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Original Article

The impact of starting dose with or without subsequent dose escalation of liposomal irinotecan on treatment outcomes in patients with metastatic pancreatic ductal adenocarcinoma

Nai-Jung Chiang[1,2], Yan-Shen Shan[3], Chung-Pin Li[1,4,5], Shih-Hung Yang[6], Yung-Yeh Su[7], Sz-Chi Chiu[8], Li-Yuan Bai[9], Shih-Chang Chuang[10], De-Chuan Chan[11], Chia-Jui Yen[12], Cheng-Ming Peng[13], Tai-Jan Chiu[14], Yen-Yang Chen[14], Jen-Shi Chen[15], Wen-Chi Chou[15]

[1]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan; [2]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; [3]Division of General Surgery, Department of Surgery, National Cheng Kung University Hospital, Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [4]Division of Clinical Skills Training, Department of Medical Education, Taipei Veterans General Hospital, Taipei, Taiwan; [5]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [6]Department of Oncology, National Taiwan University Hospital and National Taiwan University, Taipei, Taiwan; [7]National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan; [8]PharmaEngine, Inc., Taipei, Taiwan; [9]Division of Hematology-Oncology, Department of Internal Medicine, China Medical University Hospital and China Medical University, Taichung, Taiwan; [10]Division of General and Digestive Surgery, Department of Surgery, Kaohsiung Medical University Hospital and Kaohsiung Medical University, Kaohsiung, Taiwan; [11]Division of General Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; [12]Division of Hematology and Oncology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [13]Department of Surgery, Chung Shan Medical University Hospital and Chung Shan Medical University, Taichung, Taiwan; [14]Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University, Kaohsiung, Taiwan; [15]Division of Hematology-Oncology, Department of Internal Medicine, Linkou Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taoyuan, Taiwan

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Abstract: Liposomal irinotecan (nal-IRI) plus 5-fluorouracil and leucovorin (5-FU/LV) improves survival in patients with pancreatic ductal adenocarcinoma (PDAC) after progression to gemcitabine-based therapy. Few studies have examined whether the starting dose and dose escalation of nal-IRI in subsequent treatment cycles may influence patient outcomes and toxicity profiles. A total of 667 patients who received nal-IRI + 5-FU/LV for PDAC treatment between August 2018 and November 2020 at nine medical centers in Taiwan were included and retrospectively analyzed. Patients were allocated to the standard starting dose (SD), reduced starting dose (RD) without escalation, and RD with escalation of nal-IRI groups for comparison of survival outcome and safety. Propensity score matching (PSM) was performed to adjust for possible confounding variables. Nal-IRI was prescribed at SD, RD without escalation, and RD with escalation in 465 (69.7%), 147 (22.0), and 55 (8.2%), respectively. RD with escalation patients had significantly longer treatment cycles (6, range 2-25) than SD (5, range 1-42, P<0.001) and RD without escalation patients (4, range 1-26, P<0.001). The median overall survival (OS) of the patients were as follows: SD, 6.2 months (95% confidence interval [CI], 5.7-6.7); RD with escalation, 7.6 months (95% CI, 6.1-9.2); and RD without escalation, 3.6 months (95% CI, 2.6-4.5). After PSM to adjust for potential confounders, RD without escalation patients still had the poorest OS compared to the other two groups (P<0.001), while the OS difference between SD and RD with escalation patients was insignificant (P=0.10). SD patients had higher incidences of ≥ grade 3 neutropenia and febrile neutropenia than the other two groups. Administering nal-IRI at RD followed by dose escalation in subsequent treatment cycles is safe and does not compromise survival outcomes in selected patients with PDAC receiving nal-IRI plus 5-FU/LV.

Keywords: Pre-emptive dose reduction, dose escalation, nanoliposomal irinotecan, drug compliance, tolerance

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the seventh leading cause of cancer-related death worldwide [1]. Palliative chemotherapy is the most common treatment strategy for PDAC, as more than 80% of patients have unresectable or metastatic disease at the initial diagnosis [2]. Liposomal irinotecan (nal-IRI) plus 5-fluorouracil and leucovorin (5-FU/LV) is currently the standard of care for patients with metastatic PDAC who have progressed on gemcitabine-based therapy based on the pivotal phase III study, NAPOLI-1 [3].

In NAPOLI-1, patients who received nal-IRI plus 5-FU/LV had a 1.9 months absolute survival benefit compared to those who received 5-FU/LV as subsequent treatment for metastatic PDAC after progression on gemcitabine-based therapy [3]. In the Asian subgroup of NAPOLI-1, the magnitude of survival benefit was more obvious with an absolute survival difference of 5.2 [4]. However, toxicity is one of the primary limitations of nal-IRIs. The most common grade 3-4 toxicity was neutropenia at a rate of 27% in the nal-IRI plus 5-FU/LV arm compared to 1% in the 5FU/LV arm in NAPOLI-1 [3]. As a result, 33% of patients in the nal-IRI plus 5-FU/LV arm required dose reduction due to toxicity, as opposed to 4% of those in the 5-FU/LV arm in NAPOLI-1 [3].

Nal-IRI is commonly prescribed at a starting dose of 80 mg/m^2 (equivalent to 70 mg/m^2 of irinotecan base) [3]. One expanded analysis from the NAPOLI-1 showed a significant survival advantage in per-protocol (defined as patients receiving ≥80% of planned treatment during the first 6 weeks) than in non-per-protocol patients, highlighting the importance of sustained drug intensity of nal-IRI for efficacy in PDAC patients [5]. In the clinical trial setting, reduction in the nal-IRI starting dose is a common scenario that ranges from 20-40% in clinical practice based on real-world retrospective studies [6-12]. Some real-world studies have reported that reduced nal-IRI starting doses do not influence treatment efficacy [8-9]. Furthermore, our previous analysis showed a comparable survival outcome between patients receiving nal-IRI starting doses >75% and 50-75% of the standard dosage. However, significantly poor survival was observed in patients who received nal-IRI, with a standard dosage of <50% [11]. As a result, the effect of nal-IRI starting dose on survival outcome is contradictory and limited by small-scale retrospective analysis [6-10] or analysis only by multivariate analysis to adjust for possible confounders [9, 11]. Furthermore, our previous study showed that a lower nal-IRI starting dose followed by an escalation strategy could achieve survival outcomes comparable to those with a standard nal-IRI starting dose for mPDAC patients in real-world practice [12]. Unfortunately, the effect of the nal-IRI dose-escalation strategy on survival outcomes might not have been fully explored because only univariate analysis was conducted in that study [12]. Meanwhile, the present study aimed to use propensity score matching (PSM) to minimize statistical bias to examine if a reduced starting dose of nal-IRI followed by dose escalation was associated with survival differences compared to those prescribed at a standard starting dose and those prescribed at a reduced starting dose without subsequent dose escalation. Furthermore, the effect of a reduced starting dose on the total treatment duration and severe adverse events (SAEs, defined as grade III or higher adverse events) will also be investigated.

