Impact of neoadjuvant chemotherapy vs chemoradiotherapy in the treatment of esophageal adenocarcinoma: a systematic review and meta-analysis

Impact of neoadjuvant therapy of esophageal adenocarcinoma

Armand Csontos, Aliz Fazekas, Lajos Szakó, Nelli Farkas, Csenge Papp, Szilárd Ferenczi, Szabolcs Belleyei, Péter Hegyi, András Papp

Abstract

BACKGROUND

Neoadjuvant therapy is the essential modality of reducing the clinical stage of esophageal cancer, however, the superiority of neoadjuvant chemotherapy (nCT) or neoadjuvant chemoradiotherapy (nCRT) is unclear, therefore the discussion of these two modalities is necessary.

AIM

To investigate the benefits and complications of neoadjuvant modalities.

METHODS

To investigate the question, predefined criteria were established using the PICO protocol. Two independent authors performed a comprehensive search by using pre-established keywords. Statistical analyses were performed to identify significant differences. The potential publication bias was visualized on funnel plots. The quality of the data will be valued by the Risk of Bias Tool 2 (RoB2) and the GRADE approach.
RESULTS

Ten articles were included, covering a total of 1928. Significant statistical difference was detected in pathological complete response ($p < 0.001$; OR: 0.27; 95% CI: 0.16-0.46), 30-day mortality ($P = 0.015$; OR: 0.4; 95% CI: 0.22 - 0.71) favouring the nCRT; and renal failure ($P = 0.039$; OR: 1.04; 95% CI: 0.66 - 1.64) favouring the nCT. In the survivals, local or distal recurrence, other clinical or surgical complications no significant different was reported. The result of RoB2 wear moderate, and the result of GRADE approach was low or very low almost all cases.

CONCLUSION

The nCRT may has greater pCR rate, it is not defined as greater long term survival, however, nCRT also associated with higher 30-day mortality, although we did not find a specific cause for postoperative complications. In the case of nCT, toxic side effects are suspected, therefore it can decrease the quality of life. Further randomized trials are required due to the quality of the available studies.

Key Words: neoadjuvant; chemotherapy; chemoradiotherapy; esophageal cancer; adenocarcinoma


Core Tip: Patients treated with esophageal AC, neoadjuvant chemoradiation increases pathological complete response and 30-day mortality, however, it has no effect on long-term survival. Neoadjuvant chemotherapy may associate some side effects, which can decrease the quality of life.
INTRODUCTION

Epidemiology

Esophageal cancer (EC) is diagnosed as the eighth most common cancer with more than 500,000 cases, worldwide, and it is the sixth cause of tumor mortality. Squamous cell carcinoma (SCC) is still the leading subtype in the Asian Esophageal Cancer Belt, however in Western countries, such as North America, Oceania, Western and Northern Europe including Hungary, the incidence rate of adenocarcinoma (AC) has been increasing, even surpassing the incidence of the squamous cell carcinoma (SCC) [1,2].

Even in the early stages, surgery can lead to full recovery, but the advanced tumor stage at the initial diagnosis can result in high morbidity and mortality rates [3]. Esophagectomy with radical lymphadenectomy is one of the most invasive gastrointestinal operations. To improve the treatment results, a multidisciplinary approach is important, including the application of enhanced recovery after surgery (ERAS protocol) [4, 5], the minimal invasive approach of the esophagectomy (MIE) [6], and neoadjuvant oncological therapy, which can decrease the mortality by 25-35% compared to surgery alone [7-9].

Impact of the topic

The superiority of neoadjuvant therapy has been proven by several meta-analyses [7-9]. Neoadjuvant chemotherapy (nCT) or preoperative chemoradiotherapy (nCRT) can also improve oncologic endpoints [8-15], increase the overall and the progression-free surveillance, and the pathological complete response (pCR), but unfortunately, it may also be associated with numerous clinical or surgical side effects and impaired quality of life, therefore the cost-benefit of these modalities is still unclear, especially in the case of adenocarcinoma of the esophagus and esophagogastric junction (GE).

Literature background

Former meta-analyses have numerous limitations, especially including both SCC and AC as a homogenous population. Because of this fact, the results cannot be applied clearly to either subtype.

Impact of our analysis
We carried out a comprehensive, up-to-date investigation to determine whether nCT or nCRT provides more favorable results in the surgical treatment of the adenocarcinoma of the esophagus and esophageal junction.

MATERIALS AND METHODS

Protocol registration
The goals, and methods of this meta-analysis were pre-defined in protocol using PROSPERO [10]. The registration was accepted on 1 Nov 2023 under the number of CRD42023478615.

