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Timing of adjuvant chemoradiation for pancreatic cancer with positive surgical margins

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ABSTRACT

Aims: Impact of adjuvant chemoradiation timing on the outcome of pancreatic cancer patients with positive surgical margins is unknown. The aim of this study was to evaluate the effect of adjuvant chemoradiation timing for margin positive pancreatic cancer patients.

Methods: A total of 36 pancreatic adenocarcinoma patients with positive surgical margins and received adjuvant chemoradiation were included in the study. The median radiation dose was 50.4 Gy in 28 fractions. The primary study variable was the timing of chemoradiation, grouped as immediate (after ≤ 1 cycle of chemotherapy) and delayed (after two or more cycles of chemotherapy) chemoradiation. Gemcitabine (n=16) and capecitabine (n=20) were chemotherapy regimens administered with radiation.

Results: Median follow-up time was 23.7 months. Thirteen patients (36%) received immediate and 23 (64%) received delayed chemoradiation. For immediate and delayed treatment groups, median overall survival was 13.5 and 42.5 months, and disease-free survival was 6.4 and 18.8 months, respectively. Disease-free survival and overall survival were better with delayed chemoradiation (p=0.02). However, the two groups did not significantly differ in locoregional control (p=0.96).

Conclusion: Delaying chemoradiation until completion of systemic therapy improves disease-free survival and overall survival without any difference in locoregional failure compared to early chemoradiation in pancreatic cancer patients with positive surgical margins.

Keywords: Pancreatic cancer, positive margin, chemoradiation timing, prognosis

INTRODUCTION

Surgery with clear resection margins has prognostic importance for the management of pancreatic cancer and positive surgical margin is associated with poor survival.[1] Incomplete surgical resection (R1) rates following pancreatoduodenectomy for pancreatic adenocarcinoma are reported to vary from below 14% to 85%,[2-4] and postoperative 5-year survival usually does not exceed 20% irrespective of margin status.[5,6]

In patients with pancreatic cancer, chemoradiation (CRT) is generally recommended after completion of systemic chemotherapy regardless of surgical margins,[7,8] in contrast to certain gastrointestinal malignancies.[9,10] However, there is no consensus on the timing of CRT in pancreatic cancer, and to our knowledge, the impact of CRT timing in the adjuvant setting of positive surgical margins in pancreatic cancer is not investigated before.

In this study, we investigated the impact of CRT timing on the outcome of pancreatic cancer patients with positive surgical resection margins.

METHODS

The study was carried out with the permission of Marmara University Clinical Researches Ethics Committee (Date: 23.06.2022, Decision No: 09.2022.86). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Treatment results of 36 pancreatic adenocarcinoma patients with positive postoperative resection margins (R1 resection), treated with adjuvant CRT in addition to chemotherapy between January 2013 and September 2021 were evaluated. Patients with R0 resection

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(completely resected tumor with negative surgical margin) were not included in the study.

Baseline data on patients and tumor characteristics were recorded. All patients underwent surgical resection. Surgical procedures were distal pancreatectomy (n=3), total pancreatectomy (n=1), and pancreatoduodenectomy (Whipple Procedure) (n=32). Tumor (T) stage was T1 in 2, T2 in 17, T3 in 15, and T4 in 2 patients according to American Joint Committee on Cancer (AJCC, 8th edition) staging system.

Median radiotherapy dose was 50.4 (45-56) Gy in 1.8 Gy daily fractions, using intensity modulated radiation therapy or volumetric arc therapy. Tumor bed and regional (peripancreatic, celiac, superior mesenteric, porto-hepatic, and para-aortic) lymph nodes were included in the clinical target volume. Concurrent chemotherapy was either gemcitabine (n=16) or capecitabine (n=20). Adjuvant chemotherapy was gemcitabine-based in 27 patients and 5-flourourasil-based in 9 patients.

Patients were grouped according to the timing of CRT as immediate or delayed, consistently with Radiation Therapy Oncology Group (RTOG) 9704 11. Immediate CRT was defined as irradiation with or before the first cycle of adjuvant chemotherapy and delayed CRT was with or after the second cycle of adjuvant chemotherapy. The pathologic tumor (pT) stage was pT1 in 1, pT2 in 3, and pT3 in 9 patients in the immediate CRT group. In the delayed CRT group, number of patients with pT1, pT2, pT3, and pT4 tumors were 1, 14, 6, and 2, respectively. Pathologic nodal (pN) stage of the patients in immediate CRT group was pN0, pN1, and pN2 for 4, 8, and 1 patients, respectively. In delayed CRT group, number of patients with pN0, pN1, and pN2 stages were 3, 11, and 9, respectively. Patient characteristics are summarized in Table 1.

Follow-up visits were scheduled every 3 to 4 months. Disease recurrence was assessed by physical examination, computed tomography/ magnetic resonance imaging, and tumor markers.

