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Comparative effectiveness of treatment modalities in non-metastatic gastric adenocarcinoma: a propensity score matching analysis of the National Cancer Database

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ABSTRACT

Background While addition of chemotherapy and radiation to surgery improves the outcomes of non-metastatic gastric adenocarcinoma (GAC), the best treatment strategy remains controversial.

Methods To determine the effectiveness of different strategies in patients with curative surgery, we performed an analysis of GAC patients in National Cancer Database. Propensity score method was used to control for imbalances in the confounders. Overall survival (OS), the primary outcome, was analysed using Cox proportional hazard model and Kaplan-Meier curves.

Results Patients diagnosed with GAC, from 2004 to 2013, were included in this analysis and grouped according to their treatment: surgery alone (15 184), chemoradiation in the neoadjuvant (6000) or adjuvant setting (7953), and perioperative chemotherapy (PCh; 3745) or adjuvant chemotherapy (ACh; 3000). Compared with surgery alone, all adjunctive therapies resulted in an improvement in OS; neoadjuvant chemoradiation (NACRT): HR 0.9 (95% CI: 0.84 to 0.97), PCh: HR 0.73 (95% CI: 0.68 to 0.79), adjuvant chemoradiation (ACRT): HR 0.71 (95% CI: 0.67 to 0.75), and ACh: HR 0.86 (95% CI: 0.8 to 0.93). Excluding patients with surgery only, we compared different strategies to PCh. In patients with distal GAC, ACRT resulted in improved OS, (HR 0.89; 95% CI: 0.796 to 0.996), p=0.042. In patients with proximal GAC, NACRT was inferior to PCh, HR 1.101 (95% CI: 1.006 to 1.204), p=0.036.

Conclusion In this real world population, addition of chemotherapy and radiation to surgery was associated with better OS. Radiation therapy may have a role in patients with distal GAC. Future research can elucidate patient, tumour, and treatment factors that necessitate the inclusion and sequence of radiation therapy in this population.

Summary box

What is already known about this subject?

► Patients with resectable gastric adenocarcinoma are potential candidates for perioperative chemotherapy (PCh), neoadjuvant chemoradiation (NACRT), and adjuvant chemoradiation (ACRT). PCh is adopted as the standard of care in this population. Whether chemoradiation, in the adjuvant or neoadjuvant setting, is comparable to the PCh is an unanswered question.

What are the new findings?

► This comparative effectiveness analysis of National Cancer Database data included 35 882 patient with resected gastric cancer who were candidate for adjunctive therapies based on their pathological or clinical stage. An improvement in overall survival was observed for all adjunctive therapies including, NACRT, PCh, adjuvant chemotherapy, and ACRT, compared with surgery alone. This improvement was statistically significant in subgroups of proximal and distal cancers. Using propensity score matching, we found that ACRT was superior to PCh in patients with distal gastric cancer; and PCh was superior to NACRT in patients with proximal cancers.

How might it impact on clinical practice in the foreseeable future?

► This real world data highlights the fact that role of radiation in patients with resectable gastric cancer requires optimisation. In patients with resected gastric cancer who did not receive perioperative therapy, chemoradiation should be considered. Shared decision-making should include both PCh and NACRT as an option in patients with proximal gastric cancer.

BACKGROUND

Despite the substantial decline in the incidence of gastric adenocarcinoma (GAC), it remains a significant cause of mortality in the USA.[1] Roughly 50% of patients with GAC are diagnosed with a localised or regional stage disease, defined by the presence of the disease in the boundary of the stomach and regional lymph nodes. Despite extension to

local structures and spread to local and regional lymph nodes, these patients are candidates for curative therapies.[2] While surgery is the cornerstone of cure in these patients, it is established that overall survival (OS) and cure rates are improved with the use of multimodality treatment.

The multimodality treatments, herein referred to as adjunctive therapy, are delivered in the neoadjuvant, perioperative (before and after surgery), and adjuvant settings, generally with different patient selection criteria and with different toxicity profiles. The most common adjunctive therapies for patients with GAC include adjuvant chemoradiation (ACRT) or neoadjuvant chemoradiation (NACRT) as well as perioperative chemotherapy (PCh). These strategies are supported by randomised clinical data demonstrating superiority of each adjunctive treatment over surgery alone as highlighted below.

INT-0116 trial was conducted in the USA and randomised 556 patients with resected gastric cancer to surgery alone versus surgery plus ACRT. Adjuvant therapy consisted of 5-fluorouracil (5-FU) boluses for 1 month, pursued by 5-FU concurrent with radiation for 6 weeks, followed by two additional months of 5-FU. The median OS was 27 months in the surgery group versus 36 months in the surgery plus ACRT, HR for death was 1.35 (95% CI, 1.09 to 1.66; p=0.005).[3] Similarly, the Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial was conducted in Korea, where 458 patients with resected gastric cancer were randomised to surgery plus adjuvant chemotherapy (ACh) versus ACRT. ACh consisted of 4.5 months of capecitabine and cisplatin, and ACRT included 6 weeks of capecitabine and cisplatin, pursued by 6 weeks of concurrent capecitabine with radiation, followed by and additional weeks of capecitabine and cisplatin. HR for OS for ACh versus ACRT was 1.130 (95% CI, 0.775 to 1.647; p=0.527).

