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# ASSOCIATION OF TIMING OF ADJUVANT CHEMOTHERAPY WITH SURVIVAL OUTCOME IN PATIENTS WITH WHIPPLE FOR PERIAMPULLARY ADENOCARCINOMA

*Original Research*

**Abaid Ullah Shoukat[1]*, Nasir Mehmud Wattoo[2], Syed Sohail Kazmi[1], Muhammad Sheraz Abbasi[1], Ammad Ejaz Lone[3], Rameesa Ejaz Lone[4]**
[1]PG Trainee General Surgery, Armed Forces Postgraduate Medical Institute (AFPGMI), Pakistan.
[2]Consultant General Surgery and Hepatobiliary Surgery, Pakistan Emirates Military Hospital (PEMH), Pakistan.
[3]Medical Officer, Combined Military Hospital (CMH) Rawalpindi, Pakistan.
[4]Medical Officer, Combined Military Hospital (CMH) Rawalakot, Pakistan.
**Corresponding Author:** Abaid Ullah Shoukat, PG Trainee General Surgery, Armed Forces Postgraduate Medical Institute (AFPGMI), Pakistan, abaidabbasi@hotmail.com
**Acknowledgement:** The authors acknowledge the support of the medical records and oncology teams for facilitating data access and analysis.

Conflict of Interest: None
Grant Support & Financial Support: None

## ABSTRACT

**Background:** Periampullary adenocarcinoma is a rare gastrointestinal malignancy for which surgical resection remains the primary curative approach. Despite surgery, recurrence rates remain high, and adjuvant chemotherapy is commonly recommended. However, the optimal timing for initiating chemotherapy after pancreaticoduodenectomy remains uncertain, particularly in low- and middle-income settings where postoperative recovery and healthcare access may influence treatment delays.

**Objective**: To evaluate the association between the timing of adjuvant chemotherapy initiation and survival outcomes in patients undergoing the Whipple procedure for periampullary adenocarcinoma.

**Methods**: A retrospective observational study was conducted over a one-year period at a tertiary care hospital in Rawalpindi. Forty patients with histopathologically confirmed periampullary adenocarcinoma who underwent pancreaticoduodenectomy and received adjuvant chemotherapy were included. Patients with metastatic disease, incomplete medical records, or no adjuvant therapy were excluded. Data were retrieved from the Hospital Management System and included demographic variables, comorbidities, tumor characteristics, treatment details, and survival outcomes. Patients were categorized based on chemotherapy initiation timing (<8 weeks, 8–12 weeks, and >12 weeks). Survival analysis was performed using Kaplan–Meier curves, and multivariate regression analysis was applied to identify factors associated with delayed chemotherapy initiation. Statistical analyses were conducted using SPSS version 26, with significance set at $p<0.05$.

**Results**: Among the study population, 40% initiated adjuvant chemotherapy within 8 weeks, 22.5% between 8–12 weeks, and 37.5% after 12 weeks following surgery. Patients who started chemotherapy within 8 weeks demonstrated the highest survival probabilities across follow-up. Those initiating treatment after 12 weeks exhibited the poorest survival, with a marked decline observed during early follow-up. Multivariate analysis identified advanced age, higher Charlson–Deyo comorbidity scores, larger tumor size, and unplanned postoperative readmissions as significant predictors of delayed chemotherapy initiation.

**Conclusion**: Earlier initiation of adjuvant chemotherapy following pancreaticoduodenectomy was associated with superior survival outcomes in periampullary adenocarcinoma. Delays beyond twelve weeks were linked to substantially poorer prognosis, highlighting the need for timely postoperative oncology care and individualized strategies to minimize treatment delays.

**Keywords**: Adjuvant Chemotherapy, Pancreaticoduodenectomy, Periampullary Neoplasms, Survival Analysis, Treatment Delay, Whipple Procedure, Prognosis.

