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Time until definitive quality of life score deterioration as a means of longitudinal analysis for treatment trials in patients with metastatic pancreatic adenocarcinoma

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ABSTRACT

Background: The Fédération Francophone de Cancérologie Digestive phase III trial in patients with metastatic pancreatic adenocarcinoma comparing 5FU, folinic acid and cisplatin combination followed by gemcitabine (Arm A) versus the opposite sequence (Arm B) failed to demonstrate a benefit in overall survival. To longitudinally compare the quality of life (QoL) we explored different definitions of time until definitive deterioration (TUDD) of QoL scores according to minimal clinically important difference (MCID) cut-offs.

Methods: QoL was evaluated using the EORTC QLQ-C30 every 8 weeks until death. The following scores were analysed: global health, emotional functioning, physical functioning, fatigue and pain. TUDD was defined as the time interval between randomisation and the first occurrence of a decrease in QLQ-C30 score $\geqslant 5$ points without any further improvement in QoL score $\geqslant 5$ points or any further available QoL data. Analyses were repeated using a 10 point MCID and/or including death as event.

Results: From 08/2003 to 05/2006, 102 patients in Arm A and 100 in Arm B were included. Using a 5 and a 10 point MCID, TUDD curves of the 5 scores did not differ according to treatment arm., The median TUDD of global health was 5.2 months (4.3–6.2) in Arm A and 6.1 months (5.1–8.5) in Arm B (log-rank $p = 0.50$) including death as an event for a 5 point MCID. Multivariate Cox model showed that tumour localisation and progression were independently associated with TUDD ($p < 0.05$).

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Conclusions: The strategy of chemotherapy did not influence the deterioration of QoL. The TUDD approach seems to provide meaningful clinical results that are adapted to metastatic pancreatic adenocarcinoma trials.

1. Introduction

Pancreatic adenocarcinoma is the fifth cause of death from cancer in Western countries with less than 5% of patients still living at 5 years.[1] Gemcitabine-based chemotherapy is the gold standard for the systemic treatment of advanced pancreatic cancer[2] with a 5.6 month median overall survival (OS). Others trials with new therapeutic protocols[3–8] have failed to demonstrate any benefit in OS and one study has showed a modest but significant increase in OS when gemcitabine is combined with erlotinib.[9] The 5FU, folinic acid and cisplatin combination (LV5FU2-P) is an alternative option but the optimal order of the regimens needed be evaluated. The Fédération Francophone de Cancérologie Digestive no. 0301 phase III trial was performed to compare LV5FU2-P followed by gemcitabine versus gemcitabine followed by LV5FU2-P. This trial did not show any benefit in survival whatever the sequence administration.[10] The Food and Drug Administration reported that QoL is the main outcome to judge efficacy of treatment modalities when no OS differences are demonstrated.[11–15] Furthermore, because of the poor prognosis of advanced pancreatic cancer and the symptom burden, palliation and finding a balance between health-related quality of life (QoL) and OS in these therapeutic strategies is of paramount importance. Based on these therapeutic goals, Burris et al.[2] used clinical benefit (definition based on pain and performance status) as the primary aim of the phase III trial to show that gemcitabine first-line therapy was the gold standard.

The primary aim of this study was to longitudinally compare QoL according to treatment sequence of the FFCD 0301 trial The secondary aim was to explore definitions of 'time until definitive deterioration' (TUDD) in the QoL score according to the 'minimal clinically important difference' (MCID) cut-off.

2. Method

The design of this study has been described in detail elsewhere.[10]

Metastatic pancreatic adenocarcinoma (MPA) patients with WHO performance status (PS) $\leqslant 2$ and a life expectancy >2 months were randomised 1:1 (minimisation) between Arm A, LV5FU2-cisplatin followed by gemcitabine after progression and Arm B gemcitabine followed by LV5FU-cisplatin after progression. Patients were stratified according to WHO PS (0, 1 versus 2), tumour localisation (head versus other) and participating institutions (centre).

All patients signed a written informed consent and the protocol was approved by the Regional Ethics Committee (July 11th 2003, Marseille, France).