Question of the review
To define the question of this meta-analysis we applied the PICO protocol. We planned to investigate those people (P) with esophageal or cardia adenocarcinoma, who received neoadjuvant therapy before surgery. The intervention (I) was the preoperative neoadjuvant chemotherapy (nCT), which was compared (C) to neoadjuvant chemoradiotherapy (nCRT). We planned to investigate the following outcomes (O): survival, remission rate, mortality, short- and long-term clinical and surgical complications, and quality of life. At first, we planned to investigate only randomized controlled trials (RCT) to minimize the risk of bias, but to achieve a sufficient number of cases, thus providing the opportunity to draw a clear conclusion, propensity score matched (PSM) and cohort studies of good quality were also included. We excluded those trials which were not concerned strictly with AC patients.

Search strategy and the Search-key
We conducted a comprehensive search on 15 Sept 2023, in the databases of PubMed, Embase, Cochrane, Web of Science, and Scopus. We used previously defined search keys containing the ‘neoadjuvant’, ‘chemotherapy’, ‘chemoradiotherapy’, ‘esophagus cancer’, ‘esophagectomy’, and ‘random’ keywords and their variants. The downloaded datasets were imported into an EndNote (x9.3.3) library [ref].

Selection process
EndNote (EndNote X9.3.3, Alfasoft AB, Göteborg, Sweden) software was applied during the selection process. Two independent authors performed the steps of the selection process. Cohen kappa was calculated from the results. Contradictions were discussed based on mutual agreement.

Data extraction

Data were collected from text, figures, and tables of the included articles by two independent authors. Contradictions were discussed based on mutual agreement. Plot digitizer applications were used to collect those data that were not provided in a numerical format [17]. Excel (Office 365, Microsoft, Redmond, WA, USA) datasheets were used to collect and organize the datasets. Descriptive data were collected, which characterized the studies (author, year, type, number of elements, etc.), patients (age, sex, performance, etc.), the tumors (stage, location), and the therapy (neoadjuvant regimen, surgical procedure). Meta-analysis was performed from those outcomes that included at least four homogeneous datasets. Outcomes, ineligible for statistical analysis were described qualitatively. The established outcomes investigated the pathological complete response (pCR), surveillance (overall, progression-free, disease-free), mortality (30 or 90 days), tumor remission (local or distant), clinical complications (thromboembolism, respiratory and cardiac complications, renal failure, neutropenia) and surgical complication (anastomotic and chyle leak, wound infect, bleeding, vocal cord paresis).

Statistical analysis

Random-effect meta-analyses were applied. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the effect size measure. To calculate the study odds ratios and the pooled odds ratio, the total number of patients and those with the event of interest in each group separately (referred as “raw data”) was extracted or calculated from the studies where it was available. We reported the results as the odds of event of interest in the experimental group vs the odds of event of interest in the control group. Results were considered statistically significant if the pooled CI did not contain the null value. We also performed a supplementary analysis. Using the WebPlotDigitizer online
tool, we digitalized the Kaplan-Meier (KM) curves published in the involved studies. Then, applying the methodology of Guyot et al.\textsuperscript{[18, 19]}, we estimated the individual patient time-to-event data. Finally, we plotted all the available KM curves on the same figure. Using the estimated raw data, we also calculated hazard ratio (HR) within the studies, and we calculated pooled HR. A less than one HR suggests a smaller risk in the experimental group. The HR result is significant if the one is not included in the confidence interval.