Methods

Patient selection

We retrospectively reviewed the medical records of patients who received nal-IRI plus 5-FU/LV for PDAC treatment between August 2018 and November 2020 at nine medical centers in Taiwan. The inclusion criteria were as follows: age >20 years, pathological or cytological diagnosed of mPDAC, and received nal-IRI plus 5FU/LV. Patients who receipt of concurrent radiotherapy or lost of regular follow up were excluded.

The standard dosing of nal-IRI plus 5-FU/LV should be nal-IRI 80 mg/m^2 intravenously over 90 minutes, followed by LV 400 mg/m^2 intravenously over 30 minutes and 5-FU 2400 mg/m^2 over 46 hours every 2 weeks according to NAPOLI-1 [3]. However, the actual nal-IRI dosing at the beginning and subsequent treatment cycles was determined by the primary care physicians. A total of 667 patients were included in this study. This study was approved by the institutional review boards of all the investigated institutes. The requirement for informed con-

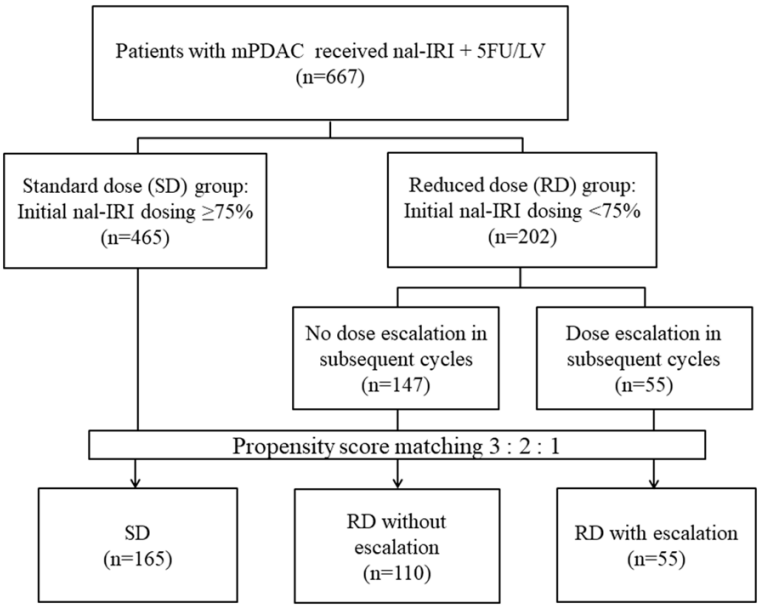

Figure 1. Study flow chart.

sent was waived because of the retrospective nature of the analysis, and all data were de-identified and encrypted.

Definition of study groups

Data on nal-IRI dosing at every treatment cycle, dose intensity, and total number of treatment cycles were obtained for each patient. All patients were first allocated to the standard dose (SD) and reduction dose (RD) groups according to the starting dose ≥75% (60 mg/m^2 nal-IRI, equivalent to 50 mg/m^2 of irinotecan base) or <75% (one more dose reduction) of the standard dose according to the NAPOLI-1 study protocol [3]. The reduction dose (RD) group was further divided into dose escalation and without dose escalation, depending on whether patients had increased ≥10% nal-IRI dose of the starting dose in any subsequent treatment cycle. **Figure 1** shows a flowchart of the study.

Data collection

We retrospectively collected data on the demographic, clinicopathological, and laboratory variables at the beginning of nal-IRI + 5-FU/LV treatment. Imaging studies were conducted during regular follow-up every 8-12 weeks or were clinically indicated during the period of chemotherapy. Tumor response was evaluated using imaging studies according to the Response Evaluation Criteria for Solid Tumors (RECIST) 1.1 [13]. Patients who required early termination of treatment or who died before the imaging studies were conducted for response assessment were determined to have experienced disease progression. Adverse events were evaluated during every clinic visit and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. All adverse events were recorded from the initiation of nal-IRI + 5-FU/LV therapy until the end of the treatment. The reason for nal-IRI cessation was obtained through a medical chart review.

The primary study outcome of interest was overall survival (OS), defined as the time between the initiation of nal-IRI + 5-FU/LV and death from any cause or date of censoring by the cutoff date of December 31, 2020. The secondary study outcomes of interest included the number of total treatment cycles and SAEs of nal-IRI plus 5-FU/LV.

Statistical analysis

Basic patient demographic data are summarized as frequencies (%) for categorical variables and medians with ranges for continuous variables. Differences between the different nal-IRI dosing groups were compared using the chi-squared (χ^2) test or Fisher's exact test if the number in any cell was less than five.

OS was calculated using the Kaplan-Meier method. Log-rank tests were used to determine statistically significant differences among the survival curves. Pairwise comparison was performed for subgroup analysis among the three dose groups. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using the Cox proportional hazards model.

Considering selection bias in non-randomized studies and achieving balanced covariates across three treatment groups, propensity score matching (PSM) via logistic regression was used with regard to patient characteristics

including age, sex, Eastern Cooperative Oncology Group (ECOG) performance, site of metastatic organ, body mass index (BMI), and prior treatment lines for metastatic PDAC. Each RD patient with escalation was matched to two RD patients without escalation and three SD patients using a greedy-match algorithm that minimizes differences in PSM [14]. In addition, PSM was being used to obtain the inverse probability weights (IPW) [15]. The idea of using IPW is to weigh individuals by the inverse of their propensity scores so that those with higher propensity scores will be assigned a lower weight and those with lower propensity scores will be assigned a higher weight. Therefore, using IPW will generate a "pseudo-sample" in which the imbalanced set of covariates becomes balanced between treatment groups [15]. A logistic regression analysis was applied to estimate the propensity of diffuse treatment dosage groups, conditioned on a pre-specified list of clinical covariates (same variables as in the PSM above) using the IPW.

