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Identifying the optimal treatment strategy in patients with resectable non-cardia gastric cancer

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Abstract

Background Multimodal treatment strategy including perioperative chemotherapy (PEC), postoperative chemoradiation therapy (POCR), and postoperative chemotherapy (POC) has been accepted as the standard of care in gastric cancer (GC). The ideal sequence and type of therapy remain undetermined.

Method The National Cancer Database was examined from 2006 to 2016 to identify patients with resectable non-cardia gastric cancer. Patient outcomes were compared based on the receipt of PEC, POCR, and POC. This comparison was repeated in a sub-group of patients who received optimal treatment. Optimal treatment was defined as initial chemotherapy within 45 days of diagnosis, resection within 45 days of diagnosis, negative margins, adjuvant chemotherapy within 90 days of resection and standard radiation dose (45 Gy). Kaplan–Meier test, log-rank test, and multivariable analysis (MVA) were performed.

Results We identified 9589 patients. Median survival was greater in the PEC group followed by POCR and POC (60.6, 42.3, and 31.2 months, respectively). On MVA, factors associated with worse overall survival included age above median ($\geq$ 63 years), Charlson–Deyo score of $\geq$ 1, non-academic/research program, poorly differentiated/undifferentiated grade, positive margins, and positive lymph nodes. Both PEC and POCR were associated with improved survival when compared to POC (HR 0.78 and 0.79; $p < 0.001$). When compared with PEC, no significant difference was noted with POCR (HR 1.01; $p = 0.987$). These results were maintained in optimally treated cohort ($n = 3418$).

Conclusion In patients with resectable non-cardia gastric cancer, both perioperative chemotherapy and postoperative chemoradiation therapy were associated with improved survival when compared to postoperative chemotherapy. No difference was noted between perioperative chemotherapy and postoperative chemoradiation therapy. These results were maintained in the optimally treated cohort.

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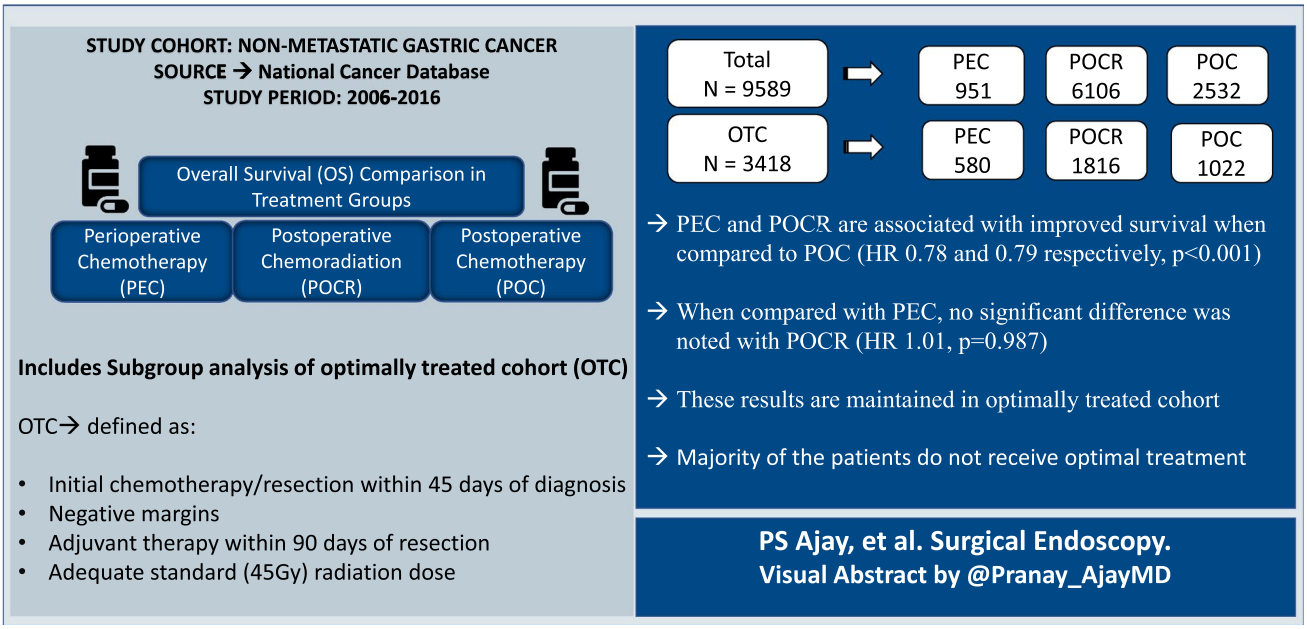
Graphical abstract



Keywords Gastric cancer · Non-cardia gastric cancer · Treatment strategies in gastric cancer

Gastric cancer (GC) is the 5th leading cause of cancer worldwide and the 3rd in terms of overall mortality [1]. It represents 1.4% of all newly diagnosed cancer cases in the USA. It has an incidence rate of 7.2 and a death rate of 2.9 per 100,000 men and women per year, with an estimated 11,180 deaths in 2021 [2]. It is commonly prevalent in Eastern and Central Asian countries, Eastern Europe, and Latin America, with a higher incidence in males [3]. The distinction between GC arising from the cardia and non-cardia gastric cancer (NCGC), based on their anatomical site, is critical as they have different epidemiologic patterns and genetic pathways of carcinogenesis [4]. Risk factors such as *Helicobacter pylori*, low socioeconomic status, and higher intake of salty and smoked foods are associated with NCGC [5]. Eradication of H. pylori infections, responsible for 90% of NCGC, has reduced the incidence of this subtype [3, 6]. More than one-third of stomach cancers are diagnosed when the cancer has metastasized reducing its 5-year relative survival rate to 5.5% from 70% for localized disease [2].