Chemo Radiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) is a Dutch trial and randomised 368 patients with resectable gastro-oesophageal junction and oesophageal cancers to surgery alone versus NACRT followed by surgery. The neoadjuvant treatment consisted of carboplatin and paclitaxel in weekly doses concurrent with radiation for 6 weeks. The median OS was 24 months is the surgery group versus 49.4 months in the NACRT followed by surgery, HR for improvement in survival was 0.66 (95% CI, 0.5 to 0.87; p=0.003).[4]

MAGIC trial is a European trial and randomised 503 patients with resectable gastric cancers to surgery versus surgery plus PCh. The probability of 5 year survival was 23% versus 36% for surgery versus surgery plus PCh, HR for improvement in survival was 0.75 (95% CI, 0.6 to 0.93; p=0.009).[5] Another European trial randomised 224 patients with resectable gastro-oesophageal junction adenocarcinoma to surgery versus surgery plus PCh. The probability of 5-year survival was 24% versus 38% for surgery versus surgery plus PCh, HR for improvement in survival was 0.69 (95% CI, 0.5 to 0.95; p=0.02).[6]

There are no comparative data to determine which adjunctive approach is best for patients with GAC. Treatment decisions are largely guided by tumour location and geography. Tumours in the proximal stomach (gastro-oesophageal junction and cardia) more often receive NACRT or PCh, and tumours in the distal stomach more commonly receive PCh or ACRT. The practice of ACRT is mainly adopted in the USA, and less commonly used in other parts of the world. ACh in patients with GAC, is an established practice in Asian countries. While there is no data in US population for this practice, its effectiveness is supported by meta-analysis.[7–9] Provider familiarity with the regimen and logistical issues in delivery of the regimen are other major determinants of choice of therapy. National Comprehensive Cancer Network guidelines endorse PCh as the preferred treatment modality at least in patients with distal GAC.[10]

This study aims to investigate the effectiveness of different adjunctive therapies in patients with non-metastatic GAC after curative surgery in the USA, using the National Cancer Database (NCDB). Given the differences in the adoption of adjunctive therapy in patients with proximal and distal gastric cancer, the impact of different adjunctive therapies on OS was explored in all patients, as well as those with proximal and distal cancers. Additionally, we sought to assess the adoption of these treatments in patients with non-metastatic GAC.

METHODS

Data source

The NCDB is a registry sponsored by both the American College of Surgeons and the American Cancer Society.[11] Over 1500 Commission on Cancer-accredited facilities in the USA participate in the programme. There is a uniform and consistent data collection process that provides a reliable source for outcome analysis with higher quality of treatment information than SEER database. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Study population

Inclusion criteria: Patients with non-metastatic GAC (ICD-O-3 site code C16.1–16.9) who were diagnosed between 2004 and 2013 were identified (figure 1).

Exclusion criteria: Patients with metastatic adenocarcinoma, small cell, squamous cell histology, lymphoma, and neuroendocrine tumours were excluded. Patients who did not undergo curative resection were excluded from the cohort. Patients with pathological stage IA were excluded from analysis, as they are not candidates for any additional therapies. Documentation of the tumour location on the record was a requirement for this analysis and patients with unknown tumour location were excluded from the analysis.

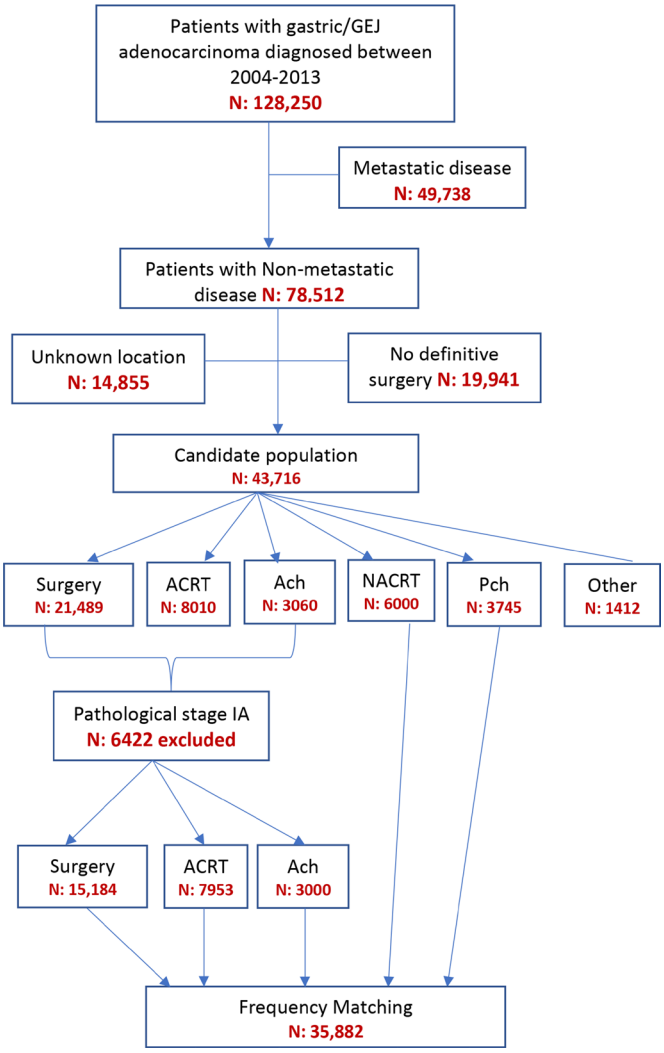

Figure 1 Consolidated Standards of Reporting Trials diagram for patient selection. ACh, adjuvant chemotherapy; ACRT, adjuvant chemoradiation; GOJ, gastro-oesophageal junction; NACRT, neoadjuvant chemoradiation; PCh, perioperative chemotherapy.

Additional variables

Using International Classification of Diseases for Oncology, third edition codes, histology was coded as adenocarcinoma (8140), diffuse (8142, 8145, and 8490), intestinal (8144), signet ring (8490), mucinous (8480, 8481), and others.

Age, gender, race, residence location, insurance status, annual income, percentage of individuals without a high school diploma in patient's area of residency, and comorbidity status using the Charlson-Deyo classification were included in the analysis.

Provider covariates included facility type (academic versus non-academic) and facility location (New England, Atlantic, East Central, West Central, or West Pacific).

Tumour grade was grouped into well-differentiated, moderately differentiated, poorly differentiated or undifferentiated, and unknown. Clinical stage was classified as cT1, cT2, cT3, or cT4 and nodal stages as cN0 or cN1.

Death from any cause following non-metastatic GAC diagnosis was abstracted. Follow-up duration was recorded as months from diagnosis until death or last contact. Patients with no follow-up for vital statistics were excluded from survival analysis.

