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Third-Line Treatment Timing After Second-Line Discontinuation in Advanced Pancreatic Cancer: A 30-Day Landmark Analysis Short title: Third-line treatment timing in pancreatic cancer

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Abstract

Purpose

Evidence for third-line systemic therapy in advanced pancreatic cancer is limited, and observational comparisons risk time-related and selection biases. We evaluated third-line initiation after second-line discontinuation using a 30-day landmark strategy, focusing on treatment timing and patient selection.

Methods

This single-center retrospective cohort included patients with advanced pancreatic cancer discontinuing second-line systemic therapy between October 2014 and October 2025. The primary analysis included ECOG performance status (ECOG PS) 0–1 patients alive and under observation at day 30. Exposure was initiation within 30 days versus no initiation by day 30, with overall survival (OS) measured from the landmark. Complementary analyses included a 45-day landmark, overlap weighting, time-dependent Cox models, and 60-day mortality after initiation.

Results

Among 130 patients, 53 received third-line therapy. The primary 30-day landmark cohort included 48 patients. Early initiation showed a directionally favorable but imprecise association with OS (aHR 0.40, 95% CI 0.15–1.04). Findings were similar at the 45-day landmark (aHR 0.33, 95% CI 0.11–1.02) and attenuated with overlap weighting (aHR 0.68, 95% CI 0.38–1.20). Death within 60 days after initiation occurred in 18.9% of recipients and was associated with ECOG PS ≥ 2.

Conclusion

Among selected patients with preserved ECOG PS alive and observed at day 30, early third-line initiation showed directionally favorable but imprecise OS. This contrast should be interpreted as early versus deferred-or-no initiation within a 30-day decision window, supporting time-bound patient selection and supportive care–integrated decision-making, not definitive causal inference.

Introduction

Advanced pancreatic cancer, most commonly pancreatic ductal adenocarcinoma (PDAC), remains a highly lethal gastrointestinal malignancy, and treatment options become progressively limited after first-line therapy[1, 2]. Combination regimens such as FOLFIRINOX and gemcitabine plus nab-paclitaxel have established modern first-line standards for selected patients[3, 4], and fluoropyrimidine-based regimens, including nanoliposomal irinotecan plus fluorouracil and folinic acid (nal-IRI/5-FU/LV), have supported evidence-based second-line treatment after first-line failure[5, 6]. In contrast, evidence for therapy

beyond the second line remains limited, and current clinical practice guidelines provide little specific direction for third-line systemic therapy[1, 2, 7, 8].

After discontinuation of second-line systemic therapy, clinicians and patients often face a narrow decision window in which to consider third-line treatment or prioritize best supportive care. This decision is not determined by disease progression alone; performance status, symptom burden, nutritional and inflammatory status, biliary complications, treatment toxicity, expected quality of life, and patient goals may change rapidly. Therefore, the clinically relevant question in this setting is not simply whether a patient ever receives third-line therapy, but whether early third-line initiation within a realistic post-discontinuation decision window is associated with subsequent survival among patients who remain plausible candidates for further treatment.

Real-world data are well suited to examine this decision point, but naive comparisons of patients who eventually receive third-line therapy with those who do not are vulnerable to guarantee-time, or immortal time, bias because patients must survive long enough to start treatment. Such comparisons are also vulnerable to selection bias, because fitter patients with lower symptom burden and better organ function are more likely to be offered treatment. A landmark strategy classifies treatment initiation status at a prespecified post-index time point and evaluates subsequent survival among patients who are alive and under observation at that point, thereby aligning the analysis with the clinical decision window and reducing time-related bias[9–12]. However, landmark analyses remain observational and cannot eliminate residual confounding.

Accordingly, this study aimed to evaluate the observational association between early third-line systemic therapy initiation and overall survival after second-line discontinuation in patients with advanced pancreatic cancer, using a prespecified 30-day landmark strategy in an eligibility-restricted cohort with ECOG PS 0–1. Complementary analyses included a 45-day landmark analysis, overlap weighting in a broader ECOG PS 0–2 cohort, exploratory time-dependent Cox models, and an early mortality assessment within 60 days after third-line initiation. The objective was not to establish a definitive causal benefit of third-line therapy, but to provide clinically interpretable evidence for time-bound patient selection and treatment timing after second-line discontinuation.

Methods

Study design and data source

This single-center retrospective cohort study used electronic health records and cancer registry data from Toyama University Hospital, a tertiary referral center in Japan. The study included consecutive adult patients (age ≥ 18 years) with advanced pancreatic cancer, defined as locally advanced unresectable or metastatic disease, who received and subsequently discontinued second-line systemic therapy between October 2014 and October 2025. Advanced pancreatic cancer was confirmed histologically or cytologically when available; when tissue confirmation was unavailable, diagnosis was based on

radiologic findings and documentation by the treating physician. Patients with a history of prior surgical resection for pancreatic cancer were excluded because the study focused on advanced de novo disease. This observational study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

The study was approved by the Institutional Review Board of Toyama University Hospital (approval no. R2025155) and was conducted in accordance with the Declaration of Helsinki. Informed consent was waived owing to the retrospective design, and an opt-out procedure was implemented according to institutional policy.