Multimodal treatment strategies that include surgery as its centerpiece have been accepted as the standard of care for non-metastatic GC patients. However, the most favorable adjunct to surgery with respect to chemotherapy or chemoradiation therapy and its sequence is yet to be established. Both, perioperative chemotherapy (PEC) and postoperative chemoradiation therapy (POCR) have been associated with improved survival over surgery alone (HR 0.75 and 1.32; $p = 0.009$ and 0.004, respectively) [7, 8]. In addition, postoperative chemotherapy (POC) has also proved to be efficacious compared to surgery alone (HR 0.74; $p = 0.04$) [9]. While independently these regimes have proven to be better compared to surgery alone, a head-to-head comparison to elucidate the best treatment strategy is missing.

The purpose of this study is to examine the National Cancer Database (NCDB) to compare PEC, POCR, and POC to identify the optimal treatment strategy in patients with resectable NCGC.

Materials and methods

Data source

The NCDB was queried to analyze patients with resectable NCGC from 2006 to 2016. The NCDB is a joint initiative of the American College of Surgeons and the American Cancer Society. It is a nationwide oncology outcomes database for more than 1500 commission-accredited cancer programs in the USA and Puerto Rico. Established in 1989, the NCDB now contains approximately 40 million records from hospital cancer registries across the USA, capturing around 72% of all newly diagnosed cancer cases. This data is used to explore trends in cancer care and serve as the basis for quality improvement [10].

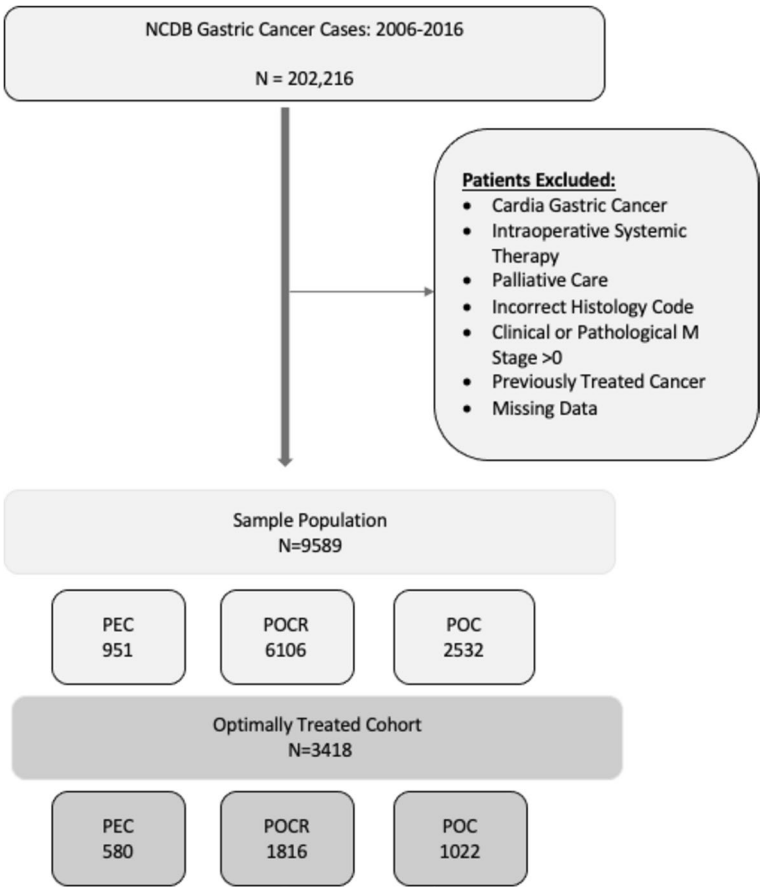


Fig. 1 Schematic depicting patient inclusion and exclusion criteria including stratification by treatment strategy. *NCDB* National Cancer Database, *PEC* perioperative chemotherapy, *POCR* postoperative chemoradiation therapy, *POCR* postoperative chemotherapy

Study patients

This study was exempt from Institutional Review Board approval and no written consent was required for this study. Patients diagnosed with non-metastatic NCGC (all sites except C 16.0) and histology codes: 8012, 8053, 8140, 8142, 8144, 8145, 8210, 8211, 8255, 8260, 8261, 8263, 8480, 8481, 8490, and 8576—according to the 3rd edition of International Classification of Diseases for Oncology (ICD-O-3), were included in this cohort. We analyzed patients aged 18 years and older, who underwent treatment with definitive surgery for resectable NCGC. Patients with GC in the cardia, stage 4 disease, patients who received intraoperative systemic therapy, patients treated with a palliative intent, and patients previously treated for cancer were excluded. Patients who received surgery alone or neoadjuvant treatment followed by surgery only and patients with an unknown sequence of treatment were also excluded.