2.1. Quality of life

QoL was assessed using EORTC QLQ-C30[16] in the waiting room before the medical consultation 7 days before randomisation and then every 8 weeks until death. The QLQ-C30 is a cancer-specific tool[17–19] composed of 30 items. Five functional scores (physical, role, cognitive, social, and emotional), a global health score ranging from 0 (worst) to 100 (best) have been developed as well as 9 symptom scores (nausea, pain, fatigue, dyspnoea, difficulty sleeping, anorexia, constipation, diarrhoea and perceived financial difficulties) ranging from 0 (best) to 100 (worse).[16,20]

We focused QoL analyses on the physical (PF), emotional (EF) and global health (GH) scores as well as on symptoms of fatigue (FA) and pain (PA).

2.2. Statistical methods

All analyses were performed on the intent-to-treat principle.

The main clinical and medical patient characteristics were described based on the completion of at least one baseline QoL questionnaire to be able to detect non-random missing patient profiles. We also reported baseline QoL scores according to treatment arm.

Qualitative and continuous variables are described using percent and mean (SD) and median (Minimum – Maximum), respectively, and then compared using the Chi^2 or Fisher exact test and the Mann and Whitney non-parametric test, respectively.

2.3. Analyses of time until definitive deterioration of a QoL score (TUDD)

The TUDD of a score was defined as the interval between randomization and the first MCID decrease in the QLQ-C30 score $\geqslant 5$ points[21] compared to the QoL score at inclusion with no further improvement in QoL score $\geqslant 5$ points or if a patient dropped-out after this $\geqslant 5$ points decrease resulting in missing data.

Patients were censored at the last follow-up when no $\geqslant 5$ point reduction in QoL score from baseline was observed or in patients with a $\geqslant 5$ point reduction in whom a secondary $\geqslant 5$ point improvement in QoL score from baseline was observed.

Patients without available QoL scores were included in the TUDD analysis but were censored at the last follow-up.

These analyses were also performed for events defined as the first $\geqslant 5$ point decrease in one of the following QLQ-C30 dimensions: GH, EF, PF, FA or PA scores.

2.4. Sensitivity analyses were performed to assess different definitions of TUDD

- With 10 point differences[21] in scores such as the MCID and/or
- considering death as an event when patients were censored.

TUDD curves were calculated using the Kaplan Meier estimation and were described using medians and the 95% CI. TUDD curves were compared using log-rank tests. The Univariate Cox model was used to calculate the hazard ratio with a 95% CI. The multivariate Cox model was constructed to explore potential prognostic factors of TUDD for at least one score including treatment (Arm B versus Arm A), age (continuous variable), gender (female versus male), tumour localisation (others versus head), WHO PS at baseline (continuous variable), occurrence of at least one grade 3/4 toxicity during treatment (yes versus no) and occurrence of at least one progression (yes versus no) during follow-up.

To evaluate TUDD definitions we reported the number of events and explored the surrogacy for OS with single-trial validation methods: prentice criteria[22] and Freedman's proportion of treatment effect explained (PTE).[23,24]

All analyses were performed with Stata software (V10) at the 0.05 level of significance.

3. Results

3.1. Population

Between August 2003 and May 2006, 102 patients were included in Arm A (LV5FU2-cisplatin first line) and 100 patients were included in Arm B (Gemcitabine first line) with a median follow-up of 44 months (Fig. 1).

According to treatment arm patient characteristics were well balanced, details had been presented elsewhere.[10]

3.2. QoL scores at baseline and completion

As shown in Fig. 2, 179 patients (88.61%) completed the QoL questionnaire at baseline, 114 at the 1st follow-up, 83 at the 2nd and 57 at the 3rd. Age, sex, prior treatments, as well as WHO performance status and body surface area did not differ significantly according to QoL completion at baseline. Men are