We visualized the findings on forest plots. Where it was applicable - the study number was large enough and not too heterogeneous -, we reported the prediction intervals (i.e. the expected range of effects of future studies) of results too. Additionally, between-study heterogeneity was described by the Higgins&Thompson’s ($I^2$) statistics (Higgins and Thompson 2002)\textsuperscript{[23]}. Publication bias was assessed by the visual inspection of Funnel-plots and calculating Harbord (modified Egger’s) test p-value\textsuperscript{[21]} for OR effect size. We planned to assume the presence of a possible small study bias if the p-value is less than 10%. (Although, we kept in mind that the test has limited diagnostic assessment below 10 study.) Potential outlier publications were explored using different influence measures and plots following the recommendation of Harrer et. al\textsuperscript{[22]}. All statistical analyses were made with R (R Core Team 2023, v4.3.0)\textsuperscript{[23]} using the meta (Schwarzer 2023, v6.2.1)\textsuperscript{[24]} package for basic meta-analysis calculations and plots, IPDfromKM for raw data estimations and dmetar (v0.0.9000)\textsuperscript{[25]} package for additional influential analysis calculations and plots. For pooling the effect size pooled OR, based on raw data was calculated by the Mantel-Haenszel method\textsuperscript{[26, 27]}. Exact Mantel-Haenszel method (without continuity correction) was used to handle zero cell counts\textsuperscript{[28, 29]}. We used a Hartung-Knapp adjustment\textsuperscript{[30, 31]} for CIs. To estimate the heterogeneity variance measure for raw data OR calculation the Paule-Mandel method\textsuperscript{[32]} (recommended by Veroniki et al.\textsuperscript{[33]}) was used with the Q profile method for confidence interval. Prediction interval calculations were based on t-distribution. In case of 0 cell counts, individual study OR with 95\%CI was calculated by adding 0.5 as continuity correction (it was used only for visualization on forest plot). The
pooled HR was calculated by classical inverse-variance meta-analysis of the log transformed HR ratios using REML heterogeneity variance estimator. Descriptive analyses were performed by calculation of mean, standard deviation, percentage. Mean estimations from median and range were using the following website [34].

Risk of bias and certain of evidence

We used the Risk of Bias Tool 2 (RoB2) and GRADE approach to assess the quality of articles and our research.

RESULTS

Searching process

1285 reports were identified from the five databases. After removing the duplications 1141 articles were screened by title and abstract, which resulted in 485 and 153 articles, respectively. After the selection process, 125 reports were examined by full text. Eight studies were included in the quantitative synthesis as the results of the selection process. Cohen kappa reported substantial agreement (Agreement: 99.74%, Cohen's k: 0.77). Reports could not be retrieved, because they were conference abstracts (28). Articles were excluded due to predefined criteria (83), containing only SCCs (9), or mixed group of ACCs and SCCs (23), mentioning no pathological subtype (1), and being preliminary trial (1). Further two articles were added by the screening of the former reviews. Overall, the analysis was performed including ten articles. More information can be seen in detail in the table above (Figure 1).

Characteristics of the studies

Ten articles were included in this meta-analysis from 2011 to 2018. Seven articles were conducted in Europe, two in Australia, and one in the USA [35-44]. We found two randomized controlled trials (RCT) [43, 44], four propensity score-matched cohorts (PMS) [39-42], and four cohorts based on prospective institutional databases (clinical cancer registry) [35-38]. Six of the articles were single-center trials [36, 39, 40, 42-44]. The articles overall contained data from 1928 patients. The nCT and the nCRT group contained 956 and 972
number of patients, respectively. All the included patients had esophagus adenocarcinoma. More information can be seen in detail in the table above (Table 1).

**Characteristics of the patients**

The estimated mean age of the patients was 60 years in both groups. The range of ages was 12-84 and 19-83 years, and the male patients were 829 (91%) and 857 (94%) in nCT and nCRT groups, respectively. Based on available data, 84%, 16% and <0.1% of the patients had I-II, III, and IV ASA scores, respectively. Patients had coronary morbidity (18%), diabetes mellitus (16%), pulmonary morbidity, or COPD (9%), malignant history (6%), and history of smoking (42%). More information can be seen in detail in the table above (Supplement Table 1).

**Characteristics of the tumor and pathological approach**

Based on available data, 99% of the tumors were diagnosed in the lower third of the esophagus or GEJ. Clinical T-stage (cT) 1 - 4 was 1%, 16%, 80%, and 3%, respectively. The nodal involvement was 367 (61%) in the nCT group and 350 (59%) in the nCRT group. Tumor differentiation was well in 2% and 1%, moderate in 36% and 31%, and poor in 57% and 64% in the groups of nCT and nCRT, respectively. Margin negative resection (R0) was 696 (81%) in nCT group, 800 (92%) in the nCRT group. Pathological T-stage (ypT) 1 - 4 was 13%, 15%, 22%, and 47%, respectively. Pathological N-stage (ypN) 0 - 3 was 45%, 31%, 14%, and 9%. Tumor regression grade (TRG, Mandard) stages 1 - 4/5 (in nCT and nCRT group) was 14% (6%-22%), 17% (7%-26%), 24% (18%-29%), and 42% (62%-22%), respectively, based on homogenous available data. More information can be seen in detail in the table above (Supplement Table 2).