Methods

We conducted a retrospective study in NCGC patients to compare the different treatment cohorts receiving PEC, POCR, or POC as an adjunct to surgery. The primary outcome was to evaluate the overall survival benefit in patients undergoing treatment with PEC, POCR, or POC. Additional sub-group analysis was performed to assess the optimal treatment strategy in patients who received optimal therapy, defined as initial chemotherapy within 45 days of diagnosis (PEC), resection within 45 days of diagnosis (POCR and POC), negative margins, adjuvant therapy within 90 days of resection (POCR and POC), and adequate standard (45 Gy) radiation dose (POCR).

Statistical analysis

Statistical analysis was carried out using SAS 9.3. Descriptive Statistics was used to summarize patient characteristics. The Kaplan–Meier method was used to estimate overall survival (OS) and survival curves were compared between PEC, POCR, and POC using log-rank tests. Univariate analysis (UA) and Multivariable analysis (MVA) utilizing cox proportional hazard model were used to compare OS between different treatment cohorts, demographics (age, race, facility type, and location), surgical variables (lymph nodes, margins), and tumor grade. For MVA, a backward selection method with an α level of removal of 0.05 was used.

Table 1 Descriptive statistics including demographics and tumor characteristics for all included patients and patients who met optimal treatment selection criteria

Variable	Level	*N* (%) = 9589 Median age = 63	Optimally treated *N* (%) = 3418 Median age = 62
Age	≤ Median	4948 (51.6)	1741 (50.9)
	> Median	4641 (48.4)	1677 (49.1)
Sex	Male	5570 (58.1)	2009 (58.8)
	Female	4019 (41.9)	1409 (41.2)
Race	White	5817 (60.7)	2063 (60.4)
	Black	2186 (22.8)	755 (22.1)
	Other	1586 (16.5)	600 (17.6)
Charlson–Deyo score	0	6806 (71.0)	2475 (72.4)
	1+	2783 (29.0)	943 (27.6)
Grade	Well/moderately differentiated	2096 (22.8)	823 (25.0)
	Poorly differentiated/undifferentiated	7112 (77.2)	2466 (75.0)
	Missing	381	129
Regional lymph nodes positive	Negative	1976 (21.2)	790 (23.6)
	Positive	7341 (78.8)	2559 (76.4)
	Missing	272	69
Surgical margins status	Negative	7585 (80.8)	3418
	Positive	1803 (19.2)	0
	Missing	201	0
Clinical T	1–2	1818 (42.3)	651 (41.7)
	3	1814 (42.3)	691 (44.2)
	4	661 (15.4)	220 (14.1)
	Missing	5296	1856
Clinical N	0	3831 (63.0)	1404 (62.7)
	1	1363 (22.4)	515 (23.0)
	2–3	891 (14.6)	320 (14.3)
	Missing	3504	1179

Results

Demographics, tumor characteristics, and treatment cohorts

We identified 202,216 patients with GC captured in the NCDB, diagnosed between 2006 and 2016 (Fig. 1). After limiting these patients to our selection criteria, 9589 patients were included in our final analysis. The median age was 63 and majority of this population was white (60.7%) and male (58.1%) (Table 1). In patients with available clinical T and N stage—42.3% (1818) were T1–2, 42.3% (1814) were T3, and the rest were T4 (15.4%, $n = 661$). Majority of the patients had no nodal disease on diagnosis (N0 = 3831, 63%) and 22.4% (1363) were N1. Clinical T and N stratified by the type of treatment received is available in Table 2. Negative margins were seen in 80.8% of the cases, while a poorly differentiated/undifferentiated grade of tumor (77.2%) and positive regional lymph nodes (78.8%) were also commonly noted. Bulk of this population was treated with POCR (6106, 64%), followed by POC (2532, 26%) and PEC (951, 10%). Other patient demographics and tumor characteristics stratified by the type of treatment received is available in Table 2.

Univariate and multivariable analyses with overall survival

Variables that had an association with OS in univariate analysis are reported in Supplemental File 1. Median survival was greater in the PEC group (60.8 months) compared to POCR and POC (42.3 and 31.2 months, respectively; $p = < 0.001$, Fig. 2). Patients who received PEC showed an improved 5-year survival rate followed by POCR and POC (50.1%, 42.2%, and 33.7%, respectively).