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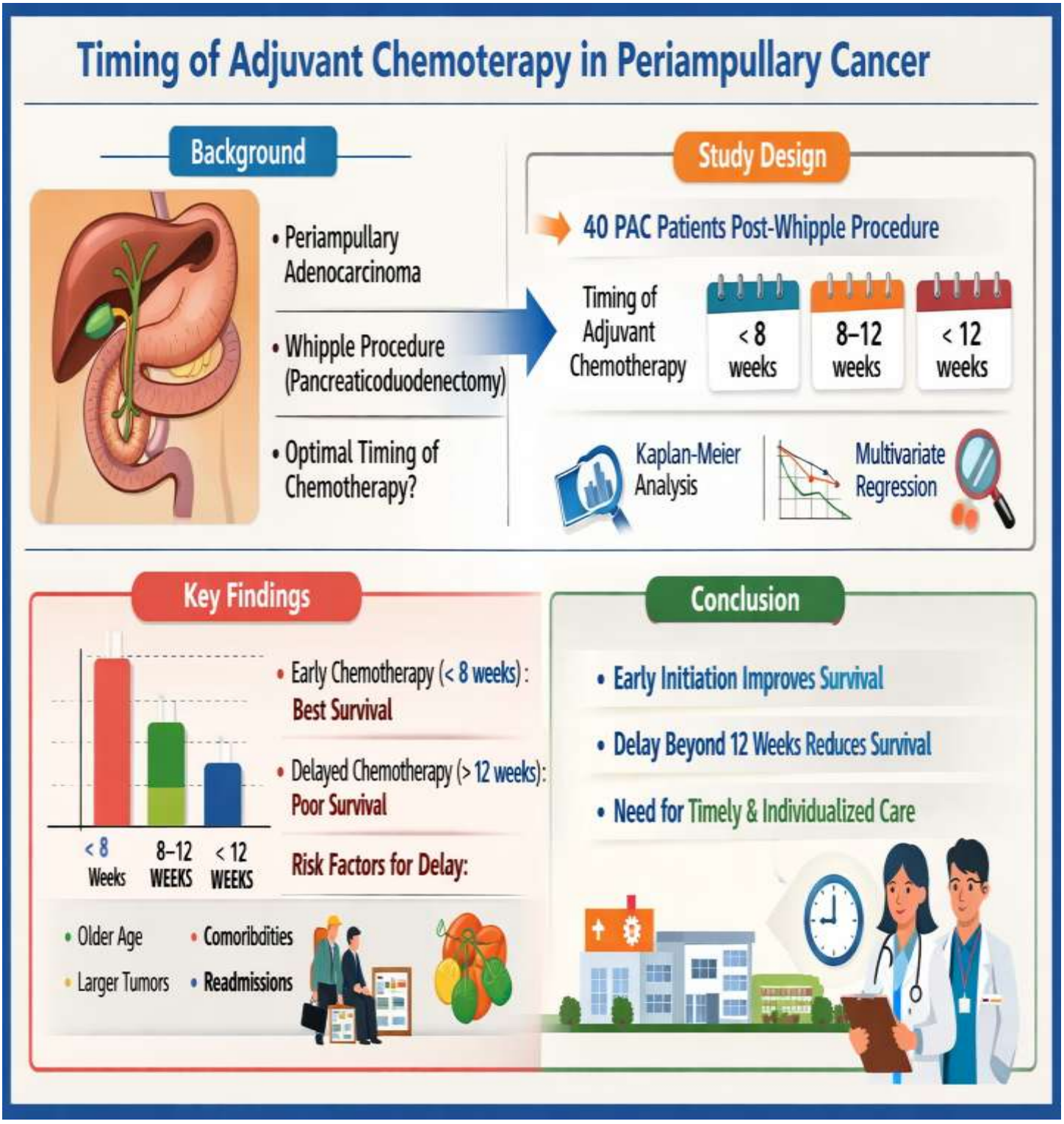