Treatment received

To determine the temporal relationship between surgery and other therapies, an NCDB variable, 'Systemic Surgery Sequence', was used to indicate the sequence of treatment. Patients were divided into five groups:

NACRT: systemic therapy before OR before and after surgery and radiation therapy before surgery.

ACRT: systemic therapy and radiation therapy after surgery.

PCh: systemic therapy before and after surgery and no radiation.

ACh: systemic therapy after surgery and no radiation.

Other adjunctive regimens (Other): other combinations for systemic and chemotherapy not fitting in the previous categories. We excluded the 'Other' group due to lack of evidence for most of the treatments offered under this category.

Given that NACRT and PCh are delivered prior to the surgery, we evaluated the median and IQR from diagnosis to surgery in each group as a measure of validity of appropriate attribution of cases to the treatment groups. In the NACRT group, median and (IQR) were 129 (111 to 154) days; in ACh, ACRT, and PCh, these values were 21 (7 to 39), 21 (8 to 36), and 131 (108 to 154) days respectively. These timing variables confirmed that the sequence variable was internally consistent.

STATISTICAL ANALYSIS

OS, defined as time from diagnosis to death or last follow-up, was used as the primary outcome measure.

Patients received treatment modalities at the discretion of their physicians. As expected, baseline patient and disease characteristics were different by treatment modality (online supplemental table 1). We used a two-stage process to address the imbalances in patient selection criteria for treatment allocation.

Stage 1: We first matched patients by age in 5-year intervals, sex, and Charlson-Deyo Score (frequency matching).[12] In this cohort, we measured the relative effectiveness of different treatment strategies compared with surgery alone.

Stage 2: To compare the effectiveness of different adjunctive therapy modalities (NACRT, ACRT, PCh, and ACh), we used propensity score matching (patients with surgery only were not included in this analysis).[13] Using generalised boosting modelling (GBM), propensity score weights for each treatment group were estimated to match the baseline pre-treatment characteristics of the entire population that were included in stage 1 analysis. GBM outperforms multivariable logistic regression model for propensity score estimation in terms of

flexibility and ease of accommodating multiple treatment groups.[14] All 13 baseline characteristics (variables are shown in table 1) and year of diagnosis were included in the propensity score estimation. Absolute standardised mean difference (ASMD) was used to show the comparability across treatment groups, with unweighted measures show the differences prior to matching and weighted measures show differences after matching. ASMD under 0.2 are considered well-balanced.

To estimate the differences in OS by four treatment modalities, we used the multivariable Cox regression model adjusting variables such as surgical margin, lymphovascular invasion, and number of examined lymph nodes that were ascertained after resection, but not known at time of diagnosis.

A landmark sensitivity analysis was conducted to check the robustness of the results and assumptions. To account for patients who would not have been a candidate for ACRT and ACh after surgery, we excluded those who died 30 and 90 days after surgery and presented the results under sensitivity analysis. The landmark analysis is not applicable to the patients who received PCh and NACRT due to the fact that we only selected for patients who underwent curative resection and those who deteriorated/progressed after neoadjuvant therapy and were not candidate for surgery were not included in our cohorts.

Given the differences in the practice of adjunctive therapy strategies for proximal versus distal GAC, we assessed the impact of treatment choice in the entire population and in proximal and distal GAC subgroups. Subgroup analyses by primary tumour site were conducted using the same analytical approach as in overall cohort.

All statistical analyses were performed by using SAS (SAS/STAT 14.1, V.9.4; SAS Institute, Cary, North Carolina) and R library(twang) (the R Foundation for Statistical Computing, Vienna, Austria). P values were two-sided at a significance level of 0.05.

RESULTS

Description of patients and treatments

A total of 35 882 patients in NCDB database met the study inclusion criteria (figure 1). Excluding patients who received 'other' therapies, 15 184 patients had surgery alone, 6000 received NACRT, 7953 received ACRT, 3745 received PCh, and 3000 received ACT.

Characteristics of all the patients who met the inclusion criteria is listed in online supplemental table 1 (35 882 patients). After frequency matching for age, sex, and Charlson-Deyo comorbidity index (stage 1), 21 384 patients were included in the comparison of the benefit of each adjunctive therapy group with surgery alone (table 1).

Recipients of adjunctive therapies had significant differences. Ninety percent of the recipients of NACRT had proximal (cardia) cancers, while 31% of the ACRT, and 36% of the PCh patients had cardia cancers. NACRT patients were younger and predominantly white males, with higher clinical T and N stages compared with the other treatment groups. The percentage of patients with higher income and private insurance was also higher among the NACRT population (data not shown). As reported in table 1, only 1% of patients with non-cardia cancers received NACRT.

With a median follow-up of 55.1 months (range: 0.03 to 131 months), median OS in the NACRT, ACRT, PCh, and ACh groups were 51 months (95% CI: 48.6 to 56.2), 77.2 months (95% CI: 70.1 to 83), 67.5 months (95% CI: 62.6 to 73.2), and 48.5 months (95% CI: 44.8 to 73.2), respectively (figure 2).

Comparison of adjunctive therapies with surgery

All adjunctive therapy modalities were associated with a better probability of survival than matched patients who received surgery alone (no adjunctive therapy), HR 0.9 (95% CI: 0.84 to 0.97) for NACRT, HR 0.73 (95% CI: 0.68 to 0.79) for PCh, HR 0.71 (95% CI: 0.67 to 0.75) for ACRT, and HR 0.86 (95% CI: 0.8 to 0.93) for ACh (table 2).

Surgical quality was assessed by margin status and nodal retrieval. Greater than 78% of all patients had negative surgical margins. The median number of lymph nodes removed was highest in the PCh group and lowest in the NACRT group (17 vs 12 lymph nodes), (table 3).

Among adjunctive therapy population, post-operative mortality (assessed as 30-day and 90-day mortality) was highest in NACRT group (table 3). The 30-day mortality in NACRT, PCh, and ACRT were 2.91, 1.68, and 0.04, respectively (p value<0.001). The 90-day mortality in NACRT, PCh, and ACRT were 7.09, 4.63, and 0.39, respectively (p value<0.001).

