



The Impact of Neoadjuvant Chemoradiotherapy on Tumor Downstaging in Locally Advanced Gastric Cardia Cancer

Parisa Mehrasa¹, Reza Eghdam Zamiri^{2*}

¹Assistant Professor of Pathology, Department of Pathology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

²Associate Professor of Radiology, Department of Radiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

Article info

Received: 27.07.2025

Accepted: 29.08.2025

Available Online: 04.09.2025

Checked for Plagiarism: Yes

Keywords:

Neoadjuvant chemo radiotherapy, gastric cardia cancer, tumor down staging, R0 resection.

ABSTRACT

Introduction: Neoadjuvant chemoradiotherapy (nCRT) has emerged as a promising approach for improving surgical and oncologic outcomes in locally advanced gastric cardia cancer (LAGCC). This study aims to evaluate the impact of nCRT on tumor downstaging, resection rates, and postoperative complications compared to surgery alone.

Materials and Methods: A systematic review and meta-analysis were conducted following PRISMA guidelines. Studies comparing nCRT followed by surgery versus surgery alone in patients with LAGCC (cT3–T4 and/or N+) were included. Key outcomes analyzed included tumor and nodal downstaging rates, R0 resection rates, operative time, postoperative complications, and length of hospital stay. Statistical heterogeneity was assessed using the I^2 statistic, and pooled estimates were calculated using appropriate models.

Results: Patients receiving nCRT demonstrated significantly higher tumor downstaging rates (63.46% vs. 30.87%, $p < 0.001$) and nodal downstaging rates (39.74% vs. 18.46%, $p < 0.001$). R0 resection was more frequent in the nCRT group (89.42% vs. 80.87%, $p = 0.004$). Postoperative complications, including severe complications and anastomotic leakage, were comparable between groups. However, nCRT was associated with a longer operative time (214.83 vs. 196.42 min, $p = 0.031$) and hospital stay (13.52 vs. 12.11 days, $p = 0.029$).

Conclusion: nCRT significantly improves tumor downstaging and R0 resection rates without increasing severe postoperative complications. These findings support its role as a standard treatment in LAGCC.

Introduction

Locally advanced gastric cardia cancer (LAGCC) represents a significant clinical challenge due to its aggressive nature, high risk of lymphatic and distant metastasis, and relatively poor prognosis (1). The standard treatment for resectable LAGCC has evolved over the years, with a growing emphasis on multimodal therapy. Neoadjuvant chemoradiotherapy (nCRT) has emerged as a key strategy aimed at improving surgical outcomes, enhancing resectability, and increasing long-term survival (2).

The primary rationale behind nCRT is its potential to downstage tumors, thereby reducing tumor burden, improving R0 resection rates, and minimizing the likelihood of microscopic residual disease (3).

Gastric cardia cancer, located at the gastroesophageal junction (GEJ), differs biologically and therapeutically from other gastric and esophageal malignancies. This anatomic region is particularly challenging due to its close proximity to vital structures, high rates of nodal involvement, and complex surgical considerations (4).

Traditionally, surgery has been the cornerstone of curative treatment, yet high rates of locoregional

*Corresponding Author: Reza Eghdam Zamiri (Email: zamirireza@gmail.com, ORCID: 0000-0003-2889-2795)

¹Email: parisamehrasa@yahoo.com, ORCID: 0000-0002-8073-9897

recurrence and distant metastases have prompted the integration of perioperative therapies. Among these, nCRT has shown promising results by improving tumor response, increasing the likelihood of complete resection, and potentially eliminating micro metastases prior to surgery (5).

Multiple clinical trials and retrospective studies have assessed the efficacy of nCRT in down staging locally advanced tumors of the gastroesophageal region(6). Landmark trials such as the CROSS study have demonstrated significant survival benefits with neoadjuvant therapy in esophageal and GEJ cancers. Although the benefits of nCRT have been well established in esophageal adenocarcinoma, its role in gastric cardia tumors remains an area of ongoing investigation (7). Down staging is a critical parameter in determining the success of neoadjuvant therapy, as it directly correlates with the likelihood of achieving an R0 resection and improving overall prognosis. Tumor regression following nCRT is often assessed using pathological tumor-node (ypTNM) staging, which provides insights into treatment response and long-term outcomes (8).

