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Scientific Article

Survival and Recurrence Patterns in Patients With Stomach Adenocarcinoma Receiving Chemotherapy or Chemoradiotherapy After D2 Gastrectomy in a Tertiary Care Cancer Institute: A Retrospective Real-World Evidence Cohort Study

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Purpose: Clinical trials comparing the efficacy of adjuvant chemotherapy (CT) and chemo radiation therapy (CTRT) for stomach adenocarcinoma have reported equivocal results. Hence, the current retrospective cohort study assessed the long-term survival and recurrence outcomes of these therapies, to generate evidence in a real-world scenario.

Methods and Materials: Pathologically confirmed patients with stomach adenocarcinoma aged ≥18 years who underwent gastrectomy and D2 lymph nodal dissection at a tertiary cancer hospital from January 2010 to October 2017 were enrolled. Hospital-based follow-up was performed until December 2021. Data were gathered from electronic medical records, supplemented by telephonic interviews for patients who could not come for physical follow-up. CT-alone and CTRT cohorts were compared in terms of survival and recurrence outcomes.

Results: The analysis included 158 patients (mean age, 56.42 years; 63.9% male; CT-alone cohort, 69; CTRT cohort, 89). Patients in the CTRT cohort had significantly worse tumor characteristics at baseline (29.2% had the diffuse type of tumor, 94.4% had stage II or III, 68.5% had lympho-vascular space invasion, and 85.4% had lymph node involvement). Recurrence was observed in 13 (19.7%) of the 76 followed-up patients. Although locoregional recurrence was higher in the CT-alone cohort (7 vs 2), distant metastasis was higher in the CTRT cohort (3 vs 1). The overall 5-year survival was 67.0% (SE, 5.0%) and 5-year recurrence-free survival (RFS) was 75.0% (SE, 5.0%). On multivariate Cox regression, no variable was significantly associated with the overall survival, whereas age, positive lymph nodes without extracapsular extension, and lymph node-negative were significantly associated with RFS. The CTRT cohort had significantly (84.0%) higher RFS (hazard ratio, 0.161; 95% CI, 0.056-0.464; $P < .001$).

Conclusions: Patients who received adjuvant CTRT after D2 dissection showed similar overall survival but significantly higher RFS than the CT-alone cohort, despite having worse baseline tumor characteristics.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.
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Introduction

Stomach cancer is the fifth most common cancer worldwide.[1] It contributes to around 1.1 million new cases and 0.8 million deaths annually.[1] Over the past decades, surgery has been the mainstay of its treatment, and significant advances have been made in surgical approaches to enhance the survival of patients with stomach cancer.[2,3] For adequate surgery, the procedure aims for complete resection of the primary tumor and any associated direct extension. For the optimum extent of regional lymphadenectomy, which varies from D0 to D2, the more extensive D2 lymphadenectomy has become the standard of care in current times.[4-6] However, very few patients present with a resectable tumor,[7-9] and even fewer survive after complete and adequate surgery.[10]

Moreover, stomach cancer is notorious for both locoregional recurrence and distant metastasis after curative resection. The high frequency of locoregional recurrence endorses the need for the addition of local treatment to systemic therapy. For this purpose, radiation therapy is combined with chemotherapy (CT) for adjuvant treatment. However, randomized controlled trials (RCTs) and meta-analyses have reported that the addition of radiation therapy may not be beneficial in terms of survival and recurrence.[11-14] However, none of these studies could evaluate the outcomes related to the effectiveness and safety of the 2 modalities in a real-world setting. Hence, the current real-world study was designed to retrospectively assess the long-term survival and recurrence outcomes of the 2 adjuvant modalities, CT alone and chemo radiation therapy (CTRT), in D2-dissected patients.

Methods and Materials

The study was conducted according to the principles expressed in the Declaration of Helsinki. The retrospective secondary data collected from electronic medical records (EMRs) were anonymized using the safe harbor method, and no identifiable information was disclosed.

Study design

The current real-world evidence (RWE) study was designed as a retrospective cohort study. The 2 cohorts of the study consisted of the patients with stomach cancer operated on at the study hospital, who received adjuvant therapy as either CT alone or CTRT. The cohort that received adjuvant CT and no radiation therapy was named the "CT-alone cohort" for this study. Similarly, the cohort that received adjuvant CTRT was named the "CTRT cohort." A chart review using EMRs of the patients was conducted from October 2021 to December 2021 for collecting data for this study.

The index date was defined as the date of assignment of adjuvant therapy by a multidisciplinary tumor (MDT) board. The preindex period started with the registration of the patient in the study hospital. A patient would either be newly diagnosed or would be reconfirmed in case the diagnosis was made before coming to the study hospital. Usually, a patient would undergo gastrectomy within 2 weeks of registration. Each case would be discussed in the MDT board meeting after receiving the histopathology report. The preindex period of the overall study population varied between 4 to 5 weeks. Baseline characteristics were collected, and eligibility criteria were applied during the preindex period. In the postindex period, data related to toxicity and follow-up were collected (Fig. 1).