Comparison of adjunctive therapies with each other

Propensity score matching was applied to reduce the imbalances of the groups for comparison of different adjunctive therapies, (online supplemental table 2) shows patient characteristics by four treatment modality with unweighted and weighted max ASMD. Propensity matching significantly reduced imbalances because the vast majority of weighted max ASMD were 0.2 or below.

We chose PCh as our reference group given that it can be used for both proximal and distal GAC populations. For the entire population, ACh was associated with a 24% higher mortality (HR 1.24, 95% CI: 1.13 to 1.36) than PCh, p value <0.001. The inferiority of ACh persisted in the proximal and distal GAC subgroups.

Given that only 1% of patients with distal cancers received NACRT, we compared the benefit of ACRT, ACh, and PCh in the distal GAC population. Compared with PCh, ACRT resulted in significantly longer OS HR (HR 0.89; 95% CI: 0.796 to 0.996), p value 0.042. In patients with proximal cancers, NACRT was inferior to PCh, HR 1.101 (95% CI: 1.006 to 1.204), p value 0.036. ACRT was equivalent to PCh in this population HR 1 (95% CI: 0.891 to 1.121), p value 0.99, (table 4).

Table 1 Patient characteristics for surgical versus adjunctive therapy comparison. The surgery-only cohort is frequency matched with the treatment group by age, sex, and comorbidity index

Original cohort	NACRT (n=6000)	PCh (n=3745)	ACRT (n=7953)	ACh (n=3000)	Surgery alone (n=15 184)	
Matched cohort	**NACRT (n=2853)**	**PCh (n=1907)**	**ACRT (n=4188)**	**ACh (n=1744)**	**Surgery alone (n=10 692)**	**Total (n=21 384)**
Age at diagnosis						
Median	67.0	68.0	70.0	72.0	69.0	69.0
Range	(20.0 to 88.0)	(24.0 to 90.0)	(19.0 to 90.0)	(23.0 to 90.0)	(18.0 to 90.0)	(18.0 to 90.0)
Sex						
Female	539 (18.9%)	667 (35%)	1600 (38.2%)	705 (40.4%)	3511 (32.8%)	7022 (32.8%)
Race/ethnicity						
White	2607 (91.4%)	1264 (66.3%)	2504 (59.8%)	1126 (64.6%)	7080 (66.2%)	14 581 (68.2%)
African American	92 (3.2%)	258 (13.5%)	739 (17.6%)	273 (15.7%)	1476 (13.8%)	2838 (13.3%)
Asian	51 (1.7%)	115 (6.1%)	449 (10.8%)	155 (8.9%)	743 (7.9%)	1613 (7.5%)
Hispanic	76 (2.7%)	234 (12.3%)	439 (10.5%)	171 (9.8%)	1030 (9.6%)	1950 (9.1%)
Other and unknown	27 (1%)	36 (1.9%)	57 (1.3%)	19 (1.1%)	263 (2.5%)	402 (1.9%)
Primary tumour location						
Cardia	2706 (94.8%)	815 (42.7%)	1066 (25.5%)	447 (25.6%)	4253 (39.8%)	9287 (43.4%)
Non-cardia	147 (5.2%)	1092 (57.3%)	3122 (74.5%)	1297 (74.4%)	6439 (60.2%)	12 097 (56.6%)
Histology						
Adenocarcinoma	2248 (78.8%)	1080 (56.6%)	2124 (50.7%)	869 (49.8%)	6156 (57.6%)	12 477 (58.3%)
Diffuse	282 (9.9%)	415 (21.8%)	1113 (26.6%)	442 (25.3%)	2071 (19.4%)	4323 (20.2%)
Intestinal	87 (3%)	192 (10.1%)	523 (12.5%)	206 (11.8%)	1186 (11.1%)	2194 (10.3%)
Mucinous	106 (3.7%)	63 (3.3%)	148 (3.5%)	55 (3.2%)	301 (2.8%)	673 (3.1%)
Others	130 (4.6%)	157 (8.2%)	280 (6.7%)	172 (9.9%)	978 (9.1%)	1717 (8%)
Grade						
Poor or undifferentiated	1387 (48.6%)	1188 (62.3%)	2895 (69.1%)	1217 (69.8%)	5946 (55.6%)	12 633 (59.1%)
Moderately differentiated	946 (33.2%)	512 (26.8%)	1020 (24.4%)	418 (24%)	3185 (29.8%)	6081 (28.4%)
Well-differentiated	126 (4.4%)	49 (2.6%)	126 (3%)	51 (2.9%)	713 (6.7%)	1065 (5%)
Unknown	394 (13.8%)	158 (8.3%)	147 (3.5%)	58 (3.3%)	848 (7.9%)	1605 (7.5%)
TNM CLIN T stage						
0	2 (0.1%)	11 (0.6%)	5 (0.1%)	2 (0.1%)	29 (0.3%)	49 (0.2%)
1	161 (5.6%)	140 (7.3%)	357 (8.5%)	169 (9.7%)	2097 (19.6%)	2924 (13.7%)
2	488 (17.1%)	323 (16.9%)	523 (12.5%)	223 (12.8%)	1515 (14.2%)	3072 (14.4%)
3	1705 (59.8%)	863 (45.3%)	605 (14.4%)	281 (16.1%)	1142 (10.7%)	4596 (21.5%)
4	80 (2.8%)	122 (6.4%)	166 (4%)	84 (4.8%)	354 (3.3%)	806 (3.8%)
Unknown	417 (14.6%)	448 (23.5%)	2532 (60.5%)	985 (56.5%)	5555 (52%)	9937 (46.5%)
TNM Clinical N Stage						
0	1027 (36%)	722 (37.9%)	1358 (32.4%)	617 (35.4%)	4858 (45.4%)	8582 (40.1%)
1	1283 (45%)	710 (37.2%)	518 (12.4%)	250 (14.3%)	924 (8.6%)	3685 (17.2%)
2	222 (7.8%)	129 (6.8%)	210 (5%)	91 (5.2%)	244 (2.3%)	896 (4.2%)
3	28 (1%)	35 (1.8%)	91 (2.2%)	39 (2.2%)	158 (1.5%)	351 (1.6%)
Unknown	293 (10.3%)	311 (16.3%)	2011 (48%)	747 (42.8%)	4508 (42.2%)	7870 (36.8%)
Academic centre						
Yes	1469 (51.5%)	1048 (55%)	1455 (34.7%)	674 (38.6%)	4665 (43.6%)	9311 (43.5%)
Insurance status						
Not Insured	51 (1.8%)	54 (2.8%)	110 (2.6%)	36 (2.1%)	319 (3%)	570 (2.7%)
Private insurance	1121 (39.3%)	660 (34.6%)	1282 (30.6%)	486 (27.9%)	3102 (29%)	6651 (31.1%)
Medicaid	105 (3.7%)	122 (6.4%)	263 (6.3%)	95 (5.4%)	647 (6.1%)	1232 (5.8%)
Medicare	1503 (52.7%)	1022 (53.6%)	2421 (57.8%)	1082 (62%)	6285 (58.8%)	12 313 (57.6%)