SAS 9.2/9.4 (SAS Institute, Cary, NC, USA) and SPSS software (version 23.0; IBM Corp, Armonk, NY, United States) were used for all statistical analyses. All statistical assessments were two-sided, and a *P* value of <0.05 was considered the threshold for statistical significance.

Results

Baseline characteristics

The basic characteristics of 667 patients are presented in **Table 1**. The median age of our cohort was 63 years (range, 27-89 years) and 56% were men. Of the 667 patients, 465 (69.7%), 147 (22.0), and 55 (8.2%) were prescribed nal-IRI at SD, RD without escalation, and RD with escalation, respectively. In the unmatched cohort, patients in the SD group had significantly better ECOG performance, a higher prevalence of distant lymph node metastases, and a higher percentage of fewer prior treatment lines. Using the 3:2:1 PSM, 165 SD patients and 110 RD patients without escalation were matched to 55 RD patients with escalation. The basic characteristics were well balanced among the three groups following PSM.

Average nal-IRI dosage over time of first six treatment cycles

The average nal-IRI dosage over time for the three patient groups is shown in **Figure 2**. The average nal-IRI starting dosage was 74 mg/m^2 for patients with SD, 47 mg/m^2 for patients with RD with escalation, and 43 mg/m^2 for patients with RD without escalation. The average nal-IRI dosage increased gradually over the first six treatment cycles in RD with escalation patients, while the average nal-IRI dosage remained consistent for SD and RD without escalation patient groups. At the sixth treatment cycle, the average nal-IRI dosage was 70 mg/m^2 for SD patients, 68 mg/m^2 for RD with escalation patients, and 42 mg/m^2 for RD without escalation patients.

Treatment cycles, discontinuing reasons, and tumor response

In the unmatched cohort, the median number of nal-IRI treatment cycles was 5 (range, 1-42), 4 (range, 1-26), and 6 (range, 2-25) for SD, RD without escalation, and RD with escalation, respectively (**Table 2**). Patients who received RD with escalation had significantly longer median treatment cycles of nal-IRI than the other two groups (P=0.001). Patients with RD without escalation had the highest probability (83.0%) of discontinuing nal-IRI because of progressive disease than SD patients (75.5%) and RD with escalation patients (69.1%) (P=0.009).

After matching, RD patients with escalation still had significantly longer median treatment cycles of nal-IRI and the lowest probability of discontinuing nal-IRI because of progressive disease than the other two patient groups. The best tumor response to nal-IRI was not significantly different between the three patient groups before and after matching.

Severe adverse event

In the unmatched cohort, patients with SD had a higher incidence of grade 3 or higher neutropenia and febrile neutropenia than the other two groups (**Table 3**). The incidence of other severe toxicities was well balanced among the three groups. Patients with SD still had a significantly higher incidence of grade 3 or higher neutropenia than the other two groups after PSM.

Survival outcome

The median follow-up duration was 12.9 (range, 2.1-28.2) months, and 475 (71.2%) of the 667 patients had died by the end of our study. In the unmatched cohort, the median OS was 6.2 months (95% CI, 5.7-6.7) for RD patients, 7.6

Table 1. Baseline patient characteristics (comparison among SD, RD with and without escalation groups)

Clinical Characteristic	Unmatched cohort				Propensity score-matched cohort			
	SD (n=465)	RD without escalation (n=147)	RD with escalation (n=55)	*p* value	SD (n=165)	RD without escalation (n=110)	RD with escalation (n=55)	*p* value
Age, years, median (range)	63 (27-89)	63 (43-86)	65 (44-82)	0.56	63 (39-89)	64 (43-86)	65 (44-82)	0.75
<65, n (%)	279 (60.0)	89 (60.5)	29 (52.7)		100 (60.6)	59 (53.6)	29 (52.7)	
≥65, n (%)	186 (40.0)	58 (39.5)	26 (47.3)		65 (39.4)	51 (46.4)	26 (47.3)	
Male, n (%)	258 (55.5)	84 (57.1)	34 (61.8)	0.65	107 (64.8)	68 (61.8)	34 (61.8)	0.85
Previous pancreatectomy, n (%)	163 (35.1)	48 (32.7)	17 (30.9)	0.75	48 (29.1)	31 (28.2)	17 (30.9)	0.94
ECOG performance, n (%)				<0.001				0.76
0-1	379 (81.5)	94 (63.9)	37 (67.3)		118 (71.5)	80 (72.7)	37 (67.3)	
2-3	86 (18.5)	53 (36.1)	18 (32.7)		47 (28.5)	30 (27.3)	18 (32.7)	
Primary tumor site of the pancreas, n (%)				0.50				0.90
Head	252 (54.2)	75 (51.0)	32 (58.2)		95 (57.6)	56 (50.9)	32 (58.2)	
Body	116 (24.9)	36 (24.5)	11 (20.0)		40 (24.2)	29 (26.4)	11 (20.0)	
Tail	89 (19.1)	29 (19.7)	11 (20.0)		26 (15.8)	22 (20.0)	11 (20.0)	
Overlapping	8 (1.7)	7 (4.8)	1 (1.8)		4 (2.4)	3 (2.7)	1 (1.8)	
Presence of liver metastases, n (%)	298 (64.1)	104 (70.7)	37 (67.3)	0.32	110 (66.7)	78 (70.9)	37 (67.3)	0.75
Presence of peritoneal metastases, n (%)	141 (30.3)	50 (34.0)	16 (29.1)	0.67	45 (27.3)	36 (32.7)	16 (29.1)	0.62
Presence of distant lymph nodes metastases, n (%)	136 (29.2)	29 (19.7)	7 (12.7)	<0.001	21 (12.7)	14 (12.7)	7 (12.7)	0.99
CA 19-9 prior to nal-IRI treatment, ug/mL, median (range)	923 (1-93,850)	1485 (2-126,770)	979 (2-27,853)	0.87	1039 (1-62,530)	1158 (2-12670)	979 (2-27,853)	0.26
Unknown, n (%)	68 (14.6)	23 (15.6)	8 (14.5)		22 (13.3)	15 (13.6)	8 (14.5)	
BMI, median (range)	21.1 (12.4-39.0)	20.8 (13.1-33.8)	22.1 (16.7-30.3)	0.17	22.3 (12.4-36.1)	22.0 (15.0-33.8)	22.1 (16.7-30.3)	0.78
Prior treatment line for metastatic disease, median (range)	1 (0-7)			<0.001				0.49
1, n (%)	316 (68.0)	76 (51.6)	28 (50.9)		99 (60.0)	62 (56.4)	28 (50.9)	
≥2, n (%)	149 (32.0)	71 (48.4)	27 (49.1)		66 (40.0)	48 43.6)	27 (49.1)	
Time from first line treatment to nal-IRI therapy, months, median (range)	7.7 (0-93.8)	8.1 (0-66.6)	6.5 (0-43.7)	0.39	7.2 (0-48.8)	7.6 (0-66.6)	6.5 (0-43.7)	0.22