**Characteristics of the neoadjuvant therapy**

Various neoadjuvant regimens were used in both groups. The most frequent neoadjuvant drugs were cisplatin, 5-fluorouracil, and docetaxel. CROSS protocol was the most common in the chemoradiation group. More information can be seen in detail in the table above 7,8,10,45-48 (Table 2).

**Characteristics of the surgical procedure**
Based on available data, Ivor-Lewis (transsthoracic), Orringer (transhiatal), McKeown (thoraco-abdomino-cervical) esophagectomy, and total gastrectomy were performed in 67%, 23%, 5%, and 4%, respectively. Minimal invasive or hybrid surgery techniques were used in 27% and 51%, respectively. Open surgery was performed only in 23%. Two-field lymphadenectomy was a standard procedure in 74%, however, three-field lymphadenectomy was performed in only 5%. More information can be seen in detail in the table above (Supplement Table 3).

**Pathological complete response**

A total of 8 studies were selected for analyses covering a total of 1547 patients [35, 36, 39-44]. The OR (the pooled effect size) was 0.27 (95%CI: 0.16-0.46). Significant statistical difference was detected, favouring the nCRT over nCT group (p < 0.001). The between-study heterogeneity expressed as I² value was 0.29 (95%CI: 0 - 0.68) (Figure 2).

**30-day mortality**

4 studies contained 899 patients were investigated [38, 40, 41, 43]. The OR was 0.4 (95%CI: 0.22 - 0.71). Significant statistical difference was detected, favouring the nCRT over nCT group (p-value = 0.015). Investigated the heterogeneity I² value was 0 (95%CI: 0 - 0.85) (Figure 3).

**90-day mortality**

Data of 1086 patients were included in four studies [38, 40-42]. The OR was 0.71 (95%CI: 0.28 - 1.84). There was no statistically significant difference between the two groups (P = 0.34). Examined the heterogeneity, I² value was 0 (95%CI: 0 - 0.85) (Supplement Figure 1).

**Overall survival**

The Kaplan-Meier curves and the logHR analysis did not find significant difference between the two groups in terms of overall survival (P = 0.82) investigated eight studies covering a total of 1540 patients [36-42, 44]. The OR was 0.98 (CI 95%: 0.77 - 1.23). The between-study heterogeneity expressed as I² value was 0.35 (95%CI: 0 - 0.71) (Figure 4, 5).

Considering the 12-month OS, nine studies were selected for analyses covering a total of 1588 patients [36-44]. The OR was 1.08 (CI 95%: 0.8 - 1.46). There was no statistically
significant difference between the two groups \((P = 0.551)\). The between-study heterogeneity expressed as \(I^2\) value was 0.05 (95% CI: 0 - 0.67) (Supplement Figure 2). Visualisation of the logHR analysis show no significant difference (Supplement Figure 3).

Regarding the 24-month survival, the OR was 1.03 (CI 95%: 0.73 - 1.45) \[^{36-44}\]. No statistically significant difference was reported between the two groups \((P = 0.858)\). Investigating heterogeneity, \(I^2\) value was 0.42 (95% CI: 0 - 0.73) (Supplement Figure 4). Visualisation of the logHR analysis show no significant difference (Supplement Figure 5).

Considering the 36-month survival, the OR was 0.93 (CI 95%: 0.54 - 1.6) between and groups \[^{36-44}\]. There was no statistically significant difference between the two groups \((P = 0.754)\). Investigating heterogeneity, \(I^2\) value was 0.73 (95% CI: 0.47 - 0.86) (Supplement Figure 6). Visualisation of the logHR analysis show no significant difference (Supplement Figure 7).

Regarding the 48-month survival, seven studies were selected for analyses covering a total of 1066 patients \[^{36-38, 40, 42-44}\]. The OR was 0.67 (95% CI: 0.27 - 0.85). There was no statistically significant difference between the two groups \((P = 0.616)\). Investigating heterogeneity, \(I^2\) value was 0.67 (95% CI: 0.27 - 0.85) (Supplement Figure 8). Visualisation of the logHR analysis show no significant difference (Supplement Figure 9).

Investigating the 60-month survival the OR was 1.15 (95% CI: 0.56 - 2.35) \[^{36-38, 40, 42-44}\]. No statistically significant difference was reported between the two groups \((P = 0.658)\). Investigating heterogeneity, \(I^2\) value was 0.67 (95% CI: 0.27 - 0.85) (Supplement Figure 10).