Continued

Table 1 Continued

Original cohort	NACRT (n=6000)	PCh (n=3745)	ACRT (n=7953)	ACh (n=3000)	Surgery alone (n=15 184)	
Matched cohort	**NACRT (n=2853)**	**PCh (n=1907)**	**ACRT (n=4188)**	**ACh (n=1744)**	**Surgery alone (n=10 692)**	**Total (n=21 384)**
Other and unknown	73 (2.5%)	49 (2.6%)	112 (2.7%)	45 (2.6%)	339 (3.2%)	618 (2.9%)
Charlson-Deyo Score						
0	1950 (68.3%)	1286 (67.4%)	2792 (66.7%)	1091 (62.6%)	7119 (66.6%)	14 238 (66.6%)
1	690 (24.2%)	479 (25.1%)	1014 (24.2%)	471 (27%)	2654 (24.8%)	5308 (24.8%)
2	213 (7.5%)	142 (7.4%)	382 (9.1%)	182 (10.4%)	919 (8.6%)	1838 (8.6%)

The numbers on the original cohort indicates the patients who met the inclusion criteria for this analysis, NACRT (6000), PCh (3745), ACRT (7953), ACh (3000), and surgery alone (15 184). The numbers for matched cohort is after matching by age, gender, and comorbidity index NACRT (2853), PCh (1907), ACRT (4188), ACh (1744), and surgery alone (10 692). The patients in the matched cohort are used to compare the outcomes between different treatments.
ACh, adjuvant chemotherapy; ACRT, adjuvant chemoradiation; ; NACRT, neoadjuvant chemoradiation; PCh, perioperative chemotherapy.

Sensitivity analysis

In the landmark analysis, excluding patients who died within 90 days after surgery in the ACh and ACRT cohorts, ACRT group had better survival compared with PCh (HR 0.917, 95% CI: 0.845 to 0.994), p value 0.035 (table 4).

An ad-hoc sub-group analysis based on age, gender, treatment facility, race, margin status, and stage is reported in online supplemental table 3). ACRT is superior in patients younger than 65 years, male, margin positive, and with pT4 tumours.

Description of treatment utilisation

We assessed the adoption of different treatment strategies in our patient population (figure 3). In general, the use of adjunctive therapies is rising and fewer patients have surgery only and no additional therapy. The use of ACh declined from 7.9% in 2004 to 2.6% in 2013 (figure 3A). The adoption pattern was assessed for proximal and distal cancers separately. In patients with proximal GAC, use of NACRT had risen from 20% in 2004 to more than 50% in 2013 (figure 3B). In the patients with distal GAC, the use of PCh had increased from 1% in 2004 to more than 20% in 2013 (figure 3C). In the same period, the number of subjects with proximal cancer in the NCDB registry had increased by 6% (data not shown).

DISCUSSION

To our knowledge, this report is the largest analysis comparing the different standard treatment modalities in patients with non-metastatic GAC in the USA. While a significant portion of patients with GAC did not get any adjunctive therapy, we show that any adjunctive therapy improved survival of patients with localised GAC when compared with surgery alone. The magnitude of survival improvement in this real-world setting, for different adjunctive therapies compared with surgery alone was comparable to that of the published randomised

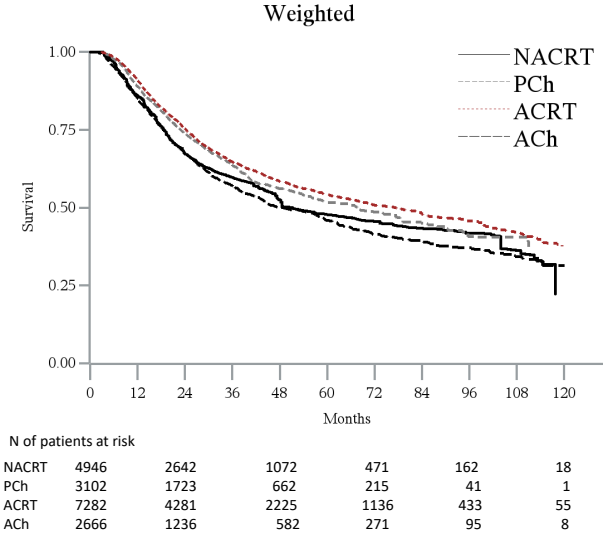

Figure 2 Survival probabilities for patients who received adjunctive therapies. With a median follow-up of 55.1 months, median OS in the NACRT, ACRT, PCh, and ACh groups were 51 months (95% CI: 48.6 to 56.2), 77.2 months (95% CI: 70.1 to 83), 67.5 months (95% CI: 62.6 to 73.2), and 48.5 months (95% CI: 44.8 to 73.2), respectively. ACh: adjuvant chemotherapy; ACRT: adjuvant chemoradiation; NACRT: neoadjuvant chemoradiation; OS, overall survival; PCh: perioperative chemotherapy,

Table 2 The HR for overall survival of different adjunctive therapies compared to surgery alone among matched cohort