Locoregional failure (LRF) was defined as recurrence at pancreatic bed or regional (peripancreatic, celiac, superior mesenteric, porto-hepatic, and para-aortic) lymph nodes. Metastases at liver, peritoneum, lung, bone or other distant sites were defined as distant failure.

Primary study endpoints were disease-free survival (DFS) and overall survival (OS). Secondary endpoint was locoregional control (LRC). OS was defined as the period (months) from the date of surgery until the last visit or death. DFS was defined as follow-up time (months) from the date of surgery to the first event.

Table 1. Baseline characteristics of patients

	Delayed CRT n (%)	Immediate CRT n (%)	p value
Age			
≤ 62	13 (56.5)	6 (46.2)	0.54
> 62	10 (43.5)	7 (53.8)	
Gender			
Female	9 (39.1)	6 (46.2)	0.68
Male	14 (60.9)	7 (53.8)	
Tumor Location			
Head	17 (73.9)	12 (92.3)	0.18
Body-Tail	6 (26.1)	1 (7.7)	
Stage			
1,2	12 (52.2)	12 (92.3)	0.05
3	11 (47.8)	1 (7.7)	
Grade			
1,2	14 (60.9)	12 (92.3)	0.06
3	9 (39.1)	1 (7.7)	
Adjuvant CT Agents			0.07
Gemcitabine based	15 (65.2)	12 (92.3)	
5-Flourouracil based	8 (34.8)	1 (7.7)	
Local Recurrence			
Yes	4 (17.4)	2 (15.4)	0.87
No	19 (82.6)	11 (84.6)	
Distant Metastasis			
Yes	7 (30.4)	9 (69.2)	0.02*
No	16 (69.6)	4(30.8)	
Local/Distant Recurrence			
Yes	11 (47.8)	11 (84.6)	0.03*
No	12 (52.2)	2 (15.4)	
Death			
Yes	9 (39.1)	10 (76.9)	0.02*
No	14 (60.9)	3 (23.1)	

CRT: Chemoradiation, CT: Chemotherapy

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows 23.0 (IBM SPSS Statistics, New York, USA). Descriptive statistics stratified by timing of adjuvant CRT were performed. The $\chi 2$ test was used to compare categorical variables, and the Kruskal-Wallis test was performed to compare the median values of continuous variables. Survival probabilities were estimated using Kaplan-Meier methodology and compared using log-rank statistics. Univariate and multivariate Cox regression models were used to generate hazard ratios. P-value < 0.5 was defined as statistical significance.

RESULTS

Median age was 62 (55-67) years. Median follow-up time was 23.7 (7-101) months. Median OS of the study population was 42.5 months (95% CI: 13.9-71.0) and median DFS was 16.1 months (95% CI: 13.2-19.0). Number of the patients received immediate and delayed CRT were 13 (36%) and 23 (64%), respectively. Median DFS for the patients treated with immediate and delayed

CRT was 6.4 and 18.8 months, respectively (p=0.02; Figure 1). Median OS was better in patients treated with delayed CRT (42.5 vs. 13.5 months; p=0.02) (Figure 2).

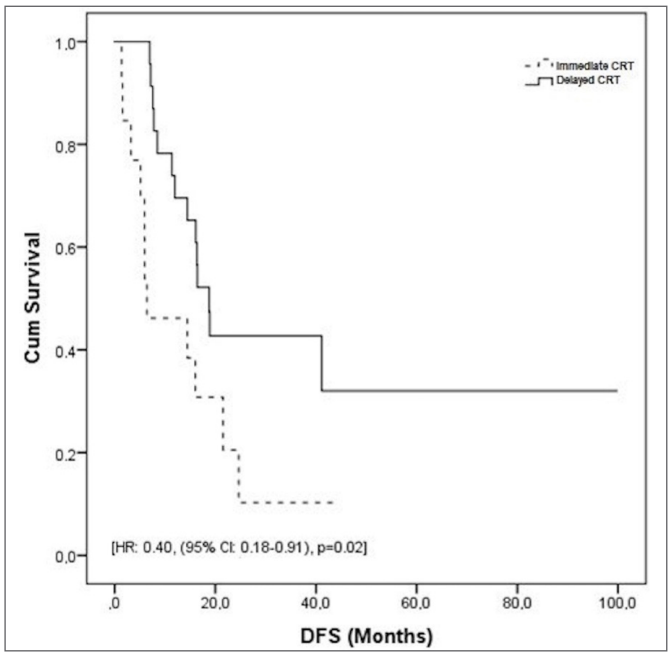

Figure 1. Disease free survival in patients treated with immediate and delayed chemoradiation

