemoradiotherapy reduces the frequency of locoregional relapses when compared with a radical course of chemoradiotherapy [15]. This study was criticized because patients did not undergo endosonography and the total dose of LT was 30 Gy, which is less than the standard induction dose. It should also be noted that patients who did not respond to treatment were excluded from the study [16].

In a study from Memorial Sloan Kettering, which included 232 patients with squamous cell carcinoma of the esophagus, Barbetta et al. They demonstrated an improvement in overall survival in patients who underwent trimodal therapy (neoadjuvant chemoradiotherapy followed by surgical treatment), compared only with radical chemoradiotherapy [17].

When analyzing the clinical recommendations of the USA (NCCN), the European Society of Medical Oncology (ESMO), the Russian Federation and Japan, several differences in the approach to the treatment of locally advanced cancer of the intra-thoracic esophagus are visible. The NCCN recommendations prefer trimodal therapy with preoperative chemoradiotherapy [18], which intersects with the clinical recommendations of the Russian Federation, the ESMO recommendations indicate that neoadjuvant chemoradiotherapy followed by esophagectomy is equivalent to radical chemoradiotherapy [19]. According to clinical guidelines in Japan, induction chemotherapy with subsequent surgical treatment is recommended in the absence of contraindications in patients [20].

Is there a place for a lifesaving esophagectomy after a radical course of chemoradiotherapy?

Analyzing the recommendations of European and Asian countries, it can be concluded that most authors adhere to the following tactics – conducting neoadjuvant therapy followed by surgery or performing radical chemoradiotherapy for patients with locally advanced squamous cell carcinoma of the esophagus. Recurrent or persistent esophageal cancer remains an urgent problem with a risk of relapse of the disease up to 60 % of cases [21].

One of the treatment options for patients with a persistent or recurrent form of the disease after

radical chemoradiotherapy is a lifesaving esophagectomy, provided that the patient's general somatic status is satisfactory within 6–12 weeks after the end of treatment if a relapse occurs.

The authors of a multicenter retrospective study, Markar S. et al., conducted a comparative analysis of the treatment results of patients (n = 308) who received lifesaving esophagectomy with a group of patients (n = 540) who received the surgical stage after induction chemoradiotherapy. In this work, a similar perioperative mortality was shown, while the incidence of anastomosis failure (17.2 % vs. 10.7 %; p = 0.007) and infectious complications was higher in the group where a radical course of CLT was performed. The overall three-year survival rate was identical and was 43.3 % versus 40.1 % (p = 0.542), respectively [22].

A meta-analysis of four studies involving 219 patients demonstrated the survival advantage of life–saving esophagectomy compared to repeated chemoradiotherapy (HR: 0.42; 95 % confidence interval: 0.21–0.86, p = 0.017). Mortality in the postoperative period was 10.3 % (3 out of 36 operated cases). The authors noted that lifesaving esophagectomy has a significant gain in long-term survival compared to repeated chemoradiotherapy but is potentially associated with high postoperative mortality [21; 22]. The data presented above are based on non-randomized studies, which may indicate a high risk of selection bias, since patients with obviously better initial characteristics received surgical treatment.

The FFCD 9102 study is noteworthy, including 451 patients who received induction therapy with a planned subsequent surgical stage of treatment. It is worth noting that 191 (42.3 %) patients out of 451 did not respond to induction therapy and were not further randomized. In 112 cases of this cohort of patients, life–saving surgery was performed, which in these 112 patients, the median overall survival did not differ from the group of randomized patients – 17.3 months versus 18.9 months (p = 0.58).

When analyzing subgroups of non-randomized patients, the median overall survival was higher in the cohort of patients who underwent surgery compared to non-operated patients and was 17 versus 5.5 months (HR = 0.39; 95 % CI: 0.25–0.61; p < 0.0001) [23]. Thus, the data presented by Vincent J. et al. they point to the advantages of performing lifesaving esophagectomy in patients with incomplete response after neoadjuvant chemoradiotherapy.

In a retrospective study of Broderick R. C. (2021), which included 97 patients with locally advanced esophageal cancer, a comparative analysis of the treatment results of patients who received a planned (less than 90 days from the end of neoadjuvant treatment) minimally invasive esophagectomy (MIE) with a group of life-saving MIE (resection for recurrent or persistent disease after a complete response to treatment or an operation performed more than 90 days after the completion of the neoCRT). Broderick et al. there were no significant differences in 30-day postoperative mortality, anastomosis failure and duration of hospitalization. Overall survival (p = 0.39) and relapse-free survival (p = 0.71) were equivalent between the two groups [24].