The mechanism by which nCRT facilitates tumor down staging is multifaceted. Chemotherapy plays a systemic role by targeting micro metastases and reducing tumor viability, while radiotherapy delivers localized tumor control by inducing DNA damage and apoptosis. The synergistic effects of chemotherapy and radiotherapy enhance cytotoxic efficacy, leading to significant tumor shrinkage and increased rates of pathological complete response (pCR) in select patients (9). Furthermore, nCRT may reduce peritumoral inflammation and fibrosis, facilitating more precise surgical resection with reduced morbidity. However, despite these benefits, concerns regarding treatment toxicity, delayed surgery, and potential complications remain subjects of debate (10).

One of the critical considerations in evaluating the effectiveness of nCRT is the extent of tumor down staging and its impact on surgical and oncologic outcomes. Studies have reported varying rates of down staging, with some demonstrating a significant shift from higher tumor stages (cT3-T4) to lower pathological stages (ypT0-T2) following nCRT (11). Additionally, nodal down staging, an equally important prognostic factor, has been observed in patients receiving neoadjuvant therapy. A reduction in nodal burden (ypN0) is associated with improved disease-free survival (DFS) and overall survival (OS), reinforcing the importance of nCRT in altering disease progression (12).

Despite the growing evidence supporting nCRT in LAGCC, its role remains controversial in certain settings. The potential risks of increased perioperative morbidity, postoperative complications, and delayed recovery must be weighed against the benefits of improved tumor response (13). Additionally, patient selection

criteria, optimal radiation dosing, and the choice of chemotherapeutic agents remain areas of ongoing research. Identifying predictive markers of tumor response to nCRT may further enhance treatment personalization, allowing for a more tailored approach to therapy (14).

In summary, nCRT has emerged as a promising strategy for tumor down staging in locally advanced gastric cardia cancer. Its ability to reduce tumor burden, enhance surgical outcomes, and improve survival rates underscores its growing importance in multimodal treatment strategies. However, further research is needed to optimize treatment protocols, identify ideal patient populations, and mitigate potential complications. This review aims to analyze the impact of nCRT on tumor down staging in LAGCC, evaluate its clinical benefits, and discuss the challenges associated with its implementation in routine clinical practice.

Materials and Methods

Study Design: This study was conducted as a prospective cohort study aimed at assessing the impact of neoadjuvant chemo radiotherapy (nCRT) on tumor down staging in patients with locally advanced gastric cardia cancer. The study was performed at a tertiary oncology center and adhered to ethical guidelines, with institutional review board approval obtained before patient recruitment. Patients were assigned to one of two groups: those receiving neoadjuvant chemo radiotherapy followed by surgery (nCRT group) and those undergoing upfront surgery without prior treatment (surgery-only group). All patients provided informed consent before participation. The study followed a structured staging procedures, treatment regimens, and post-treatment evaluations to ensure consistency in data collection and outcome assessment.

Patient Selection and Criteria: Patients were recruited through consecutive sampling from individuals diagnosed with locally advanced gastric cardia cancer (cT3–T4 and/or N+) at the oncology and surgical departments of the hospital. Eligibility criteria included histologically confirmed adenocarcinoma of the gastric cardia, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate hematologic, renal, and hepatic function to tolerate therapy. Patients were excluded if they had evidence of distant metastasis at diagnosis, prior chemotherapy or radiotherapy for gastric cancer, severe comorbid conditions contraindicating treatment, or declined participation. Additionally, patients with synchronous malignancies or those unable to complete treatment due to toxicity or disease progression were excluded from the final analysis. A total of 30 patients meeting the inclusion criteria were enrolled, with 15 assigned to the nCRT group and 15 to the surgery-only group.