On MVA, factors associated with worse OS included age above median (HR 1.34; $p = < 0.001$), treatment at

Table 2 Descriptive statistics including patient demographics and tumor characteristics in patients with non-metastatic non-cardia gastric cancer stratified by treatment received

Covariate	Statistics	Level	Treatment group			Parametric *p*-value*
			Perioperative chemotherapy *N* = 951	Postoperative chemoradiation *N* = 6106	Postoperative chemotherapy *N* = 2532	
Age	*N* (Col %)	Below median	384 (40.38)	2232 (36.55)	827 (32.66)	**< 0.001**
	N (Col %)	Above median	567 (59.62)	3874 (63.45)	1705 (67.34)	
Race	*N* (Col %)	White	620 (65.19)	3593 (58.84)	1604 (63.35)	**< 0.001**
	N (Col %)	Black	180 (18.93)	1473 (24.12)	533 (21.05)	
	N (Col %)	Other	151 (15.88)	1040 (17.03)	395 (15.6)	
Sex	*N* (Col %)	Male	565 (59.41)	3594 (58.86)	1411 (55.73)	**0.019**
	N (Col %)	Female	386 (40.59)	2512 (41.14)	1121 (44.27)	
Median income quartiles 2008–2012	*N* (Col %)	< $38,000	169 (17.83)	1414 (23.28)	573 (22.7)	**< 0.001**
	N (Col %)	$38,000–$47,999	185 (19.51)	1283 (21.12)	547 (21.67)	
	N (Col %)	$48,000–$62,999	254 (26.79)	1600 (26.34)	625 (24.76)	
	N (Col %)	≥ $63,000	340 (35.86)	1778 (29.27)	779 (30.86)	
Facility type	*N* (Col %)	Non-academic/research program	311 (34.75)	3689 (63.33)	1387 (57.82)	**< 0.001**
	N (Col %)	Academic/research program	584 (65.25)	2136 (36.67)	1012 (42.18)	
Primary payor	*N* (Col %)	Private/not insured	519 (54.57)	2935 (48.07)	1146 (45.26)	**< 0.001**
	N (Col %)	Medicare/Medicaid/other government	432 (45.43)	3171 (51.93)	1386 (54.74)	
Charlson–Deyo score	*N* (Col %)	0	720 (75.71)	4323 (70.8)	1763 (69.63)	**0.002**
	N (Col %)	1+	231 (24.29)	1783 (29.2)	769 (30.37)	
Year of diagnosis	*N* (Col %)	2006–2010	237 (24.92)	3434 (56.24)	1206 (47.63)	**< 0.001**
	N (Col %)	2011–2016	714 (75.08)	2672 (43.76)	1326 (52.37)	
Facility location	*N* (Col %)	Northeast	263 (29.39)	1368 (23.48)	542 (22.59)	**< 0.001**
	N (Col %)	Midwest	233 (26.03)	1228 (21.08)	483 (20.13)	
	N (Col %)	West	171 (19.11)	971 (16.67)	438 (18.26)	
	N (Col %)	South	228 (25.47)	2258 (38.76)	936 (39.02)	
Grade	*N* (Col %)	Well/Moderately differentiated	177 (20.37)	1366 (23.13)	553 (22.72)	0.192
	N (Col %)	Poorly differentiated/undifferentiated	692 (79.63)	4539 (76.87)	1881 (77.28)	
Regional lymph nodes positive	*N* (Col %)	Negative	387 (41.93)	1119 (18.7)	470 (19.49)	**< 0.001**
	N (Col %)	Positive	536 (58.07)	4864 (81.3)	1941 (80.51)	
Clinical T	*N* (Col %)	1–2	219 (29.36)	1153 (46.87)	446 (41.03)	**< 0.001**
	N (Col %)	3	443 (59.38)	939 (38.17)	432 (39.74)	
	N (Col %)	4	84 (11.26)	368 (14.96)	209 (19.23)	
Clinical N	*N* (Col %)	0	408 (47.55)	2439 (66.06)	984 (64.1)	**< 0.001**
	N (Col %)	1	327 (38.11)	723 (19.58)	313 (20.39)	
	N (Col %)	2–3	123 (14.34)	530 (14.36)	238 (15.5)	
Pathologic T	*N* (Col %)	0–2	226 (29.27)	1116 (25.18)	372 (20.03)	**< 0.001**
	N (Col %)	3	364 (47.15)	2009 (45.33)	787 (42.38)	
	N (Col %)	4	182 (23.58)	1307 (29.49)	698 (37.59)	
Pathologic N	*N* (Col %)	0	360 (42.45)	968 (19.68)	433 (21.44)	**< 0.001**
	N (Col %)	1	194 (22.88)	1613 (32.8)	555 (27.48)	
	N (Col %)	2	135 (15.92)	1177 (23.93)	461 (22.82)	
	N (Col %)	3	159 (18.75)	1160 (23.59)	571 (28.27)	

Table 2 (continued)