Treatment modality	HR*	95% CI	Wald p value
NACRT	0.904	0.842 to 0.971	0.006
PCh	0.732	0.677 to 0.793	<0.001
ACRT	0.709	0.674 to 0.746	<0.001
ACh	0.863	0.803 to 0.928	<0.001
Surgery alone	Reference		

*Based on the multivariable Cox regression model including surgical margins, lymphovascular invasion, number of lymph nodes examined and all variables in table 1 except per cent no high school degree quartiles. Data stratified by year of diagnosis.
ACh, adjuvant chemotherapy; ACRT, adjuvant chemoradiation; NACRT, neoadjuvant chemoradiation; PCh, perioperative chemotherapy.

trials.[3–5 7] We found that ACRT was comparable to PCh in US patients with GAC who had undergone curative resection, but in the subgroup of patients with distal cancers, ACRT conferred a statistically significant survival benefit over PCh (HR 0.89; 95% CI: 0.796 to 0.996; p value 0.042). Similarly, in the subgroup of proximal cancers, NACRT was inferior to PCh (HR 1.101; 95% CI: 1.006 to 1.204; p value 0.036). However, it must be noted that these CI are very close to one for a sample size of the magnitude.

The findings suggest that there is room for optimum use of radiation in the management of curable patients with GAC. Radiation improved the outcomes when administered in the adjuvant setting in patients with distal gastric cancers. Yet, its benefit in the proximal cancers in the neoadjuvant setting was questionable.

The role of radiation in the adjuvant setting for GAC remains a debated topic and is a practice that is not well adopted outside of the USA. The ARTIST study

Table 3 Surgical characteristics by treatment modality

	NACRT (n=6000)	PCh (n=3745)	ACRT (n=7953)	ACh (n=3000)	Surgery alone (n=15 184)	Total (n=35 882)
Surgical Procedure, Days from Dx						
Median	129	131	21	21	23	34
IQR	111 to 154	108 to 154	8 to 36	7 to 39	6 to 44	12 to 103
Range	(0 to 616)	(0 to 740)	(0 to 738)	(0 to 895)	(0 to 772)	(0 to 895)
Surgical margins						
Negative	5361 (89.4%)	3158 (84.3%)	6362 (80%)	2334 (77.8%)	12 340 (81.3%)	30 606 (82.2%)
Positive	410 (6.8%)	465 (12.4%)	1406 (17.7%)	565 (18.8%)	2048 (13.5%)	5114 (13.7%)
Unknown	229 (3.8%)	122 (3.3%)	185 (2.3%)	101 (3.4%)	796 (5.2%)	1516 (4.1%)
Regional nodes examined						
Median	12	17	15	16	11	13
Range	(0 to 90)	(0 to 90)	(0 to 90)	(0 to 90)	(0 to 90)	(0 to 90)
0 to 15	3820 (63.7%)	1594 (42.6%)	4067 (51.1%)	1472 (49.1%)	9775 (64.4%)	21 542 (57.9%)
>15	1956 (32.6%)	2071 (55.3%)	3803 (47.8%)	1476 (49.2%)	5148 (33.9%)	14 952 (40.2%)
Unknown	224 (3.7%)	80 (2.1%)	83 (1%)	52 (1.7%)	261 (1.7%)	742 (2%)
Lymphovascular invasion						
Absent	1845 (30.8%)	967 (25.8%)	960 (12.1%)	408 (13.6%)	2574 (17%)	6933 (18.6%)
Present	608 (10.1%)	822 (21.9%)	1512 (19%)	677 (22.6%)	1908 (12.6%)	5673 (15.2%)
Unknown	3547 (59.1%)	1956 (52.2%)	5481 (68.9%)	1915 (63.8%)	10 702 (70.5%)	24 630 (66.1%)
Pathological TNM						
0	141 (2.4%)	39 (1%)	0 (0%)	0 (0%)	0 (0%)	180 (0.5%)
I	1011 (16.9%)	623 (16.6%)	914 (11.5%)	316 (10.5%)	4044 (26.6%)	7062 (19%)
II	1417 (23.6%)	992 (26.5%)	2397 (30.1%)	787 (26.2%)	3373 (22.2%)	9346 (25.1%)
III	1502 (25%)	1317 (35.2%)	3563 (44.8%)	1297 (43.2%)	3572 (23.5%)	11 730 (31.5%)
IV	73 (1.2%)	132 (3.5%)	545 (6.9%)	335 (11.2%)	790 (5.2%)	1962 (5.3%)
Unknown	1856 (30.9%)	642 (17.1%)	534 (6.7%)	265 (8.8%)	3405 (22.4%)	6956 (18.7%)
90-Day mortality						
Yes	202 (8.6%)	87 (5.8%)	19 (0.50%)	56 (3.7%)	1305 (13.9%)	1669
No	2055 (91.1%)	1412 (94.2%)	3778 (99.5%)	1440 (96.3%)	8106 (86.1%)	16 791

ACh, adjuvant chemotheray; ACRT, adjuvant chemoradiation; NACRT, neoadjuvant chemoradiation; PCh, perioperative chemotherapy.

Table 4 The HR for overall survival of different adjunctive therapies in the entire population and subgroups, and sensitivity analysis for patients who died after surgery in the treatment groups in which surgery was first in the sequence of therapy

	NACRT HR (95%CI)*	ACRT HR (95%CI)*	ACh HR (95%CI)*	PCh
All patients				
	1.163 (1.006 to 1.344)	0.928 (0.856 to 1.006)	1.243 (1.134 to 1.363)	1
P value	0.041	0.069	<0.001	
All patients (excluding patient who died after surgery in ACRT and ACh)				
Excluding subjects who died ≤30 days after surgery	1.164 (1.006 to 1.345)	0.923 (0.852 to 1.000)	1.241 (1.131 to 1.361)	1
P value	0.041	0.051	<0.001	
Excluding subjects who died ≤90 days after surgery	1.165 (1.007 to 1.348)	0.917 (0.845 to 0.994)	1.194 (1.088 to 1.311)	1
P value	0.040	0.035	<0.001	
Proximal	1.101 (1.006 to 1.204)	1.000 (0.891 to 1.121)	1.291 (1.118 to 1.491)	1
P value	0.036	0.99	<0.001	
Distal		0.890 (0.796 to 0.996)	1.215 (1.075 to 1.373)	1
P value		0.042	0.002	