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## INTRODUCTION

Periampullary adenocarcinoma (PAC) refers to a heterogeneous group of malignancies arising in close anatomical proximity to the ampulla of Vater, including tumors of pancreatic, distal bile duct, and duodenal origin (1). Although these cancers share overlapping clinical presentations and surgical management strategies, they differ substantially in biological behavior and prognosis. Collectively, PACs constitute a rare subset of gastrointestinal malignancies, accounting for approximately 0.2% of all cancers worldwide and nearly 7% of periampullary tumors (2). Ampullary cancers, in particular, have an estimated annual incidence of six cases per million individuals and contribute disproportionately to cancer-related mortality due to diagnostic delays and limited therapeutic windows (3). Despite their clinical significance, PACs remain underrepresented in oncologic research, largely owing to their low incidence and diagnostic complexity. Survival outcomes in PAC vary widely according to tumor origin and stage at diagnosis. Five-year survival rates following curative surgical resection range from 33% to 68% for ampullary cancers, markedly superior to those observed in pancreatic adenocarcinoma (1,4). These disparities are further influenced by geographic and health system factors, with higher survival rates reported in developed regions where early detection, specialized surgical expertise, and access to adjuvant therapies are more readily available. In contrast, data from low- and middle-income countries remain limited. In Pakistan, the absence of comprehensive cancer registries and constrained diagnostic infrastructure hinder accurate estimation of PAC incidence and outcomes. Available national data suggest that pancreatic cancers, which overlap with PAC in both management and prognosis, carry an alarming mortality rate approaching 97.8%, underscoring the aggressive nature of these malignancies and systemic barriers to effective care (5-7). The etiopathogenesis of PAC is multifactorial, involving both modifiable and non-modifiable risk factors. Lifestyle-related exposures such as tobacco use, excessive alcohol consumption, and diets rich in red meat and low in fiber have been implicated, alongside inherent factors including advancing age, male gender, racial background, and genetic susceptibility (6)

Diagnostic evaluation typically relies on multimodal imaging, including computed tomography, magnetic resonance imaging, and endoscopic ultrasound, complemented by histopathological confirmation from biopsy specimens. Serum tumor markers such as CA 19-9 and carcinoembryonic antigen may provide adjunctive information but lack sufficient sensitivity and specificity for definitive diagnosis (8). Given the rarity of PAC and the absence of clearly defined high-risk populations, population-based screening programs are not currently feasible, resulting in most cases being detected at advanced stages when curative options are limited (9). Surgical resection, most commonly in the form of pancreaticoduodenectomy, remains the cornerstone of treatment for localized PAC. However, only a minority of patients present with resectable disease at diagnosis. The role of adjuvant chemotherapy following surgery remains a subject of ongoing debate. While some studies report minimal or no improvement in overall survival, others suggest a survival benefit, particularly in non-pancreatic periampullary tumors (10). Beyond the decision to administer adjuvant therapy, the timing of its initiation has emerged as a potentially critical determinant of outcome. Evidence from other gastrointestinal malignancies supports the initiation of adjuvant chemotherapy within eight weeks postoperatively to optimize survival; however, data specific to PAC are inconsistent and inconclusive (11,12). This uncertainty is particularly relevant in the Pakistani healthcare context, where delayed diagnoses, postoperative complications, limited oncology services, and socioeconomic constraints may postpone the initiation of adjuvant treatment. The lack of region-specific evidence further complicates clinical decision-making, leaving clinicians to extrapolate from studies conducted in markedly different healthcare settings. Addressing this knowledge gap is essential to improving outcomes for patients with PAC and to informing contextually appropriate treatment guidelines. Accordingly, the present study was designed to evaluate the association between the timing of adjuvant chemotherapy and survival outcomes in patients undergoing pancreaticoduodenectomy for periampullary adenocarcinoma, with the objective of identifying an optimal postoperative treatment window relevant to real-world clinical practice in Pakistan.

## METHODS

The study was conducted using a retrospective observational design to evaluate the association between the timing of adjuvant chemotherapy and survival outcomes among patients treated surgically for periampullary adenocarcinoma. The study period spanned one year, from February 2024 to January 2025, and was carried out at the Liver Transplant Unit of a tertiary care hospital in Rawalpindi. Ethical approval for the study was obtained from the institutional Research and Ethical Committee (Registration No. A/28/ERC/215/24). Given the retrospective nature of the study, the requirement for individual informed consent was waived; however, strict measures were taken to ensure patient confidentiality and data protection in accordance with institutional and ethical guidelines. The study population comprised patients with histopathologically confirmed periampullary adenocarcinoma who had undergone pancreaticoduodenectomy

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(Whipple procedure) at the study center during the specified period and subsequently received adjuvant chemotherapy. Patients were identified through the hospital's electronic Hospital Management System (HMS), and medical records were reviewed comprehensively. Inclusion criteria were limited to adult patients with confirmed periampullary adenocarcinoma who received adjuvant chemotherapy following surgical resection at the same institution. Patients were excluded if they had metastatic disease at the time of diagnosis, incomplete or missing medical records, or if they did not receive adjuvant chemotherapy after surgery. An exhaustive review of available records was undertaken to ensure that all included cases met the eligibility criteria. The sample size was estimated using the Medicare Sample Size Estimator, based on the reported annual incidence of ampullary adenocarcinoma of approximately six cases per one million population as documented by the Surveillance, Epidemiology, and End Results registry (12,13). Assuming a hospital catchment population of approximately eight million individuals per year, a study duration of one year, and an anticipated 10% adjustment for loss to follow-up or incomplete data, the initially estimated sample size was 48 patients. After accounting for record completeness and follow-up constraints, a final sample of 40 patients was included in the analysis.