Covariate	Statistics	Level	Treatment group			Parametric *p*-value*
			Perioperative chemotherapy *N* = 951	Postoperative chemoradiation *N* = 6106	Postoperative chemotherapy *N* = 2532	
Surgical margins status	*N* (Col %)	Negative	816 (87.74)	4846 (80.82)	1923 (78.11)	**< 0.001**
	N (Col %)	Positive	114 (12.26)	1150 (19.18)	539 (21.89)	
Chemotherapy type	*N* (Col %)	Chemotherapy administered, type and number of agents not documented	17 (1.79)	498 (8.16)	331 (13.07)	–
	N (Col %)	Single-agent chemotherapy	16 (1.68)	3066 (50.21)	658 (25.99)	
	N (Col %)	Multiagent chemotherapy	918 (96.53)	2540 (41.6)	1532 (60.51)	
	N (Col %)	None/unknown	0	2(0.03)	11(0.44)	
Surgery type	*N* (Col %)	Unknown	136 (14.31)	1390 (22.75)	355 (14.10)	–
	N (Col %)	Gastrectomy, NOS	172 (18.09)	1327 (21.73)	593 (23.42)	
	N (Col %)	Antrectomy, lower	29 (3.05)	201 (3.29)	79 (3.12)	
	N (Col %)	Lower distal gastrectomy	178 (18.72)	1209 (19.8)	520 (20.54)	
	N (Col %)	Upper (proximal) gastrectomy	20 (2.1)	186 (3.05)	65 (2.57)	
	N (Col %)	Near total or total gastrectomy	8 (0.84)	73 (1.2)	31 (1.22)	
	N (Col %)	Near total gastrectomy	19 (2)	114 (1.87)	47 (1.86)	
	N (Col %)	Total gastrectomy	178 (18.72)	594 (9.73)	316 (12.48)	
	N (Col %)	Gastrectomy**	8 (0.84)	45 (0.74)	26 (1.03)	
	N (Col %)	Partial or subtotal gastrectomy**	35 (3.68)	297 (4.86)	124 (4.9)	
	N (Col %)	Near total or total gastrectomy**	52 (5.47)	98 (1.6)	65 (2.57)	
	N (Col %)	Gastrectomy^^	16 (1.68)	64 (1.05)	41 (1.62)	
	N (Col %)	Partial or subtotal^^	39 (4.1)	260 (4.26)	140 (5.53)	
	N (Col %)	Near total or total gastrectomy^^	44 (4.63)	142 (2.33)	67 (2.65)	
	N (Col %)	Radical gastrectomy^^	14 (1.47)	83 (1.36)	37 (1.46)	
	N (Col %)	Gastrectomy, NOS	0 (0)	16 (0.26)	9 (0.36)	
	N (Col %)	Surgery, NOS	3 (0.32)	7 (0.11)	15 (0.59)	

Bold values indicate statistical significance

NOS not otherwise specified

*The parametric *p*-value is calculated by χ^2 test

**Gastrectomy with resection of a portion of esophagus

^^Gastrectomy with a resection in continuity with the resection of other organs

non-academic/research hospital (HR 1.20; $p = < 0.001$) compared to academic/research hospital, Charlson–Deyo score of 1 + (HR 1.07; $p = 0.027$) compared to score 0, poorly differentiated/undifferentiated grade (HR 1.37; $p = < 0.001$) compared to well/moderately differentiated grade, positive regional lymph nodes (HR 2; $p = < 0.001$), and positive surgical margins (HR 1.98; $p = < 0.001$, Table 3). Patients treated with PEC and POCR had an association with improved OS (HR 0.78 and 0.79, respectively; $p = < 0.001$) compared to POC. When we reanalyzed, with patients weighted against PEC, no significant difference was noted between POCR (HR 1.01; $p = 0.987$) and PEC.

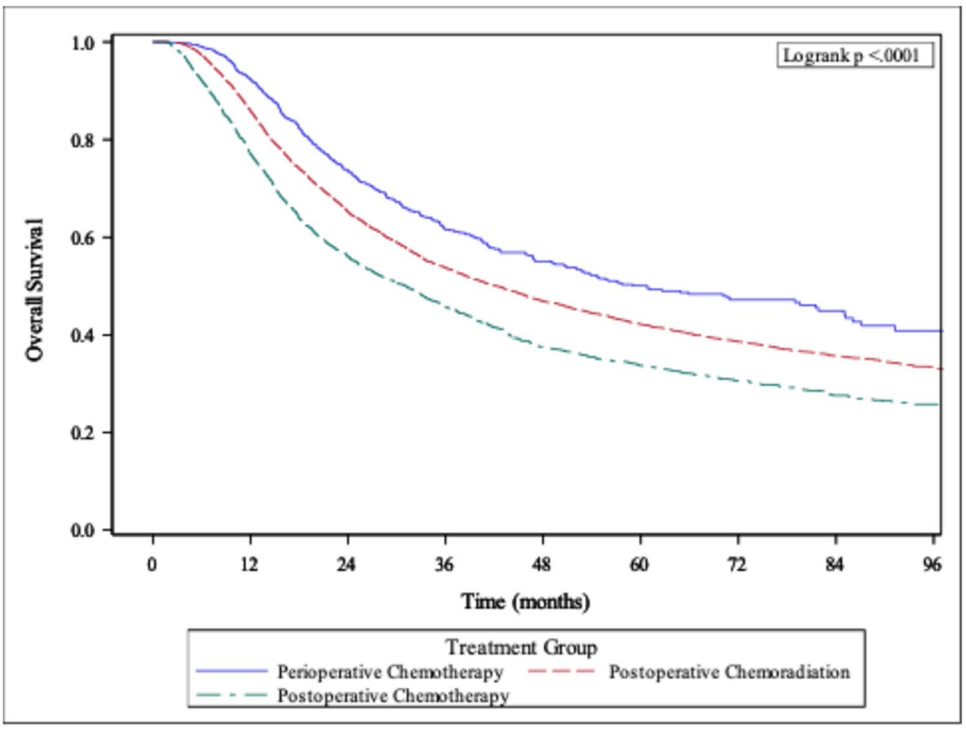


Fig. 2 Kaplan–Meier survival curves for all patients treated with perioperative chemotherapy, postoperative chemoradiation therapy, and postoperative chemotherapy. Median survival, 5-year, and 10-year survival rates included. *CI* confidence interval