*Based on Cox regression model with propensity score matching and adjusted for surgical margin, regional lymph nodes examined, and lymphovascular invasion.
ACh, adjuvant chemotherapy; ACRT, adjuvant chemoradiation; NACRT, neoadjuvant chemoradiation; PCh, perioperative chemotherapy.

suggests that for lymph node-positive patients, adjuvant chemoradiotherapy may be superior to chemotherapy alone, leading to the confirmatory ARTIST2 trial (NCT0176146).[15] In our study, ACRT compared with surgery alone improved the survival by 29%, HR 0.71 (95% CI, 0.67 to 0.75); this is comparable to results of INT-0116 (HR 0.65, 95% CI: 0.34 to 0.91).[3] Several factors suggest that contemporary delivery of ACRT compared with INT-0116 is improved. First, INT-0116 study had been criticised for inadequate lymph node resection and that radiation in essence compensated for inadequate surgery. In our population, the median number of lymph nodes removed was 15, and better than INT-0116 population. Second, in the INT-0116 trial, only 64% of patients who were randomised to chemoradiation completed their treatment; primarily due to toxicities of the treatment. INT-0116 used bolus 5-FU regimen, toxicity of infusional 5-FU and capecitabine is significantly better than that of bolus 5-FU and there has been a shift in using capecitabine or infusional 5-FU in this setting.[16–18] Finally, the central review of radiation fields of the INT-0116 trial identified significant violations, which prompted the issuing of a consensus recommendation for treatment of this population.[19 20]

The Chemo Radiotherapy after Induction chemo Therapy In Cancer of the Stomach (CRITICS) trial raises doubts about the benefit of adjuvant radiation in patients with GAC. CRITICS used neoadjuvant platinum-based chemotherapy in all patients with post-surgery randomisation to ACh or chemoradiotherapy. CRITICS did not show a survival benefit for addition of chemoradiation versus continuation of chemotherapy after surgery HR 1.01 (95 CI% 0·84 to 1·22; p=0·90).[21] This is interpreted as switching from pre-operative chemotherapy to post-operative chemoradiation, and is not beneficial. ACRT in our population is delivered only to those who did not get any neoadjuvant therapy and is not comparable to that of CRITICS trial. Indeed, we have no cohort of patients comparable to CRITICS treatment.

NACRT is considered a standard of care for most patients with oesophageal and gastro-oesophageal junction adenocarcinoma. Our analysis revealed that NACRT was inferior to PCh in patients with proximal gastric cancer, HR 1.101 (95% CI: 1.006 to 1.204), p value 0.036. The higher 90-day mortality of the NACRT group (7.09%) compared with PCh (4.36%) may be the explanation for this bewildering finding in our analysis. In the CROSS trial, the adjusted HR for improvement in the OS for the adenocarcinoma was 0.74 (95% CI: 0.536 to 1.024), and thus insufficient to conclude that NACRT improved the survival of patients with adenocarcinoma compared with surgery alone.[4] Finally, our results suggest that the benefit of NACRT seen in oesophageal cancer may be less substantial in proximal GAC. Our findings are in line with that of the Pre Operative therapy in Esophagogastric adenocarcinoma Trial (POET) study, where PCh was compared with the same strategy plus radiation. POET was closed early due to poor accrual. Nevertheless, radiation did not result in a statistical improvement in survival rates.[22]

With more than 90% of patients in the PCh group receiving multidrug chemotherapy, our PCh group compared with surgery alone had 27% improvement in survival (HR 0.73, 95% CI: 0.68 to 0.79). This is comparable to the reported HR in National French Federation of Cancer Centers System (HR 0.69, 95% CI: 0.50 to

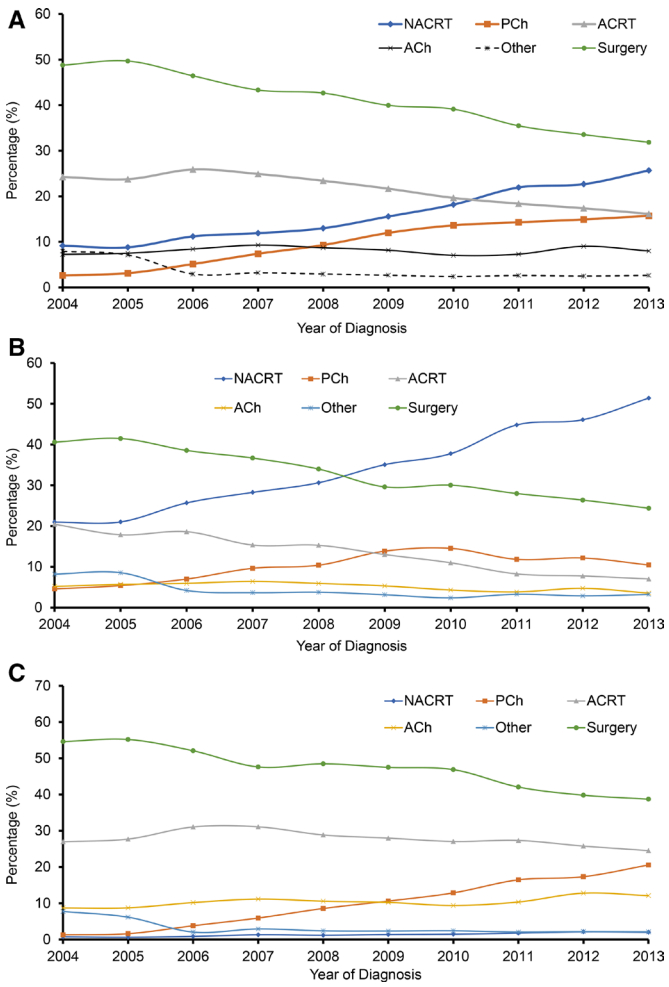

Figure 3 Adoption of adjunctive therapies over the study period for all patients (A), in patients with proximal cancers (B), and in patients with distal cancers (C). The number of patients who received surgery only is decreasing overtime. ACh, adjuvant chemotherapy; ACRT, adjuvant chemoradiation; NACRT, neoadjuvant chemoradiation; PCh, perioperative chemotherapy.