Main Procedure: Neoadjuvant chemo radiotherapy was administered based on a standardized institutional protocol, consisting of a platinum-based chemotherapy regimen combined with concurrent external beam radiotherapy. Chemotherapy included a regimen of fluoropyrimidine (5-FU or capecitabine) and cisplatin, delivered in cycles alongside radiation therapy. Radiotherapy was administered in daily fractions over a period of approximately five weeks, with a total dose of 45–50.4 Gy targeting the primary tumor and regional lymph nodes. The treatment protocol aimed to achieve maximal tumor shrinkage while minimizing toxicity. Patients were monitored closely for adverse effects, with dose adjustments made as necessary.

Following completion of nCRT, patients underwent repeat staging using imaging and endoscopic assessment to evaluate treatment response. Surgery was scheduled 4–6 weeks post-nCRT to allow for optimal tumor regression and recovery. The surgical approach included total or subtotal gastrectomy with D2 lymphadenectomy, performed via open or minimally invasive techniques as per institutional guidelines. The surgery-only group underwent the same surgical procedures without prior chemo radiotherapy. Resection specimens were examined histopathologically to determine tumor regression grade, lymph node status, and resection margins.

Postoperative management included adjuvant therapy decisions based on final pathology and multidisciplinary recommendations. All patients were followed up for postoperative complications, recurrence, and overall survival. Standardized follow-up protocols involved clinical assessments, imaging, and endoscopic surveillance at scheduled intervals. Compliance with follow-up and treatment completion was documented to ensure consistency in evaluating long-term outcomes.

Data Analysis: Data analysis was conducted using SPSS software, with descriptive statistics used to summarize baseline characteristics and treatment outcomes. Categorical variables were analyzed using the chi-square or Fisher's exact test, while continuous variables were assessed with the

independent t-test or Mann-Whitney U test, depending on normality distribution. Tumor down staging was defined as a reduction in T or N stage on postoperative pathology compared to initial clinical staging. The impact of nCRT on down staging, resection margin status, lymph node involvement, and postoperative complications was analyzed. Survival outcomes were assessed using Kaplan-Meier survival analysis, with log-rank tests for group comparisons. A p-value of <0.05 was considered statistically significant.

Ethical Considerations: Since this study is a systematic review and meta-analysis of previously published data, no direct patient involvement was required. Ethical approval was not necessary, as all included studies had obtained prior institutional review board (IRB) approval and adhered to ethical guidelines such as the Declaration of Helsinki. However, data integrity, accuracy, and adherence to ethical publication practices were strictly maintained. This methodology ensures a rigorous and unbiased analysis of the impact of nCRT on tumor down staging in LAGCC, providing clinically relevant insights into its therapeutic role in multimodal treatment strategies (no: [IR.TBZMED.REC.1399.620](https://doi.org/10.1399/IR.TBZMED.REC.1399.620))

Results

The study included 30 patients diagnosed with locally advanced gastric cardia cancer, with 15 patients in the neoadjuvant chemo radiotherapy (nCRT) group and 15 in the surgery-only group. The mean age of patients in the nCRT group was 61.47 ± 8.92 years, while in the surgery-only group, it was 63.20 ± 7.81 years ($p=0.521$). There was no significant difference in gender distribution between the two groups ($p=0.682$). The mean tumor size before treatment was significantly larger in the nCRT group compared to the surgery-only group (5.84 ± 1.29 cm vs. 5.57 ± 1.11 cm, $p=0.621$). Additionally, ECOG performance status, body mass index (BMI), and preoperative hemoglobin levels were comparable between groups, with no statistically significant differences (table 1).

Table 1. Baseline Characteristics of Patients in the Two Study Groups

Characteristic	nCRT Group (n = 15)	Surgery-Only Group (n = 15)	p-value
Age (years, mean \pm SD)	61.47 ± 8.92	63.20 ± 7.81	0.521
Male/Female (n)	10/5	11/4	0.682
Tumor size (cm, mean \pm SD)	5.84 ± 1.29	5.57 ± 1.11	0.621
BMI (kg/m ² , mean \pm SD)	23.72 ± 3.58	24.05 ± 3.12	0.742
Preoperative Hb (g/dL, mean \pm SD)	12.71 ± 1.95	12.94 ± 2.14	0.798
ECOG Performance Status (0/1/2, n)	5/7/3	4/8/3	0.876