Disease-free survival

The Kaplan-Meier curves and the logHR analysis did not find significant difference between the two groups in terms of overall survival \((P = 0.85)\) investigated three studies including 578 patients \[^{36, 38, 42}\]. The OR was 1.04 (CI 95%: 0.5 - 2.16). Investigating heterogeneity, \(I^2\) value was 0.49 (95% CI: 0 - 0.85) (Supplement Figure 11, 12).
In terms of 12-month DFS, the OR was 0.93 (95% CI: 0.44 - 1.97) [36, 38, 42]. There was no statistically significant difference between the two groups (P = 0.702). Investigating heterogeneity, $I^2$ value was 0.07 (95% CI: 0 - 0.9) (Supplement Figure 13). Visualisation of the logHR analysis show no significant difference (Supplement Figure 14).

Regarding the 24-month DFS, the OR was 0.95 (95% CI: 0.49 - 1.86) [36, 38, 42]. There was no statistically significant difference between the two groups (P = 0.789). Investigating heterogeneity, $P$ value was 0 (95% CI: 0 - 0.9) (Supplement Figure 15). Visualisation of the logHR analysis show no significant difference (Supplement Figure 16).

Considering the 36-month DFS, the OR was 0.96 (95% CI: 0.4 - 2.28) [36, 38, 42]. No statistically significant difference was reported between the two groups (P = 0.846). Examined the heterogeneity, $I^2$ value was 0.05 (95% CI: 0 - 0.9) (Supplement Figure 17). Visualisation of the logHR analysis show no significant difference (Supplement Figure 18).

In terms of 48-month DFS, the OR was 1.04 (95% CI: 0.31 - 3.51) [36, 38, 42]. There was no statistically significant difference between the two groups (P = 0.904). Examined the heterogeneity, $I^2$ value was 0.32 (95% CI: 0 - 0.93) (Supplement Figure 19). Visualisation of the logHR analysis show no significant difference (Supplement Figure 20).

Regarding the 60-month DFS, the OR was 1.04 (95% CI: 0.3 - 3.64) [36, 38, 42]. There was no statistically significant difference between the two groups (P = 0.913). Investigated the heterogeneity $I^2$ value was 0.32 (95% CI: 0 - 0.93) (Supplement Figure 21).

**Progression-free survival**

Regarding the 12-month PFS, three studies were selected for analyses including 340 patients [40, 43, 44]. The OR was 0.73 (95% CI: 0.47 - 1.16). There was no statistically significant difference between the two groups (P = 0.101). Investigating the heterogeneity, $I^2$ value was 0 (95% CI: 0 - 0.9) (Supplement Figure 22).

Considering the 24-month PFS, the OR was 0.78 (95% CI: 0.1 - 6.18) [40, 43, 44]. There was no statistically significant difference between the two groups (P = 0.652). Investigating the heterogeneity, $I^2$ value was 0.72 (95% CI: 0.04 - 0.92) (Supplement Figure 23).
In terms of 36-month PFS, the OR was 1.04 (95%CI: 0.1 - 11.05) [40, 43, 44]. There was no statistically significant difference between the two groups ($P = 0.946$). Investigating the heterogeneity, $I^2$ value was 0.81 (95%CI: 0.39 - 0.94) (Supplement Figure 24).

**Locoregional recurrence**

Data of 1037 patients were investigated in six studies [36, 37, 41-44]. The OR was 0.98 (95%CI: 0.35 - 2.77). There was no statistically significant difference between the two groups ($P = 0.966$). Investigated heterogeneity, $I^2$ value was 0.76 (95%CI: 0.47 - 0.89) (Supplement Figure 25). Locoregional recurrence occurred in 12% of the patients.

**Distant metastasis recurrence**

Investigating 910 patients in five studies [37, 41-44], The OR was 1.12 (95%CI: 0.76 - 1.64). There was no statistically significant difference between the two groups ($P = 0.462$). Examined heterogeneity, $I^2$ value was 0 (95%CI: 0 - 0.79) (Supplement Figure 26). Distal metastasis recurrence occurred in 39% of the patients.

**Thromboembolism events**

Data of 818 patients were investigated in four studies [35, 40, 42, 43]. The OR was 1.93 (95%CI: 0.1 - 38.65). There was no statistically significant difference between the two groups ($P = 0.535$). Examined heterogeneity $I^2$ value was 0.72 (95%CI: 0.22 - 0.90) (Supplement Figure 27).

**Cardiac complication**

Investigating 1580 patients in seven studies [35, 36, 38, 40-43]. The OR was 0.8 (95%CI: 0.42 - 1.52). There was no statistically significant difference between the two groups ($P = 0.425$). Examined heterogeneity, $I^2$ value was 0.46 (95%CI: 0 - 0.77) (Supplement Figure 28).