SD, Standard Starting Dose; RD, Reduced Starting Dose; ECOG, Eastern Cooperative Oncology Group; CA 19-9, Carbohydrate Antigen 19-9; BMI, Body Mass Index.

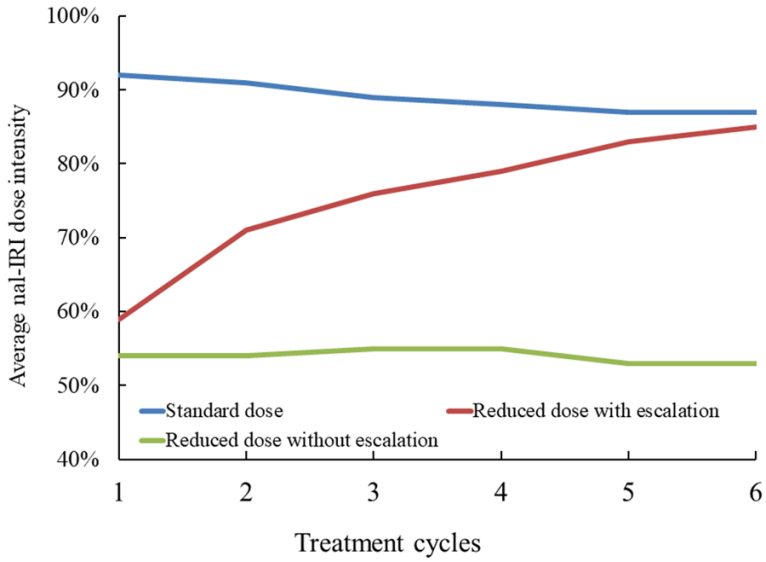

Figure 2. Changes in average nal-IRI dose intensity over time of first six treatment cycles.

months (95% CI, 6.1-9.2) for RD with escalation patients, and 3.6 months (95% CI, 2.6-4.5) for RD patients without escalation (**Figure 3A**). RD without escalation patients had a significantly poorer OS than the other two groups (P<0.001), while there was no significant OS difference between the SD and RD with escalation groups (P=0.08).

After matching, the median OS in SD, RD with escalation, and RD without escalation patients were 6.8 months (95% CI, 5.3-8.3), 7.6 months (95% CI, 6.1-9.2) months, and 3.6 months (95% CI, 2.8-4.4), respectively (**Figure 3B**). Patients with RD without escalation still had the poorest OS compared with the other two groups. RD patients with escalation had an insignificant survival difference compared to SD patients (P=0.10).

Table 4 presents the results of univariate and multivariate analyses examining overall survival. RD without escalation was a negative prognosticator compared to SD patients. In multivariate analysis (IPW adjusted to clinical variables of age, sex, ECOG performance, site of metastatic organ, BMI, and prior treatment lines for metastatic PDAC), RD without escalation remained an independent negative prognosticator OS. Whereas RD with escalation was an independent positive prognosticator for OS in patients with mPDAC.

Selected subgroup analyses for OS are shown in **Figure 4**. RD with escalation patients exhibited a trend toward better survival outcomes than SD patients among our pre-planned subgroups (**Figure 4A**). Patients aged ≥65 years gained a significant OS benefit when prescribed nal-IRI at RD with escalation than when prescribed at SD. After matching, there was still an OS advantage among patients aged ≥65 years who were prescribed nal-IRI in the RD escalation group than that prescribed at SD (HR 0.48; 95% CI, 0.25-0.94; P=0.031).

In the subgroup analysis comparing RD with escalation and RD without escalation (**Figure 4B**), RD with escalation patients had significantly better OS than RD without escalation across all pre-planned subgroups. After matching, the survival advantage of RD with escalation patients continued in almost all pre-planned subgroups.

Discussion

Previous small-scale real-world studies have suggested that using a reduced starting nal-IRI dosage is common in clinical practice and might achieve better tolerability without compromising treatment efficacy in patients with mPDAC [6-10]. Using a large-scale multicenter database across Taiwan, we compared the survival outcome and toxicity profiles through PSM analyses among 667 PDAC patients who received nal-IRI either at a standard starting dose or at a reduced starting dose, and whether the nal-IRI dose was subsequently escalated. Our study showed that patients who received a reduced nal-IRI starting dose followed by subsequent dose escalation did not have compromised OS relative to those receiving the standard starting dose, while patients receiving a reduced starting dose who did not have dose escalation had the worst OS. In addition, compared to RD patients without escalation, RD patients with escalation had longer median treatment cycles, lower probability of

Table 2. Summary of Outcomes (comparison among SD, RD with escalation, and RT without escalation before and after matching)

Treatment outcomes	Unmatched cohort				Propensity score-matched cohort			
	SD (n=465)	RD without escalation (n=147)	RD with escalation (n=55)	*p* value	SD (n=165)	RD without escalation (n=110)	RD with escalation (n=55)	*p* value
Treatment cycle, median (range)	5 (1-42)	4 (1-26)	6 (2-25)	0.001	5 (1-27)	3 (1-26)	6 (2-25)	0.003
Reason for discontinuing, n (%)				0.009				0.001
Progressive disease	351 (75.5)	122 (83.0)	38 (69.1)		129 (78.2)	95 (86.4)	38 (69.1)	
Toxicity	41 (8.8)	9 (6.1)	1 (1.8)		16 (9.7)	6 (5.5)	1 (1.8)	
Patient preferences or others	73 (15.7)	16 (10.9)	16 (29.1)		20 (12.1)	9 (8.2)	16 (29.1)	
Best tumor response, n (%)				0.25				0.36
Partial response	42 (9.0)	10 (6.8)	4 (7.3)		13 (7.9)	6 (5.5)	4 (7.3)	
Stable disease	138 (29.7)	33 (22.4)	19 (34.5)		51 (30.9)	25 (22.7)	19 (34.5)	
Progressive disease	285 (61.3)	104 (70.7)	32 (58.2)		101 (61.2)	79 (71.8)	32 (58.2)	

SD, Standard Starting Dose; RD, Reduced Starting Dose.