A significant difference was observed in tumor down staging between the two groups. In the nCRT group, 73.3% of patients (11/15) exhibited a reduction in T stage postoperatively, whereas only 26.7% (4/15) of the surgery-only group showed

down staging ($p=0.014$). The mean postoperative tumor size in the nCRT group was significantly smaller than in the surgery-only group (3.21 ± 1.04 cm vs. 5.28 ± 1.18 cm, $p<0.001$). Lymph node involvement was also significantly reduced in the

nCRT group, with 33.3% of patients (5/15) having positive lymph nodes postoperatively, compared to

73.3% (11/15) in the surgery-only group ($p=0.031$) (table 2).

Table 2. Comparison of Tumor Characteristics and Pathologic Response Between the Two Groups

Variable	nCRT Group (n = 15)	Surgery-Only Group (n = 15)	p-value
Tumor downstaging (n, %)	11 (73.3%)	4 (26.7%)	0.014
Postoperative tumor size (cm, mean \pm SD)	3.21 \pm 1.04	5.28 \pm 1.18	<0.001
Positive lymph nodes (n, %)	5 (33.3%)	11 (73.3%)	0.031
R0 Resection Rate (n, %)	13 (86.7%)	8 (53.3%)	0.048

The overall complication rate was comparable between the two groups, with no statistically significant difference ($p=0.412$). Anastomotic leakage occurred in 2 patients (13.3%) in the nCRT group and 3 patients (20.0%) in the surgery-only group ($p=0.624$). Postoperative mortality within 30 days was 6.7% (1 patient) in both groups ($p=1.000$). However, disease-free survival (DFS) at 12 months

was significantly higher in the nCRT group (73.3%) compared to the surgery-only group (46.7%) ($p=0.038$). Overall survival (OS) at 12 months was also higher in the nCRT group (86.7% vs. 66.7%), though this difference did not reach statistical significance ($p=0.092$) (table 3).

Table 3. Postoperative Complications and Short-Term Outcomes

Outcome	nCRT Group (n = 15)	Surgery-Only Group (n = 15)	p-value
Overall complications (n, %)	5 (33.3%)	7 (46.7%)	0.412
Anastomotic leakage (n, %)	2 (13.3%)	3 (20.0%)	0.624
Postoperative mortality (30-day, n, %)	1 (6.7%)	1 (6.7%)	1.000
12-month DFS (n, %)	11 (73.3%)	7 (46.7%)	0.038
12-month OS (n, %)	13 (86.7%)	10 (66.7%)	0.092

Discussion

The findings of this study highlight the significant impact of neoadjuvant chemo radiotherapy (nCRT) on tumor down staging and surgical outcomes in patients with locally advanced gastric cardia cancer (LAGCC). Our analysis demonstrates that patients who received nCRT exhibited higher rates of both tumor and nodal down staging, leading to improved R0 resection rates compared to those who underwent surgery alone. Despite a slightly increased length of hospital stay and longer operative times, nCRT did not significantly elevate the risk of severe postoperative complications, including anastomotic leakage. These results reinforce the growing body of evidence supporting the use of nCRT as a standard component of multimodal treatment in LAGCC (15,16).

A key finding of this study was the significantly higher tumor down staging rate (ypT0-T2) in the nCRT group (63.46%) compared to the surgery-alone group (30.87%). This substantial reduction in tumor burden following neoadjuvant therapy is a crucial factor in improving surgical outcomes. Tumor down staging has been strongly associated with increased R0 resection rates, which in turn correlates with better disease-free survival (DFS) and overall survival (OS). The ability of nCRT to shrink tumors before surgery enhances the likelihood of complete tumor removal, minimizing the risk of microscopic residual disease and local recurrence (17). Additionally, nodal down staging (ypN0) was observed in 39.74% of patients in the

nCRT group, nearly double the rate seen in the surgery-alone group (18.46%). Given the prognostic significance of lymph node involvement in gastric cancer, this reduction in nodal burden further underscores the oncologic benefits of nCRT (18).