Study setting and participants

The study was conducted in a single tertiary care cancer hospital in India. Participants were selected by consecutive sampling from the list of patients with stomach adenocarcinoma registered at the hospital between January 2010 and October 2017. Eligible for inclusion were patients with pathologically confirmed stomach adenocarcinoma aged more than 18 years, who underwent exploratory laparotomy with gastrectomy and D2 nodal dissection at the study hospital, followed by either CT alone or CTRT as the adjuvant therapy. The adjuvant therapy provided to the patient was the exposure of interest. Patients who were operated on elsewhere, who visited the hospital only for consultation or supportive/palliative care, or who presented with metastatic disease at the time of the first consultation were considered ineligible and were excluded from the study.

All the patients were required to visit the hospital for follow-up every 3 months during the first 2 years, every 6 months for the next 3 years, and yearly after that. Follow-up data were collected from EMRs until the death of the patient or until the last day of the follow-up period (December 31, 2021), whichever was earlier. At the time of data collection, patients who did not come for in-person follow-up visits were called to collect outcome data telephonically. If patients were not contactable even on the phone, they were labeled as lost to follow-up.

Clinical procedures

As a part of the routine care at the institute for patients with stomach adenocarcinoma, depending on the location of the tumor, the patient underwent total or subtotal gastrectomy. Total gastrectomy was performed for tumors of the gastroesophageal junction or upper gastric body, whereas subtotal gastrectomy was performed for tumors in the lower body, antrum, or pylorus. The adjuvant therapy was started 4 to 6 weeks after surgery, depending on

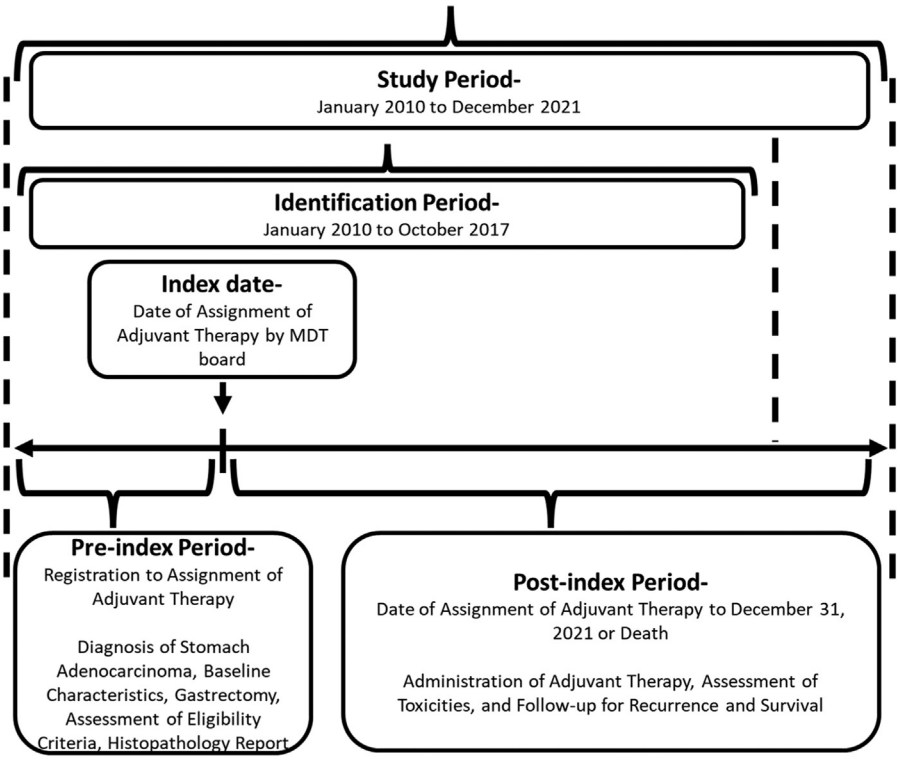

Figure 1 Study design.

the recovery time. The type of adjuvant therapy (CT alone or CTRT) was chosen on a case-to-case basis after a discussion in the MDT board meeting.

Adjuvant therapy in the CT-alone cohort

Based on the clinical judgment of the medical oncologist, within the framework of the guidelines, postoperative fluoropyrimidine-based doublet CT was administered as either 5-fluorouracil continuous infusion or capecitabine, along with oxaliplatin or cisplatin.

