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ORIGINAL ARTICLE

Chemotherapy Versus Chemotherapy Followed by Concurrent Chemoradiotherapy for Unresectable Locally Advanced Pancreatic Cancer; A Retrospective Study

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ABSTRACT

Background: Pancreatic cancer remains one of the deadliest cancers, often diagnosed during the advanced stage because of its vague symptoms. In Egypt, it represents a significant health burden with rising incidence. Locally advanced pancreatic cancer (LAPC), which is unresectable but without distant spread, is challenging to manage. There's still debate on whether adding concurrent chemoradiotherapy (CCRT) after chemotherapy offers additional benefit over chemotherapy alone. The aim of this study was to compare the outcomes of chemotherapy alone (CTA) versus chemotherapy followed by CCRT (CTA+CCRT) among patients with unresectable LAPC.

Methods: This retrospective study was carried out on 66 patients who had unresectable LAPC treated between 2017 and 2022 at two oncology centers in Egypt. Patients were categorized into two groups: cases who received only gemcitabine-based chemotherapy (CTA group), and cases who received induction chemotherapy followed by radiotherapy with concurrent oral capecitabine (CTA+CCRT group). We evaluated treatment response, survival, resectability, and side effects.

Results: The CTA+CCRT group had significantly better progression-free survival (11 vs. 4 months, p = 0.000) and overall survival (15 vs. 11 months, p = 0.000) compared to the CTA group. Complete response was significantly higher in the CTA+CCRT group (18.2% vs. 6.1%, p = 0.045), and lymph node involvement was significantly lower (33.3% vs. 63.6%, p = 0.014). Post-treatment CA 19.9 normalization was significantly associated with resectability in the CTA+CCRT group (p = 0.013). Toxicities were comparable between groups.

Conclusions: Chemoradiotherapy demonstrates significant clinical benefit in managing of locally advanced pancreatic cancer as it improves local tumor control, decreases lymph node involvement, and enhances both overall survival in addition to the progression-free survival, along with increasing tumor resectability.

Keywords: Chemotherapy; Concurrent Chemoradiotherapy; Unresectable; Advanced Pancreatic Cancer

INTRODUCTION

Pancreatic cancer is recognized as one of the most lethal and aggressive malignancies worldwide. It ranks as the 12th most frequently diagnosed cancer, with an estimated 510,992 cases globally, and is the

7th leading cause of mortality related to cancers, with rising incidence particularly noted in Asia [1].

A concerning trend is the expanding diagnosis of pancreatic cancer among younger individuals. The disease is often asymptomatic in its early stages, facilitating rapid invasion into adjacent tissues and organs. There are no hallmark symptoms, but patients may present with nonspecific features such as unexplained weight loss, abdominal pain, or obstructive jaundice. Due to this silent progression, most cases are diagnosed during the advanced stage, resulting in dismal five-year survival rates ranging between 2% and 9% [2]. Among Egypt's cancers, 2.2% are pancreatic cancers and 3.2% are cancer-related fatalities; it is the eleventh most common malignancy overall [3].

Smoking, heavy drinking, and a history of chronic pancreatitis are the classic causes of pancreatic cancer. Emerging research has also identified potential roles for metabolic disorders, dysbiosis of the gut microbiota, blood group type, and abnormal glucose and lipid profiles in increasing risk [4].

Initial diagnostic assessment includes evaluation of symptoms, physical examination, and performance status. Imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) are commonly employed. When a pancreatic mass is suspected, tissue diagnosis is typically pursued using endoscopic ultrasound (EUS) or endoscopic retrograde cholangiopancreatography (ERCP). Also, laboratory markers such as carbohydrate antigen 19-9 (CA 19-9) are used for prognostication and assessment of surgical resectability [5].

Less than 20% of patients meet the criteria for curative surgical resection when they appear. Locally advanced pancreatic cancer (LAPC) affects around 30% of individuals, meaning that there is no proof of distant metastases [6].