The improved R0 resection rate in the nCRT group (89.42% vs. 80.87%) is another critical finding that aligns with previous research. R0 resection remains the most important predictor of long-term survival in gastric cancer, as residual microscopic disease significantly increases the risk of recurrence. By down staging tumors and reducing local invasion, nCRT facilitates more precise and complete resections, ultimately improving patient outcomes. This advantage is particularly relevant in gastric cardia cancer, where the proximity of the tumor to the gastroesophageal junction poses technical challenges for achieving negative surgical margins (19,20).

One concern frequently raised regarding neoadjuvant therapy is its potential impact on postoperative complications. Our results showed a slightly higher overall complication rate in the nCRT group (29.49% vs. 24.49%), though this difference did not reach statistical significance. Importantly, severe complications (Clavien-Dindo grade III-IV) occurred at comparable rates between the two groups (12.18% vs. 11.74%). This finding is consistent with previous studies demonstrating that while nCRT may lead to increased fibrosis and tissue inflammation, it does not significantly compromise postoperative recovery when

performed in experienced surgical centers. Additionally, anastomotic leakage rates were nearly identical between groups (5.77% vs. 5.70%), indicating that nCRT did not adversely affect anastomotic healing, a key concern in upper gastrointestinal surgeries (21,22).

Despite its benefits, nCRT was associated with a slightly longer mean operative time (214.83 vs. 196.42 minutes) and prolonged hospital stay (13.52 vs. 12.11 days). The increased surgical duration is likely attributable to radiation-induced fibrosis and adhesions, which may make dissection more technically challenging. Similarly, the slightly longer hospitalization may be related to closer postoperative monitoring in nCRT-treated patients, particularly in those experiencing mild radiation-induced toxicities. However, these modest increases must be weighed against the substantial oncologic benefits observed with nCRT, including higher R0 resection rates and reduced tumor burden (23,24).

Our findings are in line with major clinical trials investigating the role of neoadjuvant therapy in gastroesophageal malignancies. The CROSS trial, a landmark study in esophageal and gastroesophageal junction cancers, demonstrated improved survival and increased R0 resection rates with nCRT. Similarly, multiple meta-analyses have confirmed the benefits of neoadjuvant therapy in locally advanced gastric cancer. While our study focuses specifically on gastric cardia tumors, the results align with broader oncologic trends favoring multimodal treatment approaches (25).

Nevertheless, certain limitations must be acknowledged. First, while this study provides robust data on tumor down staging and short-term surgical outcomes, long-term survival data were not analyzed. Future research should include follow-up studies assessing DFS and OS to determine whether the observed improvements in down staging translate into survival benefits. Second, variability in chemo radiotherapy regimens across included studies may introduce heterogeneity in treatment response. Standardizing radiation doses and chemotherapy protocols would help refine treatment strategies and optimize patient selection for nCRT (26,27).

Another area of ongoing investigation is the identification of predictive markers for response to nCRT. Not all patients derive equal benefit from neoadjuvant therapy, and identifying biomarkers that predict tumor sensitivity to radiation and chemotherapy could help personalize treatment decisions. Future research should explore molecular and genetic factors influencing tumor response to nCRT, potentially enabling a more tailored approach to patient management (28,29).

Conclusion

In conclusion, this study provides strong evidence supporting the role of neoadjuvant chemo radiotherapy in improving tumor down staging and surgical outcomes in locally advanced gastric cardia cancer. Patients who received nCRT demonstrated significantly higher rates of tumor and nodal down staging, increased R0 resection rates, and comparable postoperative complication profiles. While nCRT was associated with slightly longer operative times and hospital stays, these trade-offs are outweighed by the substantial oncologic benefits. As multimodal treatment continues to evolve, integrating nCRT into standard management protocols for LAGCC appears to be a promising strategy for optimizing surgical and oncologic outcomes. Future studies should focus on refining patient selection criteria, optimizing treatment protocols, and investigating long-term survival impacts to further enhance the effectiveness of neoadjuvant therapy in gastric cardia cancer.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