Index date and exposure definition

The index date was the date of second-line systemic therapy discontinuation. This date was determined by chart review and defined operationally as the final documented administration date of the second-line regimen before definitive treatment cessation. If subsequent resumption of the same second-line regimen was identifiable after a planned delay or temporary interruption, the index date was reassigned to the final administration preceding definitive discontinuation.

The exposure of interest was initiation of third-line systemic therapy after the index date. Third-line therapy was defined as any cytotoxic chemotherapy, targeted therapy, or investigational anticancer treatment initiated as the third sequential line of systemic therapy. Best supportive care (BSC) was defined as symptom-directed care without further systemic anticancer therapy and was recorded when documented in clinical notes or when no subsequent systemic therapy was administered before death or last follow-up.

To reduce guarantee-time (immortal time) bias, the main strategy comparisons used prespecified landmark analyses in which treatment strategy was defined by whether third-line therapy had been initiated within a fixed post-index decision window [9–12]. In the primary 30-day landmark analysis, patients were classified as having initiated third-line therapy within 30 days after the index date versus no initiation by day 30. Patients in the no-initiation-by-day-30 group could subsequently initiate third-line therapy after the landmark; therefore, this comparator represents a deferred-or-no-initiation-within-30-days strategy rather than a strict never-treated group. Complementary time-dependent Cox models treated third-line initiation as a time-varying exposure but were considered exploratory because evolving clinical status may influence both treatment initiation and mortality risk.

Analytic cohorts

The overall cohort comprised all eligible patients with ECOG PS 0–4 who discontinued second-line systemic therapy during the study period. This cohort was used for patient-flow description, treatment-characteristic summaries among third-line recipients, index-based descriptive analyses, and complementary time-dependent Cox models.

The primary eligibility-restricted cohort comprised patients with ECOG PS 0–1 at or near the index date (within 7 days before or after second-line discontinuation) who were alive and under observation at 30 days after the index date. This restriction was intended to approximate patients who would generally remain plausible candidates for third-line therapy and to reduce confounding driven by poor functional status. Under observation was defined as having documented clinical contact, including outpatient visits, hospitalization, laboratory testing, or imaging assessments, on or after the landmark date. The eligibility-restricted cohort was used for the primary 30-day landmark analysis and for baseline-characteristic summaries according to eventual third-line initiation after the index date.

The 45-day landmark sensitivity analysis used the same eligibility-restricted framework, with treatment strategy classified at day 45 and survival measured from day 45. A broader overlap-weighted cohort included patients with ECOG PS 0–2 at the index date who were alive and under observation at the 45-day landmark. This cohort was used for propensity score overlap weighting to estimate a weighted 45-day landmark association among patients with measured covariate profiles compatible with either treatment strategy. Additional analyses in the overall cohort were used to describe how associations changed when patients with poorer functional status were included.

Baseline variables and data collection

Baseline variables were assessed at or closest to the index date; a 14-day window was allowed when values on the exact index date were unavailable. Variables included age, sex, ECOG PS, serum albumin, C-reactive protein (CRP), total bilirubin, carbohydrate antigen 19 – 9 (CA19-9), peritoneal dissemination, liver metastasis, and progression-free survival (PFS) during second-line therapy. Second-line PFS was defined as the time from initiation of second-line therapy to documented radiographic or clinical disease progression or death, whichever occurred first.

For patients who received third-line therapy, regimen category, treatment duration, and reason for third-line discontinuation were abstracted from the medical record. For the exploratory 60-day mortality analysis, ECOG PS and laboratory variables were assessed at or near third-line initiation when available.

The modified Glasgow Prognostic Score (mGPS) was calculated as follows: score 0 for CRP ≤ 1.0 mg/dL; score 1 for CRP > 1.0 mg/dL and albumin ≥ 3.5 g/dL; and score 2 for CRP > 1.0 mg/dL and albumin < 3.5 g/dL [13].

Outcome measures

Outcome measures

The primary outcome was all-cause overall survival (OS). For descriptive analyses from the index date, OS was measured from the index date to death from any cause. For landmark analyses, OS was measured from the landmark date (day 30 or day 45) to death. Patients without a confirmed date of

death were censored at the date of last known clinical contact. Index-based descriptive OS and landmark OS were therefore interpreted as distinct quantities.

As an exploratory patient-selection analysis among patients who initiated third-line therapy, early mortality was defined as death within 60 days after third-line initiation. This pragmatic window was used to describe patients who died before having a plausible opportunity to derive benefit from further systemic therapy. The analysis was intended to identify clinical factors associated with early mortality and was not designed to develop or validate a prediction model.

Statistical analysis

Baseline characteristics are summarized as median (interquartile range [IQR]) for continuous variables and number (percentage) for categorical variables. Group comparisons used the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. For Table 1, groups were defined by eventual initiation of third-line therapy after the index date, not by 30-day landmark strategy. OS was estimated using the Kaplan-Meier method.