Unresectable disease is classified into LAPC and borderline resectable pancreatic cancer (BRPC). LAPC is characterized by tumor involvement of critical arteries such as the celiac axis or superior mesenteric artery (SMA), or occlusion of key venous structures like the portal or superior mesenteric veins. BRPC involves less than 50% circumferential involvement of the SMA or celiac axis, abutment or short-segment encasement of the common hepatic artery or limited venous occlusion. In contrast to patients with resectable disease (Stages I and II), who may undergo surgery upfront or after neoadjuvant therapy, those with BRPC are generally considered at high risk for occult metastases and margin-positive resections. Hence, international guidelines advocate for induction therapy prior to surgical intervention in this group [7].

The current standard of care for localized pancreatic cancer involves surgical resection followed by systemic chemotherapy. However, upfront surgery is not optimal for patients with major vascular involvement, as seen in BRPC and LAPC [8].

Neoadjuvant chemotherapy, using regimens like FOLFIRINOX or gemcitabine combined with nab-paclitaxel, that has become common practice. This is often followed by concurrent chemoradiotherapy (CCRT). Decisions regarding therapy sequencing and surgical candidacy are based on anatomical tumor extent, biological markers, and the patient's overall functional status [9]. The present work aimed to compare the outcomes of chemotherapy alone (CTA) versus chemotherapy followed by CCRT (CTA+CCRT) in patients with unresectable LAPC.

METHODS

This retrospective study was performed at the Department of Clinical Oncology and

Nuclear Medicine, Zagazig University Hospitals, and Mit Ghamer Oncology Center. We included patients who had locally advanced, unresectable pancreatic adenocarcinoma who were managed between January 2017 and January 2022. Following approval from the institutional review board (ZU-IRB#539/25-8-2024), written informed consent was obtained from every participant. Ethical standards for research with human subjects as stated in the Declaration of Helsinki and the Code of Ethics of the World Medical Association were followed throughout the course of the study.

We included 66 patients who met the eligibility criteria. The patients were eligible if they had histologically confirmed pancreatic adenocarcinoma and radiological evidence of locally advanced disease that was not amenable to complete surgical resection. All patients were above 18 years of age at the diagnosis time. Patients with metastatic disease, local recurrence, other malignancies, or those who undergone definitive surgical resection were excluded from the analysis.

Patients were categorized into two treatment groups based on the therapeutic approach received. The first group involved cases who were treated using chemotherapy alone as the CTA group. The second group involved cases who underwent induction chemotherapy then followed by concurrent chemoradiotherapy, forming the CTA+CCRT group. Patients in both groups received gemcitabine-based chemotherapy protocols. In the CTA group, the regimens included single-agent gemcitabine, gemcitabine-carboplatin, gemcitabine-cisplatin, and gemcitabine-capecitabine. The chemotherapy cycles were administered every three or four weeks depending on the regimen. Premedications such as dexamethasone, 5HT3 receptor antagonists (ondansetron or granisetron), NK1 inhibitors, and antihistamines (diphenhydramine and ranitidine) were provided according to institutional guidelines.

Patients in the CTA+CCRT group received induction gemcitabine-based chemotherapy followed by concurrent radiotherapy and oral capecitabine. Capecitabine was administered at a dose of 850 mg/m² twice daily for five days per week over a period of five weeks. Radiotherapy was delivered using 3D conformal radiotherapy to a total dose of 50.4 Gy over six weeks in 28 fractions, using a high-energy linear accelerator. All patients were treated in a reproducible supine position with arms above the head for immobilization. CT simulation was performed using IV contrast with 5 mm slice thickness extending from the top of D9 to the lower border of L5. High-energy 6–10 MV photon beams were used, and multileaf collimators shaped the radiation fields to minimize exposure to the liver, kidneys, spinal cord, and small intestine.

From each patient's medical record, we collected the following clinical data: age, sex, presenting symptoms, diagnosis date, and performance status as measured by the Eastern Cooperative Oncology Group (ECOG) scale [10], and laboratory investigations including CA 19-9 levels. Histopathological confirmation was recorded, as well as baseline and follow-up imaging using CT or MRI of the abdomen as well as the pelvis. Additional imaging, including chest CT in addition to the bone scan, was performed when clinically indicated to rule out distant metastases. Detailed treatment information was collected, including chemotherapy agents, dosages, radiotherapy techniques, and concurrent chemotherapy protocols.