**Respiratory complication**

Data of 1580 patients in seven studies [35, 36, 38, 40-43]. The OR was 1.04 (95%CI: 0.66 - 1.64). There was no statistically significant difference between the two groups ($P = 0.835$). Investigated heterogeneity, $I^2$ value was 0.59 (95%CI: 0.04 - 0.82) (Supplement Figure 29).

**Renal failure**

Data of 650 patients investigated in three studies [35, 42, 43]. The OR was 2.43 (95%CI: 1.12 - 5.28). Significant statistical difference was detected, favouring the nCT over nCRT group.
(p-value = 0.039). Examined heterogeneity, $I^2$ value was 0 (95% CI: 0 - 0.9) (Supplement Figure 30).

**Neutropenia**

Investigating 560 patients in three studies \cite{35,40,43}. The OR was 0.97 (95% CI: 0.09 - 10.29). There was no statistically significant difference between the two groups ($P = 0.964$).

Examined heterogeneity, $I^2$ value was 0.47 (95% CI: 0 - 0.84) (Supplement Figure 31).

**Anastomotic leakage**

Data of 1580 patients were investigated in seven studies \cite{35,36,38,40-43}. The OR was 0.83 (95% CI: 0.41 - 1.68). There was no statistically significant difference between the two groups ($P = 0.539$). Investigated the heterogeneity, $I^2$ value was 0.75 (95% CI: 0.48 - 0.88) (Supplement Figure 32).

**Chylie leakage**

1366 patients were investigated in six studies \cite{35,36,40-43}. The OR was 0.99 (95% CI: 0.61 - 1.61). There was no statistically significant difference between the two groups ($P = 0.961$).

Examined the heterogeneity $I^2$ value was 0 (95% CI: 0.48 - 0.75) (Supplement Figure 33).

**Wound infection**

Examined five studies including 1022 patients \cite{35,38,40,42,43}. The OR was 1.04 (95% CI: 0.36 - 3.02). There was no statistically significant difference between the two groups ($P = 0.930$). Investigating heterogeneity, $I^2$ value was 0.37 (95% CI: 0 - 0.76) (Supplement Figure 34).

**Bleeding**

Examined 849 patients in four studies \cite{35,36,40,42}. The OR was 1.4 (95% CI: 0.425 - 7.79). There was no statistically significant difference between the two groups ($P = 0.581$).

Investigated heterogeneity, $I^2$ value was 0 (95% CI: 0 - 0.85) (Supplement Figure 35).

**Vocal cord paresis**

Investigated three studies including 733 patients \cite{35,40,42}. The OR was 1.21 (95% CI: 0.04 - 41.98). There was no statistically significant difference between the two groups ($P = 0.537$). Examined heterogeneity, $I^2$ value was 0.5 (95% CI: 0 - 0.85) (Supplement Figure 36).

**Leukopenia**
Two studies were selected for descriptive analyses covering a total of 485 patients [35, 40]. In the nCT group, leukopenia occurred in 8% compared to 12% in the nCRT group.

Anemia

Two studies were selected for descriptive analyses covering a total of 485 patients [35, 40]. In the nCT group, anemia occurred in 1% compared to 0.4% in the nCRT group.

Nausea or Vomiting

Three studies were selected for descriptive analyses covering a total of 560 patients [35, 40, 43]. In the nCT group, nausea or vomiting occurred in 9% compared to 3% in the nCRT group.

Diarrhea

Two studies were selected for descriptive analyses covering a total of 485 patients [35, 40]. In the nCT group, diarrhea occurred in 7% compared to no cases in the nCRT group.

Hospital stay

Two studies were selected for descriptive analyses covering a total of 430 patients [40, 42]. The estimated mean of hospital stay was 20 days (range: 7-97) in the nCT group compared to 18 days (range: 7-75) in nCRT group.

Risk of Bias

As we expected, the included two randomized controlled trials carried a low risk of bias. In the case of other included trials, ROB2 resulted in some concern, mainly due to the randomization process (D1). In the case of the measurement process of one trial, some concerns were also mentioned, because of the application of the plot digitizer [17]. No high risk of bias has been reported. More information can be seen in detail in the table above (Table 3).

GRADE approach

The GRADE approach judges our findings low in most of the outcomes, moderate in 30-day mortality, very low in 12-month OS, 36-month PFS and in the thromboembolism events. RoB2 reported moderate risk in all outcomes. High heterogeneity was reported in the outcome of 36-month PFS and the thromboembolism events. Imprecision declared in the outcome of pCR and the 12-month OS. The high variation of oncological treatment
also decreases the evidence. Large effect size increases the quality of pCR and 30-day mortality.\(^{40}\) (Supplement Table 4).