Table 1
Baseline characteristics in the eligibility-restricted cohort (ECOG PS 0–1)

Characteristic	Third-line after index (n = 40)	No third-line/BSC (n = 8)	p-value
Age, years	66 (56–73)	68 (62–72)	0.729
Male sex, n (%)	25 (62.5)	2 (25.0)	0.115
ECOG performance status at index, n (%)			0.320
0	8 (20.0)	0 (0.0)	
1	32 (80.0)	8 (100.0)	
Second-line PFS, days	123 (71–186)	102 (75–186)	0.978
CRP, mg/dL	0.8 (0.2–2.1)	0.7 (0.2–3.2)	0.843
Albumin, g/dL	3.6 (3.1–3.8)	3.4 (3.2–3.6)	0.743
Total bilirubin, mg/dL	0.4 (0.3–0.7)	0.5 (0.5–0.5)	0.698
CA19-9, U/mL	742 (47–4506)	182 (72–9646)	0.802
Missing	3	1	
Peritoneal dissemination, n (%)	13 (32.5)	3 (37.5)	1.000
Liver metastasis, n (%)	36 (90.0)	4 (50.0)	0.018

Values are median (interquartile range) or n (%), unless otherwise indicated. Groups are defined by eventual initiation of third-line therapy after the index date, not by 30-day landmark strategy classification. P-values were calculated using the Mann-Whitney U test or Fisher's exact test, as appropriate. mGPS was calculated using CRP and albumin at index: mGPS = 2 if CRP > 1.0 mg/dL and albumin < 3.5 g/dL; mGPS = 1 if only one criterion was met; mGPS = 0 if neither criterion was met.

In the primary 30-day landmark analysis, patients alive and under observation at day 30 were classified according to initiation of third-line therapy within 30 days versus no initiation by day 30, and OS was estimated from day 30 onward. Multivariable Cox proportional hazards regression was used to estimate the association between the 30-day strategy and OS. The 30-day window was selected as a clinically plausible decision period after second-line discontinuation, allowing time for recovery from treatment toxicity, reassessment of disease status, and shared decision-making regarding third-line therapy.

The primary estimand was a conditional treatment strategy association among patients with ECOG PS 0–1 at index who were alive and under observation at day 30. Accordingly, the estimate should not be interpreted as the effect of third-line therapy in the entire index cohort. Prespecified covariates for adjusted Cox models included age, sex, albumin, CRP, total bilirubin, PFS during second-line therapy,

peritoneal dissemination, and liver metastasis. Models in the overall cohort additionally included ECOG PS. The proportional hazards assumption was assessed using Schoenfeld residuals.

A 45-day landmark sensitivity analysis used the same approach, with exposure classified at day 45 and survival estimated from day 45 onward [9–11].

For the overlap-weighted sensitivity analysis, propensity scores for initiation of third-line therapy by the 45-day landmark were estimated using logistic regression with prespecified baseline covariates: age, sex, ECOG PS, albumin, CRP, total bilirubin, PFS during second-line therapy, peritoneal dissemination, and liver metastasis. Overlap weights were defined as 1 - propensity score for patients who initiated third-line therapy by the landmark and as the propensity score for those who did not. Weighted Cox regression was then performed from day 45 to death or censoring. Covariate balance after weighting was assessed using standardized mean differences (SMDs), with SMD < 0.10 considered adequate balance; the effective sample size after weighting was calculated.

Time-dependent Cox regression models were fitted as exploratory or complementary analyses in both the eligibility-restricted cohort and the overall cohort, with third-line initiation modeled as a time-varying exposure. These models were used to address exposure classification over follow-up but were interpreted cautiously because time-varying clinical deterioration could confound both treatment initiation and mortality.

For the exploratory early mortality analysis among patients receiving third-line therapy, univariable and multivariable logistic regression evaluated associations between clinical variables assessed at or near third-line initiation and death within 60 days after treatment initiation. ECOG PS ≥ 2, mGPS = 2, and total bilirubin were prespecified for the multivariable model to maintain parsimony given the limited number of events. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. The apparent area under the receiver operating characteristic curve (AUC) was calculated for the multivariable model, without internal or external validation.

All multivariable models used complete-case analysis without imputation for missing covariate data. Patients with missing values in any covariate included in a given model were excluded from that model; missingness in adjusted models is summarized in Supplementary Table S1 in Online Resource 1. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria) with the survival, survminer, PSweight, and pROC packages.

Results

Patient selection and analytic cohorts

Figure 1 shows the patient flow and analytic cohorts. Between October 2014 and October 2025, 130 consecutive patients with advanced pancreatic cancer discontinued second-line systemic therapy and

met the inclusion criteria. Of these, 53 patients (40.8%) subsequently initiated third-line systemic therapy, whereas 77 (59.2%) did not receive further systemic treatment and were managed with best supportive care or died without additional chemotherapy. Among patients who initiated third-line therapy, the median interval from second-line discontinuation to third-line initiation was 10 days (IQR, 6–23 days).