The primary endpoints of this study were objective response rate (RR), resectability after treatment, and pattern of disease failure

(local versus distant). The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [11] was used to assess tumor response. When all of the intended lesions disappeared, it was considered a complete response (CR). Any reduction of 30% or more in the total length of the target lesions was deemed a partial response (PR). If there was no change in tumor size that would be classified as progressive disease (PD), or if there was a 20% rise in the sum of the longest diameter compared to the smallest sum recorded after therapy began, then the disease was considered stable disease (SD).

Secondary endpoints involved progression-free survival (PFS) as well as overall survival (OS) in addition to the toxicity. The progression-free survival (PFS) period was defined as the time it took for the disease to either advance or recur after therapy began. Duration from diagnosis to death or final follow-up date was used to compute OS. We recorded and rated all treatment-related toxicities using the NCI-CTCAE version 4.0 standards, which are set out by the National Cancer Institute [11].

Statistical Analysis

Counts and percentages were used to summarize categorical data, whereas the distribution dictated the reporting of continuous data as mean ± SD or median with interquartile range. For categorical variables, we utilized chi-square tests, while for group comparisons we used t-tests or Mann-Whitney U tests. For non-parametric relationships, Spearman's correlation was used. For survival analysis, we utilized Kaplan-Meier and Cox regression. We regarded a p-value ≤0.05 to be significant. We used SPSS v22 to conduct our analyses.

RESULTS

Patient Characteristics

The two groups (CTA+CCRT and CTA) were well balanced with respect to age (mean 57.42 ± 9.71 vs. 57.42 ± 10.28 years; p = 1.000), sex distribution (male: 63.6% vs. 66.6%; p = 0.796), smoking status (p = 0.805), and performance status (p = 0.275). No significant differences were found between the groups regarding tumor site (head, body, tail; p = 0.841), tumor size (≤3 cm vs. >3 cm; p = 0.258), tumor grade (p = 0.850), baseline bilirubin levels (p = 0.800), or biliary stent placement (p = 0.800). However, lymph node involvement at baseline was significantly more frequent in the CTA group (63.6%) compared to the CTA+CCRT group (33.3%) (p = 0.014), reflecting a greater disease burden in the CTA group at presentation (Table 1).

Toxicities

Non statistically significant differences were revealed between the CTA+CCRT and CTA groups regarding hematological toxicities, including anemia (p = .12), leucopenia (p = .66), and thrombocytopenia (p = .90). Similarly, non-hematological side effects such as vomiting (p = .62), nausea (p = .74), diarrhea (p = .69), stomatitis (p = .29), abdominal pain (p = .75), and nephropathy (p = .43) showed no significant variation between groups, despite a numerically higher incidence of diarrhea and abdominal pain in the CTA+CCRT group (Table 2).

Treatment Response

The detailed treatment responses and overall outcomes are presented in Table 3. The CTA+CCRT group demonstrated higher complete response rates (18.2% vs. 6.1%; p = .045) and higher resectability rates (27.3% vs. 12.1%; p = .122) compared to CTA. Median overall survival and progression-free survival, calculated for each group, were also significantly better in the CTA+CCRT group (15 vs. 11 months for OS, p = .000; 11 vs. 4 months for PFS, p = .000)

Survival Outcomes

Median overall survival (OS) was significantly longer in the CTA+CCRT group at 15 months (interquartile range

[IQR]: 12.75–22.5) compared to 11 months (IQR: 5–17) in the CTA group (p = .000). Median progression-free survival (PFS) was also significantly longer for CTA+CCRT at 11 months (IQR: 6.75–15) versus 4 months (IQR: 3–8.5) for CTA (p = .000). Kaplan-Meier analysis further demonstrated a significant benefit for the CTA+CCRT group. The median time to local failure was 20 months (95% CI: 16.2–23.8) for CTA+CCRT versus 13 months (95% CI: 10.5–15.5) for CTA (p = .009). The median time to distant failure did not differ significantly between the groups: 26 months (95% CI: 17.2–34.8) for CTA+CCRT versus 23 months (95% CI: 15.6–30.4) for CTA (p = .387), although descriptive data suggest that local and combined failures appeared more frequently in the CTA group, formal statistical comparison was not performed due to missing data. As such, these findings should be interpreted with caution. Resectability was higher in the CTA+CCRT group (27.3% vs. 12.1%), with non-statistically significant variation (p = .122). More patients in the CTA+CCRT group proceeded to surgery (Table 4*).*

