Neoadjuvant Chemoradiotherapy for Locally Advanced Gastric Cancer

Subjects: Oncology

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Locally advanced gastric cancer (LAGC) has a poor prognosis with surgical resection alone, and neoadjuvant treatment has been recommended to improve surgical and oncological outcomes. Although neoadjuvant chemotherapy has been established to be effective for LAGC, the role of neoadjuvant chemoradiotherapy (NCRT) remains under investigation. Clinical experience and research evidence on esophagogastric junction adenocarcinoma (e.g., cardia gastric cancers) indicate that the likelihood of achieving sustainable local control is higher through NCRT than through resection alone. Furthermore, NCRT also has an acceptable treatment-related toxicity and adverse event profile. In particular, it increases the likelihood of achieving an R0 resection and a pathological complete response (pCR). Moreover, NCRT results in higher overall and recurrence-free survival rates than surgery alone; however, evidence on the survival benefits of NCRT versus neoadjuvant chemotherapy (NCT) remains conflicting. For noncardia gastric cancer, the efficacy of NCRT has mostly been reported in retrospective studies, and several large clinical trials are ongoing. Consequently, NCRT might play a more essential role in unresectable LAGC, for which NCT alone may not be adequate to attain disease control.

Keywords: locally advanced gastric cancer ; neoadjuvant treatment ; chemoradiation therapy

1. Introduction

One of the most common cancers, gastric cancer, constitutes a leading cause of cancer-related death despite improvements in treatment and the widespread eradication of *Helicobacter pylori* [1][2][3]. The suboptimal prognosis of this disease is likely attributable to its aggressive biological behavior and to its frequently advanced stage at diagnosis (in more than 50% of cases) [4]. Although surgical resection provides the highest chance of recovery, it is usually insufficient or inapplicable for locally advanced gastric cancer (LAGC). A multimodal strategy includes systemic and local therapies that are based on the tumor characteristics [5][6]; it can induce disease control, facilitate complete resection, and improve survival outcomes [7]. This principle applies not only to initially resectable disease but also unresectable LAGC [8].

LAGC is typically defined as a tumor of the stomach or esophagogastric junction (EGJ); it is a type of histologically confirmed adenocarcinoma staged under the clinical tumor, node, and metastasis (TNM) staging system as cT3–cT4b, lymph node metastasis (N1–N3) without distant metastases (M0) [9]. In this context, tumors exhibiting mesenteric root invasion, para-aortic lymphadenopathy, or major vessel encasement are considered unresectable. For resectable disease, neoadjuvant chemotherapy (NCT) has demonstrated clear survival benefits over those of initial surgery, regardless of whether adjuvant chemotherapy was implemented [10][11][12]. Moreover, NCT might result in the downstaging of LAGC, facilitating subsequent resection [13][14][15]. Little information is available on the addition of radiotherapy, namely, neoadjuvant chemoradiotherapy (NCRT), to LAGC treatment programs.

A network meta-analysis concluded that combining radiotherapy and chemotherapy leads to more favorable local control relative to modality alone [16]. According to clinical trials on esophageal or EGJ adenocarcinomas, NCRT is associated with a significantly lower local failure rate and higher pathological complete response (pCR) and R0 resection rates in subsequent surgery [17][18][19]. Furthermore, NCRT results in a more satisfactory clinical response than NCT, suggesting its viability as a treatment modality. Prognostic data for LAGC are less abundant than those for esophageal and EGJ cancers. Notably, several clinical trials exploring the efficacy and safety of NCRT in LAGC are ongoing [20][21][22][23].