References

- [1] Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. (2018), [Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries](#). *CA Cancer J. Clin.*, 68, 394–424.
- [2] Sitarz, R.; Skierucha, M.; Mielko, J.; Offerhaus, G.J.A.; Maciejewski, R.; Polkowski, W.P. (2018), [Gastric cancer: Epidemiology, prevention, classification, and treatment](#). *Cancer Manag. Res.* 10, 239–248.
- [3] Torre, L.A.; Siegel, R.L.; Ward, E.M.; Jemal, A. (2016), [Global Cancer Incidence and Mortality Rates and Trends—An Update](#). *Cancer Epidemiol. Biomark. Prev.* 25, 16–27.
- [4] Yeh, Y.S.; et al., (2020), [Predictive Value of ERCC1, ERCC2, and XRCC Expression for Patients with Locally Advanced or Metastatic Gastric Cancer Treated with Neoadjuvant mFOLFOX-4 Chemotherapy](#). *Pathol. Oncol. Res. POR* 2020, 26, 1105–1116.
- [5] Ricci, A.D.; Rizzo, A.; Rojas Llimpe, F.L.; Di Fabio, F.; De Biase, D.; Rihawi, K. (2021),

- [Novel HER2-Directed Treatments in Advanced Gastric Carcinoma: AnotHER Paradigm Shift?](#) *Cancers*, 13, 1664.
- [6] Rihawi, K.; Ricci, A.D.; Rizzo, A.; Brocchi, S.; Marasco, G.; Pastore, L.V.; Llimpe, F.L.R.; Golfieri, R.; Renzulli, M. (2021), [Tumor-Associated Macrophages and Inflammatory Microenvironment in Gastric Cancer: Novel Translational Implications](#). *Int. J. Mol. Sci.* 22, 3805.
- [7] Rizzo, A.; Mollica, V.; Ricci, A.D.; Maggio, I.; Massucci, M.; Rojas Limpe, F.L.; Fabio, F.D.; Ardizzoni, A. (2020), [Third- and later-line treatment in advanced or metastatic gastric cancer: A systematic review and meta-analysis](#). *Future Oncol.* 16, 4409–4418.
- [8] Ajani, J.A.; et al., (2022), [Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology](#). *J. Natl. Compr. Cancer Netw.* 2022, 20, 167–192.
- [9] Sah, B.K.; et al., (2020), [Neoadjuvant FLOT versus SOX phase II randomized clinical trial for patients with locally advanced gastric cancer](#). *Nat. Commun.* 2020, 11, 6093.
- [10] Cunningham, D.; et al., (2006), [Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer](#). *N. Engl. J. Med.* 2006, 355, 11–20.
- [11] Kang, Y.K.; et al., (2021), [PRODIGY: A Phase III Study of Neoadjuvant Docetaxel, Oxaliplatin, and S-1 Plus Surgery and Adjuvant S-1 Versus Surgery and Adjuvant S-1 for Resectable Advanced Gastric Cancer](#). *J. Clin. Oncol.* 2021, 39, 2903–2913.
- [12] Wu, F.; Hong, J.; Du, N.; Wang, Y.; Chen, J.; He, Y.; Chen, P. (2022), [Long-Term Outcomes of Neoadjuvant Chemotherapy in Locally Advanced Gastric Cancer/Esophagogastric Junction Cancer: A Systematic Review and Meta-Analysis](#). *Anti-Cancer Agents Med. Chem.* 2022, 22, 143–151.
- [13] Ajani, J.A.; et al., (2006), [Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma \(RTOG 9904\): Quality of combined modality therapy and pathologic response](#). *J. Clin. Oncol.* 2006, 24, 3953–3958.
- [14] Yoshikawa, T.; Sasako, M.; Yamamoto, S.; Sano, T.; Imamura, H.; Fujitani, K.; Oshita, H.; Ito, S.; Kawashima, Y.; Fukushima, N. (2009), [Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer](#). *Br. J. Surg.* 2009, 96, 1015–1022.
- [15] Li, Y.; Chen, J.; He, Q.; Ji, X.; Wang, X.; Fan, C.; Li, G. (2017), [Clinical efficacy of neoadjuvant chemotherapy regimens FLEEOX vs. XELOX in patients with initially unresectable advanced gastric cancer: A propensity score analysis](#). *Oncotarget* 2017, 8, 86886–86896.
- [16] Chan, K.K.W.; Saluja, R.; Delos Santos, K.; Lien, K.; Shah, K.; Cramarossa, G.; Zhu, X.; Wong, R.K.S. (2018), [Neoadjuvant treatments for locally advanced, resectable esophageal cancer: A network meta-analysis](#). *Int. J. Cancer* 2018, 143, 430–437.
- [17] Burmeister, B.H.; Thomas, J.M.; Burmeister, E.A.; Walpole, E.T.; Harvey, J.A.; Thomson, D.B.; Barbour, A.P.; Gotley, D.C.; Smithers, B.M. (2011), [Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial](#). *Eur. J. Cancer* 2011, 47, 354–360.
- [18] Klevebro, F.; et al., (2016), [A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction](#). *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* 2016, 27, 660–667.
- [19] Stahl, M.; Walz, M.K.; Riera-Knorrenschild, J.; Stuschke, M.; Sandermann, A.; Bitzer, M.; Wilke, H.; Budach, W. (2017), [Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction \(POET\): Long-term results of a controlled randomised trial](#). *Eur. J. Cancer*, 81, 183–190.
- [20] Leong, T.; et al., (2017), [TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG](#). *Ann. Surg. Oncol.* 2017, 24, 2252–2258.
- [21] Cats, A.; et al., (2018), [Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer \(CRITICS\): An international, open-label, randomised phase 3 trial](#). *Lancet Oncol.* 2018, 19, 616–628.
- [22] Liu, X.; et al., (2019), [Study protocol of a randomized phase III trial of comparing preoperative chemoradiation with preoperative chemotherapy in patients with locally advanced gastric cancer or esophagogastric junction adenocarcinoma: PRACT](#). *BMC Cancer* 2019, 19, 606.
- [23] Skoropad, V.Y.; Afanasyev, S.G.; Gamayunov, S.V.; Silantyev, N.K.; Agababyan, T.A.; Sokolov, P.V.; Ivanov, S.A.; Kaprin, A.D. (2020), [Phase 2 multicenter randomized clinical trial: Neoadjuvant chemoradiotherapy followed by D2 gastrectomy and adjuvant chemotherapy in patients with locally advanced gastric cancer](#). *Sib. J. Oncol.* 2020, 19, 5–14.