Table 3. Grade 3 or higher adverse events (comparison of SD, RD with escalation, and RT without escalation before and after matching)

Toxicity	Unmatched cohort				Propensity score-matched cohort			
	SD (n=465)	RD without escalation (n=147)	RD with escalation (n=55)	*p* value	SD (n=165)	RD without escalation (n=110)	RD with escalation (n=55)	*p* value
Anemia	97 (20.9)	32 (21.8)	12 (21.8)	0.97	34 (20.6)	23 (20.9)	12 (21.8)	0.98
Neutropenia	124 (26.7)	22 (15.0)	7 (12.7)	0.002	42 (25.5)	15 (13.6)	7 (12.7)	0.019
Thrombocytopenia	31 (6.7)	16 (10.9)	1 (1.8)	0.062	9 (5.5)	9 (8.2)	1 (1.8)	0.25
Febrile neutropenia	19 (4.1)	4 (2.7)	1 (1.8)	0.048	4 (2.4)	2 (1.8)	1 (1.8)	0.34
Aspartate Aminotransferase	21 (4.5)	6 (4.1)	3 (5.5)	0.92	7 (4.2)	4 (3.6)	3 (5.5)	0.86
Alanine Aminotransferase	19 (4.1)	2 (1.4)	2 (3.6)	0.29	6 (3.6)	0	2 (3.6)	0.19
Jaundice	36 (7.7)	12 (8.2)	7 (12.7)	0.45	10 (6.1)	7 (6.4)	7 (12.7)	0.23
Hypokalemia	71 (15.3)	24 (16.3)	8 (14.5)	0.94	25 (15.2)	14 (12.7)	8 (14.5)	0.85
Fatigue	7 (1.5)	4 (2.7)	0	0.36	4 (2.4)	4 (3.6)	0	0.36
Vomiting	17 (3.7)	5 (3.4)	2 (3.6)	0.76	8 (4.8)	3 (2.7)	2 (3.6)	0.66
Diarrhea	12 (2.6)	4 (2.7)	2 (3.6)	0.13	7 (4.2)	3 (2.0)	2 (3.6)	0.10

discontinuing nal-IRI because of progressive disease, and similar safety profiles.

The concept that a standard drug dose would undoubtedly be associated with better efficacy in fit patients or those with an advanced tumor burden [16]. As a result, our SD patients were characterized by better performance status, higher incidences of distant lymph node metastases, and received nal-IRI treatment in an earlier treatment line than RD patients. Using PSM to adjust for these potential confounders, our study showed that RD with escalation patients had comparable OS to SD patients. Our data suggest that prescribed nal-IRI at a reduced starting dose following subsequent dose escalation might be an alternative treatment strategy for patients who do not have adequate performance or who are heavily treated for PDAC.

Although 33% of patients in the nal-IRI + 5-FU/LV arm of NAPOLI-1 needed a dose reduction due to intolerance of adverse events [3], the nal-IRI dose intensity was consistent in the first six treatment cycles in our SD patients. A relatively lower starting dose (74 mg/m^2 vs. 80 mg/m^2) and better toxicity profiles with a lower incidence of vomiting (3.7% vs. 11%), diarrhea (2.6% vs. 13%), and fatigue (1.5% vs. 14%) in our SD patients compared to those in NAPOLI-1 might explain the lower proportion of nal-IRI dose modifications in our SD cohort. Although the incidence of these subjective SAEs might be underestimated by retrospective analysis,

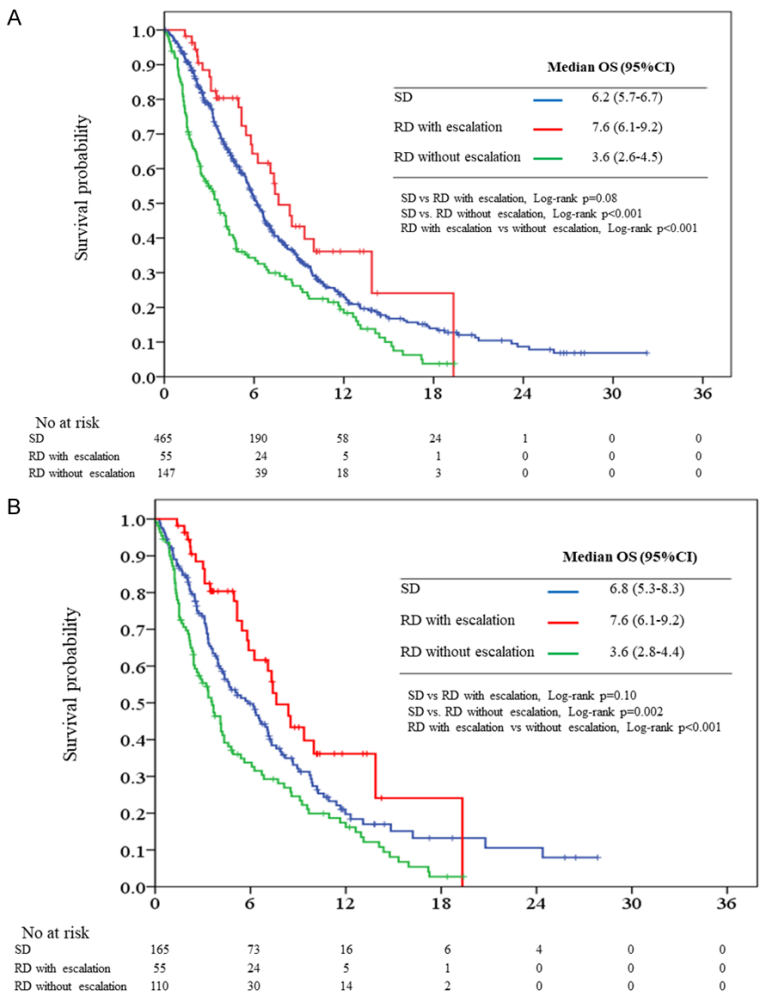

Figure 3. Overall survival according to different nal-IRI dosing group before (A) and after propensity score matching (B).

the lower incidence of SAEs in our SD cohort might encourage clinicians to prescribe adequate nal-IRI doses at the beginning of treatment.