According to the above studies, most authors adhere to neoadjuvant therapy with subsequent surgery, or performing radical chemoradiotherapy for patients with locally advanced squamous cell carcinoma of the esophagus. A number of studies have shown that the overall and relapse-free survival in patients after life-saving esophagectomy is higher than in patients after repeated chemoradiotherapy, especially in patients with recurrent squamous cell carcinoma of the esophagus.

Neoadjuvant therapy in the treatment of operable locally advanced esophageal cancer

The absence of modern randomized studies comparing different regimens of drug therapy alone with chemoradiotherapy followed by the surgical stage of treatment creates a dilemma of choosing the optimal treatment tactics in patients with satisfactory general somatic status and operable esophageal tumor [25]. To date, induction chemoradiotherapy remains the standard of treatment for squamous locally advanced intra-thoracic esophageal cancer, according to data obtained from the results of the CROSS study and published in 2012. and having a number of limitations described above. Recently, several clinical trials have been conducted on the neoadjuvant treatment of resectable esophageal cancer.

In the JCOG1109 (NExT) study, launched in 2012, the authors conducted a comparative analysis of the results of treatment of patients with locally advanced squamous cell carcinoma of the esophagus, who

underwent various preoperative therapy. The first group included patients who underwent 2 cycles of neoadjuvant chemotherapy with cisplatin 80 mg/m^2 on day 1 and 5-fluorouracil 800 mg/m^2 from 1 to 5 days, a cycle every 21 days (CF), in the second group 3 cycles of PCTs were used according to the DCF scheme (docetaxel 70 mg/m^2 in 1 day; cisplatin 70 mg/m^2 in 1 day; 5-fluorouracil 750 mg/m^2 from 1 to 5 days, cycle every 21 days) and in the third group, chemoradiotherapy with 23 fractions up to 41.4 Gy was performed as a neoadjuvant treatment with 2 cycles of radiomodification according to the scheme: cisplatin 75 mg/m^2 on 1 day and 5-fluorouracil 1000 mg/m^2 with 1 for 4 days, a cycle every 21 days [26].

In 2022, at the conference of the American Society of Clinical Oncology (ASCO) on diseases of the gastrointestinal tract, the main results of this study were reported for the first time. The results of treatment of 601 patients were analyzed. The CF group included 199 patients, the DCF group included 202, and 200 patients were registered in the chemoradiotherapy group in the period from December 2012 to July 2018. The median age was 65 years (30–75 years), patients with clinical stage III accounted for 62.6 %.

The average follow-up time was 4.2 years (0–8.5 years). The median overall survival in the CF group was 4.6 years, in the chemoradiotherapy group – 6 years, in the DCF group – was not achieved, three-year overall survival was 62.6 %, 68.3 % and 72.1 %, respectively (log-rank test: p = 0.006 for CF compared to DCF and p = 0.12 for CF compared to CF-RT). According to the stratified Cox regression analysis for the overall survival rate, the risk ratio is 0.68 [95 % CI: 0.50–0.92] in the comparison groups CF with DCF and 0.84 [0.63–1.12] for CF compared to chemoradiotherapy with the CF radiomodification scheme.

When analyzing adverse events, it is noted that grade 3–4 neutropenia, febrile neutropenia and hyponatremia were more common in the DCF group than in the CF and chemoradiotherapy groups. Grade 3–4 esophagitis was more common in the chemoradiotherapy group than in the neoadjuvant chemotherapy groups (Table 1).

Thus, the researchers note that the addition of docetaxel to neoadjuvant therapy with cisplatin and fluorouracil is accompanied by an improvement in overall survival and acceptable toxicity, compared with the CF regimen. The authors believe that this scheme may be a new standard of treatment for locally advanced intracoracic squamous cell carcinoma of the esophagus [27].

In 2021, Wang et al. The results of a multicenter randomized trial that examined the comparative analysis of the safety and efficacy of neoadjuvant chemotherapy with chemoradiotherapy followed by minimally invasive esophagectomy were published. The study included 264 patients with esophageal squamous cell carcinoma and cT3-T4aN0/1M0 tumor prevalence who received chemotherapy with paclitaxel and cisplatin. The total dose of radiation therapy was 40 Gy (20 fractions of 2 Gy), starting from the first day of chemotherapy.