Treatment Group	OS (Months)	Survival Rate(95% CI)
Perioperative Chemotherapy	60	50.1% (46.1%, 53.9%)
	120	29.7% (14.0%, 47.2%)
Postoperative Chemoradiation	60	42.2% (40.8%, 43.6%)
	120	28.5% (26.8%, 30.3%)
Postoperative Chemotherapy	60	33.7% (31.6%, 35.8%)
	120	21.9% (19.2%, 24.7%)

Sub-group analysis of optimally treated cohort

We identified 3418 patients in our optimally treated cohort. Descriptive statistics was similar to our all-patient analysis (see Table 1). The majority of these patients received POCR (53%), followed by POC (30%) and PEC (17%). Variables associated with OS on UA are reported in Supplemental File 2. Alike to our all-patient analysis, median survival was greater in PEC (70.1 months) followed by POCR (56.1 months) and POC (33.5 months) ($p = < 0.0001$, Fig. 3). Patients who received PEC showed an improved 5-year survival rate of 52.3%, followed by POCR and POC (48.1% and 37.8%, respectively). MVA of optimally treated cohort was associated with an improved OS in patients treated with PEC and POCR (HR 0.76 and 0.72; $p = 0.002$ and < 0.001, respectively) when compared to POC (Table 4). When weighted against PEC, no significant difference was noted between POCR (HR 0.95; $p = 0.502$) and PEC.

Discussion

The purpose of this study was to identify the optimal treatment strategy in resectable NCGC patients by examining a large population database, like the NCDB. Our analysis revealed that both PEC and POCR showed a statistically significant association with improved OS when compared to POC in resectable NCGC patients. This result was maintained in our optimally treated cohort.

Treatment strategies including the use of multimodal therapy in non-metastatic GC patients is based on preference of the treating physician or institution, without clear evidence of optimal therapy. Our study showed no significant

Table 3 Multivariate Analysis of all patients with resectable non-cardia gastric cancer treated with perioperative chemotherapy, postoperative chemoradiation therapy, and postoperative chemotherapy

Covariate	Level	OS (months)		
		Hazard ratio (95% CI)	HR *p*-value	Overall *p*-value
Treatment group weighted to POC	Perioperative chemotherapy	0.78 (0.70–0.89)	**< 0.001**	**< 0.001**
	Postoperative chemoradiation	0.79 (0.74–0.84)	**< 0.001**	
	Postoperative chemotherapy	–	–	
Treatment group weighted to PEC	Postoperative chemoradiation	1.01 (0.89–1.12)	0.987	**< 0.001**
	Postoperative chemotherapy	1.27 (1.12–1.44)	**< 0.001**	
	Perioperative chemotherapy	–	–	
Age	Above median	1.34 (1.27–1.43)	**< 0.001**	**< 0.001**
	Below median	–	–	
Race	Black	1.00 (0.93–1.07)	0.952	**< 0.001**
	Other	0.76 (0.69–0.83)	**< 0.001**	
	White	–	–	
Facility type	Non-academic/research program	1.20 (1.13–1.28)	**< 0.001**	**< 0.001**
	Academic/research program	–	–	
Charlson–Deyo score	1+	1.07 (1.01–1.14)	**0.027**	**0.027**
	0	–	–	
Facility location	Northeast	0.75 (0.70–0.82)	**< 0.001**	**< 0.001**
	Midwest	1.02 (0.95–1.10)	0.564	
	West	0.90 (0.83–0.99)	**0.025**	
	South	–	–	
Grade	Poorly differentiated/undifferentiated	1.36 (1.27–1.47)	**< 0.001**	**< 0.001**
	Well/moderately differentiated	–	–	
Regional lymph nodes positive	Positive	2.00 (1.84–2.18)	**< 0.001**	**< 0.001**
	Negative	–	–	
Surgical margins status	Positive	1.98 (1.85–2.12)	**< 0.001**	**< 0.001**
	Negative	–	–	

Bold values indicate statistical significance

CI confidence interval, *PEC* perioperative chemotherapy, *POCR* postoperative chemoradiation therapy, *POC* postoperative chemotherapy

*Number of observations in the original dataset = 9589. Number of observations used = 8410