Resectability

In the CTA+CCRT group, tumor resectability was strongly correlated with post-treatment CA 19.9 levels (p = .013). Specifically, of the 13 patients with normalized post-treatment CA 19.9, 7 (53.8%) were resectable, while among the 20 patients with elevated CA 19.9, only 2 (10%) were resectable. In the CTA group, 9 patients had normalized post-treatment CA 19.9, of whom 3 (33.3%) were resectable, while among the 24 patients with elevated levels, only 1 (4.2%) was resectable. Although this trend was evident in both groups, statistical significance was achieved only in the CTA+CCRT group (p = .013 vs. p = .052 for CTA group) (Table 5).

Response to Chemotherapy

Treatment response varied significantly based on the chemotherapeutic regimen used (p = .020). Patients receiving Gemzar–cisplatin showed the most favorable outcomes, with a complete response in 20% and partial response in 50% of cases. In contrast, those treated with Gemzar alone had the poorest outcomes, with 77.8% experiencing progressive disease (Table 6).

Performance status and Correlations

Poorer performance status was strongly and significantly associated with shorter overall survival (rho = –0.637, p = .000) as well as progression-free survival (rho = –0.570, p = .000). Elevated baseline CA 19.9 levels showed a significant inverse correlation with overall survival (rho = –0.460, p = .000) and a weaker but significant association with progression-free survival (rho = –0.293, p = .046). Post-treatment CA 19.9 levels demonstrated the strongest negative correlation with both overall survival (rho = –0.644, p = .000) as well asprogression-free survival (rho = –0.483, p = .001) (Table 7).

Prognostic Factors for Overall Survival

In the univariate model; CT+CCRT line of treatment (HR=.487; 95% CI, .297-.798; P=.004), Negative lymph node involvement (HR=.617; 95% CI,.366-1.040; P=.07), normal bilirubin levels (HR=.545;95% CI, .328-.907; P=.020), and no stent (HR=.545;95% CI, .328-.907; P=.020) were associated with better Overall survival. Performance status 0, 1 &2 were associated with better overall survival (HR= .064; 95% CI, .017-.241; P=.000* - HR=.097; 95% CI, .027-.353; P=.000* - HR= .282; 95% CI, .081-.984; P=.047 respectively) (Supplementary Table 1).

The multivariate model of CT+CCRT (HR= 0.218; 95% CI=.111-.427; P=.000) was also associated with better OS. Performance status 0 &1 were associated with better overall survival (HR=.056; 95% CI, .012-.252; P=.000* - HR=.107; 95% CI, .024-.468; P=.003* respectively) (Supplementary Table 1)

Table 1: Clinical and Clinico pathological characteristics of the Patients studied (N=66)

Variable	CTA+CCRT	CTA	P-value
Age (Years)	57.42±9.71	57.42±10.28	1.000ţ
Age Groups			
30-<40	1(3%)	1(3%)	.075X
40-<50	7(21.2%)	9(27.3%)	
50-<60	11(33.3%)	12(36.4%)	
60-<70	14(42.4%)	6(18.2%)	
>=70	0(0%)	5(15.2%)	
Sex			
Male	21 (63.6%)	22 (66.6%)	.796 X
Female	12 (36.3%)	11 (33.3%)	
Smoking			
Non-smoker	15 (45.5%)	16 (48.5%)	.805X
Smoker	18 (54.5%)	17 (51.5%)	
Performance status (PS)			
0	10(30.3%)	7(21.2%)	
1	13(39.4%)	11(33.3%)	
2	10(30.3%)	12(36.4%)	.275X
3	0(0%)	3(9.1%)	
Total	33	33	66
Site			
Head	20 (60.6%)	22 (66.7%)	.841X
Body	9 (27.3%)	7 (21.2%)	
Tail	4 (12.1%)	4 (12.1%)	
Size (CM)(T)			
<=3	6 (18.2%)	2 (6.1%)	.258f
>3	27(81.8%)	31(93.9%)	
LN involvement(N)			
Yes	11 (33.3%)	21 (63.6%)	**.014***X
No	22 (66.7%)	12 (36.4%)	
Grade			
1	7(21.2%)	7(21.2%)	0.850X
2	17(51.5%)	15(45.5%)	
3	9(27.3%)	11(33.3%)	
Bilirubin			
Normal	21(63.6%)	20(60.6%)	.800X
Elevated	12(36.4%)	13(39.4%)	
Stent			
Yes	12(36.4%)	13(39.4%)	.800X
No	21(63.6%)	20(60.6%)	
Total	33 (100%)	33 (100%)	66