Adjuvant therapy in the CTRT cohort

Adjuvant therapy in the CTRT cohort was administered as per a modified institutional protocol based on the intergroup (INT) 0116 trial.[15] From day 1 to 5, 425 mg/m^2 of body surface area fluorouracil and 20 mg/m^2 leucovorin were administered per day. Radiation therapy planning was initiated after the first cycle of CT, 1 or 2 days ahead of the planned date for radiation therapy. A computed tomography scan–based simulation was carried out with the patient placed in the supine position and aligned straight by crosswire lasers. A thermoplastic cast was fabricated in the treatment position, isocenters were marked using radiopaque fiducials, and a planning computed tomography scan was acquired with intravenous contrast administration. The patient data set was transferred to the workstations for contouring and planning. Contouring was performed according to the standard Radiation Therapy Oncology Group target volume delineation guidelines, based on the histopathologic features, tumor location, and organs at risk. A dose of radiation therapy ranging from 45 to 50.4 Gy in 25 to 28 fractions was prescribed to the planning target volume. Conformal radiation therapy in the form of intensity modulated radiation therapy (IMRT) was used to deliver the dose through image guided radiation therapy. The medical physics team in the radiation oncology department optimized the plan. The treating radiation oncologist approved and verified the final plan. Around 28 days after the start of this initial cycle of CT, the radiation therapy was delivered on 6 megavoltage linear accelerator after patient-specific quality assurance, set-up verification, cone beam computed tomography based online imaging and matching, and application of shifts. Radiation therapy was delivered 5 days a week, along with 20 mg/m^2 leucovorin and 400 mg/m^2 fluorouracil on the first 4 and the last 4 days of the radiation therapy.[16] One month after the completion of radiation therapy, 3 additional cycles of 425 mg/m^2 fluorouracil plus 20 mg/m^2 leucovorin were given 1 month apart. In patients having grade 3 or 4 toxic effects, the dose of CT was modified accordingly. During each follow-up visit by patients in both cohorts, a clinical examination was carried out, and if indicated, a positron emission tomography computed tomography or

computed tomography scan, ultrasonography, or endoscopy was performed.

Measurement of variables

The primary outcomes of the study were overall survival (OS) and recurrence-free survival (RFS) in the 2 adjuvant treatment cohorts. OS was calculated from the date of the surgery to the date of death or the date of the last follow-up. RFS was calculated from the date of the surgery to the date of a clinically confirmed recurrence. Recurrence was defined as the presence of a recurrent tumor on biopsy or imaging. Furthermore, a recurrence was classified as locoregional or distant metastasis, where the former was defined as a recurrence to the regional lymph nodes and surgical bed including remnant stomach (if any) and/or anastomotic site, whereas the latter was defined as spread to distant sites. In the histopathologic reports, margin status was described as R0 for microscopically negative, R1 if microscopic tumor cells were present in the resection margins, and R2 if macroscopic tumor cells were present in the resection margins. Assessment methods were similar for both CT-alone and CTRT cohorts.

Data related to demographic profile, tumor characteristics, treatment, adjuvant modalities, survival outcomes, and recurrence were retrospectively extracted from EMRs into Microsoft Excel (2019 v2301) sheets. These variables were compared between the 2 cohorts to determine the factors associated with the outcomes. Host factors of the patients, including genetic makeup, may have introduced bias. The compliance of the patients and variations in prescriptions and treatment methods based on the preferences of the treating oncologist may have affected survival and recurrence.

Statistical considerations

To compare survival in 2 independent cohorts, the sample size was calculated assuming equal allocation, α as 5% and β as 20%. To achieve a relative hazard for OS of at least 0.2, a minimum of 12 events (10 in the CT-alone cohort and 2 in the CTRT cohort) were needed in the entire study population. With an assumed baseline event rate of at least 10%, a censoring rate of 0.5 equally applied to both the cohorts, and the average study period or follow-up period of 112.5 months, at least 59 participants were needed to be recruited in each arm, after a continuity correction.[17] Enrollment was continued until October 2017 even after the sample size was achieved.

Data analysis was performed using the Statistical Package for Social Sciences (v 28). Descriptive statistics related to categorical variables are presented as percentages. Continuous variables are represented as means and standard deviations. The Pearson χ^2 test and the Fisher-Freeman-Halton exact test were used for bivariate analysis. An independent-samples t test was used to compare the mean age in the 2 cohorts. Kaplan-Meier curves were plotted for OS and RFS. Hypothesis testing was done through the Tarone-Ware test and log-rank test. Cox proportional-hazards regression analysis was performed for identifying variables with significant prognostic value and for calculating univariate and multivariate hazard ratios (HR) with their 95% CI. A P value of $\leq .05$ was considered statistically significant. All statistical tests were 2-tailed. To provide a comparable denominator for Cox regression, indicators for lymph node involvement and extracapsular extension (ECE) were combined to compute a new variable related to lymph node positivity with/without ECE.

Results

Participants

Out of 2419 patients with stomach adenocarcinoma who visited the study center from January 2010 to October 2017, 158 patients were eligible for inclusion (Fig. 2), and all of them were included in the final analysis. Complete baseline data for all 158 enrolled patients (69 in the CT-alone cohort and 89 in the CTRT cohort) were available in the EMRs without any missing data point. Data generated during a physical follow-up visit to the study hospital were also available in the EMRs without any missing data point. However, only recurrence and survival data could be collected from 16 patients who were interviewed telephonically for follow-up.

Descriptive data

Demographic and tumor characteristics

The median age of the entire study population was 58 (range, 17-87) years. At baseline, patients in the CTRT cohort had significantly worse tumor characteristics (29.2% had a diffuse type of tumor, 94.4% had stage II or III, 68.5% had lympho-vascular space invasion, and 85.4% had an involvement of lymph nodes, including 61.8% [47/76] who had an ECE) than those in the CT-alone cohort (Table 1).