2. NCRT for EGJ and Gastric Cardia Cancers

2.1. NCRT versus Surgery Alone

Multimodal treatment has been advocated for locally advanced EGJ and esophageal cancer because of the poor survival rate afforded by radical surgery alone [24][25][26]. Specifically, NCRT or perioperative chemotherapy is recommended for

EGJ adenocarcinoma [27]. EGJ adenocarcinoma can be further classified as esophageal or gastric cancer, with a distinct staging system for each type of cancer under a staging system slightly different from the TNM staging system. In general, EGJ tumors are staged as gastric cancer if they extend more than 2 cm to the proximal stomach; otherwise, they are staged as esophageal cancer [28][29]. Under the Siewert classification, which is widely applied to the classification of EGJ cancers, type I and type II/III tumors are more appropriately staged as esophageal and gastric cancer, respectively [30]. However, gastric cardia cancers are frequently included with EGJ adenocarcinoma in clinical studies, and their management is largely the same.

The superior survival benefits conferred by NCRT over surgery alone for locally advanced esophageal cancer and EGJ cancer were first demonstrated in an Irish clinical trial in which 113 patients with esophageal adenocarcinoma were randomly assigned to receive either NCRT or surgery alone. The 3 year overall survival (OS) rate achieved through NCRT was significantly higher than that achieved through surgery (32% vs. 6%, $p = 0.01$) [31]. In another trial, CALGB 9781, in which patients with esophageal adenocarcinoma constituted the majority, NCRT also resulted in more favorable survival over surgery alone (median OS, 4.48 vs. 1.79 years, $p = 0.02$) [32]. Moreover, in the phase III CROSS trial [33], NCRT was associated with a higher R0 resection rate (92% vs. 69%, $p < 0.001$) and OS (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.49–0.87) than surgery alone. The rate of major adverse events associated with NCRT was acceptable (6% leukopenia and 5% anorexia), and in-hospital mortality did not differ between the two groups. Furthermore, the survival benefits afforded by NCRT persisted over 10 years in the long-term follow-up [34]. Although both squamous cell cancer and adenocarcinoma were considered in the trial, 75% of the patients had adenocarcinoma, and NCRT led to survival benefits in both types of cancer.

Other trials have reported negative results for NCRT. Aside from two studies that were underpowered due to the low number of cases [35][36], the FFCD 9901 trial, which included patients with stage I and II esophageal cancer, found that NCRT did not provide any survival benefits over surgery alone. Instead, it reported a significantly higher postoperative mortality rate of 11.1% of NCRT versus 3.4% of NCT ($p = 0.049$) [37]. These discrepant findings may be explained by between-study differences in patient characteristics; only 29.2% of the patients had adenocarcinoma, and most tumors were located at the middle-third of the esophagus. Although subgroup analysis for stage I and II tumors was not performed, the present study indicated that NCRT should be considered with caution for earlier stage disease. On the other hand, meta-analyses have consistently indicated that NCRT confers greater survival benefits than surgery alone for locally advanced esophageal and EGJ adenocarcinoma [38][39][40], and that these benefits may be more pronounced in younger patients (patients aged ≤55 years) [39]. The clinical studies discussed thus far are summarized in **Table 1**.

Table 1. Studies examining neoadjuvant chemoradiotherapy (NCRT) for esophagogastric junction (EGJ) cancer or gastric cardia cancer (GCC).

Author	Trial Name	Patients	Group	Chemotherapy	Radiotherapy	R0 Resection of NCRT (%)	pCR of NCRT (%)	Survival Outcomes
Walsh et al., 1996 [31]		113 EGJ AC	NCRT vs. surgery	PF × 2 4-weekly	40 Gy, 2D/3D EBRT	92.9	25	3 year OS rate was higher under NCRT vs. surgery alone (32% vs. 6%, $p = 0.01$).
Tepper et al., 2008 [32]	CALGB-9781	56 EC (75% EGJ AC)	NCRT vs. surgery	PF × 2 monthly	50.4 Gy, EBRT	NA	40	Median OS was 4.48 years vs. 1.79 years, favoring NCRT ($p = 0.002$).
van Hagen et al., 2012 [33]	CROSS	366 EC (75% EGJ AC)	NCRT vs. surgery	CP × 5 every week	41.4 Gy, 3D EBRT	92	29	Median OS was 49.4 months vs. 24.0 months, favoring NCRT ($p = 0.003$).
Urba et al., 2001 [35]		100 EC (75% EGJ AC)	NCRT vs. surgery	PF × 2 + vinblastine	45 Gy, 3D EBRT	NA	28	Median OS was 17.6 months with surgery alone vs. 16.9 months with NCRT. ($p = 0.15$).