The authors note that there was no significant difference in the frequency of postoperative complications between both groups: 47.4 % in the neoCRT group (54 out of 114) and 42.6 % in the neoHT group (46 out of 108; p = 0.48); the degree of complications according to the Clavien-Dindo classification was the same. Postoperative mortality was 3.5 % (4 out of 114) in the group of neoadjuvant chemoradiotherapy and 2.8 % (3 out of 108) in the group of chemotherapeutic treatment only (p = 0.94). When evaluating the results of a remote surgical preparation in patients in the chemoradiotherapy group, a complete morphological response was more common (35.7 % vs. 3.8 %; p < 0.001), as well as a smaller number of affected lymph nodes (ypN0: 66.1 % vs. 46.2 %; p = 0.03), which directly affects survival rates.

The authors conclude that the difference in the safety profile between neoadjuvant chemotherapy and chemoradiotherapy is insignificant, however, in the neoCRT group, the indicators of pathomorphological response were recorded more often [28]. Of the various chemotherapy regimens, the DCF scheme is the most preferable as a neoadjuvant component, accompanied by an improvement in overall survival rates, which may enter new standards for the treatment of squamous locally advanced esophageal cancer.

Adjuvant therapy possibilities and the introduction of immunotherapy

Although neoadjuvant therapy is associated with improved survival compared to surgery alone, most patients do not have a complete pathomorphological response, which directly affects the prognosis of relapse.

In a retrospective study involving 118 patients treated from 2000 to 2016 with squamous cell carcinoma who received neoadjuvant (*n* = 59) or perioperative chemotherapy (*n* = 59), Yan et al. there were no differences in relapse-free or overall survival [29]. In another randomized study that examined the results of treatment of 346 patients with squamous cell carcinoma of the esophagus treated in hospitals of Xi'an Jiaotong University since January 2005. By April 2007, the effectiveness of preoperative and perioperative chemotherapy was evaluated using the PCF scheme (paclitaxel 100 mg/m^2 and cisplatin 60 mg/m^2 on day 1, followed by infusion of 5-fluorouracil (700 mg/m^2 mg per day for 5 days). Patients were randomized into 2 groups: group A (*n* = 175) included patients who received perioperative chemotherapy (2 + 2), group B (*n* = 171) – 4 neoadjuvant cycles.

Median follow-up was 60 and 61 months in groups A and B, respectively. The development of locoregional relapse was diagnosed in 25 patients (14.2 %) in group A and in 35 (20.5 %) – in group B, distant metastasis – in 41 (23.4 %) and 62 (36.3 %) cases, respectively. The median relapse-free survival was 23 months in group A compared to 15 in group B. Five-year relapse-free survival was 35.0 % (95 % CI: 26.1–47.2) in the perioperative chemotherapy group compared with 19.1 % (95 % CI: 15.3–28.7) in the neoadjuvant therapy group only ($p < 0.01$). In patients receiving perioperative chemotherapy, the improvement in five-year survival was 16 % (38 % *vs* 22 %; $p < 0.01$) [30].

A breakthrough study that opens a new adjuvant therapy option for patients with radically operated locally advanced squamous cell carcinoma of the esophagus was the Checkmate 577 study. This randomized double-blind placebo-controlled study included the results of treatment of 794 patients with stage II or III who underwent radical surgical treatment (R0) with incomplete pathomorphological response (ypT1 or ypN1) after induction chemoradiotherapy. Patients were randomized in a 2:1 ratio into groups receiving PD-1 inhibitor (nivolumab) (*n* = 532) or placebo (*n* = 262). Patients were treated with nivolumab at a dose of 240 mg every 2 weeks / placebo for 16 weeks with a transition to a 4-week administration of 480 mg of nivolumab or placebo [31].

According to the results of the study, it was shown that the addition of nivolumab in adjuvant mode is accompanied by a satisfactory safety profile: adverse events of 3–4 degrees were observed in 71 out of 532 patients (13 %) in the PD-1 checkpoint inhibitor group, and in the placebo group this indicator was 6 % (15 out of 260). The most frequent adverse events of any severity were fatigue, diarrhea, itching and rash in patients in the nivolumab group; diarrhea, fatigue – in patients in the placebo group. When assessing the quality of life, the percentage of patients who answered "I am not at all concerned about the

Table 1. JCOG1109 (NExT) research results

	CF (*n* = 199)	DCF (*n* =202)	CRT (*n* = 200)
Median relapse-free survival rate Б	2.7 years	Not achieved	5.3 years
Three-year relapse-free survival rate	47.7 %	61.8 %	58.5 %
Undesirable events			
Neutropenia level > 3	23.4 %	85.2 %	44.5 %
Febrile neutropenia	1 %	16.3 %	4.7 %
Hyponatremia	6.2 %	26.0 %	11.0 %
Esophagitis, level > 3	1 %	1 %	89 %
Mortality rate	3 (15 %)	4 (20 %)	2 (1.0 %)

side effects of treatment" in the questionnaire was the same in both groups. The quality-of-life indicator (FACT-E and EQ-5D-3L questionnaires) remained satisfactory throughout the treatment period.