Treatment-related factors

The majority (61.4%) of patients (37/69 in the CT-alone cohort and 60/89 in the CTRT cohort) underwent subtotal gastrectomy, whereas the remaining 38.6% underwent total gastrectomy. All the patients underwent D2 lymphadenectomy. For adjuvant therapy, 69 (43.7%) patients received CT alone, whereas 89 (56.3%) received CTRT. Seven of the 16 patients, who had the involvement

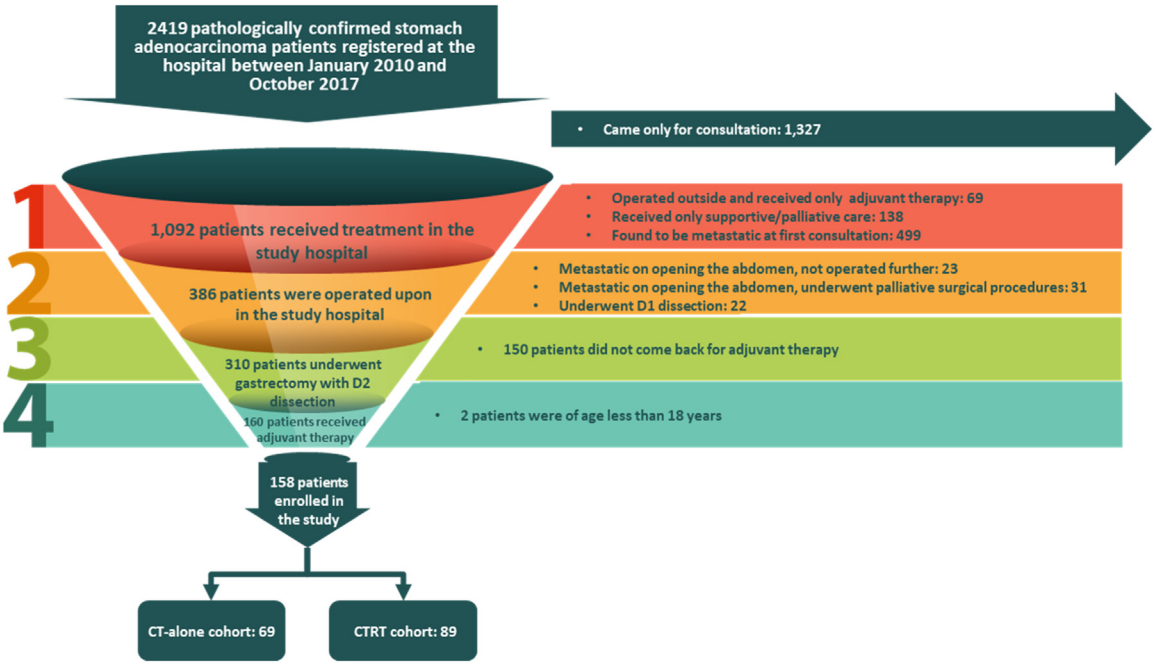

Figure 2 Funnel diagram showing attrition of study participants.

of margins at baseline, refused radiation therapy, and hence were provided only CT (Table 1).

Outcome data

Of 158 patients, 82 (51.9%) patients were lost-to-follow-up, comprising 36/69 (52.2%) patients in the CT-alone cohort and 46/89 (51.7%) patients in the CTRT cohort. Hence, outcome data could be collected for 76 (47.8%) patients (33 in the CT-alone cohort and 43 in the CTRT cohort). Out of these, 60 patients were followed up physically in the study hospital, and 16 patients (or the family members who survived them) were contacted telephonically to collect the outcome data.

Out of the 76 patients having outcome data, 44 (57.9%) patients were alive at the time of the analysis. Out of 13 (19.7% of 76) patients who developed a recurrence after treatment, 8 patients eventually died. The overall recurrence (24.2% or 8/33 vs 11.6% or 5/43) and locoregional recurrence (7 vs 2) were higher in the CT-alone cohort than in the CTRT cohort, although the Fisher-Freeman-Halton exact test (P = .095) did not show any significant difference between the 2 cohorts (Table 2). Out of 82 patients lost to follow-up, 12 (14.6%) had locoregional recurrence, and 2 (2.4%) had distant metastasis before they were lost to follow-up (Note E1 and Table E1). Acute toxicities during the time of treatment were documented in 156 (98.7%) of 158 patients (Note E2 and Table E2). Most patients (148/156) had mild (grade 1 or 2) toxicities. No death occurred in either cohort during the treatment period.

Main results

Survival analysis

The 5-year survival of the complete study population was 67.0% (SE, 5.0%). It was higher in the CT-alone cohort (75.0%; SE, 7.0%) than in the CTRT cohort (61.0%; SE, 8.0%). Kaplan-Meier plots (Fig. 3A) showed that the CT-alone cohort had initially worse OS, which became better than the CTRT cohort after around 20 months, although the Tarone-Ware test was not significant (P = .954). The lower OS in the CTRT cohort, despite low recurrence, may have occurred because of worse initial tumor characteristics, although because of censoring of patients who were lost to follow-up, it is difficult to comment on the precise reason. Further, on multivariate Cox proportional-hazards regression, there was no statistically significant difference in OS in the 2 cohorts (HR, 0.908; 95% CI, 0.394-2.094; P = .822), suggesting that overall, both the cohorts had similar OS. Moreover, this analysis further revealed that no variable was significantly associated with OS, although, on univariate analysis, the variable for lymph node-negative was significantly associated with OS (Table 3).