Instead of the standard starting dose followed by subsequent dose modifications in a clinical trial setting, our study showed that 30% of the patients received a reduced starting nal-IRI dose in real-world clinical practice. The percentage of patients with starting dose reductions in our study was comparable to that of other retrospective studies of nal-IRI + 5FU/LV treatment in patients with PDAC [6-10]. Interestingly, our study showed that 55 of the 202 patients (27%) prescribed a reduced starting nal-IRI dose received dose escalation in subsequent treatment cycles. As a result, the average nal-IRI dosage of six treatment cycles in RD with escalation patients was close to that of SD patients. These data suggest that a substantial number of patients could gradually tolerate higher nal-IRI dosages by slow titration manipulation. Our data support a gradual increase in nal-IRI dosage in patients receiving a reduced starting dose to approximate the standard treatment dose to enhance the therapeutic efficacy of nal-IRI in patients with PDAC.

In clinical practice, choosing a lower starting dose may be obligatory to achieve a balance between lower toxicity profiles and minimal compromise in treatment efficacy. Considering the characteristics of our RD patients, we speculated that a reduced starting nal-IRI dose was prescribed because of treatment tolerance for patients who were heavily treated or who were too frail [11]. Unfortunately, the use of lower nal-IRI doses reduced the occurrence of severe adverse events in patients with shorter treatment durations and poorer efficacy in patients with RD without escalation. Our previous study showed that starting nal-IRI dosage <50% of the standard dose is a poor prognosticator in patients with PDAC receiving nal-IRI + 5-FU/LV treatment [11]. Consistent with our previous report, patients with RD without escalation experienced significantly worse OS, shorter treatment cycles, and a higher probability of discontinuing nal-IRI due to progressive disease than the other two groups.

The benefits of palliative chemotherapy in patients with PDAC include disease control and relief of symptoms of distress [17]. It is well known that gemcitabine monotherapy provides a tumor response rate of 11% for PDAC, while 27% of the patients had improved performance and ameliorated tumor pain after receiving treatment [18]. Similarly, some of our sick

Table 4. Univariate and multivariate analyses examining overall survival

Variable	Unmatch cohort						Propensity score-matched cohort					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P	Adjusted HR#	95% CI	P	HR	95% CI	P	Adjusted HR#	95% CI	P
SD	reference			reference			reference			reference		
RD without escalation	1.59	1.29-1.96	<0.001	1.83	1.48-2.26	<0.001	1.47	1.12-1.93	0.006	1.66	1.26-2.19	<0.001
RD with escalation	0.71	0.48-1.06	0.090	0.63	0.42-0.94	0.025	0.65	0.43-0.99	0.046	0.61	0.41-0.95	0.027

inverse probability weights adjusted to clinical variables of age, sex, Eastern Cooperative Oncology Group Performance Status, site of metastatic organ, body mass index, and prior treatment lines for metastatic PDAC.

patients who received a lower starting nal-IRI dose might have clinical benefits with improved performance status and decreased physical distress after receiving treatment with nal-IRI. Therefore, they were able to tolerate higher therapeutic doses in subsequent cycles. The use of RD with escalation might be most beneficial in nal-IRI responders who are insufficiently fit for the standard nal-IRI dose.

Old age is a well-known negative predictor of antitumor therapy in various cancer types [19, 20]. However, elderly patients had similar treatment efficacy and toxicity profiles to younger patients who received nal-IRI + 5-FU/LV for the treatment of PDAC in the NAPOLI-1 trial [21]. In our study, a subgroup analysis of OS revealed the possibility of a survival benefit in patients aged ≥65 years who received RD with escalation compared to SD. We speculated that, compared to younger patients, elderly cancer patients might be associated with higher treatment-related toxicity if a standard starting dose of nal-IRI was prescribed. Initial treatment with a lower drug intensity of nal-IRI might allow elderly patients a greater probability to tolerate the treatment to maximize nal-IRI therapeutic efficacy. The impact of age on the treatment efficacy and toxicity of nal-IRI in a real-world setting requires further exploration.

This is the first PSM study to analyze the association between the starting nal-IRI dose and subsequent dose escalation and survival outcomes in patients with PDAC. This study was strengthened by the inclusion of a large number of patients from multiple centers across Taiwan. Nevertheless, this study has some limitations. First, the retrospective nature with selection bias represented the most important issue; however, we implemented PSM in statistical analysis to reduce this bias. Second, the decision to prescribe a reduced starting dose and dose escalation in subsequent cycles was influenced by multiple factors related to considerations of physicians and patients, which could not be fully addressed in our analysis. Third, the RD patients were further divided into those with and without escalation depending on whether dose escalation was performed in the subsequent treatment cycles. There is no consistent principle for dose escalation in clinical practice; however, we were unable to analyze whether the magnitude of dose escalation might affect treatment efficacy and toxicity profiles. Therefore, prospective studies are required to address these issues.

Conclusion

This study showed that starting with a reduced dose followed by dose escalation in subsequent treatment cycles did not compromise OS compared to starting with a standard dose in patients with PDAC receiving nal-IRI + 5-FU/LV after propensity score matching for multiple clinical variables. RD patients with escalation experienced longer treatment cycles, lower probability of discontinuing nal-IRI because of progressive disease, and similar safety profiles to RD patients without escalation. Taken together, the results of our study suggest that prescribed nal-IRI at a reduced starting dose followed by dose escalation in subsequent treatment cycles is an effective and safe clinical practice for PDAC patients.