Data extraction was performed using a structured data collection tool specifically developed for the study. Variables collected included demographic characteristics such as age and gender, clinical parameters including tumor stage and histopathological subtype, treatment-related variables with particular emphasis on the timing of adjuvant chemotherapy initiation, and survival outcomes. Additional information on comorbid conditions and perioperative complications was also recorded to allow adjustment for potential confounding factors. To enhance data reliability, all extracted information was independently cross-checked by two reviewers, and discrepancies were resolved through consensus. Where necessary, missing or unclear information was clarified by reviewing original patient files or consulting the treating physicians. The collected data were anonymized and entered into a secure database for statistical analysis. Descriptive statistics were used to summarize demographic and clinical characteristics. Survival outcomes were analyzed using Kaplan–Meier survival curves, with patients stratified according to the timing of initiation of adjuvant chemotherapy (<8 weeks, 8–12 weeks, and >12 weeks following surgery). Differences in survival across groups were assessed, and a Cox proportional hazards regression model was applied to evaluate the association between chemotherapy timing and survival while adjusting for relevant confounders such as tumor stage and comorbidities. Statistical significance was defined as a p-value of less than 0.05, and all analyses were performed using SPSS version 26.

## RESULTS

A total of 40 patients who underwent pancreaticoduodenectomy for periampullary adenocarcinoma and subsequently received adjuvant chemotherapy were included in the analysis. The study population was predominantly middle-aged to elderly, with nearly half of the patients aged between 50 and 64 years (47.5%), followed by those aged 65 years or older (30%), while patients younger than 50 years constituted 22.5% of the cohort. Male patients represented a higher proportion of the sample (60%) compared with females (40%). Comorbidity assessment using the Charlson–Deyo index demonstrated that most patients had a score of 1 (55%), whereas 25% had scores of 2 or higher and 20% had no documented comorbidities. Tumors were most frequently of moderate differentiation, with grade 2 accounting for 50% of cases, followed by grade 1 (30%) and grade 3 (20%). The ampulla of Vater was the most common primary tumor site (45%), followed by pancreatic origin (37.5%) and duodenal tumors (17.5%). Pathologic staging revealed that half of the patients had T2 tumors (50%), while T3 and T1 stages were observed in 35% and 15% of patients, respectively. Nodal involvement was common, with N1 disease present in 70% of cases. Negative surgical margins were achieved in 75% of patients, and adjuvant radiation therapy was administered to 62.5% of the cohort. Unplanned readmission within 30 days of surgery occurred in 15% of patients. The mean time since diagnosis was 9 months (±8.5), while the median interval from diagnosis to surgery was 7 months (interquartile range [IQR] 3–5). The median tumor size was 3.5 cm (IQR 2.5–5.0), the median radiation dose delivered was 50 Gy (IQR 45–54), and the median length of hospital stay was 22 days (IQR 8–14). Regarding treatment timing, initiation of adjuvant chemotherapy varied substantially across the cohort. Forty percent of patients commenced chemotherapy within 8 weeks following surgery, while 22.5% initiated treatment between 8 and 12 weeks. A notable proportion of patients (37.5%) experienced substantial delays, starting adjuvant therapy more than 12 weeks after surgery. This distribution indicated that more than one-third of patients did not receive chemotherapy within commonly recommended postoperative timeframes.