The 5-year RFS (including locoregional recurrence and distant metastasis) of the complete study population was 75.0% (SE, 5.0%). It was higher in the CTRT cohort (83.0%; SE, 6.0%) compared with the CT-alone cohort (63.0%; SE, 7.0%). On Kaplan-Meier plots (Fig. 3B), the CT-alone cohort had significantly worse RFS than the CTRT cohort throughout the study period (log-rank test P = .004). Cox regression further confirmed significantly

Table 1 Comparison of baseline variables in the 2 cohorts

Variables	Categories/details	Total study population (N = 158)	CT-alone cohort (N = 69)	CTRT cohort (N = 89)	CT-alone vs CTRT cohort test statistic (df)	CT-alone vs CTRT cohort *P* value (2 tailed)*
Demographic variables						
Age (y)	Mean (SD)	56.42 (12.240)	57.91 (12.904)	55.27 (11.641)	1.350† (156)	.179
Sex	Male	101 (63.9%)	45 (65.2%)	56 (62.9%)	0.089‡ (1)	.766
	Female	57 (36.1%)	24 (34.8%)	33 (37.1%)		
Tumor characteristics						
Tumor location	Antro-pyloric	98 (62.0%)	41 (59.4%)	57 (64.0%)	6.519‡ (3)	.089
	GEJ	9 (5.7%)	7 (10.1%)	2 (2.2%)		
	Fundus	37 (23.4%)	13 (18.8%)	24 (27.0%)		
	Cardia	14 (8.9%)	8 (11.6%)	6 (6.7%)		
Tumor type	Intestinal	30 (19.0%)	8 (11.6%)	22 (24.7%)	19.218§	<.001*
	Diffuse	32 (20.3%)	6 (8.7%)	26 (29.2%)		
	Mixed	5 (3.2%)	3 (4.3%)	2 (2.2%)		
	Undifferentiated	91 (57.6%)	52 (75.4%)	39 (43.8%)		
Pathologic stage	I	24 (15.2%)	19 (27.5%)	5 (5.6%)	14.561‡ (2)	<.001*
	II	49 (31.0%)	19 (27.5%)	30 (33.7%)		
	III	85 (53.8%)	31 (44.9%)	54 (60.7%)		
Grade	1	10 (6.3%)	4 (5.8%)	6 (6.7%)	4.236§	.341
	2	56 (35.4%)	29 (42.0%)	27 (30.3%)		
	3	85 (53.8%)	32 (46.4%)	53 (59.6%)		
	4	1 (0.6%)	1 (1.4%)	0 (0.0%)		
	Unknown	6 (3.8%)	3 (4.3%)	3 (3.4%)		
Involvement of the lymph nodes	Positive lymph nodes with ECE	73 (46.2%)	26 (37.7%)	47 (52.8%)	16.591‡ (2)	<.001*
	Positive lymph nodes without ECE	42 (26.6%)	13 (18.8%)	29 (32.6%)		
	Lymph nodes-negative (not involved)	43 (27.2%)	30 (43.5%)	13 (14.6%)		
Perineural invasion	Positive	70 (44.3%)	29 (42.0%)	41 (46.1%)	0.257‡ (1)	.612
	Negative	88 (55.7%)	40 (58.0%)	48 (53.9%)		

(*continued on next page*)

Table 1 (*Continued*)

Variables	Categories/details	Total study population (N = 158)	CT-alone cohort (N = 69)	CTRT cohort (N = 89)	CT-alone vs CTRT cohort test statistic (df)	CT-alone vs CTRT cohort *P* value (2 tailed)*
Lympho-vascular space invasion	Positive	94 (59.5%)	33 (47.8%)	61 (68.5%)	6.920‡ (1)	.009*
	Negative	64 (40.5%)	36 (52.2%)	28 (31.5%)		
Involvement of margins	Positive	16 (10.1%)	7 (10.1%)	9 (10.1%)	0.000‡ (1)	NA‖
	Negative	142 (89.9%)	62 (89.9%)	80 (89.9%)		

Abbreviations: CT = chemotherapy; CTRT = chemoradiation therapy; df = degree of freedom; ECE = extracapsular extension; GEJ = gastroesophageal junction; NA = not applicable.

* $P \leq .05$ was considered significant.

† *t*-Test statistic using independent samples *t* test. Equal variance assumed because Levene's test for equality of variances had a *P* value more than .05 ($P = .271$).

‡ Pearson χ^2 test.

§ Because >20% of cells had an expected count of less than 5, the Fisher-Freeman-Halton exact test was applied. The df is not reported with this test.

‖ Because there was no difference in the proportion of positive results in the 2 groups, *P* value was not applicable.

better RFS in the CTRT cohort and showed an 84.0% lower hazard of recurrence in this cohort (HR, 0.161; 95% CI, 0.056-0.464; $P < .001$). This analysis also showed that age, positive lymph nodes without ECE, lymph node-negative, and the type of adjuvant therapy were significantly associated with RFS (Table 3). No additional analysis was carried out for any subcohorts and interactions. No sensitivity analyses were performed.