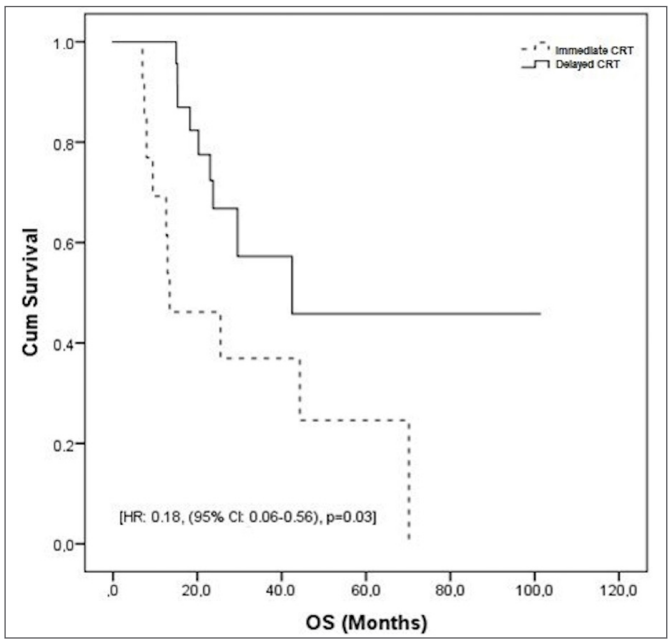

Figure 2. Overall survival in patients treated with immediate and delayed chemoradiation

Primary sites of distant failure were liver in 6 (17%) patients, peritoneum in 4 (11%), lung in 4 (11%), and bone in one (2%) patient. Median recurrence-free survival (RFS) of the study population was 7.2 months (95% CI: 0.2-14.8). Median RFS for delayed and immediate CRT groups was 11.95 and 11.38 months, respectively (p=0.96). Six (17%) patients developed local failure. Median time to LRF was 11.95 vs. 13.7 months for delayed and immediate CRT groups, respectively (p=0.96) (Table 2).

Table 2. Patients' outcome based on adjuvant CRT timing

	Immediate CRT	Delayed CRT	p-value
Median OS (Months)	13.5	42.5	
2-year OS (%)	38.5	47.8	0.02*
Median RFS (Months)	11.38	11.95	
2-year RFS (%)	38.5	39.1	0.96
Median time to LRF	13.7	11.95	
2-year LRC (%)	38.5	39.1	0.96

CRT: Chemoradiation, OS: Overall survival, RFS: Recurrence free survival, LRF: Locoreginal failure, LRC: Locoregional control

DISCUSSION

Results of our study showed that compared to immediate adjuvant CRT, OS and DFS were better with delayed adjuvant CRT in margin-positive pancreatic cancer patients.

Conflicting results are reported about the impact of CRT in the adjuvant setting of resected pancreatic cancer.[12-15] A meta-analysis by Butturini et al.[16] showed an increased survival benefit with adjuvant CRT in patients with R1 resection compared to R0 resection. In daily clinical practice, CRT is almost always delayed until completion of systemic therapy irrespective of margin status due to the aggressive nature of the disease and the importance of systemic control.[8]

Previous studies reported that timing of CRT in the adjuvant setting of pancreatic cancer did not significantly affect DFS or OS, regardless of the margin status.[17] However, the impact of adjuvant CRT timing on outcomes of patients with positive surgical margins has not been studied before.

Timing of adjuvant CRT after resection of pancreatic cancer was investigated by Wo et al.[17] and they reported that early or late adjuvant CRT for resectable disease did not significantly affect LRC or OS. They found that resection margin positivity was significantly associated with LRF but not OS. However, they did not analyze patients' survival and recurrence patterns in terms of immediate or delayed postoperative radiotherapy. In our study, delaying CRT after completion of systemic therapy in margin positive patients showed better DFS and OS, although the patients in these group had more advanced stages.

Early CRT is preferred in patients with margin positive gastric or gastroesophageal/esophageal cancers in adjuvant setting.[9,10] However, delaying CRT until completion of systemic chemotherapy is preferred in patients with margin positive pancreatic cancer, though there is no study conducting the effectiveness of early or late CRT.[8]

In our study, OS and DFS were better in the delayed CRT group. Surprisingly, LRR rates were not affected by the timing of CRT. This may be due to the low number of

patients in the immediate CRT group. Treating patients with systemic therapy first may result in the abandonment of early radiotherapy and this may explain the low number of patients in the immediate treatment group.

Our study has some limitations. It is a retrospective study and despite the collection of nine years of data, the patient number is very small due to strict selection criteria.

CONCLUSION

Treating margin-positive pancreatic cancer patients with adjuvant CRT following multi-agent systemic therapy increases OS and DFS compared to immediate treatment. LRC does not change with CRT timing. Further studies with larger patient numbers are needed to evaluate these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Marmara University Clinical Researches Ethics Committee (Date: 23.06.2022, Decision No: 09.2022.86).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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