Author	Trial Name	Patients	Group	Chemotherapy	Radiotherapy	R0 Resection of NCRT (%)	pCR of NCRT (%)	Survival Outcomes
Burmeister et al., 2005 [36]		128 EC (62% EGJ AC)	NCRT vs. surgery	PF × 1	35 Gy, 2D EBRT	80	NA	Similar OS (HR: 0.89, 95% CI: 0.67–1.19) and RFS (HR 0·82, 95% CI 0.61–1.10) were observed between NCRT and surgery.
Mariette et al., 2014 [37]	FFCD-9901	195 EC (28% EGJ AC) Stage I-II	NCRT vs. surgery	PF × 2 biweekly	45 Gy, 3D EBRT	93.8	33.3	NCRT had a similar 3 year OS rate (47.5% vs. 53.0%, $p = 0.94$) but a higher postoperative mortality rate (11.1% vs. 3.4%, $p = 0.049$).
Stahl et al., 2017 [19][41]	POET	126 Pts (EGJ AC/GCC)	NCRT vs. NCT	*NCRT*: Induction PLF × 2 then PE *NCT*: PLF × 2.5	30 Gy, 3D EBRT	69.5	15.6	NCRT had a similar 5 year OS rate (39.5% vs. 24.4%, $p = 0.055$) but higher local RFS (HR: 0.37, 95% CI 0.16–0.85) vs. NCT.
Reynold et al., 2021 [42]	Neo-AEGIS	377 Pts (EGJ or Esophageal AC)	NCRT vs. NCT	*NCRT*: CP × 5 every week *NCT*: FLOT	41.4 Gy 3D/4D EBRT	95	16	3 year OS rate was similar (56% with NCRT vs. 57% with NCT, HR: 1.02, 95% CI: 0.74–1.42, *p*-value was not available).
Tsai et al., 2020 [43]		5,371 GCC	NCRT vs. NCT	NA (US national database)	NA	91.4	NA	Multivariable analysis revealed similar OS (HR 0.95, 95% CI 0.86–1.05).
Klevebro et al., 2016 [18]		181 Pts (72% EGJ/28% Esophageal AC)	NCRT vs. NCT	*NCRT*: PF × 3 every 3 week *NCT*: PF × 3	40 Gy, 3D EBRT	87	28	3 year OS rate was similar (47% with NCRT vs. 49% with NCT, $p = 0.77$). RFS was 44% in both groups.

AC: adenocarcinoma; EC: esophageal cancer; pCR: pathological complete response; OS: overall survival; RFS: recurrence-free survival; PF: cisplatin plus fluorouracil; CP: carboplatin plus paclitaxel; EBRT: external beam radiation therapy; PLF: cisplatin, leucovorin, and fluorouracil; PE: cisplatin and etoposide; FLOT: fluorouracil plus leucovorin, oxaliplatin, and docetaxel; HR: hazard ratio; CI: confidence interval; US: United States; NCT: neoadjuvant chemotherapy; NA: not available.