There were 396 cases of relapse or death. The incidence of distant foci was lower in the nivolumab group (in 154 out of 532 patients – 29 %) than in the placebo group (in 103 out of 262 patients – 39 %), as was the development of locoregional relapses (12 % vs. 17 %, respectively). The authors note that the risk of long–term relapse or death was 26 % lower during adjuvant therapy with nivolumab than in the placebo group (HR 0.74; 95 % CI: 0.60–0.92). The median relapse–free survival in the nivolumab group was 22.4 months (95 % CI: 16.6–34.0) compared with 11.0 months (95 % CI: 8.3–14.3) of placebo patients ($p < 0.001$) [31].

The results of this study allow us to recommend adjuvant therapy with nivolumab to all patients with squamous cell carcinoma of the esophagus and incomplete morphological response after induction therapy and esophagectomy [18].

It is also worth noting that the number of studies studying the use of checkpoint inhibitors as one of the components of neoadjuvant treatment of patients with esophageal cancer is growing.

In 2022, Liu J. et al. The results of a multicenter, single-group phase II study of ShiCTR1900026240 were published, which studied the addition of a PD-1 inhibitor (camrelizumab) produced in China to carboplatin + paclitaxel chemotherapy in the neoadjuvant treatment of patients with locally advanced squamous cell carcinoma of the esophagus with affected mediastinal lymphatic collectors. All patients underwent 2 cycles of neoadjuvant therapy, including 200 mg of camrelizumab, nab-paclitaxel 100 mg/m^2 (day 1, 8, 15) and carboplatin AUC-5 on 1 day, every 3 weeks.

The study included 60 patients, of whom the full course of treatment was completed in 55 (91.7 %) patients. 58 patients (96.7 %) were diagnosed with treatment-related adverse events, the most common of which was hematological toxicity (leukopenia) – 86.7 % of cases. It should be noted that 34 patients (56.7 %) had adverse events of the 3rd degree or higher, in 1 (1.7 %) case the patient died of pneumonia and acute respiratory failure. The surgical stage of treatment was received by 51 patients, resection of R0 was achieved in 50 cases. Postoperative complications were diagnosed in 47.1 % of cases (24/51). Hospital and postoperative mortality of 30 and 90 days was not recorded.

A noteworthy factor is that this study was conducted on patients with clinically detectable lymph node lesion N2–3. According to the results of the removed surgical material, a complete pathomorphological response (ypT0N0) was achieved in 20 (39.2 %) patients, and 5 (9.8 %) patients had a complete response of the primary tumor, but with the presence of tumor cells in the lymph nodes (ypT0N+). The authors also note that there was no significant correlation between the status of PD-L1 and the pathological response in squamous cell carcinoma of the esophagus, regardless of the method of evaluating PD-L1 expression [32].

According to the CROSS study, the addition of radiation therapy to chemotherapy in the neoadjuvant mode can significantly contribute to reducing the size of the tumor and increasing the frequency of complete pathomorphosis [13]. According to a number of researchers, immuno-chemoradiotherapy can enhance the body's response to a tumor and increase the frequency of a complete pathomorphological response compared to standard chemoradiotherapy [33; 34]. To date, a number of studies have been

Table 2. Comparative analysis of studies that studied neoadjuvant chemo-immuno-radiation therapy

Research	*N*	Treatment algorythm	pCR	% pCR
PALACE-1	20	Pembrolizumab + CROSS	10/18	55.6
NCT02844075	28	Pembrolizumab + CROSS	12/26	46.2
CROSS	41	DCT + PCT acccording to TC scheme	18/37	48.6

Table 3. Comparative analysis of studies about neoadjuvant chemoimmunotherapy [37]