**DISCUSSION**

The benefits of neoadjuvant therapy were proved before.\(^{7-9}\) Former meta-analyses examined the question of the amplification of the neoadjuvant chemo- and chemoradiotherapy in a mixed population of AC and SCC. In the nCRT group, they found advantages in the 3-year survival by R0 resection; however, the pCR rate has no effects on long-term survival. They also found more common perioperative mortality and cardiovascular complications among patients with AC in the nCRT group.\(^{50}\) A former network meta-analysis proved that triplet-based chemoradiation increased overall survival and disease-free survival in the case of AC of the stomach or GE.\(^{51}\).

Pathological complete response (pCR) is defined as the lack of tumor in the resected specimen or lymph nodes (pT0 pN0 cM0)\(^{15, 36}\). A 5-year survival rate can be 88% in patients with pCR compared to 39% without pCR.\(^{15, 52}\). According to an up-to-date investigation, tumor regression after neoadjuvant treatment is significantly associated with long-term survival regardless of the treatment regimen. They compared the long-term survival of total population, and TRG 1 to TRG 2 patient, who underwent neoadjuvant chemotherapy or chemoradiotherapy before operation.\(^{53}\) Another retrospective cohort study found improved OS and DFS of pCR patients, who underwent nCT against the lower rate of pCR, compared to nCRT. They found a significant relation between TRG and survival in both groups. In addition, it was found that pCR cases in nCRT do not have as good survival as in nCT, although their proportion is higher in nCRT. Based on this, it seems that esophageal adenocarcinoma should be considered more as a systemic disease and should be treated accordingly.\(^{53, 54}\). However, other trials found that a larger number of pCR does not improve overall survival.\(^{55}\). In this meta-analysis, we found significantly higher pCR in the nCRT group, however, no differentiation was found in OS, DFS and PFS, supported former meta-analysis.\(^{50, 55}\).

From this finding, we suspected the no relation between the pCR and OS, therefore pCR
usage as a prognostic factor should be considered, in the case of AC. A 2023 study also support our findings, that high number of pCR after CROSS is not clearly associated with longer overall survival [56]. Another study concluded only clinical complete response without nodal metastasis connected to long-term survival, therefore the “watch-and-wait”, strategies should be considered carefully, applied only total pCR patients [57]. The application of pCR as a prognostic indicator of neoadjuvant therapy is still questionable, which proves numerous large numbers of randomized studies are necessary, in the future.

None of the investigated groups were superior considering the local recurrence based on our investigation, and a former meta-analysis supported this finding [50]. This proves that the higher local control provided by radiotherapy did not reduce the incidence of local recurrence. We also did not detect a significant difference among in terms of metastases, which occurred in 39% compared to 12% of local recurrence, therefore AC should be treated as a systematic disease, therefore the “watch-and-wait” strategies should be considered critically.

Our findings showed a significantly higher risk of 30-day mortality in the chemoradiotherapy group. This fact can be attributed to complications arising in the postoperative period, however difference in the outcomes of surgical complications were not detected, which is supported by a former meta-analysis, in which no difference was reported in the case of anastomotic leakage [50]. A former meta-analysis also found a higher risk of mortality in the postoperative period among patients with AC, therefore further investigation of nCRT effect of the postoperative complication is needed in the future [50]. Only descriptive analysis was performed, and the duration of postoperative hospitalization was similar in both groups [40, 42].

We found no difference in any of the clinical complications; however, a former meta-analysis found a higher risk of cardiovascular complication in the nRCT group, which can be a toxic side effect of this modality.

Neoadjuvant chemotherapy and radiotherapy may also be related to adverse events. Thromboembolic events, neutropenia, leukopenia, anemia, nausea or vomiting, and
diarrhea are listed among several toxic side effects. Renal failure occurs more often in the nCT group, which also had a toxic side effect, however difference was not reported in the case of cardiac failure, against former meta-analysis. According to previous investigations neutropenia is not statistically associated with either neoadjuvant modality. In the descriptive analysis, leukopenia occurs 4% more often in the nCRT group, therefore these patients may be more vulnerable to developing infections. Low number of cases of anemia were observes in both groups. Quality of Life (QoL) can be measured by the EORTC QLQ-C30 questionnaire, which contains the side effects of nausea, vomiting, and diarrhea, which developed in the nCT group almost 7% more often.