Table 2
Association between third-line initiation strategies and overall survival

Analysis	**Adjusted HR (95% CI)**	**p-value**	**Sample size analyzed/eligible**
ECOG PS 0–1 cohort			
30-day landmark	0.40 (0.15–1.04)	0.060	47/48
45-day landmark	0.33 (0.11–1.02)	0.055	45/46
Time-dependent Cox	0.15 (0.05–0.51)	0.002	47/48
Overall cohort (ECOG PS 0–4)			
Time-dependent Cox	0.54 (0.31–0.95)	0.031	n = 127
Overlap-weighted 45-day landmark (ECOG PS 0–2)	0.68 (0.38–1.20)	0.183	n = 77

Hazard ratios are adjusted for prespecified covariates described in the Methods section. For these observational analyses, effect estimates and confidence intervals should be emphasized over p-values. Sample sizes reflect complete-case analyses for covariates included in each model and, for landmark analyses, only patients who were alive at the landmark time. Landmark analyses classified exposure as initiation of third-line therapy by the landmark and estimated survival from the landmark among patients alive at that time; the primary analysis was the 30-day landmark strategy comparison in the eligibility-restricted cohort (ECOG PS 0–1). Time-dependent Cox models treated third-line initiation as a time-varying exposure and are presented as exploratory/complementary analyses only; these estimates may remain vulnerable to time-varying confounding and should not be interpreted as stronger evidence of treatment benefit. Multivariable models were adjusted for age, sex, albumin, CRP, total bilirubin, PFS during second-line therapy, peritoneal dissemination, and liver metastasis; models in the overall cohort additionally adjusted for ECOG PS. The overlap-weighted analysis used propensity score-based overlap weights at the 45-day landmark in the ECOG PS 0–2 cohort. Complete-case analyses excluded patients with missing values in any covariates included in the respective models. In the primary 30-day landmark model, one patient was excluded due to missing CRP data (final n = 47).

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS, progression-free survival; PS, performance status.

The primary 30-day landmark cohort comprised 48 patients with ECOG PS 0–1 at the index date who were alive and under observation at day 30. Within this cohort, 36 patients had initiated third-line therapy by day 30, and 12 had not. The 45-day landmark sensitivity analysis included 46 patients at risk. Complete covariate data were available for 47 of 48 patients in the primary multivariable model; missing data for adjusted models are summarized in Supplementary Table S1 in Online Resource 1.

Third-line treatment characteristics

Among the 53 patients who received third-line therapy, the most common regimens were fluoropyrimidine-based therapy (45.3%), gemcitabine-based therapy (26.4%), nanoliposomal irinotecan-based therapy (15.1%), and other regimens or clinical trial agents (13.2%). The median duration of third-line therapy was 65 days (IQR, 35–98 days). The main reason for discontinuing third-line therapy was disease progression (73.6%), followed by PS deterioration (15.1%), patient preference (7.5%), and death during treatment (3.8%). Nanoliposomal irinotecan plus fluorouracil/folinic acid (nal-IRI/5-FU/LV) was categorized separately.

Baseline characteristics in the primary analytic population

Baseline characteristics of the eligibility-restricted cohort are summarized in Table 1 according to eventual initiation of third-line therapy after the index date (third-line, n = 40; no third-line/BSC, n = 8). Patients who subsequently received third-line therapy and those who did not were generally similar with respect to age, ECOG PS, second-line PFS, inflammatory and nutritional markers, bilirubin, CA19-9, and peritoneal dissemination.

Liver metastasis was more frequent among patients who subsequently received third-line therapy than among those who did not (90.0% vs. 50.0%; p = 0.018). This imbalance indicates that treatment allocation after second-line discontinuation was shaped by clinical trajectories and other measured or unmeasured factors; accordingly, subsequent survival analyses should be interpreted as observational associations rather than causal effects.

Primary 30-day landmark strategy comparison

For clinical context, in the eligibility-restricted cohort (ECOG PS 0–1; n = 48), median OS from the index date was 142 days (95% CI, 98–200) among patients who eventually received third-line therapy (n = 40) and 100 days (95% CI, 35–190) among those who did not (n = 8). These index-based estimates do not account for time-related bias or treatment decisions occurring after second-line discontinuation.

The primary analysis compared strategies defined at the 30-day landmark: initiation of third-line therapy within 30 days versus no initiation by day 30. In the 30-day landmark analysis, initiation by day 30 was associated with longer subsequent OS from the landmark, although the estimate was imprecise and the confidence interval included the null (aHR 0.40, 95% CI 0.15–1.04; Table 2; Fig. 2A). Among the 12 patients who had not initiated third-line therapy by day 30, 4 (33%) subsequently initiated therapy after the landmark, whereas 8 (67%) did not initiate during follow-up. Thus, the comparator group represents a deferred-or-no-initiation strategy within the prespecified decision window rather than a strict never-treated group.

Sensitivity and complementary analyses

Sensitivity and complementary analyses are summarized in Table 2. In the 45-day landmark sensitivity analysis, the direction of association was similar but remained imprecise (aHR 0.33, 95% CI 0.11–1.02; Fig. 2B). For the overlap-weighted analysis, the 45-day ECOG PS 0–2 overlap cohort included 78 eligible patients before complete-case analysis and 77 patients in the weighted Cox model, consistent with the missing-data summary in Online Resource 1.

In the overall cohort (ECOG PS 0–4; n = 130), the time-dependent multivariable Cox model suggested a directional association between third-line initiation and longer OS (aHR 0.54, 95% CI 0.31–0.95). By contrast, landmark analyses in the overall cohort produced attenuated estimates (30-day landmark: aHR 0.68, 95% CI 0.39–1.17; 45-day landmark: aHR 0.55, 95% CI 0.30–1.01). In the ECOG PS 0–2 overlap cohort, propensity score overlap weighting at the 45-day landmark yielded a similarly attenuated estimate (aHR 0.68, 95% CI 0.38–1.20).