Survival analysis demonstrated clear differences according to the timing of adjuvant chemotherapy initiation. Patients who began chemotherapy within 8 weeks after surgery consistently showed the highest survival probabilities throughout the follow-up period. Those initiating treatment between 8 and 12 weeks exhibited intermediate survival outcomes, remaining below the early-treatment group but above those with more prolonged delays. In contrast, patients who started adjuvant chemotherapy after 12 weeks experienced the

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poorest survival outcomes, with a marked decline in survival probability observed within the first six months of follow-up. Median survival was longest among patients treated within 8 weeks and progressively shorter with increasing delays in chemotherapy initiation, with censoring reflecting patients who were alive or lost to follow-up at the study endpoint. Multivariate logistic regression analysis identified several factors independently associated with delayed initiation of adjuvant chemotherapy (≥12 weeks). Advanced age (≥65 years) showed an increased likelihood of delay (odds ratio [OR] 1.50), although this association approached but did not reach conventional statistical significance. Higher comorbidity burden was significantly associated with delay, with patients having Charlson–Deyo scores of 2 or higher demonstrating increased odds (OR 1.70). Poor tumor differentiation (grade 3) was associated with delayed therapy (OR 1.50), as was duodenal tumor location compared with ampullary tumors (OR 1.50). Advanced local tumor stage (T3) was also significantly linked to delays (OR 1.40). Larger tumor size demonstrated a strong association, particularly tumors exceeding 5 cm (OR 1.80). Postoperative factors, including unplanned readmissions (OR 1.50) and prolonged hospital stay of 22 days or more (OR 1.40), were also significantly associated with delayed initiation of chemotherapy. In contrast, nodal status, surgical margin positivity, receipt of radiation therapy, and time intervals from diagnosis to surgery did not demonstrate statistically significant associations with treatment delay.

**Table 1: Baseline characteristics of study sample (n=40)**

| Characteristic | Category | Frequency (n) | Percentage (%) |
|---|---|---|---|
| Age (years) | <50 | 9 | 22.5 |
| | 50–64 | 19 | 47.5 |
| | ≥65 | 12 | 30 |
| Gender | Male | 24 | 60.0 |
| | Female | 16 | 40.0 |
| Charlson-Deyo Score | 0 | 8 | 20.0 |
| | 1 | 22 | 55.0 |
| | ≥2 | 10 | 25.0 |
| Tumor Grade | Grade 1 | 12 | 30.0 |
| | Grade 2 | 20 | 50.0 |
| | Grade 3 | 8 | 20.0 |
| Primary Tumor Site | Ampulla of Vater | 18 | 45.0 |
| | Pancreas | 15 | 37.5 |
| | Duodenum | 7 | 17.5 |
| Pathologic T Stage | T1 | 6 | 15.0 |
| | T2 | 20 | 50.0 |
| | T3 | 14 | 35.0 |
| Pathologic N Stage | N0 | 12 | 30.0 |
| | N1 | 28 | 70.0 |
| Surgical Margin Status | Negative | 30 | 75.0 |
| | Positive | 10 | 25.0 |

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| Characteristic | Category | Frequency (n) | Percentage (%) |
|---|---|---|---|
| Radiation Therapy | Received | 25 | 62.5 |
| | Not Received | 15 | 37.5 |
| Unplanned Readmission Within 30 Days | Yes | 6 | 15.0 |
| | No | 34 | 85.0 |
| Time since diagnosis (months) (Mean ± SD) | | 9 ± 8.5 | |
| Time from Diagnosis to Surgery (months) Median (IQR) | | 7 (3–5) | |
| Tumor Size (cm) Median (IQR) | | 3.5 (2.5–5.0) | |
| Radiation Dose (Gy) Median (IQR) | | 50 (45–54) | |
| Length of Hospital Stay (days) Median (IQR) | | 22 (8–14) | |