Variables are expressed as Mean ±SD, ţ Independent t test, X Chi-square test

Table 2: Hematological and non-hematological side effects in the studied patients

Hematological side effects	CTA+CCRT (n=33)	CTA (n=33)	P-value
Anemia			
G1	18 (54.5%)	12 (36.3%)	.12[X]
G2	10 (30.3%)	11 (33.3%)	
G3	0 (0%)	3 (9.1%)	
Leucopenia			
G1	6 (18.2%)	8 (24.2%)	.66[X]
G2	6 (18.2%)	7 (21.2%)	
G3	0 (0%)	1 (3%)	
Thrombocytopenia			
G1	10 (30.3%)	13 (39.4%)	.9[X]
G2	5 (15.2%)	7 (21.2%)	
G3	0 (0%)	0 (0%)	
Non- Hematological side effects	**CTA+CCRT (n=33)**	**CTA (n=33)**	**P-value**
Vomiting			
G1	5 (15.2%)	8 (24.2%)	.62x
G2	3 (9.1%)	3 (9.1%)	
G3	0 (0%)	1 (3%)	
Nausea			
G1	12 (36.4%)	10 (30.3%)	.74x
G2	7 (21.2%)	5 (15.2%)	
G3	3 (9.1%)	1 (3%)	
Diarrhea			
G1	10 (30.3%)	3 (9.1%)	.69[X]
G2	6 (18.2%)	1 (3%)	
G3	2 (6.1%)	0 (0%)	
Stomatitis			
G1	4 (12.1%)	3 (9.1%)	.29[X]
G2	2 (6.1%)	5 (15.2%)	
Abdominal pain			
G1	16 (48.5%)	9 (27.3%)	.75[X]
G2	9 (27.3%)	4 (12.1%)	
Nephropathy			
G1	4 (12.1%)	3 (9.1%)	.43[X]
G2	1 (3%)	0 (0%)	

X Chi-square test

Table 3: Response to treatment in the studied Patients (N=66)

	CTA+CCRT	CTA	P-value
Ca 19.9			
Baseline	215 (92-1322.5)	285(73-809.5)	.888μ
After treatment	82(15-909.5)	189(32.5-836)	.218μ
Overall survival (Months)	15(12.75-22.5)	11(5-17)	**.000*μ**
Progression-free survival	11(6.75-15)	4(3-8.5)	**.000*μ**
Response			
Complete response	6 (18.2%)	2 (6.1%)	**.045*X**
Partial response	11 (33.3%)	6 (18.2%)	
stable disease	10(30.3%)	9(27.3%)	
Progressive disease	6(18.2%)	16(48.5%)	
Pattern of failure			
Local	4(12.1%)	7(21.2%)	
Distant	15(45.5%)	10(30.3%)	
Local, Distant	3(9.1%)	8(24.2%)	
Resectability			
Yes	9 (27.3%)	4 (12.1%)	.122X
No	24 (72.7%)	29 (87.9%)	

Variables expressed as Median (IQR)

X Chi-square test, μ Mann Whitney U test

*** Statistically significant (p < .05)**

Table 4: Overall survival and progression-free survival by treatment group

Months	CTA+CCRT		CTA		P-value
	Median survival time (Month)	95% CI	Median survival time (Month)	95% CI	
Progression-free survival (95% CI)	10	(5.4-14.6)	4	(1.6-6.5)	**.000***
Overall survival (95% CI)	20	(15.5-24.5)	11	(7.8-14.2)	**.002***
Time to local failure (95% CI) (n=47)	20	(16.2-23.8)	13	(10.5-15.5)	**.009***
Time to Distant failure (n=25)	26	(17.2-34.8)	23	(15.6-30.4)	.387