After overlap weighting, measured covariates were well balanced between strategies (all standardized mean differences < 0.10), and the effective sample size was 43.3. Taken together, these analyses suggest that the favorable association observed in the ECOG PS 0–1 primary landmark cohort was less pronounced in broader and more clinically heterogeneous populations.

An exploratory time-dependent Cox model in the eligibility-restricted cohort showed a numerically stronger association (aHR 0.15, 95% CI 0.05–0.51; p = 0.002; Table 2). This analysis was used only to assess the direction of association under time-varying exposure classification. Because time-dependent models may be affected by changes in clinical status that simultaneously influence treatment initiation and mortality risk, this estimate should not be interpreted as stronger evidence of treatment benefit.

Early mortality after third-line initiation

Among the 53 patients who initiated third-line therapy, 10 (18.9%) died within 60 days of treatment initiation. Among these 10 patients, the median OS from third-line initiation was 27 days (IQR, 17–46 days). In univariable logistic regression, ECOG PS ≥ 2 at initiation was strongly associated with 60-day mortality (OR 14.39, 95% CI 2.89–71.57; p = 0.001; Table 3). An mGPS of 2 showed a borderline association (OR 4.36, 95% CI 0.98–19.34; p = 0.053), whereas total bilirubin was not associated with 60-day mortality (OR per 0.1 mg/dL increase, 1.09, 95% CI 0.95–1.25; p = 0.210). In the multivariable model, ECOG PS ≥ 2 remained associated with early mortality (OR 13.17, 95% CI 2.32–74.92; p = 0.004), whereas mGPS = 2 and total bilirubin were not statistically significant.

Table 3
Exploratory analysis of 60-day mortality after third-line initiation among third-line recipients (events: 10/53)

Predictor	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
ECOG PS ≥ 2	14.39 (2.89–71.57)	0.001	13.17 (2.32–74.92)	0.004
mGPS = 2	4.36 (0.98–19.34)	0.053	2.02 (0.36–11.49)	0.427
Total bilirubin (per 0.1 mg/dL)	1.09 (0.95–1.25)	0.210	1.10 (0.93–1.30)	0.248
The multivariable model included ECOG PS ≥ 2, mGPS = 2, and total bilirubin. Given the small number of events (10 deaths within 60 days), this analysis is exploratory and intended to support clinical interpretation rather than to develop a definitive prediction model or risk score.				

The exploratory ROC analysis for the multivariable model showed an apparent AUC of 0.83 (Supplementary Figure S1 in Online Resource 1). Because this estimate was derived from a small number of events without internal validation or calibration, it should not be interpreted as a validated prediction model. Rather, the early mortality analysis indicates that ECOG PS ≥ 2 may mark a subgroup at high risk for early death after third-line initiation, supporting careful patient selection when considering treatment beyond second line.

Discussion

In this single-center retrospective cohort of patients with advanced pancreatic cancer who discontinued second-line systemic therapy, the primary 30-day landmark strategy comparison showed a directionally favorable but imprecise association between third-line initiation within 30 days and subsequent OS among patients with ECOG PS 0–1 who were alive and under observation at the landmark. The adjusted point estimate favored early initiation (aHR 0.40, 95% CI 0.15–1.04), but the confidence interval included the null. The 45-day landmark sensitivity analysis showed a similar direction (aHR 0.33, 95% CI 0.11–1.02), whereas overlap weighting in a broader ECOG PS 0–2 cohort attenuated the association (aHR 0.68, 95% CI 0.38–1.20). Exploratory time-dependent Cox models yielded numerically stronger estimates, but these estimates should be interpreted cautiously. The 60-day mortality analysis further suggested that ECOG PS ≥ 2 may mark patients at high risk for death soon after third-line initiation.

These findings are most relevant to the short clinical decision window after second-line discontinuation. In advanced pancreatic cancer, this period often requires rapid reassessment of disease progression, recovery from treatment toxicity, biliary complications, nutritional decline, pain, expected quality of life, and patient goals. The comparison in this study was not third-line therapy versus no therapy. Rather, it was early initiation versus deferred-or-no initiation by day 30 among patients who remained alive and observable at that decision point. Therefore, the results should not be read as a blanket recommendation for third-line therapy. They instead support a time-bound approach in which the feasibility of further

systemic therapy is reassessed promptly and explicitly, while best supportive care planning and goals-of-care discussions proceed in parallel rather than being deferred until treatment options are exhausted.

The analytic design is central to this interpretation. A landmark strategy is not merely a statistical device; in this setting, it approximates the timing of the post-second-line treatment decision. Naive comparisons between patients who ever receive third-line therapy and those who do not can be misleading because treated patients must survive long enough to start treatment. By defining treatment status at a prespecified landmark and estimating subsequent survival only among patients alive and under observation at that time, the landmark approach reduces guarantee-time bias and aligns the estimand with a clinically recognizable decision point[9–12]. However, the resulting estimate remains conditional on survival and observation to the landmark and should not be interpreted as an intention-to-treat effect for the entire index cohort. Although time-dependent Cox models address changing exposure status during follow-up, they may still be affected by time-varying clinical deterioration that influences both treatment initiation and mortality. The attenuation in the ECOG PS 0–2 overlap-weighted cohort is therefore informative rather than contradictory: it suggests that the association observed in the primary ECOG PS 0–1 landmark cohort may not generalize to a broader population with greater functional heterogeneity.