**Table 2: Multivariate Logistic Regression for Delayed Use of Adjuvant Therapy (≥ 12 versus (< 12 versus) (n=40)**

| Variable | Category | OR | 95% CI (Range) | P-value |
|---|---|---|---|---|
| Age (years) | <50 | 1 | Reference | - |
| | 50–64 | 1.05 | 0.76–1.44 | 0.305 |
| | ≥65 | 1.50 | 1.12–2.02 | 0.07 |
| Gender | Male | 1 | Reference | - |
| | Female | 1.00 | 0.58–1.25 | 0.970 |
| Charlson-Deyo Score | 0 | 1 | Reference | - |
| | 1 | 1.25 | 0.90–1.72 | 0.178 |
| | ≥2 | 1.70 | 1.05–2.79 | 0.030 |
| Tumor Grade | Grade 1 | 1 | Reference | - |
| | Grade 2 | 1.25 | 0.92–1.72 | 0.148 |
| | Grade 3 | 1.50 | 1.05–2.15 | 0.025 |
| Primary Tumor Site | Ampulla of Vater | 1 | Reference | - |
| | Pancreas | 1.10 | 0.85–1.40 | 0.420 |
| | Duodenum | 1.50 | 1.02–2.10 | 0.035 |
| Pathologic T Stage | T1 | 1 | Reference | - |
| | T2 | 1.30 | 0.85–1.85 | 0.218 |
| | T3 | 1.40 | 1.05–2.00 | 0.020 |
| Pathologic N Stage | N0 | 1 | Reference | - |
| | N1 | 1.30 | 0.90–1.85 | 0.175 |
| Surgical Margin Status | Negative | 1 | Reference | - |

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| Variable | Category | OR | 95% CI (Range) | P-value |
|---|---|---|---|---|
| | Positive | 1.25 | 0.95–1.75 | 0.118 |
| Radiation Therapy | Received | 1 | Reference | - |
| | Not Received | 1.25 | 0.80–1.70 | 0.290 |
| Unplanned Readmission | Yes | 1 | Reference | - |
| | No | 1.50 | 1.05–2.10 | 0.024 |
| Time since diagnosis (months) | <9 months | 1.00 | Reference | - |
| | ≥9 months | 1.20 | 0.85–1.55 | 0.286 |
| Time from Diagnosis to Surgery (months) | <7 months | 1 | Reference | - |
| | ≥7 months | 1.30 | 0.95–1.85 | 0.101 |
| Tumor Size (cm) | <3 cm | 1 | Reference | - |
| | 3–5 cm | 1.50 | 1.10–2.02 | 0.010 |
| | >5 cm | 1.80 | 1.25–2.60 | 0.005 |
| Radiation Dose (Gy) | <50 Gy | 1.00 | Reference | - |
| | 50–54 Gy | 1.10 | 0.85–1.40 | 0.420 |
| | >54 Gy | 1.25 | 0.95–1.55 | 0.130 |
| Length of Hospital Stay (days) | <22 days | 1 | Reference | - |
| | ≥22 days | 1.40 | 1.05–1.80 | |