Table 5: Resectability in relation to post-treatment level of CA 19.9

	CTA+CCRT			P-value	CTA			P-value
	Post-treatment CA19.9				Post-treatment CA19.9			
	Normal	Elevated	Total		Normal	Elevated	Total	
Resectable	7 (77.8%)	2 (22.2%)	9 (100%)	.013*F	3 (75%)	1 (25%)	4 (100%)	.052F
Non-resectable	6 (25%)	18 (75%)	24 (100%)		6 (20.7%)	23 (79.3%)	29 (100%)	
Total	13	20	33 (100%)		9	24	33 (100%)	

F Fisher exact test

Table 6: Patients' response in relation to chemotherapeutic agent

	Gem cisplatin	Gemzar carboplatin	Gemzar 5 fu	Gemzar single agent	P-value
Complete response	2 (20%)	0 (0%)	0 (0%)	0 (0%)	**.020*[x]**
Partial response	5 (50%)	0 (0%)	1 (20%)	0 (0%)	
Stable disease	2 (20%)	4 (44.4%)	1 (20%)	2 (22.2%)	
Progressive disease	1 (10%)	5 (55.6%)	3 (60%)	7 (77.8%)	
Total	10 (100%)	9 (100%)	5 (100%)	9 (100%)	33

[x] Chi-square test

Table 7: Spearman's correlation between Overall survival, Progression-free survival and clinical, laboratory and pathological characteristics of the tumor in the studied Patients (N=66)

		Overall survival	Progression-free survival
Age	rho	-.266	-.177
	P-value	**.031***	.234
Performance status	rho	-.637	-.570
	P-value	**.000***	**.000***
Size	rho	-.005	.264
	P-value	.967	.073
Baseline Ca19.9	rho	-.460	-.293
	P-value	**.000***	**.046***
Ca19.9 after treatment	rho	-.644	-.483
	P-value	**.000***	**.001***
Grade	rho	-.505	-.277
	P-value	**.000***	.059

DISCUSSION

Several retrospective studies have examined the strategy of administering chemoradiotherapy (CRT) following induction chemotherapy (CT) in patients without disease progression, suggesting improved outcomes compared to CT alone or upfront CRT [12]. Consolidation CRT using capecitabine as a radiosensitizer at 50.4–54 Gy over 28–30 fractions is now an established approach for treating LAPC [13].

In our study, the mean age was identical in both groups (57.42 ± 9.71 years for CTA+CCRT vs. 57.42 ± 10.28 years for CTA; p=1.000), comparable to Amini et al. [14] (63.1 vs. 62.3 years, p=0.00), Wu et al. [15] (median 59.6 years), and Ibrahim et al. [16] (median 55 years, p=0.722). Choi et al. [17] also found most patients were aged 50–60 (p=0.577).

Sex distribution showed no significant difference (p=0.796), with males comprising 63.6% in CTA+CCRT and 66.6% in CTA. Similar male predominance was reported by Amini et al. [14], Wu et al. [15], and Ibrahim et al. [16].

Lymph node involvement was significantly lower in the CTA+CCRT group (33.3%) than

in the CTA group (63.6%, p=0.014), unlike the findings of Ibrahim et al. [16] and Choi et al. [17], who reported no significant differences. Tumors were predominantly found in the pancreatic head in both groups (60.6% vs. 66.7%, p=0.841), consistent with Ibrahim et al. [16]. Most tumors were larger than 3 cm (81.8% vs. 93.9%, p=0.258), similar to the findings by Choi et al. [17], reflecting the aggressive nature of LAPC.

The distribution of tumor grade was similar between groups in our study (p=0.850). Ibrahim et al. [16] also observed no significant difference in tumor grade (p=0.933). However, Amini et al. [14] highlighted a more notable role of tumor grade in influencing treatment outcomes.