Research paper	Phase	Start-point and endpoint	Median	*N*	Neodjuvant therapy	pCR	R0 resections	AEs Grade 3-4 (%)	CTCAE
ChiCTR1900026240 (Liu, 2022)	2	pCR	-	60	Camrelizumab + TC	20/51	50/51	34/60	5.0
TD-NICE (Yan, 2022)	2	MPR	-	45	Tisrelizumab + TC	18/36	29/36	19/45	-
ESONICT-1 (Zhang, 2021)	2	pCR, AEs	6 m	30	Sintilimab + nab-paclitaxel + cicplatin	4/23	23/23	1/30	5.0
Shen, 2021	-	Safety, feasibility	6 m	28	PD-1 inhibitor+ TC	9/27	26/27	2/28	5.0
Zhang, 2020	2	MPR	7.9 m	24	Toripalimab + nab-paclitaxel + S-1	3/18	-	-	-
ChiCTR2000028900 (Yang, 2022)	1	Safety, feasibility	13.8 m	23	Camrelizumab + TC	5/20	20/20	11/23	5.0
SIN-ICE (Duan, 2021)	NA	pCR	-	23	Sintilimab + platinum-containing chemotherapy	6/17	16/17	7/23	4.03
NCT04177797 (He, 2022)	2	Safety, feasibility and MPR	-	20	Toripalimab + TC	3/16	14/16	4/20	4.03
KEEP-G 03 (Gu, 2020)	1/2	Safety, feasibility	-	17	Sintilimab + lipo-paclitaxel + cisplatin + S-1	4/15	15/15	6/17	5.0
Li, 2020	2	pCR, MPR	4.5 m	17	Toripalimab + TC	2/12	12/12	2/17	-
Yang, 2021	-	pCR	-	16	Camrelizumab + TC	5/16	15/16	-	5.0
NCT03985670 (Xing, 2021)	2	pCR	-	15	Toripalimab (day 3) + TP (day 1)	4/11	11/11	3/15	5.0
				15	Toripalimab (day 1) + TP (day 1)	1/13	13/13	7/15	
FRONTiER (Yamamoto, 2021; Matsuda, 2022)	1	Toxicity	-	6	Nivolumab + CF (Group A)	2/6	6/6	-	4.03
				12	Nivolumab + DCF (Group C and D)	4/12	11/12	-	

Note: pCR – complete pathomorphologic response; AEs Grade 3–4 – unwanted events grade 3–4; MPR – maximal pathomorphologic response; TS – chemotherapy according to the scheme: carboplatin + paclitaxel.

conducted examining the addition of immunochemotherapy to radiation therapy (Table 2).

A study examining the effect of the addition of a checkpoint inhibitor (Pembrolizumab) to chemoradiotherapy according to the CROSS-scheme is a single-center, prospective, single-group study of PALACE-1. Of the 20 patients included in the study, 19 (95 %) received a full course of preoperative treatment, one patient was not given a course of CT due to hematological toxicity. In 18 (90 %) cases, patients underwent the surgical stage of treatment (1 patient had metastatic lesion after the end of neoadjuvant therapy and in 1 case death occurred due to arrosive bleeding).

According to the results of the morphological study, the frequency of complete pathomorphological response was 55.6 % for neoadjuvant therapy with pembrolizumab in combination with chemoradiotherapy [35].

In the NCT02844075 study, out of 28 included patients who received Pembrolizumab with neoadjuvant chemoradiotherapy, esophagectomy was performed in 26 cases. A complete pathomorphological response in the primary tumor was achieved in 46.1 % of patients who underwent resection (95 % CI: 28.8–64.6). Overall survival rates after 6, 12 and 18 months were 89.3 %, 80.8 % and 73.1 %, respectively [36].

Analyzing prospective studies examining the attachment of monoclonal antibodies in neoadjuvant mode to patients with trimodal therapy, Zhu J. et al. (2022) it has been shown that immunotherapy does not significantly improve the frequency of complete pathomorphological responses in squamous cell carcinoma of the esophagus but leads to an increase in the frequency of adverse events of 3–4 degrees [37].

The multicenter randomized phase III trials that have begun should show the effect of neoadjuvant immunotherapy on long-term survival.

CONCLUSIONS

To date, the recommendations for the treatment of locally advanced esophageal cancer vary in different countries. Thus, according to ESMO recommendations, preference is given to a radical course of chemoradiotherapy, in the USA and the Russian Federation – trimodal therapy with preoperative chemoradiotherapy. Clinical guidelines from Asian countries recommend induction chemotherapy followed by surgical treatment in operable patients. In addition to economic factors, the histological type of tumor is of leading importance. The CROSS study shows the effectiveness of chemoradiotherapy followed by surgical treatment in patients with esophageal cancer, but it is worth noting that T4 tumors were not included in the trial. Thus, when the tumor spreads to adjacent structures and with potential operability, neoadjuvant polychemotherapy according to the DCF scheme is indicated.

Over the past decade, immunotherapy with monoclonal antibodies has been active in the treatment of patients with esophageal cancer, blocking the interaction between the programmed death receptor (PD-1) and its ligands (PD-L1 and PD-L2). Thus, the addition of nivolumab in adjuvant mode in patients with incomplete pathomorphological response after trimodal therapy is accompanied by a satisfactory safety profile and improved survival rates, which led to the inclusion of this treatment option in clinical recommendations.

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