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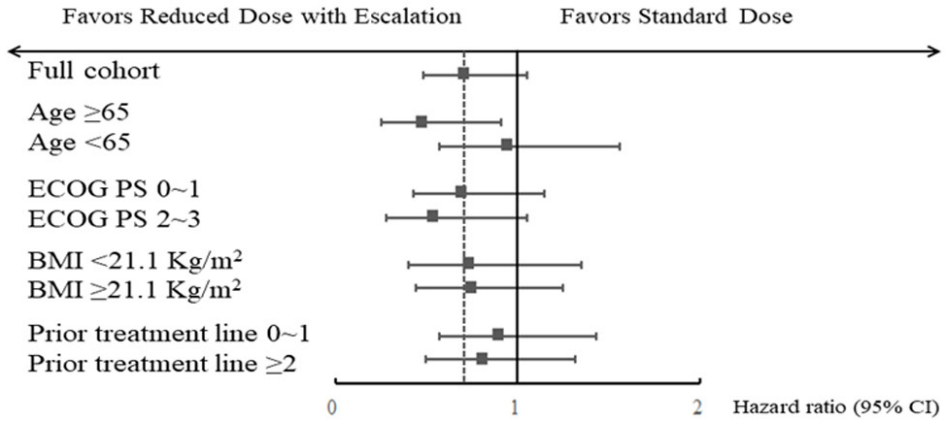
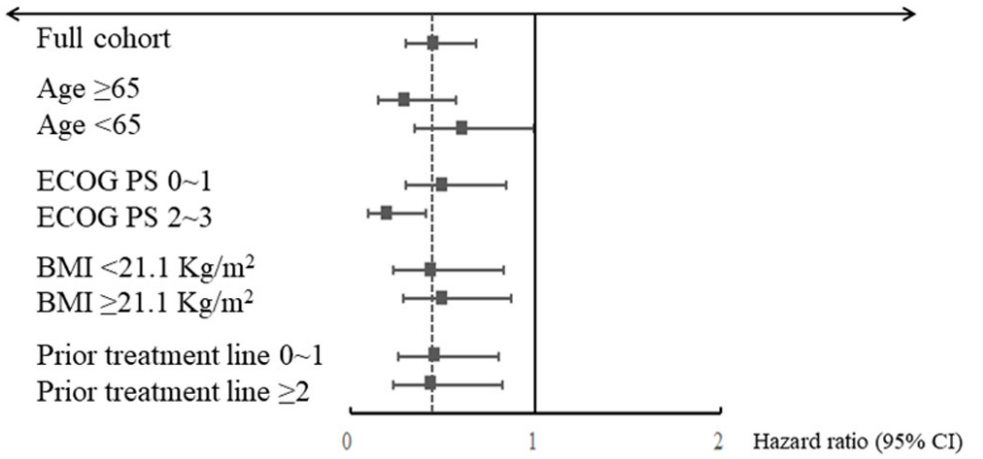
A



Overall survival (months)	Standard Dose	RD with Escalation	HR (95% CI)	P	HR (95% CI)	P+
Full cohort	5.9 (4.3-7.4)	7.6 (6.1-9.2)	0.71 (0.48-1.05)	0.09	0.72 (0.47-1.09)	0.12
Age ≥ 65	4.2 (2.5-7.4)	6.4 (3.9-9.1)	0.48 (0.25-0.91)	**0.024**	0.48 (0.25-0.94)	**0.031**
Age < 65	6.9 (4.9-9.4)	7.9 (5.9-10.1)	0.95 (0.57-1.56)	0.84	0.99 (0.57-1.72)	0.96
ECOG PS 0~1	7.1 (5.8-8.4)	8.5 (6.0-11.0)	0.70 (0.43-1.15)	0.16	0.72 (0.42-1.21)	0.22
ECOG PS 2~3	2.6 (1.7-3.6)	5.5 (1.9-9.0)	0.54 (0.28-1.05)	0.07	0.67 (0.33-1.34)	0.25
BMI < 21.1 Kg/m2	3.9 (2.8-5.1)	8.4 (1.8-14.5)	0.74 (0.40-1.35)	0.33	0.67 (0.35-1.29)	0.23
BMI ≥ 21.1 Kg/m2	7.1 (4.9-9.3)	7.6 (6.0-9.2)	0.75 (0.44-1.25)	0.27	0.80 (0.46-1.39)	0.43
Prior treatment line 0~1	6.6 (4.4-8.7)	9.4 (7.3-11.5)	0.90 (0.57-1.43	0.65	0.72 (0.41-1.26)	0.25
Prior treatment line ≥ 2	4.6 (2.3-7.0)	7.1` (4.9-9.3)	0.81 (0.50-1.32)	0.41	0.67 (0.36-1.26)	0.21

B



Overall survival (months)	RD without Escalation	RD with Escalation	HR (95% CI)	P	HR (95% CI)	P+
Full cohort	3.6 (2.6-4.5)	7.6 (6.1-9.2)	0.45 (0.30-0.68)	**<0.001**	0.44 (0.29-0.68)	*<0.001*
Age ≥ 65	2.4 (1.1-3.8)	6.4 (3.9-9.1)	0.30 (0.15-0.57)	**<0.001**	0.28 (0.14-0.56)	*<0.001*
Age < 65	4.1 (3.2-5.0)	7.9 (5.9-10.1)	0.61 (0.35-0.99)	0.049	0.66 (0.37-1.02)	0.07
ECOG PS 0~1	4.8 (3.2-6.4)	8.5 (6.0-11.0)	0.50 (0.30-0.84)	**0.009**	0.50 (0.29-0.85)	**0.010**
ECOG PS 2~3	1.4 (1.1-1.6)	5.5 (1.9-9.0)	0.20 (0.10-0.41)	**<0.001**	0.21 (0.10-0.45)	**<0.001**
BMI < 21.1 Kg/m2	3.1 (2.2-4.0)	8.4 (1.8-14.5)	0.44 (0.23-0.83)	**0.012**	0.40 (0.20-0.77)	**0.006**
BMI ≥ 21.1 Kg/m2	4.8 (2.8-6.8)	7.6 (6.0-9.2)	0.50 (0.29-0.87)	**0.015**	0.51 (0.29-0.90)	**0.020**
Prior treatment line 0~1	4.1 (2.5-5.8)	9.4 (7.3-11.5)	0.46 (0.26-0.80)	**0.006**	0.46 (0.26-0.82)	**0.008**
Prior treatment line ≥ 2	3.3 (2.2-4.5)	7.1` (4.9-9.3)	0.44 (0.23-0.82)	**0.010**	0.41 (0.21-0.77)	**0.006**

Figure 4. Selected subgroup analyses for OS between RD with escalation patients and SD patients (A), as well as RS with escalation patients and RD without escalation patients (B). ECOG PS, Eastern Cooperative Oncology Group Performance Status; BMI, Body Mass Index.