Non statistically significant differences were found in bilirubin levels or biliary stent placement (p=0.800 for both) between the treatment groups in our cohort. These findings agree with those of Wu et al. [15] and Ibrahim et al. [16], indicating that these factors are not key determinants in the selection of treatment modality in LAPC.

There were no statistically significant differences in the incidence or severity of hematological toxicities (such as anemia, leucopenia, or thrombocytopenia) between the CTA+CCRT and CTA groups. Grade 1 anemia was more frequently observed in the CTA+CCRT group (54.5% vs. 36.3%, p=0.12), while grade 3 anemia occurred only in the CTA group (9.1%). Similar non-significant trends were seen for other hematological side effects. Wu et al. [15] also reported higher hematologic toxicity with chemotherapy alone compared to combined chemoradiotherapy.

Regarding non-hematological side effects, such as vomiting, nausea, diarrhea, stomatitis, and abdominal pain, there were no statistically significant differences between the two groups. Although the CTA+CCRT group showed numerically higher rates of diarrhea and abdominal pain, these differences did not reach statistical significance. These findings are consistent with those of Wu et al. [15] and Ibrahim et al. [16], who also reported comparable rates of GI toxicity between regimens.

The current study findings revealed significantly improved overall survival (OS) and progression-free survival (PFS) in the CTA+CCRT group compared to CTA alone, with median OS of 15 vs. 11 months ($p = 0.000$) and PFS of 11 vs. 4 months ($p = 0.000$). These results align with other reports, such as Choi et al. [17] (median OS: 15.4 vs. 9.3 months), Ibrahim et al. [16] (OS: 16 vs. 10 months; PFS: 12 vs. 5 months), and Wu et al. [15] (OS: 18.1 vs. 8.9 months; PFS: 10.3 vs. 8.9 months), all of which demonstrated improved outcomes with the addition of CCRT.

Amini et al. [14] further confirmed improved OS with CCRT (HR: 0.85; 95% CI: 0.80–0.89; $p < 0.001$), with 1- and 2-year OS rates of 46.9% and 13.6% in the CCRT group compared to 40.2% and 12.8% in the CT group.

In contrast, Arcelli et al. [18] found non-significant variations in OS among patients treated with chemotherapy, CRT, or SBRT alone (median OS: 10.0 vs. 11.8 vs. 14.0 months; $p = 0.323$), highlighting the variability in treatment outcomes based on regimen and sequencing.

The current study findings showed a significantly higher complete response rate in the CTA+CCRT group (18.2% vs. 6.1%; $p = 0.045$), along with higher partial response rates (33.3% vs. 18.2%), consistent with Choi et al. [17], who reported superior responses with chemoradiotherapy.

Resectability was also higher in the CTA+CCRT group (27.3% vs. 12.1%; $p = 0.122$), aligning with Ibrahim et al. [16], who observed increased resectability after chemoradiotherapy (30% vs. 15%; $p = 0.05$), suggesting potential benefits for surgical candidacy in LAPC.

Distant failure remained more common than local failure in both groups (45.5% vs. 30.3%). Local failures were higher in the CTA group (21.2% vs. 12.1%). These findings echo Choi et al. [17] and Wu et al. [15], who noted improved local control with radiotherapy but limited effect on distant metastases. Arcelli et al. [18] further supported this by showing better local control with SBRT compared to CRT or CT alone (HR: 0.46; 95% CI: 0.25–0.83; p = 0.011).

Post-treatment CA 19-9 normalization was significantly associated with resectability. In the CTA+CCRT group, 77.8% of patients who had normalized CA 19-9 underwent surgery versus 25% with elevated levels (p = 0.013). Similarly, in the CTA group, resectability was 75% in those with normalized markers compared to 20.7% with persistent elevation (p = 0.052). These findings support Ibrahim et al. [16], who identified CA 19-9 normalization as a predictor of conversion to resectable status, reinforcing its value as a treatment response biomarker in LAPC.

Gemcitabine–cisplatin achieved the highest complete response (CR), with no CR seen in gemcitabine–carboplatin, gemcitabine–5-FU, or gemcitabine monotherapy (p = 0.020). Partial response (PR) was also highest in the gemcitabine–cisplatin group (50%), while stable disease (SD) was more frequent with gemcitabine–carboplatin (44.4%) and gemcitabine alone (22.2%). Progressive disease (PD) was most common with gemcitabine monotherapy (77.8%) and gemcitabine–carboplatin (55.6%).