Discussion

In our study, the CTRT cohort showed lower locoregional recurrence, higher distant metastasis, and significantly higher RFS, whereas no significant difference in OS was observed in the 2 cohorts. Many clinical trials have assessed the advantages of adjuvant therapies. The Southwest Oncology Group Directed Intergroup Study 0116 (INT-0116) compared adjuvant CTRT with surgery alone. The trial demonstrated a statistically significant OS and RFS advantage of adjuvant CTRT,[15] which was maintained even after 10 years, as shown in the updated results of the same patient cohort.[18] However, the trial also reported certain toxicities due to radiation therapy, because of which 17.0% of the 281 enrolled patients could not complete the postoperative protocol treatment.[16,19] In contrast, all the patients in the CTRT cohort of our study could complete the study protocol with mild adverse events. This could be because of the more advanced technique of IMRT used in our center. Additionally, 90.0% of patients enrolled in the INT-0116 study did not undergo D2 lymph node dissection, which triggered the debate around whether the same survival advantage could have been achieved with D2 dissection.[16,18,19] Comparatively, all the patients in our current study underwent D2 dissection.

Another trial, ARTIST 1, compared adjuvant CT with CTRT in patients who had undergone D2 gastrectomy. The trial concluded that the addition of radiation therapy did not significantly reduce recurrence. Although, on a subgroup analysis that was not prespecified, a subset of the trial participants who had involvement of lymph nodes showed significantly better RFS after CTRT, with no advantage in OS.[11] To further clarify the advantage of CTRT in patients with worse tumor characteristics, the ARTIST 2 trial compared the adjuvant CTRT with 2 adjuvant CTs in D2-dissected patients who had lymph node involvement and stage II/III at baseline. The trial concluded that there was no additional significant benefit of administering adjuvant radiation therapy with CT in reducing recurrence in any subset of patients. However, even this trial had limitations. One of its limitations was that it recruited fewer patients than planned (546 patients rather than 900), which reduced the statistical power of the study. Furthermore, early reporting of disease-free survival performed in the trial could have led to an

Table 2 Recurrence and survival data comparison between the followed-up patients of the 2 cohorts

Variable categories	Total study population (N = 158)	CT-alone cohort (N = 69)	CTRT cohort (N = 89)	CT-alone vs CTRT cohort test statistic (df)	CT-alone vs CTRT cohort *P* value (2 tailed)*
Recurrence	(n = 76)	(n = 33)	(n = 43)	4.988†	.095
Locoregional recurrence	9 (11.8%)	7 (21.2%)	2 (4.7%)		
Lymph node	9	7	2		
Distant metastasis	4 (5.3%)	1 (3.0%)	3 (7.0%)		
Bone	1	1	0		
Brain	1	0	1		
Lung	1	0	1		
Omentum	1	0	1		
No recurrence	63 (82.9%)	25 (75.8%)	38 (88.3%)		
Survival status	(n = 76)	(n = 33)	(n = 43)	0.789*,‡ (1)	.374
Alive	44 (57.9%)	21 (63.6%)	23 (53.5%)		
Locoregional recurrence	4	3	1		
Distant metastasis	1	0	1		
No recurrence	39	18	21		
Dead	32 (42.1%)	12 (36.4%)	20 (46.5%)		
Locoregional recurrence	5	4	1		
Distant metastasis	3	1	2		
No recurrence	24	7	17		

Abbreviations: CT = chemotherapy; CTRT = chemoradiation therapy; df = degree of freedom.

* $P \leq .05$ was considered significant.

† Because >20% of cells had an expected count of less than 5, the Fisher-Freeman-Halton exact test was applied. The df is not reported with this test.

‡ Pearson's χ^2 test.

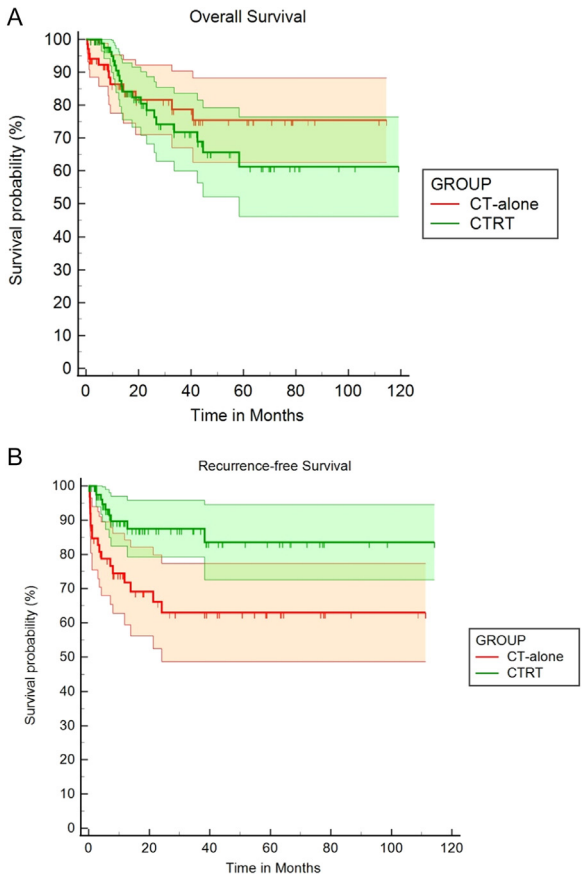

Figure 3 Kaplan-Meier plots of the 2 cohorts. (A) Overall survival comparison in chemotherapy-alone and chemo radiation therapy cohorts. (B) Recurrence-free survival comparison in chemotherapy-alone and chemo radiation therapy cohorts.