**Backward selection with an α level of removal of 0.05 was used. The following variables were removed from the model: Primary Payor, Median Income Quartiles 2008–2012, Sex, and Year of Diagnosis

difference in OS between POCR and PEC, but both were associated with improved survival when compared to POC. The ARTIST trial in 2012, compared POC (capecitabin plus cisplatin) with POCR in patients with D2-resected GC. The addition of radiation therapy to chemotherapy was not associated with improved disease-free survival (DFS, $p = 0.08$). POCR showed an association with improved DFS only in a sub-group of patients with node-positive disease (3-year DFS: 76% vs. 72%; $p = 0.04$) and intestinal-type (3-year DFS: 94% vs. 83%; $p = 0.01$) GC [11]. The ARTIST-II trial in 2021 analyzed patients with node-positive GC after D2 resection and compared single agent POC (S1), multiagent POC (S1 + oxaliplatin), and POCR (S1 + oxaliplatin + radiation) in a 1:1:1 ratio [12]. DFS with single agent POC was significantly shorter when compared with multiagent POC (HR 0.61, $p = 0.016$) and a trend toward statistical significance was noted when compared to POCR (HR 0.68, $p = 0.057$). No difference in DFS between multiagent POC and POCR was noted (HR 0.91, $p = 0.66$). Our study results are different from ARTIST 1 and 2 trials as both these trials use multiagent chemotherapy in combination with radiation therapy, while practice in the USA is to use single agent chemotherapy in combination with radiation for POCR. Unfortunately, the exact type of chemotherapeutic agent used, dosage, and frequency is not available in the National Cancer Database. Our study population included both node-positive and node-negative patients which differs from the ARTIST 2 trials' selection criteria.

Our study demonstrated an independent association with improved OS with PEC when compared to POC. The JCOG0501 study in 2021 compared PEC (neoadjuvant

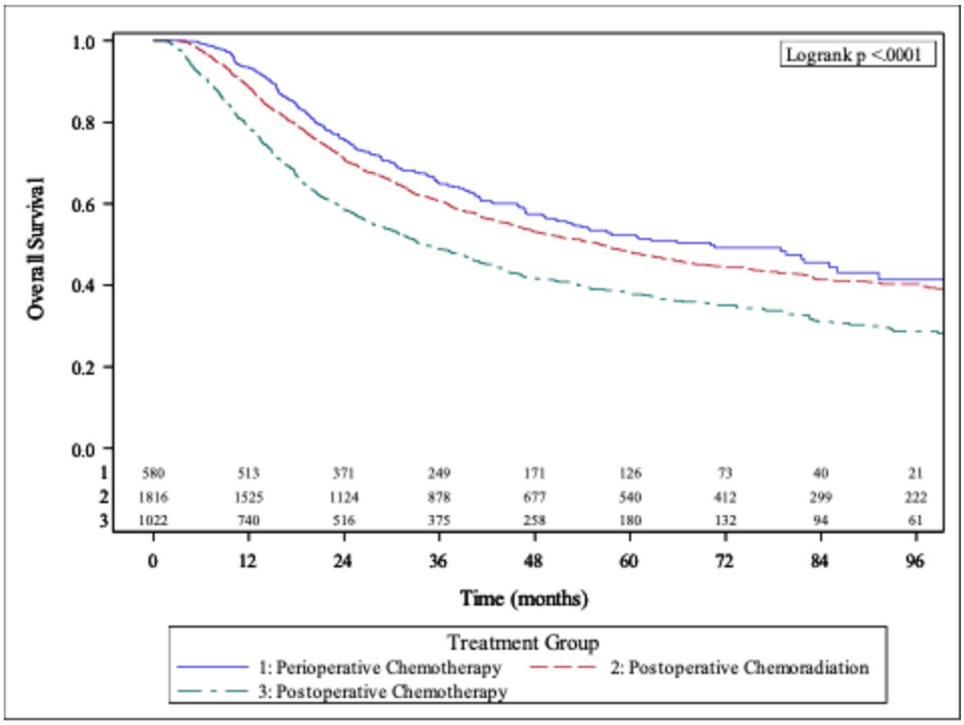


Fig. 3 Kaplan–Meier survival curves for patients treated with perioperative chemotherapy, postoperative chemoradiation therapy, and postoperative chemotherapy in patients who met optimal treatment selection criteria. Median survival, 5-year, and 10-year survival included. *N* number, *CI* confidence Interval

Treatment Group	OS (Months)	Survival Rate(95% CI)
Perioperative Chemotherapy	60	52.3% (47.2%, 57.1%)
	120	41.4% (34.2%, 48.4%)
Postoperative Chemoradiation	60	48.1% (45.5%, 50.7%)
	120	35.8% (32.6%, 39.0%)
Postoperative Chemotherapy	60	37.8% (34.3%, 41.2%)
	120	25.1% (20.5%, 30.0%)