Evidence for third-line systemic therapy in advanced pancreatic cancer remains limited, and most available data are retrospective or strongly shaped by patient selection, regimen availability, and local treatment practice[14–18]. Previous reports have generally described outcomes among patients who actually received third-line chemotherapy, compared treatment categories, or explored prognostic factors after third-line initiation. The present study addresses a different question: how early versus deferred-or-no initiation within a defined post-second-line window relates to subsequent survival among patients who remain plausible candidates for further therapy. Contemporary guidelines provide clearer evidence-based options for first- and second-line treatment, whereas recommendations beyond second line remain less specific and emphasize careful selection, PS, and supportive care considerations[1, 2, 7, 8]. In this context, the contribution of this study is not to establish third-line therapy as a standard treatment, but to frame post-second-line management as a short-window strategy question. Although treatment access, regimen sequencing, and supportive care pathways vary across health systems, the rapid reassessment of candidacy for further systemic therapy after second-line discontinuation is a shared challenge in advanced pancreatic cancer practice. The findings may therefore be most generalizable as a decision-making framework rather than as regimen-specific efficacy evidence.

The exploratory early mortality analysis provides a complementary patient-selection perspective. Among the 53 patients who initiated third-line therapy, 10 (18.9%) died within 60 days, and their median OS from third-line initiation was 27 days. ECOG PS ≥ 2 at initiation was strongly associated with early mortality, whereas the apparent AUC of the multivariable model should be regarded as optimistic because it was derived from a small number of events without validation. This analysis should therefore not be used as a clinical prediction model or decision rule. Nevertheless, it underscores the need to incorporate early

mortality risk, symptom burden, nutritional and inflammatory status, goals of care, and timely supportive care integration when considering treatment beyond second line[19, 20].

This study has several strengths. It used a consecutive real-world cohort, focused on a clinically relevant post-second-line decision point, prespecified a landmark strategy to reduce guarantee-time bias, evaluated robustness using complementary analytic approaches, and explicitly assessed early mortality after third-line initiation. The limitations are substantial and should guide interpretation. This was a retrospective single-center study with a small sample size, a small comparator group at the 30-day landmark, and wide confidence intervals. Residual confounding remains likely despite adjustment, particularly from unmeasured factors such as symptom burden, frailty, nutritional decline, contraindications to chemotherapy, physician judgment, and patient preference. The landmark estimand is conditional on being alive and under observation at the landmark and is not generalizable to all patients at second-line discontinuation. Second-line discontinuation timing may also have been misclassified when treatment pauses or temporary interruptions were difficult to distinguish from definitive cessation. Finally, the early mortality analysis was exploratory and unvalidated, and the findings require confirmation in larger, preferably multicenter cohorts.

In conclusion, initiation of third-line systemic therapy within 30 days after second-line discontinuation showed a directionally favorable but imprecise association with longer subsequent survival among carefully selected patients with advanced pancreatic cancer, preserved ECOG PS, and survival to the 30-day landmark. This finding should be interpreted as early initiation versus deferred-or-no initiation within a defined clinical decision window, not as evidence of a definitive treatment-versus-no-treatment effect or causal benefit. Third-line treatment decisions should be individualized, time-bound, and integrated with assessment of symptoms, functional status, patient goals, and supportive care needs. Prospective and multicenter studies are needed to clarify which patients are most likely to derive meaningful benefit from further systemic therapy after second-line discontinuation.

Abbreviations

BSC
best supportive care
CA19-9
carbohydrate antigen 19 – 9
CRP
C-reactive protein
ECOG
Eastern Cooperative Oncology Group
mGPS
modified Glasgow Prognostic Score
PFS
progression-free survival

PS
performance status.

Declarations

Authors' contributions: KN and SK conceived the study. KN and SK curated data. KN, SK, YN, YU, IM, AT, BO, HK, JS, TE, and NH contributed to data acquisition and interpretation. KN and SK performed the analyses and drafted the manuscript. IY provided critical revisions. All authors read and approved the final manuscript.

Ethics Approval: The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Toyama University Hospital (approval no. R2025155).

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References

1. Okusaka T, Nakamura M, Yoshida M, Kitano M, Ito Y, Mizuno N, et al. Clinical Practice Guidelines for Pancreatic Cancer 2022 from the Japan Pancreas Society: a synopsis. Int J Clin Oncol. 2023;28(4):493–511. 10.1007/s10147-023-02317-x.