overestimation of the treatment effect of the evaluated modalities. Moreover, only 178 disease-free survival events reported during the trial necessitated an additional period of follow-up to substantiate the conclusion, which could not be ensured in a clinical trial setting.[12] Another limitation reported in the ARTIST 2 trial was that despite having prespecified subgroups in the protocol, the study could not enroll participants accordingly.[12] Compared with the ARTIST 2 trial, the current study enrolled a comprehensive patient population and had a long study period. Moreover, the current study used a modern technique of administering IMRT in all patients and showed a significant reduction in recurrence in the CTRT cohort despite the worse tumor characteristics.

Another crucial, multicentric trial, CRITICS 1, compared perioperative CT with neoadjuvant CT and adjuvant CTRT in D1+ dissection. Adjuvant CTRT did not improve OS in this trial,[13] which is similar to the findings of our study. Further, ongoing trials CRITICS 2 and TOPGEAR aim to optimize perioperative, neoadjuvant, and adjuvant therapies to yield better outcomes in patients with stomach adenocarcinoma.[20,21]

The findings of the clinical trials raise a concern regarding adding radiation therapy to the adjuvant therapy because it carries increased toxicity without any evidence of benefit in OS. Although RCTs are the gold standard for evaluating the efficacy and safety of a treatment modality,[22] they suffer from limitations such as stricter eligibility criteria, leading to reduced generalizability, shorter follow-up period, and lack of information on effectiveness. Besides, the study population of a clinical trial may not be representative of the target population that avails the treatment modality in clinical practice. Furthermore, the rigid protocol followed in clinical trials does not reflect the standard of care in routine practice. RWE studies help to overcome the limitations of RCTs.

The current study was designed as an RWE study. It had less strict inclusion criteria and a 10-year-long follow-up time. A pragmatic approach was adopted for decision-making for treatment modalities. The decision on the type of adjuvant therapy was made through the existing process of discussion in the MDT board meeting. Adjuvant CT in the CT-alone cohort was administered based on the judgment of the medical oncologist within the framework of the guidelines. No additional clinical procedure was carried out because of the study, besides the routine clinical practice of the institute. For the patients who could not visit the hospital for a follow-up, the study team conducted interviews by telephone. Another strength of the current study was that the care provided to the participants was advanced as per the current time. All the patients enrolled in the current study underwent D2 dissection and received radiation therapy in the CTRT cohort using IMRT.

However, the current study was not without limitations. It used secondary data that were collected retrospectively by various care providers. Furthermore, although the study hospital caters to patients from many Indian states and neighboring countries, the results of this study cannot be generalized over the entire population, as the data were collected from only 1 hospital.

Another limitation of the study was that the 2 cohorts were not comparable at baseline concerning tumor characteristics, where CTRT was offered to patients with worse tumor characteristics and CT alone was offered to patients with better tumor characteristics. Selection bias is inherent in a real-world study, because we are not able to "randomize" the participants in 2 arms. The fact that the study enrollment was not based on rigid criteria helped in making the study population representative of the target population that avails the treatment modality in clinical practice. Additionally, the study could reflect the preferences of the practitioners, where they prescribe adjuvant CTRT to patients with worse tumor characteristics, which is indicative of more trust in this modality over CT alone, and needs a RWE study design to validate the same.

Table 3 Cox proportional-hazards regression analysis of the overall survival and recurrence-free survival of patients