0.95).[6] In the MAGIC trial only 69.3% of patients underwent curative surgery, and in the contemporary CRITICS trial 82% of patients underwent curative surgery due to disease progression.[21] It is critical to point out that our cohort only included patients with GAC who had undergone surgery, therefore those who deteriorated after chemotherapy are not represented in our population. This makes our cohort slightly different from the intent to treat populations in the neo-adjuvant or perioperative strategies in the published trials.

Snyder *et al* showed that rates of adjunctive therapy in Medicare population was low and that medical oncology consultation was associated with increased rates of adjunctive therapy.[23] It remains concerning that a significant proportion of patients in our cohort did not receive any adjunctive therapy (31% in 2013). However, it is encouraging that the rates of patients having surgery alone is declining and more patients receive adjunctive therapies. The increase in the PCh and NACRT indicates an increased engagement of the medical oncology in the care of these patients early on. This shift coincides with scientific presentations and publications of adjunctive therapy regimens and supports that importance of multimodality treatment in early stage GAC patients.

The novelty of our approach is in limiting the analysis population to those who had undergone curative surgery. To verify that surgeries performed were curative, the intent of therapy was verified by using the 'palliative-care' variable, a NCDB variable to distinguish between curative and palliative treatments. The intent of therapy was curative in 98.1% of surgery only group. For NACRT, PCh, ACRT, and ACh, treatment was curative in 98.3%, 99%, 99.2%, and 97.8% respectively. Therefore, assuming 'fitness' for aggressive therapy. We have accounted for all available clinical variables that can impact the selection of patients for aggressive therapy, including age and comorbidities and setting of care (academic versus non-academic setting) as a proxy for expertise. While, the adequacy of staging in these patients are unknown and may impact the findings, only a minority of patients in each treatment group have pathological stage IV (table 3). Therefore, it is unlikely that staging practices had a significant impact on our findings.

We acknowledge that this is a retrospective study with limitations in the accuracy of the coded data. We selected propensity score analysis to overcome the limitations of biasses in treatment allocation. Given the rigorous process for selecting the patients and sorting therapies, our findings reflect the realistic outcomes of patients treated outside of the clinical trials.

In summary, our analysis provides a comprehensive assessment of care delivery to the population of resectable GAC and a comparative effectiveness for available adjunctive therapy modalities. We establish that in real world setting, adjunctive therapies improve survival over surgery alone. These results should be taken into consideration for patients who undergo upfront surgery. Future trials to better define the role of radiation in the care of GAC is warranted.

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REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66:7–30.
2 Howlader N, Noone A M, Krapcho M, *et al*. *Seer cancer statistics review, 1975-2012*. Bethesda, MD: National Cancer Institute, 2013.
3 Macdonald JS, Smalley SR, Benedetti J, *et al*. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725–30.
4 van Hagen P, Hulshof MCCM, van Lanschot JJB, *et al*. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074–84.
5 Cunningham D, Allum WH, Stenning SP, *et al*. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11–20.
6 Ychou M, Boige V, Pignon J-P, *et al*. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011;29:1715–21.
7 GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Paoletti X, Oba K, *et al*. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA* 2010;303:1729–37.
8 Noh SH, Park SR, Yang H-K, *et al*. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (classic): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014;15:1389–96.
9 Sakuramoto S, Sasako M, Yamaguchi T, *et al*. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007;357:1810–20.
10 NCCN clinical practice guidelines in oncology (NCCN Guidelines®), 2018. Available: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf [Accessed 16 May 2018].
11 National cancer data base. Available: https://www.facs.org/quality-programs/cancer/ncdb [Accessed 1 Jul 2018].
12 Melbye M, Wohlfahrt J, Olsen JH, *et al*. Induced abortion and the risk of breast cancer. *N Engl J Med* 1997;336:81–5.
13 Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med* 2014;33:1242–58.
14 McCaffrey DF, Griffin BA, Almirall D, *et al*. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med* 2013;32:3388–414.
15 Park SH, Sohn TS, Lee J, *et al*. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. *J Clin Oncol* 2015;33:3130–6.
16 Glynne-Jones R, Dunst J, Sebag-Montefiore D. The integration of oral capecitabine into chemoradiation regimens for locally advanced rectal cancer: how successful have we been? *Ann Oncol* 2006;17:361–71.
17 Kim JS, Kim JS, Cho MJ, *et al*. Comparison of the efficacy of oral capecitabine versus bolus 5-FU in preoperative radiotherapy of locally advanced rectal cancer. *J Korean Med Sci* 2006;21:52–7.
18 Dahan L, Atlan D, Bouché O, *et al*. Postoperative chemoradiotherapy after surgical resection of gastric adenocarcinoma: can LV5FU2 reduce the toxic effects of the MacDonald regimen? A report on 23 patients. *Gastroenterol Clin Biol* 2005;29:11–15.
19 Tepper JE, Gunderson LL. Radiation treatment parameters in the adjuvant postoperative therapy of gastric cancer. *Semin Radiat Oncol* 2002;12:187–95.
20 Smalley SR, Gunderson L, Tepper J, *et al*. Gastric surgical adjuvant radiotherapy consensus report: rationale and treatment implementation. *Int J Radiat Oncol Biol Phys* 2002;52:283–93.
21 Cats A, Jansen EPM, van Grieken NCT, *et al*. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (critics): an international, open-label, randomised phase 3 trial. *Lancet Oncol* 2018;19:616–28.
22 Stahl M, Walz MK, Stuschke M, *et al*. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009;27:851–6.
23 Snyder RA, Penson DF, Ni S, *et al*. Trends in the use of evidence-based therapy for resectable gastric cancer. *J Surg Oncol* 2014;110:285–90.