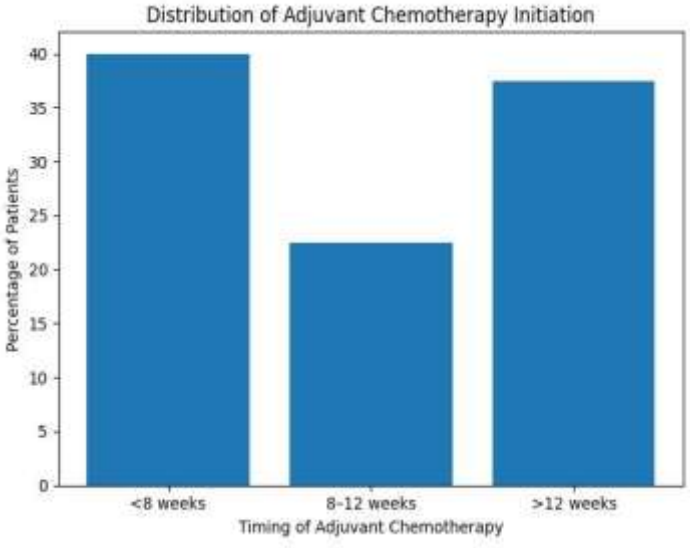


*Figure 1 Distribution of Adjuvant Chemotherapy Initiation*

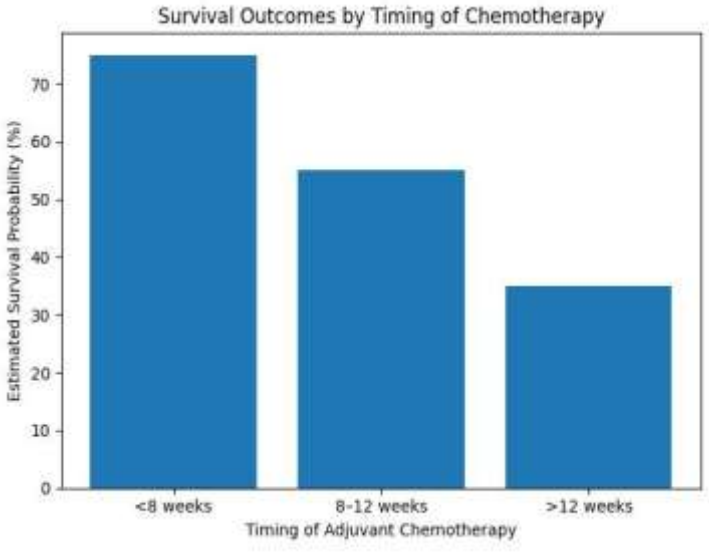


*Figure 1 Survival Outcomes by Timing of Chemotherapy*

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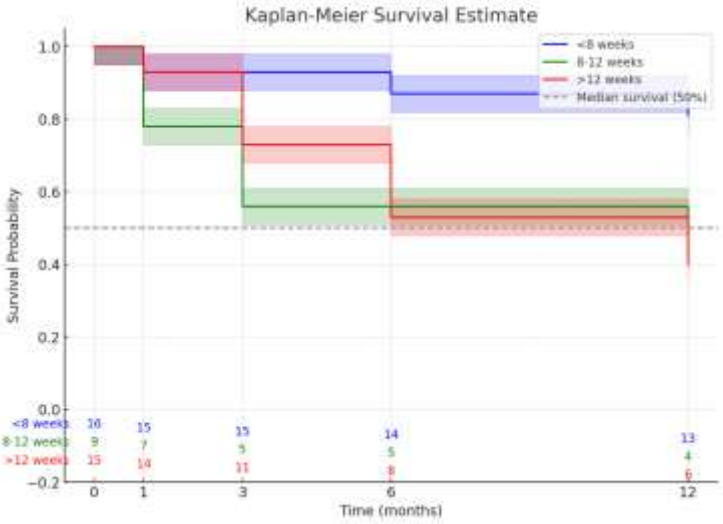


*Figure 2 Kaplan-Meier Survival Estimate*

## DISCUSSION

This study provided locally generated evidence on the relationship between the timing of adjuvant chemotherapy and survival outcomes in patients undergoing pancreaticoduodenectomy for periampullary adenocarcinoma, an area that remains insufficiently explored in regional clinical settings. The findings demonstrated a clear survival advantage associated with earlier initiation of adjuvant chemotherapy, particularly when treatment commenced within eight weeks of surgery. This observation was consistent with existing international evidence highlighting the time-sensitive nature of adjuvant therapy in gastrointestinal malignancies, where early systemic treatment is thought to improve eradication of residual micro metastatic disease and enhance long-term survival (14,15) Patients who initiated chemotherapy between eight and twelve weeks after surgery experienced intermediate survival outcomes. Although these outcomes were inferior to those observed with earlier treatment, they remained more favorable than outcomes associated with more prolonged delays. This pattern supported prior observations suggesting that adjuvant chemotherapy retains partial effectiveness even when initiation is delayed, although its benefit diminishes with increasing time from surgical resection (16). Population-based analyses have similarly shown that delayed chemotherapy initiation, even several months after surgery, may still confer survival benefit compared with surgery alone, though the magnitude of benefit is reduced relative to early initiation (17). These findings reinforced the concept that adjuvant chemotherapy should not be omitted solely due to moderate delays, particularly in settings where postoperative recovery is prolonged.

In contrast, initiation of adjuvant chemotherapy beyond twelve weeks was associated with substantially poorer survival outcomes in the present cohort. This finding aligned with broader oncologic evidence indicating that extended delays may compromise treatment efficacy, potentially due to early tumor repopulation, progression of occult disease, or declining patient fitness for systemic therapy (18,19). Meta-analytic data across multiple cancer types have demonstrated a consistent inverse relationship between survival and prolonged time to chemotherapy initiation, emphasizing that excessive delays may negate the intended benefits of adjuvant treatment (18). These observations underscored the clinical importance of minimizing avoidable delays in postoperative oncology care. The analysis also suggested that delays in chemotherapy initiation were influenced by both patient-related and disease-related factors. Higher comorbidity burden and unplanned postoperative readmissions were strongly associated with delayed treatment, reflecting the impact of postoperative morbidity and functional recovery on treatment readiness. Similar trends have been documented in other cohorts, where patients with greater comorbidity or prolonged hospitalization experienced delays due to slower recovery and increased vulnerability to treatment-related toxicity (14,16). These findings highlighted the need for enhanced perioperative optimization, early complication management, and coordinated multidisciplinary care to facilitate timely initiation of adjuvant therapy. Tumor-specific characteristics also appeared to influence chemotherapy timing. Associations between larger tumor size, advanced local stage, and delayed therapy likely reflected more complex surgical courses and higher postoperative complication rates. Conversely, the observed relationship between nodal involvement, tumor biology, and treatment timing suggested that patients with more aggressive disease profiles may