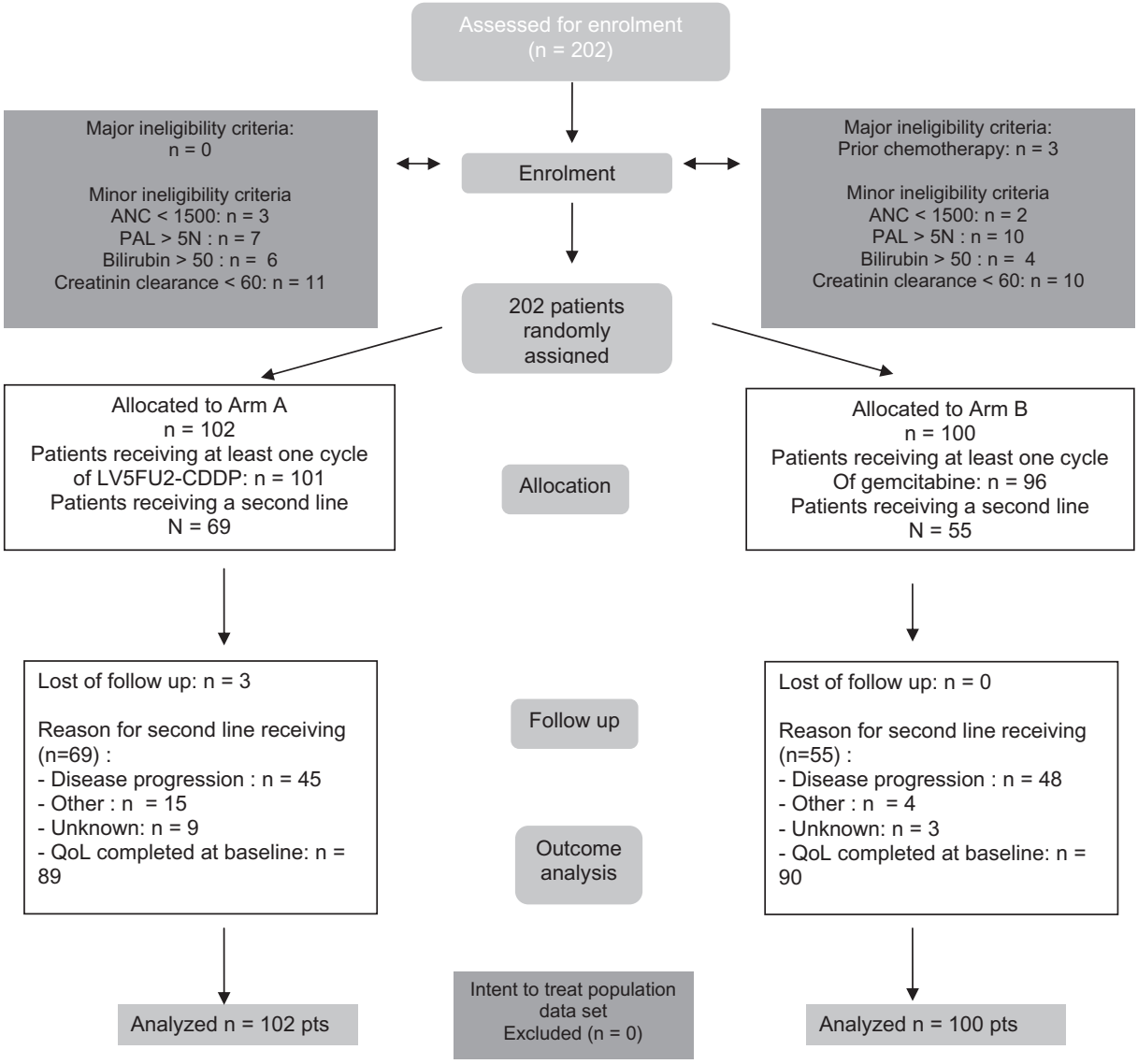
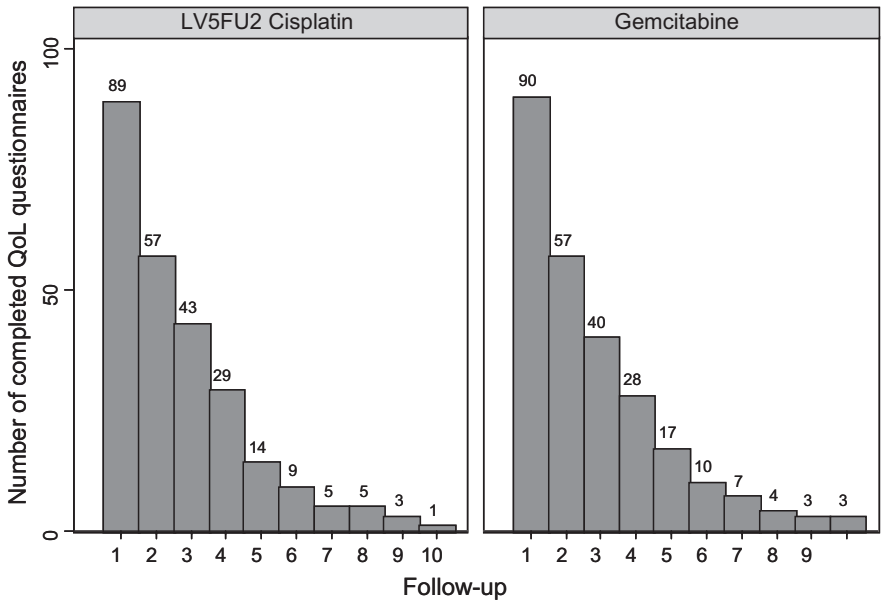


Fig. 1 – Consort diagram.