We consider our meta-analysis to be the most comprehensive and recent summary of the data considering the question of interest. It is also exclusive for the cases of esophageal adenocarcinoma. In addition, plenty of outcomes were analysed including sufficient number of cases. The data of this study accurately reflects the population of the esophageal AC. No significant difference of demographical aspects was reported between the sample of the two examined groups.

Some limitation of our study should be mentioned. Deviating from the protocol we also included propensity score matches studies, and cohort trials, which are less reliable than randomized controlled trials, and can carry potentially significant biases. All the trials were made in Western countries, which is characteristic of AC, therefore the results cannot be referred to the Asian population or other countries. Several types of neoadjuvant regimens were applied, and some included articles did not separate the preoperative and perioperative therapy, therefore these facts also carry some limitations. The evidence of most outcomes was low, therefore the true effect may be substantially different from the estimate.

In summary, one might question the lack of impact of radiotherapy on overall survival, despite improvements in measures of pathological regression, known to correlate with survival. This discrepancy can be attributed to the modification of these crucial measures by local therapy. In the context of modern surgical techniques, the systemic component
of the disease is the primary determinant of survival for esophageal and gastro-oesophageal junction adenocarcinoma. Hence, the addition of systemic chemotherapy, new immunotherapy, and targeted treatments capable of addressing distant disease holds greater potential to enhance patient survival in the future.

CONCLUSION
Patients treated with esophageal AC, neoadjuvant chemoradiation increases pathological complete response and 30-day mortality, however, it has no effect on long-term survival. Neoadjuvant chemotherapy may associate some side effects, which can decrease the quality of life. Further randomized trials are required due to the quality of the available studies.

ARTICLE HIGHLIGHTS
Research background
The number of the adenocarcinoma (AC) of the esophagus is increasing especially in the Western countries, contrary to the squamous cell carcinoma (SCC). In the progressed stages neoadjuvant therapy before surgery can improve the survival. The superiority of the neoadjuvant modalities is not clear, especially of the adenocarcinoma. Former meta analysis have numerous limitations, including pooled population of ACC and SCC, therefore their results cannot played to either subtype.

Research motivation
The superiority of neoadjuvant therapy has proven before, but which modality has higher benefit is questionable, especially of the adenocarcinoma of the esophagus. We carried out a comprehensive, up-to-date investigation to determine whether nCT or nCRT provides more favorable results in the surgical treatment of the adenocarcinoma of the esophagus and esophageal junction.

Research objectives
To define the question of this meta-analysis we applied the PICO protocol. We planned to investigate those people (P) with esophageal or cardia adenocarcinoma, who received neoadjuvant therapy before surgery. The intervention (I) was the preoperative neoadjuvant chemotherapy (nCT), which was compared (C) to neoadjuvant chemoradiotherapy (nCRT). We planned to investigate the following outcomes (O): survival, remission rate, mortality, short- and long-term clinical and surgical complications, and quality of life.

**Research methods**

PICO protocol was used to define our clinical question. Two independent author perform the comprehensive search in multiple databases by predefined criteria. Statistical analysis were performed by biostatistician co-workers. We calculated odds ratio (OR) and hazard ratio (HR) with the 95% confidence intervals. We visualized our findings on forest plots and Kaplan-Meier curves. We use the Risk of Bias Tool 2 and GRADE approach to measure the quality of our results.

**Research results**

After selection methods ten articles were included. After statistical analysis we found, the 30-day mortality ($P = 0.015$) and pathological complete response ($p < 0.001$) was higher risk in the nCRT group, however significant difference was not found in the long term survival. Develop of the risk of renal failure ($P = 0.039$) was higher in the nCT group, and the occurrence of nausea or vomiting was 9% in the nCT group compared to 3%. Significant difference was not reported in the case of other clinical or surgical complications.

**Research conclusions**

Superiority of neoadjuvant therapy has proved before. However nCRT may increase the pCR and the 30-day mortality however it cannot increase the long term survival. In the case of nCT some adverse effect were mentioned which can decrease the quality of life.
Research perspectives

The present study predominantly processes retrospective data, which may involve significant bias, therefore a new, more detailed randomized study would be necessary.
Arom Choi, Incheol Park, Hye Sun Lee, Jinseok Chung, Min Joung Kim, Yoo Seok Park. "Usefulness of complete blood count parameters to predict poor outcomes in cancer patients with febrile neutropenia presenting to the emergency department", Annals of Medicine, 2022