2.2. NCRT versus NCT for EGJ and Gastric Cardia Cancers

Since the MAGIC trial reported that perioperative chemotherapy with ECF regimen (i.e., epirubicin, cisplatin, and fluorouracil) resulted in a significantly more favorable clinical response and significantly higher OS over surgery alone for distal esophageal and gastric cardia adenocarcinoma [10], researchers have devoted efforts to determining whether NCRT or NCT is more suitable for gastric cardia cancers. The German POET trial is the only randomized controlled Phase III trial designed for EGJ cancer that compares NCRT and NCT [19][41]. Patients undergoing NCRT had a higher rate of local recurrence-free survival (RFS; HR 0.37, 95% CI 0.16–0.85) as well as a higher rate of pCR (14.3% vs. 1.9%, $p = 0.03$) and a trend toward higher 5 year OS (39.5% vs. 24.4%, HR 0.65, 95% CI 0.42–1.01). Notably, the subgroup analysis

suggested that patients with cardia cancers (Siewert type II) gained more benefits from NCRT relative to patients with Siewert type I cancers.

Conversely, the phase III NEO-AEGIS trial [42] and a Swedish trial [18] indicated that NCRT did not confer greater benefits in terms of OS and RFS than NCT, despite the association of NRT with higher pCR and R0 resection rates. Moreover, a meta-analysis suggested that NCRT is associated with higher postoperative mortality rates than is NCT (relative risk (RR) 1.58, 95% CI 1.00–2.49) [16]. In summary, evidence from locally advanced EGJ cancer indicates that NCRT is the modality of choice in terms of local control, although whether it affords greater survival benefits over NCT remains unclear. Until more evidence from clinical trials is presented, the implementation of NCRT in cases of gastric cardia cancer can be considered [19][42][43].

Recently, the results of the recent phase II/III FLOT4 trial [44] suggest a new standard for perioperative chemotherapy for EGJ cancers and LAGC. The perioperative FLOT regimen, which comprises fluorouracil plus leucovorin, oxaliplatin, and docetaxel, provided superior OS (median, 50 vs. 35 months, HR: 0.77, 95% CI 0.63–0.94) relative to the ECF or ECX (i.e., epirubicin, cisplatin, and capecitabine) regimens. Although numerous patients may benefit from perioperative FLOT, whether it can be a substitute for NCRT remains unclear [44], and a clearer answer may emerge after the completion of the ESOPEC trial, which directly compares the perioperative FLOT and CROSS regimens.

3. NCRT for Locally Advanced, Resectable Noncardia Gastric Cancer

Based on the experience of and evidence from research on EGJ and cardia cancers, the main advantage of NCRT is that it achieves a higher rate of local control to enable subsequent curative surgery. Compared with its use in EGJ and cardia cancers, the use of NCRT for noncardia gastric cancer is less validated due to the lack of phase III randomized controlled trials. Evidence from mostly uncontrolled studies [13][45][46][47][48][49][50][51][52] indicates that NCRT led to R0 resection and pCR rates of approximately 70–80% and approximately 20–25%, respectively. A review of the performances of NCRT and other modalities is presented as follows.

3.1. NCRT versus Adjuvant Therapy for Resectable LAGC

A small trial found that NCRT afforded no clinical benefits over adjuvant chemoradiotherapy [53]. However, two recent studies with propensity score matching suggested that NCRT is preferred over adjuvant chemotherapy [54] or chemoradiotherapy [55]. In a Chinese cohort, NCRT was associated with a significantly higher pCR rate (17.0% vs. 4.0%, $p = 0.001$), RFS (HR, 0.63; 95% CI 0.43–0.92, $p = 0.014$), and local-recurrence-free survival rates (HR, 0.40; 95% CI 0.23–0.69, $p = 0.0019$) but a significantly higher proportion of grade 3/4 adverse events (52% vs. 34%, $p = 0.01$). The OS did not differ significantly between treatments (HR, 0.45; 95% CI 0.51–1.11, $p = 0.15$) [54]. In contrast, in a Korean cohort, NCRT was associated with significantly improved OS (HR 0.57, 95% CI 0.36–0.91, $p = 0.020$) and R0 resection rates (HR 0.50, 95% CI 0.27–0.90, $p = 0.021$) as well as lower grade 3/4 toxicity (10% vs. 54%, $p < 0.001$) than adjuvant chemoradiotherapy [55].