LV5FU2 cisplatin: Arm A, LV5FU2-cisplatin followed by gemcitabine
Gemcitabine: Arm B, gemcitabine followed by LV5FU-cisplatin
Time interval between follow-up was theoretically planned every 8 weeks, observed median time interval between follow-up was 2 months.

Fig. 2 – QoL questionnaires completed during follow-up among the 202 patients of ITT population in each arm.

in majority with a median age about 63 years and head primary tumour localisation.

The median delay between QoL follow-up was 2 months (0–25) and median delay between completion of the final QoL questionnaire and last follow-up or death was 3 months in each arm. The mean QoL scores at baseline were similar between arms except for EF, with, respectively, 61.4 in Arm A versus 71.7 in Arm B ($p = 0.007$) (Table 1).

3.3. *TUDD of global health score*

3.3.1. *Minimal clinically important difference (MCID) ⩾5 points*

At the data cut-off, 23 and 19 patients, respectively, experienced a definitive deterioration of GH score ⩾5 points in Arms A and B while the median TUDD for GH was not reached (Fig. 3)

3.3.2. *MCID ⩾5 points or death*

At the data cut-off, 95 and 99 patients experienced a definitive deterioration of GH score ⩾5 points or death, respectively, in Arms A and B with a median TUDD of 5.19 months (4.3–6.2) and 6.11 months (5.1–8.5) (Fig. 3).

3.3.3. *MCID ⩾10 points*

In Arms A and B, respectively, 17 and 13 patients experienced a definitive deterioration of GH score ⩾10 points although the median TUDD was not reached (log-rank $p = 0.24$). The Univariate Cox HR of Arm B versus A was 0.64 (0.31–1.35).

3.3.4. *MCID ⩾10 points or death*

In Arms A and B, respectively, 95 and 98 patients experienced a definitive deterioration of GH score ⩾10 points or death with a median TUDD of 5.58 months (4.5–6.9) and 7.43 months (5.3–9.3) (log-rank $p = 0.57$) and a HR of 0.92 (0.69–1.22).

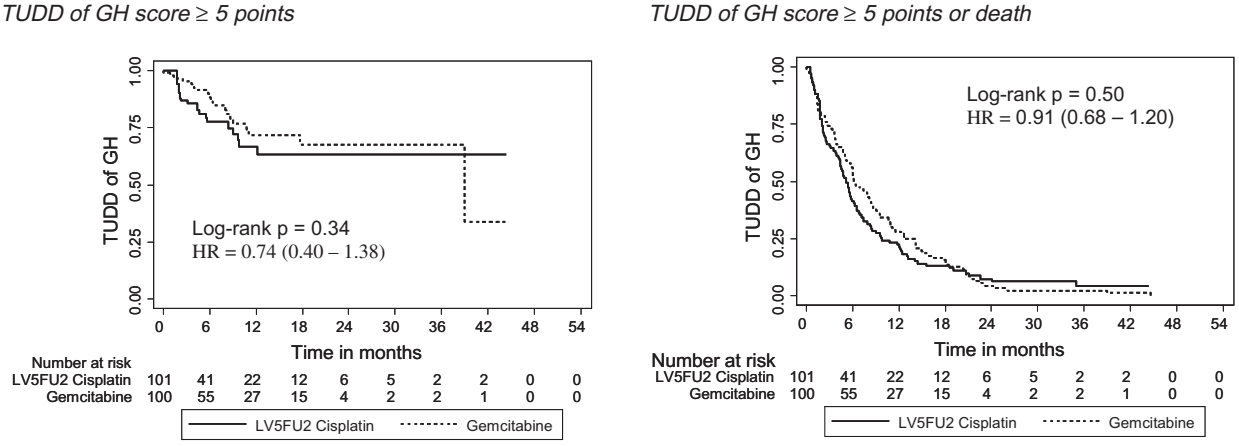
3.4. *TUDD of physical functioning score*

3.4.1. *MCID ⩾5 points*

In Arms A and B, respectively, 30 and 32 patients experienced a definitive deterioration of PF score ⩾5 points with a median TUDD of 18.92 months (11.0–NR) and 19.91

Table 1 – QoL scores at baseline by treatment arm.