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Disclosure of conflict of interest

Author Sz-Chi Chiu was employed by the company PharmaEngine, Inc. The remaining authors declare that there is no conflict of interest.

Address correspondence to: Dr. Wen-Chi Chou, Division of Hematology-Oncology, Department of Internal Medicine, Linkou Chang Gung Memorial Hospital, 5 Fu-Hsing Street, Kwei-Shan Shiang, Taoyuan, Taiwan. Tel: 886-3281200 Ext. 8825; Fax: 886-3-3285818; E-mail: wenchi3992@yahoo.com.tw

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.

[2] Ryan DP, Hong TS and Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med 2014; 371: 1039-1049.

[3] Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, Macarulla T, Lee KH, Cunningham D, Blanc JF, Hubner RA, Chiu CF, Schwartsmann G, Siveke JT, Braiteh F, Moyo V, Belanger B, Dhindsa N, Bayever E, Von Hoff DD and Chen LT; NAPOLI-1 Study Group. 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: 545-557.

[4] Bang YJ, Li CP, Lee KH, Chiu CF, Park JO, Shan YS, Kim JS, Chen JS, Shim HJ, Rau KM, Choi HJ, Oh DY, Belanger B and Chen LT. Liposomal irinotecan in metastatic pancreatic adenocarcinoma in Asian patients: subgroup analysis of the NAPOLI-1 study. Cancer Sci 2020; 111: 513-527.

[5] Chen LT, Siveke JT, Wang-Gillam A, Li CP, Bodoky G, Dean AP, Shan YS, Jameson GS, Macarulla T, Lee KH, Cunningham D, Blanc JF, Chiu CF, Schwartsmann G, Braiteh FS, Mamlouk K, Belanger B, de Jong FA and Hubner RA. Survival with nal-IRI (liposomal irinotecan) plus 5-fluorouracil and leucovorin versus 5-fluorouracil and leucovorin in per-protocol and non-per-protocol populations of NAPOLI-1: expanded analysis of a global phase 3 trial. Eur J Cancer 2018; 105: 71-78.

[6] Kieler M, Unseld M, Bianconi D, Scheithauer W and Prager GW. A real-world analysis of second-line treatment options in pancreatic cancer: liposomal-irinotecan plus 5-fluorouracil and folinic acid. Ther Adv Med Oncol 2019; 11: 1758835919853196.

[7] Barzi A, Miksad R, Surinach A, Corvino FA, Wang S, Torres AZ, Mamlouk K, Pulgar S, Valderrama A, Bekaii-Saab T and Ahn D. Real-world dosing patterns and outcomes of patients with metastatic pancreatic cancer treated with a liposomal irinotecan regimen in the United States. Pancreas 2020; 49: 193-200.

[8] Glassman DC, Palmaira RL, Covington CM, Desai AM, Ku GY, Li J, Harding JJ, Varghese AM, O'Reilly EM and Yu KH. Nanoliposomal irinotecan with fluorouracil for the treatment of advanced pancreatic cancer, a single institution experience. BMC Cancer 2018; 18: 693.

[9] Su YY, Chiang NJ, Tsai HJ, Yen CJ, Shan YS and Chen LT. The impact of liposomal irinotecan on the treatment of advanced pancreatic adenocarcinoma: real-world experience in a Taiwanese cohort. Sci Rep 2020; 10: 7420.

[10] Tossey JC, Reardon J, VanDeusen JB, Noonan AM, Porter K and Arango MJ. Comparison of conventional versus liposomal irinotecan in combination with fluorouracil for advanced pancreatic cancer: a single-institution experience. Med Oncol 2019; 36: 87.

[11] Chiu TJ, Su YY, Yang SH, Li CP, Bai LY, Chiang NJ, Chuang SC, Shan YS, Chan DC, Chen LT, Yen CJ, Peng CM, Chen YY, Chen JS and Chou WC. Liposomal irinotecan pre-emptive dose reduction in patients with pancreatic ductal adenocarcinoma: 667 patients' experience within a population-based study. Ther Adv Med Oncol 2021; 13: 17588359211058255.

[12] Su YY, Chiang NJ, Li CP, Yen CJ, Yang SH, Chou WC, Chen JS, Chiu TJ, Chen YY, Chuang SC, Bai LY, Chiu CF, Peng CM, Chan DC, Chiu SC, Yang YH, Shan YS and Chen LT. Dosing pattern and early cumulative dose of liposomal irinotecan in metastatic pancreatic cancer: a real-world multicenter study. Front Oncol 2022; 12: 800842.

[13] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.

[14] Rosenbaum P. Observational studies. New York: Springer-Verlag; 2002.

[15] Wang G and Aban I. Application of inverse probability weights in survival analysis. J Nucl Cardiol 2015; 22: 611-613.

[16] Shah M, Rahman A, Theoret MR and Pazdur R. The drug-dosing conundrum in oncology-when less is more. N Engl J Med 2021; 385: 1445-1447.
[17] Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP and Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol 2007; 25: 2607-2615.
[18] Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD and Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15: 2403-2413.
[19] Kish JA, Zhang Q, Langer CJ, Nguyen-Tân PF, Rosenthal DI, Weber RS, List MA, Wong SJ, Garden AS, Hu K, Trotti AM, Bonner JA, Jones CU, Yom SS, Thorstad W, Schultz CJ, Ridge JA, Shenouda G, Harris J and Le QT. The impact of age on outcome in phase III NRG Oncology/RTOG trials of radiotherapy (XRT) +/- systemic therapy in locally advanced head and neck cancer. J Geriatr Oncol 2021; 12: 937-944.
[20] Macarulla T, Blanc JF, Wang-Gillam A, Chen LT, Siveke JT, Mirakhur B, Chen J and de Jong FA. Liposomal irinotecan and 5-fluorouracil/leucovorin in older patients with metastatic pancreatic cancer-a subgroup analysis of the pivotal NAPOLI-1 trial. J Geriatr Oncol 2019; 10: 427-435.
[21] VanderWalde N, Moughan J, Lichtman SM, Jagsi R, Ballo M, VanderWalde A, Mohiuddin M, Meropol NJ, Kachnic L, Berger A, Ajani J, Anne R, Hopkins JL, Arora A, Meyer J, Ellsworth SG, Lee RJ, Green N and Crane CH. The association of age with acute toxicities in NRG oncology combined modality lower GI cancer trials. J Geriatr Oncol 2022; 13: 294-301.