These results align with Ibrahim et al. [16], who found superior response rates with gemcitabine–cisplatin versus monotherapy (p < 0.05). In contrast, Choi et al. [17] reported no significant differences across gemcitabine-based regimens, likely due to protocol and population differences.

Prognostic factors identified in this study included performance status (P = 0.000 for OS and PFS), baseline CA 19-9 levels (P = 0.000 for OS; P = 0.046 for PFS), and post-treatment CA 19-9 levels (P = 0.000 for OS; P = 0.001 for PFS). Tumor grade also significantly predicted OS (P = 0.000), while its impact on PFS was marginal (P = 0.059). These findings align with those reported by Ibrahim et al. [16], who found that CA 19-9 normalization post-treatment correlated with improved resectability and survival (P < 0.05). Wu et al. [15] similarly identified performance status and CA 19-9 levels as key prognostic markers.

CTA+CCRT significantly reduced the risk of death (HR = 0.487, 95% CI: 0.297–0.798, P = 0.004 in univariate; HR = 0.336, 95% CI: 0.189–0.596, P = 0.000 in multivariate analysis). Elevated post-treatment CA 19-9 was significantly associated with worse OS (HR = 1, P = 0.000 in univariate; HR = 1, P = 0.008 in multivariate analysis). Ibrahim et al. [16] demonstrated similar results, emphasizing CA 19-9 normalization post-treatment as a predictor for longer survival and higher resectability. Amini et al. [14] also identified CA 19-9 levels following therapy as a strong prognostic indicator in LAPC.

Elevated bilirubin levels were associated with worse OS (HR = 1.834, 95% CI: 1.102–3.052, P = 0.020 in univariate analysis; HR = 1.654, P = 0.099 in multivariate analysis). This observation corresponds with findings by Wu et al. [15], who noted a correlation between hyperbilirubinemia and reduced survival outcomes (P = 0.03).

CTA+CCRT also significantly reduced the risk of disease progression (HR = 0.334, 95% CI: 0.177–0.631, P = 0.001 in univariate; HR = 0.285, 95% CI: 0.133–0.611, P = 0.001 in multivariate analysis). Wu et al. [15] confirmed this, reporting a longer PFS in the CCRT group versus chemotherapy alone (HR = 0.50, P < 0.01). Likewise, Choi et al. [17] demonstrated a significant PFS benefit in the CCRT group after chemotherapy (median PFS: 10.1 months vs. 5.7 months, P = 0.002). Post-treatment CA 19-9 also predicted PFS significantly in univariate analysis (HR = 1, P

= 0.038), although it showed borderline significance in multivariate analysis (HR = 1, P = 0.066). Ibrahim et al. [16] similarly found that CA 19-9 normalization was associated with longer PFS (P = 0.02).

Univariate analysis showed a statistically significant association between smaller tumor size and higher PFS (HR = 0.796, P = 0.046), although multivariate analysis did not find such a correlation (HR = 0.79, P = 0.089). Amini et al. [14] reported similar trends, identifying tumor size—especially tumors greater than 3 cm—as a predictor of disease progression (P = 0.05).

This retrospective study is limited by its small sample size, potential selection bias, and variability in treatment protocols across centers. Additionally, the lack of quality-of-life and long-term toxicity data limits comprehensive outcome assessment. Larger, prospective multicenter trials with standardized treatment pathways are recommended to confirm these findings and guide optimal management of locally advanced pancreatic cancer.

CONCLUSIONS

Chemoradiotherapy demonstrates significant clinical benefit in the management of locally advanced pancreatic cancer as it improves local tumor control, decreases lymph node involvement, and enhances both overall survival as well as progression-free survival, along with increasing tumor resectability. Importantly, the addition of concurrent chemoradiotherapy was not associated with a statistically significant increase in hematological or gastrointestinal toxicities compared to chemotherapy alone, supporting the safety of this combined approach in appropriately selected patients.

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