2. Conroy T, Pfeiffer P, Vilgrain V, Lamarca A, Seufferlein T, O'Reilly EM, et al. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(11):987–1002. 10.1016/j.annonc.2023.08.009.
3. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25. 10.1056/NEJMoa1011923.
4. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703. 10.1056/NEJMoa1304369.
5. Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016;387(10018):545–57. 10.1016/s0140-6736(15)00986-1.
6. Pelzer U, Schwaner I, Stieler J, Adler M, Seraphin J, Dörken B, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. Eur J Cancer. 2011;47(11):1676–81. 10.1016/j.ejca.2011.04.011.
7. Conroy T, Ducreux M. ESMO Clinical Practice Guideline Express Update on the management of metastatic pancreatic cancer. ESMO Open. 2025;10(4):104528. 10.1016/j.esmoop.2025.104528.
8. Springfeld C, Bailey P, Büchler MW, Neoptolemos JP. ESMO 2023 pancreatic cancer guidelines signal stepwise progress. Hepatobiliary Surg Nutr. 2024;13(2):362–5. 10.21037/hbsn-24-37.
9. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol. 2008;167(4):492–9. 10.1093/aje/kwm324.
10. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol. 2013;31(23):2963–9. 10.1200/jco.2013.49.5283.
11. Zabor EC, Assel M. On the Need for Landmark Analysis or Time-dependent Covariates. J Urol. 2023;209(6):1060–2. 10.1097/ju.0000000000003459.
12. Tsuruda KM, Hektoen HH, Costa DR, Andreassen BK. Immortal time bias in survival outcomes when comparing treatment with chemotherapy versus immunochemotherapy for non-small cell lung cancer. Translational Lung Cancer Res. 2025;14(1):300–2.
13. Fu W, Wang K, Yan S, Wang X, Tang B, Chang J, et al. Prognostic Significance of the Modified Glasgow Prognostic Score in Patients With Pancreatic Cancer: A Meta-Analysis. Dose Response. 2020;18(3):1559325820942065. 10.1177/1559325820942065.
14. Talbot A, Talbot T, Shaughnessy E, Glass A, Das A, Watanabe Y, et al. Overall survival and treatment modalities in pancreatic adenocarcinoma: a retrospective analysis of a single centre in Western Australia. J Gastrointest Oncol. 2023;14(5):2221–8.
15. Evrard C, Pelras A, Rivet S, Bachet J-B, Dubreuil O, Pointet A-L, et al. Predictive and prognostic factors of efficacy of third-line chemotherapy in patients with unresectable pancreatic cancer: a

cohort-based study. Oncologist. 2025;30(6):oyaf125. 10.1093/oncolo/oyaf125.

16. Miwa K, Kawasaki R, Shimokawa M, Otsuka T, Tanaka T, Fukahori M, et al. Efficacy of third-line chemotherapy following nanoliposomal irinotecan combined with fluorouracil and folinic acid as second-line treatment for unresectable pancreatic cancer. Front Oncol. 2025;15:1626689. 10.3389/fonc.2025.1626689.
17. Adashek JJ, Moran JA, Le DT, Kurzrock R. Lessons learned from a decade of immune checkpoint inhibition: The good, the bad, and the ugly. Cancer Metastasis Rev. 2025;44(2):43. 10.1007/s10555-025-10260-8.
18. Lu HR, Zhu PF, Deng YY, Chen ZL, Yang L. Third-line treatment options in metastatic pancreatic cancer patients: a real-world study. Front Oncol. 2023;13:1251258. 10.3389/fonc.2023.1251258.
19. Ho PYP, Lee HFV. Factors correlating with shorter survival after treatment: aiding oncologists to choose who (not) to receive palliative systemic therapy. Annals Palliat Med. 2019;9(6):4430–45.
20. Law B, Windsor J, Connor S, Koea J, Srinivasa S. Best supportive care in advanced pancreas cancer: a systematic review to define a patient-care bundle. ANZ J Surg. 2024;94(7–8):1254–9. https://doi.org/10.1111/ans.18906.