Variables	Overall survival				Recurrence-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value*	HR (95% CI)	*P* value*	HR (95% CI)	*P* value*	HR (95% CI)	*P* value*
Age	0.991 (0.962, 1.021)	.539	1.002 (0.971, 1.035)	.885	1.026 (0.992, 1.061)	.138	1.040 (1.001, 1.080)	.042*
Sex								
Male†								
Female	1.890 (0.945, 3.781)	.072	1.751 (0.709, 4.323)	.225	0.782 (0.342, 1.786)	.559	0.994 (0.349, 2.828)	.991
Tumor location								
Antro-pyloric†								
GEJ	0.795 (0.184, 3.433)	.759	0.679 (0.133, 3.461)	.642	0.557 (0.074, 4.211)	.571	0.630 (0.068, 5.834)	.684
Fundus	1.486 (0.667, 3.313)	.333	1.906 (0.811, 4.480)	.139	0.835 (0.306, 2.279)	.725	0.640 (0.197, 2.075)	.457
Cardia	1.071 (0.315, 3.638)	.912	1.144 (0.284, 4.601)	.850	1.978 (0.724, 5.405)	.183	1.170 (0.298, 4.590)	.822
Tumor type								
Intestinal	0.796 (0.300, 2.113)	.647	0.808 (0.248, 2.630)	.723	0.654 (0.222, 1.925)	.441	1.391 (0.375, 5.168)	.622
Diffuse	0.634 (0.256, 1.572)	.325	0.494 (0.169, 1.441)	.196	0.327 (0.097, 1.108)	.073	0.525 (0.129, 2.131)	.367
Mixed	0.000 (0.000)	.981	0.000 (0.000, 2.604E +174)	.959	0.633 (0.085, 4.734)	.656	0.000 (0.000, 1.168E +244)	.968
Undifferentiated†								
Pathologic stage								
I†								
II	76,736.942 (0.000, 1.925E +95)	.916	74,109.659 (0.000, 1.761E +85)	.905	3.135 (0.366, 26.870)	.297	2.756 (0.263, 28.865)	.398
III	93,691.244 (0.000, 2.349E +95)	.914	66,178.417 (0.000, 1.573E +85)	.906	7.685 (1.031, 57.289)	.047*	5.765 (0.550, 60.379)	.144
Grade								
1	0.000 (0.000)	.976	0.000 (0.000, 1.185E +136)	.942	0.473 (0.030, 7.586)	.597	0.273 (0.013, 5.544)	.398
2	0.585 (0.129, 2.641)	.485	0.224 (0.037, 1.354)	.103	0.853 (0.108, 6.739)	.880	0.106 (0.010, 1.152)	.065
3	0.606 (0.141, 2.603)	.500	0.242 (0.045, 1.310)	.100	0.866 (0.114, 6.561)	.889	0.248 (0.027, 2.277)	.218
4	0.000 (0.000)	.992	0.063 (0.000)	.996	4.477 (0.277, 72.286)	.291	16,022.996 (0.000, 2.147E +253)	.974

(*continued on next page*)

Table 3 (*Continued*)

Variables	Overall survival				Recurrence-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value*	HR (95% CI)	*P* value*	HR (95% CI)	*P* value*	HR (95% CI)	*P* value*
Unknown†								
Involvement of lymph nodes								
Positive lymph nodes with ECE†								
Positive lymph nodes without ECE	0.800 (0.364, 1.759)	.579	0.737 (0.322, 1.688)	.471	0.504 (0.201, 1.264)	.144	0.360 (0.132, 0.981)	.046*
Lymph node-negative (not involved)	0.230 (0.068, 0.775)	.018*	0.285 (0.058, 1.401)	.122	0.147 (0.034, 0.632)	.010*	0.093 (0.014, 0.630)	.015*
Perineural invasion								
Positive†								
Negative	0.543 (0.270, 1.094)	.088	1.020 (0.443, 2.346)	.963	0.499 (0.233, 1.071)	.074	0.562 (0.197, 1.602)	.281
Lympho-vascular space invasion								
Positive†								
Negative	0.538 (0.249, 1.164)	.115	1.472 (0.542, 3.996)	.448	0.596 (0.261, 1.362)	.220	1.793 (0.535, 6.001)	.344
Involvement of margins								
Positive†								
Negative	0.584 (0.225, 1.520)	.271	0.470 (0.156, 1.416)	.180	0.559 (0.193, 1.619)	.284	0.870 (0.264, 2.867)	.819
Adjuvant treatment								
Chemotherapy alone†								
Chemo radiation therapy	1.208 (0.590, 2.473)	.606	0.908 (0.394, 2.094)	.822	0.326 (0.146, 0.726)	.006*	0.161 (0.056, 0.464)	<.001*

Abbreviations: CI = confidence interval; ECE = extracapsular extension; GEJ = gastroesophageal junction; HR = hazard ratio.

* $P \leq .05$ was considered significant.

† Reference category.

Further, the complete study population could never reach the median OS (Fig. E1A) or the median RFS (Fig. E1B) during the study period. Moreover, a higher number of total patients were lost to follow-up, although loss to follow-up was similar in both cohorts. Some of the possible reasons for the high number of patients lost to follow-up can be a change in phone number, a long distance from the study site, seeking follow-up care in other hospitals nearer to their hometowns, and the COVID-19 pandemic. The study being a real-world study, loss of data is anticipated by design, because the procedure of follow-up was pragmatic, unlike an RCT, where the retention of participants is better. Still, we could draw meaningful conclusions from the available data using censoring methods in survival analysis.

Despite all limitations, the study generated RWE for the use of adjuvant CTRT in patients with stomach adenocarcinoma undergoing D2 dissection and demonstrated the use of RWE studies in the future course of evidence generation for establishing the long-term effectiveness of various treatment modalities.

Conclusion

The current study showed that the CTRT cohort had a significantly higher RFS than the CT-alone cohort without severe adverse events during therapy. Further, the CTRT cohort showed similar OS to the CT-alone cohort, despite worse tumor characteristics. Based on these results, we conclude that patients who receive CTRT using IMRT after D2 dissection during surgery have a better clinical outcome than those who receive CT alone, although the findings of this retrospective cohort study need to be confirmed by future RWE studies and RCTs.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101280.

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