S1 + cisplatin followed by surgery and adjuvant S1) with POC (S1) in gastric cancer patients in Japan. This study showed no difference in OS between the two treatment strategies (3-year OS rates: 60.9% vs. 62.4%, respectively; HR 0.91 for PEC against POC, $p = 0.28$) [13]. The eligibility criteria for this study included only patients with Borrmann's type IV or large type III (≥ 8 cm) tumors which are known to be more aggressive compared to the other types [14]. This was not a part of our study's inclusion criteria and hence our study population and results differ from this study. Our study results are in concordance with the recently concluded PRODIGY trial in 2021 which compared PEC (docetaxel, oxaliplatin, and S1 in the neoadjuvant setting followed by surgery and S1 adjuvant chemotherapy) with POC (adjuvant S1) in locally advanced gastric cancer patients in Asia [15]. Patients in the PRODIGY trial who received PEC (HR 0.70, $p = 0.02$) had an association with improved DFS compared to POC. This study solely focuses on Eastern population. Studies have noted differences in survival between Eastern and Western cohorts, with better OS seen in Eastern populations [16]. Significant biological differences exist between Eastern and Western population groups, and this may influence geographical differences in clinical outcomes [17]. Factors such as abnormal E-cadherin and c-erbB2 expression are more common in the Western populations [18, 19]. These are factors associated with increased depth of invasion and metastasis [19, 20]. The location and histology of the tumor also differ between these two populations [21]. A higher incidence of proximal gastric cancer and diffuse and signet ring cell histology seen in Western

Table 4 Multivariate analysis of optimally treated cohort in resectable non-cardia gastric cancer patients treated with perioperative chemotherapy, postoperative chemoradiation therapy, and postoperative chemotherapy

Covariate	Level	OS (months)		
		Hazard ratio (95% CI)	HR *p*-value	Overall *p*-value
Treatment group weighted to POC	Perioperative chemotherapy	0.76 (0.64–0.91)	**0.002**	**< 0.001**
	Postoperative chemoradiation	0.72 (0.65–0.81)	**< 0.001**	
	Postoperative chemotherapy	–	–	
Treatment group weighted to PEC	Postoperative chemoradiation	0.95 (0.80–1.11)	0.502	**< 0.001**
	Postoperative chemotherapy	1.31 (1.10–1.55)	**0.002**	
	Perioperative chemotherapy	–	–	
Age	Above median	1.24 (1.10–1.40)	**< 0.001**	**< 0.001**
	Below median	–	–	
Race	Black	1.01 (0.89–1.15)	0.879	**< 0.001**
	Other	0.71 (0.60–0.83)	**< 0.001**	
	White	–	–	
Facility type	Non-academic/research program	1.12 (1.01–1.25)	**0.036**	**0.036**
	Academic/research program	–	–	
Primary payor	Private/not insured	0.86 (0.76–0.97)	**0.012**	**0.012**
	Medicare/Medicaid/other government	–	–	
Facility location	Northeast	0.77 (0.67–0.89)	**< 0.001**	**< 0.001**
	Midwest	1.09 (0.95–1.24)	0.217	
	West	1.00 (0.85–1.18)	0.981	
	South	–	–	
Grade	Poorly differentiated/undifferentiated	1.32 (1.17–1.50)	**< 0.001**	**< 0.001**
	Well/moderately differentiated	–	–	
Regional lymph nodes positive	Positive	2.28 (1.96–2.64)	**< 0.001**	**< 0.001**
	Negative	–	–	

Bold values indicate statistical significance

CI confidence interval, *PEC* perioperative chemotherapy, *POCR* postoperative chemoradiation therapy, *POC* postoperative chemotherapy

*Number of observations in the original dataset = 3418. Number of observations used = 3046

**Backward selection with an α level of removal of 0.05 was used. The following variables were removed from the model: Charlson–Deyo Score, Median Income Quartiles 2008–2012, Sex, and Year of Diagnosis

populations could explain some of the differences in survival as these are known to be more aggressive in nature [22, 23]. Data from the above trials should be extrapolated to the Western population with caution. The CRITICS trial in 2018 showed POCR did not improve survival when compared to POC in patients with resectable GC treated with preoperative chemotherapy and surgery [24]. Only 60% of the patients started the allocated postoperative treatment, when compared to 95% of the patients who proceeded to surgery following neoadjuvant therapy. This study laid ground for future studies to focus on preoperative treatment strategies, forming the basis for CRITICS-II trial, on which no data have been published to date [25]. Our study population differs from CRITICS trial as the neoadjuvant treatment group in our study did not receive adjuvant radiation therapy and hence the comparison groups are different.

Limitations of this study include the retrospective nature of this design, leading to a selection bias. The NCDB does not contain longitudinal data, such as disease-free survival and the lack of details on systemic therapy (name, dose, duration, and cycles). Additionally, complications during hospital course, toxicity of treatment regimes, and cause of death are not captured. The exact number of patients who started treatment with neoadjuvant therapy is unknown as only resected patients were analyzed. However, studies have indicated that the drop-off rate is only close to 5% after preoperative therapy [25]. The availability of data only till 2016 is another limitation of this study. Despite these limitations, our study represents an analysis of a large population dataset and compares PEC, POCR, and POC along with a sub-group analysis of optimally treated patients who received these three treatment strategies.

Conclusion

In our analysis, both perioperative chemotherapy and postoperative chemoradiation therapy are acceptable treatment strategies over postoperative chemotherapy when multimodal treatment is indicated in patients with non-metastatic resectable non-cardia gastric cancer. Postoperative chemotherapy alone may not be optimal.

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Declarations

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