A recent randomized controlled trial examined adjuvant XELOX chemotherapy administered to 60 patients with LAGC and compared the outcomes of adjuvant XELOX chemotherapy with and without NCRT [56]. NCRT resulted in a significantly higher RFS rate (60.0% vs. 33.3%, $p = 0.019$) and a significantly lower local recurrence rate (11.5% vs. 36.7%, $p = 0.039$) for up to 3 years, without an increase in perioperative complications (23.1% vs. 30.0%, $p = 0.560$). No significant difference in OS was observed (63.3% vs. 50.0%, $p = 0.215$). These findings, which are summarized in **Table 2**, indicate that NCRT is more effective than adjuvant treatments in achieving and maintaining local control. To determine whether long-term OS can be improved under NCRT, further investigations are warranted.

Table 2. Studies examining neoadjuvant chemoradiotherapy (NCRT) for locally advanced gastric cancers (LAGC) in comparison with surgery alone or adjuvant therapies.

Author	Trial Name	Patients	Group	Chemotherapy	Radiotherapy	R0 Resection of NCRT (%)	pCR ofNCRT (%)	Survival Outcomes
Ajani et al., 2006 [13]	RTOG-9904	43 NCGC	NCRT	Induction PF × 1 then cisplatin + paclitaxel	45 Gy, 3D EBRT	77	26	Median OS was 23.2 months. R0 resection and pCR were associated with improved outcomes (*p*-value not shown).
Ajani et al., 2004 [45]		33 NCGC (all resectable)	NCRT	Induction PF × 1 then fluorouracil	45 Gy, 2D EBRT	70	30	Median OS was 33.7 months.
Pepek et al., 2013 [47]		48 GC (73% proximal)	NCRT	Various	45 Gy, 3D EBRT	86	19	3 year OS and RFS rates were 50% and 41%, respectively.
Rostom et al., 2013 [48]		41 GC/EGJ AC (68% NCGC)	NCRT	Induction PF × 2 then fluorouracil	45 Gy, 3D EBRT	70.7	24	3 year OS rate was 47.3%. R0 resection (p = 0.027) and pCR (p = 0.01) were associated with improved outcomes.
Trip et al., 2014 [49]		24 NCGC	NCRT	Carboplatin plus paclitaxel × 5	45 Gy, 3D IMRT	72	16	Median OS was 15 months.
Badgwell et al., 2015 [50]		192 (74% GC)	NCRT	NA	NA	93	20	5 year OS was 56% (median OS: 5.8 years).
Saedi et al., 2014 [53]		25 NCGC	NCRT vs. Surgery	PF × 1 then Adjuvant ECX	45 Gy, 2D EBRT	NA	NA	5 year OS rates were similar (38.5% with NCRT vs. 16.7% with surgery, p = 0.169).
Kim et al., 2022 [55]		152 GC/EGJ AC (42% NCGC)	NCRT vs. ACRT	Various	50.4 Gy, IMRT	95	26	NCRT was independently associated with improved OS (HR: 0.57, 95% CI: 0.36–0.91).
Wang et al., 2021 [56]		60 NCGC	NCRT vs. ACT	XELOX × 2	50.4 Gy, 3D EBRT	84.6	NA	3 year OS rates were similar (60% with NCRT vs. 50% with ACT, p = 0.215).

NCGC: noncardia gastric cancer; EGJ: esophagogastric junction; AC: adenocarcinoma; pCR: pathological complete response; OS: overall survival; RFS: recurrence-free survival; PF: cisplatin plus fluorouracil; EBRT: external beam radiation therapy; IMRT: intensity modulated radiation therapy; ECX: epirubicin, cisplatin, and capecitabin; XELOX: oxaliplatin plus capecitabine; NCT: neoadjuvant chemotherapy; ACT: adjuvant chemotherapy; ACRT: adjuvant chemoradiotherapy; HR: hazard ratio; CI: confidence interval.

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