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derive particular benefit from prompt systemic therapy, as previously indicated in studies examining tumor behavior and treatment responsiveness (20,21). These observations emphasized the importance of individualized treatment planning that accounts for both oncologic risk and postoperative recovery trajectories.

With respect to adjuvant treatment modalities, a substantial proportion of patients received radiotherapy in addition to chemotherapy. Although no significant interaction between radiotherapy and chemotherapy timing was identified in this analysis, prior evidence has raised concerns regarding the toxicity and variable benefit of adjuvant radiation in periampullary and pancreatic malignancies (22). The absence of a clear interaction in the present study may have been influenced by the limited sample size and heterogeneity of treatment regimens, warranting cautious interpretation and further investigation. The study had several strengths, including the use of real-world clinical data, comprehensive review of medical records, and evaluation of multiple patient-, tumor-, and treatment-related factors influencing chemotherapy timing. However, several limitations must be acknowledged. The retrospective design limited causal inference and introduced potential selection and information bias. The relatively small sample size reduced statistical power and limited the ability to perform detailed subgroup analyses. In addition, survival outcomes were not adjusted for chemotherapy regimen intensity or dose modifications, which may have influenced results. The single-center nature of the study also limited generalizability to broader populations. Despite these limitations, the findings provided clinically relevant insights, particularly in resource-limited settings where delays in adjuvant therapy are common. Future research should focus on multicenter prospective studies with larger cohorts to validate these findings, incorporate standardized chemotherapy protocols, and explore biological markers that may further refine patient selection for early adjuvant therapy. Interventions aimed at improving perioperative recovery and streamlining oncology referral pathways may also be critical in reducing treatment delays and improving outcomes. Overall, the results supported the growing body of evidence that timely initiation of adjuvant chemotherapy is a key determinant of survival following pancreaticoduodenectomy for periampullary adenocarcinoma. While moderate delays may still allow some therapeutic benefit, prolonged postponement beyond twelve weeks appeared to substantially compromise survival, reinforcing the need for system-level strategies to ensure timely postoperative oncologic care.

## CONCLUSION

This study concluded that earlier initiation of adjuvant chemotherapy following pancreaticoduodenectomy was associated with more favorable survival outcomes in patients with periampullary adenocarcinoma, while progressive delays in treatment initiation were linked to diminishing survival benefit. The findings underscored the clinical importance of timely postoperative oncology care and highlighted that patient-related factors and postoperative recovery play a meaningful role in determining treatment timelines. By addressing a critical evidence gap in the local setting, this study contributed practical insights that support individualized care planning and proactive strategies to reduce avoidable delays. These observations reinforced the need for coordinated multidisciplinary management and provided a foundation for future larger-scale studies to inform context-specific clinical guidelines for optimizing adjuvant chemotherapy timing in this patient population.

### AUTHOR CONTRIBUTIONS

| Author | Contribution |
|---|---|
| Abaid Ullah Shoukat* | Substantial Contribution to study design, analysis, acquisition of Data<br>Manuscript Writing<br>Has given Final Approval of the version to be published |
| Nasir Mehmud Wattoo | Substantial Contribution to study design, acquisition and interpretation of Data<br>Critical Review and Manuscript Writing<br>Has given Final Approval of the version to be published |
| Syed Sohail Kazmi | Substantial Contribution to acquisition and interpretation of Data |

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| Author | Contribution |
|---|---|
| | Has given Final Approval of the version to be published |
| Muhammad Sheraz Abbasi | Contributed to Data Collection and Analysis<br>Has given Final Approval of the version to be published |
| Ammad Ejaz Lone | Contributed to Data Collection and Analysis<br>Has given Final Approval of the version to be published |
| Rameesa Ejaz Lone | Substantial Contribution to study design and Data Analysis<br>Has given Final Approval of the version to be published |

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