Figures

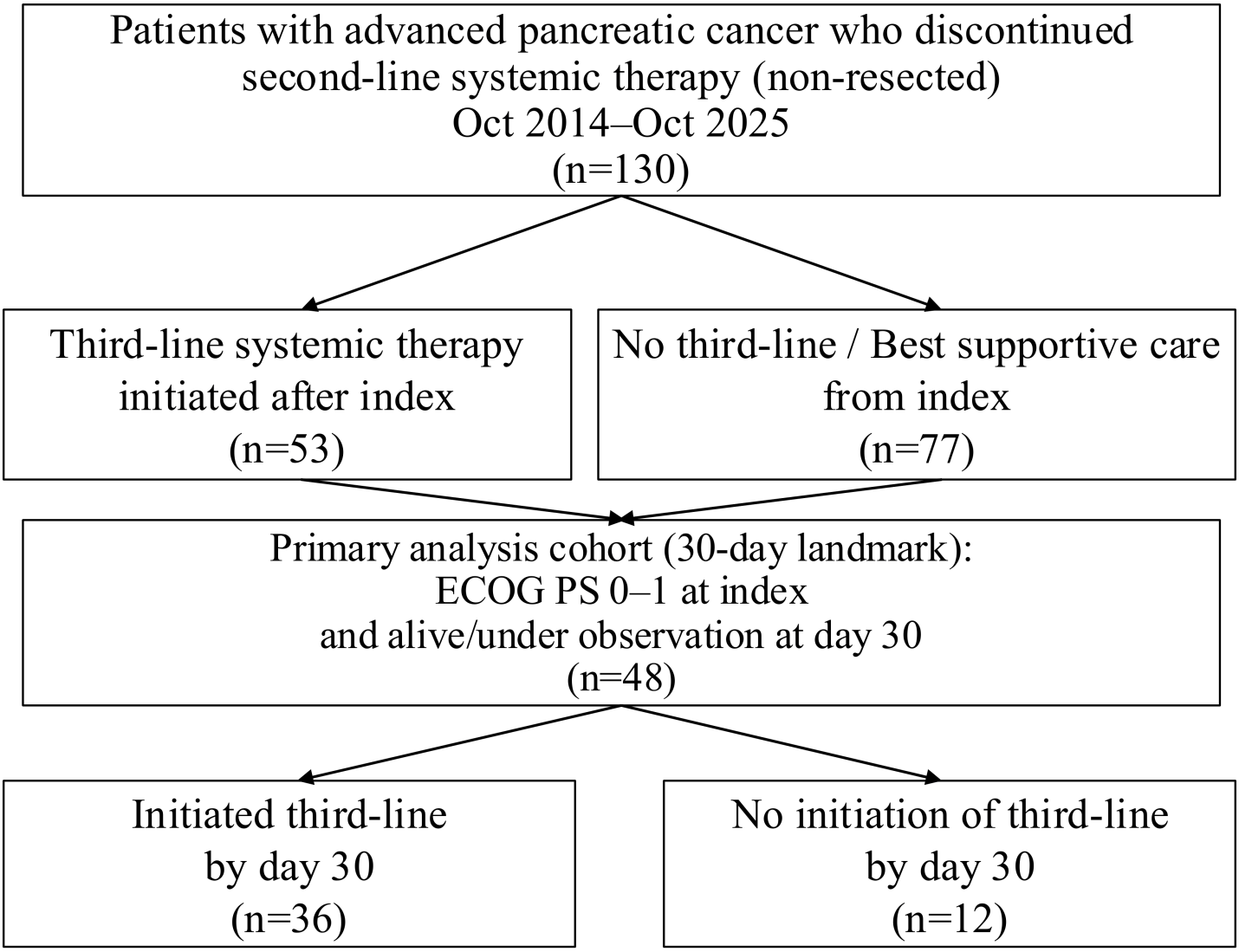
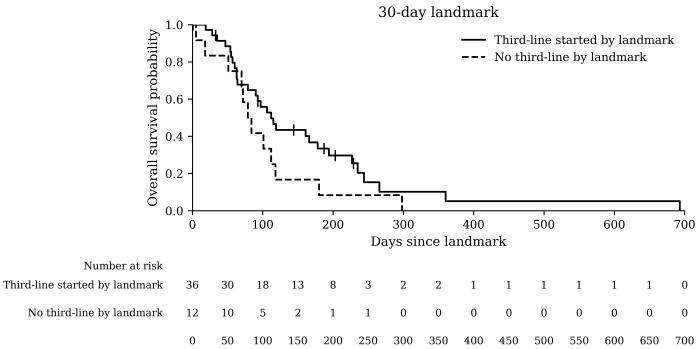


Figure 1

Patient flow and analytic cohorts

The index date was defined as the date of second-line discontinuation. The eligibility-restricted cohort comprised patients with ECOG PS 0-1 at index. The primary analysis cohort (30-day landmark) included patients from this eligibility-restricted cohort who were alive and under observation at day 30. For the 30-day landmark strategy comparison, 48 patients were alive and under observation at day 30 (initiated third-line by day 30, n = 36; no initiation by day 30, n = 12) and were followed for OS from day 30 onward. For the 45-day landmark sensitivity analysis, 46 patients were at risk at day 45 (initiated by day 45, n = 37; no initiation by day 45, n = 9). Patients classified as no initiation by the landmark could still initiate third-line therapy after the landmark. Table 1 summarizes baseline characteristics according to eventual initiation of third-line therapy at any time after index (n = 40 vs. n = 8), which differs from the landmark risk-set definitions used in Figure 2 and Table 2.



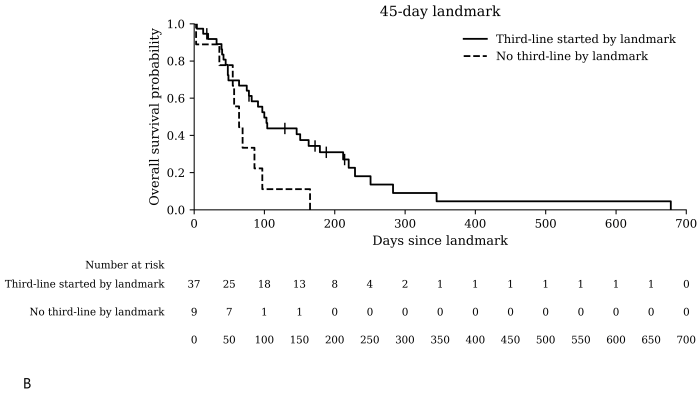


Figure 2

Landmark Kaplan-Meier curves for overall survival in the eligibility-restricted cohort (ECOG PS 0-1 at index)

Panel A shows the 30-day landmark analysis, and Panel B shows the 45-day landmark sensitivity analysis. Time zero corresponds to the landmark time point after second-line discontinuation, and follow-up is measured from the landmark onward. At the 30-day landmark, 36 patients had initiated third-line therapy by day 30 and 12 had not; at the 45-day landmark, 37 had initiated by day 45 and 9 had not. The no-initiation-by-landmark group may include patients who initiated third-line therapy after the landmark. Abbreviations: ECOG, Eastern Cooperative Oncology Group; KM, Kaplan-Meier; OS, overall survival; PS, performance status.

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