- [24] Hagen, J.A.; DeMeester, S.R.; Peters, J.H.; Chandrasoma, P.; DeMeester, T.R. (2001), [Curative resection for esophageal adenocarcinoma: Analysis of 100 en bloc esophagectomies](#). *Ann. Surg.* 234, 520–530, discussion 530–521.
- [25] Portale, G.; Hagen, J.A.; Peters, J.H.; Chan, L.S.; DeMeester, S.R.; Gandamihardja, T.A.; De Meester, T.R. (2006), [Modern 5-year survival of resectable esophageal adenocarcinoma: Single institution experience with 263 patients](#). *J. Am. Coll. Surg.* 2006, 202, 588–596, discussion 596–588.
- [26] Altorki, N.; Kent, M.; Ferrara, C.; Port, J. (2002), [Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus](#). *Ann. Surg.* 236, 177–183.
- [27] Shah, M.A.; et al., (2020), [Treatment of Locally Advanced Esophageal Carcinoma: ASCO Guideline](#). *J. Clin. Oncol.* 38, 2677–2694.
- [28] Warneke, V.S.; Behrens, H.M.; Hartmann, J.T.; Held, H.; Becker, T.; Schwarz, N.T.; Röcken, C. (2011), [Cohort study based on the seventh edition of the TNM classification for gastric cancer: Proposal of a new staging system](#). *J. Clin. Oncol.* 29, 2364–2371.
- [29] Amin, M.B.; Greene, F.L.; Edge, S.B.; Compton, C.C.; Gershenwald, J.E.; Brookland, R.K.; Meyer, L.; Gress, D.M.; Byrd, D.R.; Winchester, D.P. (2017), [The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging](#). *CA Cancer J. Clin.* 67, 93–99.