	Arm A 1st line LV5FU2-cisplatin N = 102				Arm B 1st line gemcitabine N = 100				*p* Mann and Whitney
QLQ-C30 scores	N	Mean (SD)	Median	Min–Max	N	Mean (SD)	Median	Min–Max	
Global health	72	53.2 (22.3)	50	0–100	87	50.6 (20.8)	50	0–100	0.33
Physical functioning	75	73.8 (24.1)	83	7–100	88	77.2 (20.3)	80	20–100	0.59
Emotional functioning	75	61.4 (25.0)	58	0–100	89	71.7 (19.2)	75	25–100	0.007
Pain	74	42.1 (32.9)	33	0–100	89	33.5 (27.4)	33	0–100	0.10
Fatigue	75	51.3 (28.7)	44	0–100	88	47.3 (28.0)	33	0–100	0.35



LV5FU2 cisplatin: Arm A, LV5FU2-cisplatin followed by gemcitabine
Gemcitabine: Arm B, gemcitabine followed by LV5FU-cisplatin

Fig. 3 – Time until definitive deterioration (TUDD) of global health (GH) score according to treatment arm (Kaplan Meier estimation).

months (11.0–NR) (log-rank $p = 0.90$) and an HR of 1.03 (0.62–1.71).

3.4.2. *MCID ⩾5 points or death*

In Arms A and B, respectively, 97 and 98 patients experienced a definitive deterioration of PF score ⩾5 points or death with a median TUDD of 4.76 months (3.0–5.8) and 4.86 months (3.7–6.5) (log-rank $p = 0.96$) and an HR of 1.01 (0.76–1.34).

3.4.3. *MCID ⩾10 points*

In Arms A and B, respectively, 22 and 27 patients experienced a definitive deterioration of PF score ⩾10 points while the median TUDD was not reached (log-rank $p = 0.70$) with an HR of 1.12 (0.63–1.99).

3.4.4. *MCID or ⩾10 points or death*

In Arms A and B, respectively, 96 and 98 patients experienced a definitive deterioration of PF score ⩾10 points or death with median TUDD of 5.36 months (4.2–6.5) and 5.85 months (3.8–8.5) (log-rank $p = 0.88$) with an HR of 0.98 (0.74–1.30).

3.5. *TUDD of emotional functioning score*

3.5.1. *MCID ⩾5 points*

In Arms A and B, respectively, 18 and 27 patients experienced a definitive deterioration of EF score ⩾5 points while the median TUDD was not reached in Arm A and was 28.12 months (13.0–NR) in Arm B (log-rank $p = 0.20$) with an HR of 1.49 (0.81–2.74).

3.5.2. *MCID ⩾5 points or death*

In Arms A and B, respectively, 96 and 99 patients experienced a definitive deterioration of EF score of ⩾5 points or death with a median TUDD of 5.58 months (4.5–7.4) and 5.98 months (4.5–8.1) (log-rank $p = 0.85$) with an HR of 1.03 (0.77–1.37).

3.5.3. *MCID ⩾10 points*

In Arms A and B, respectively, 14 and 21 patients experienced a definitive deterioration of EF score of ⩾10 points or death while the median TUDD was not reached (log-rank $p = 0.26$) with an HR of 1.47 (0.74–2.92).

3.5.4. *MCID ⩾10 points or death*

In Arms A and B, respectively, 96 and 98 patients experienced a definitive deterioration of EF score of ⩾10 points or death with a median TUDD of 5.91 months (4.9–8.0) and 6.08 months (4.8–9.5) (log-rank $p = 0.97$) and an HR of 1.01 (0.76–1.34).

3.6. *TUDD of pain score*

3.6.1. *MCID ⩾5 points (or ⩾10 points)*

In Arms A and B, respectively, 15 and 23 patients experienced a definitive deterioration of PA score ⩾5 points (or 10 points) while the median TUDD was not reached (log-rank $p = 0.22$) and an HR of 1.50 (0.78–2.89).

3.6.2. *MCID ⩾5 points (or ⩾10 points) or death*

In Arms A and B, respectively, 95 and 99 patients experienced a definitive deterioration of PA score ⩾5 points (or 10 points) or death with median TUDD of 5.82 months (4.8–7.5) and 6.05 months (4.9–9.5) (log-rank $p = 0.92$) and an HR of 0.98 (0.74–1.31).

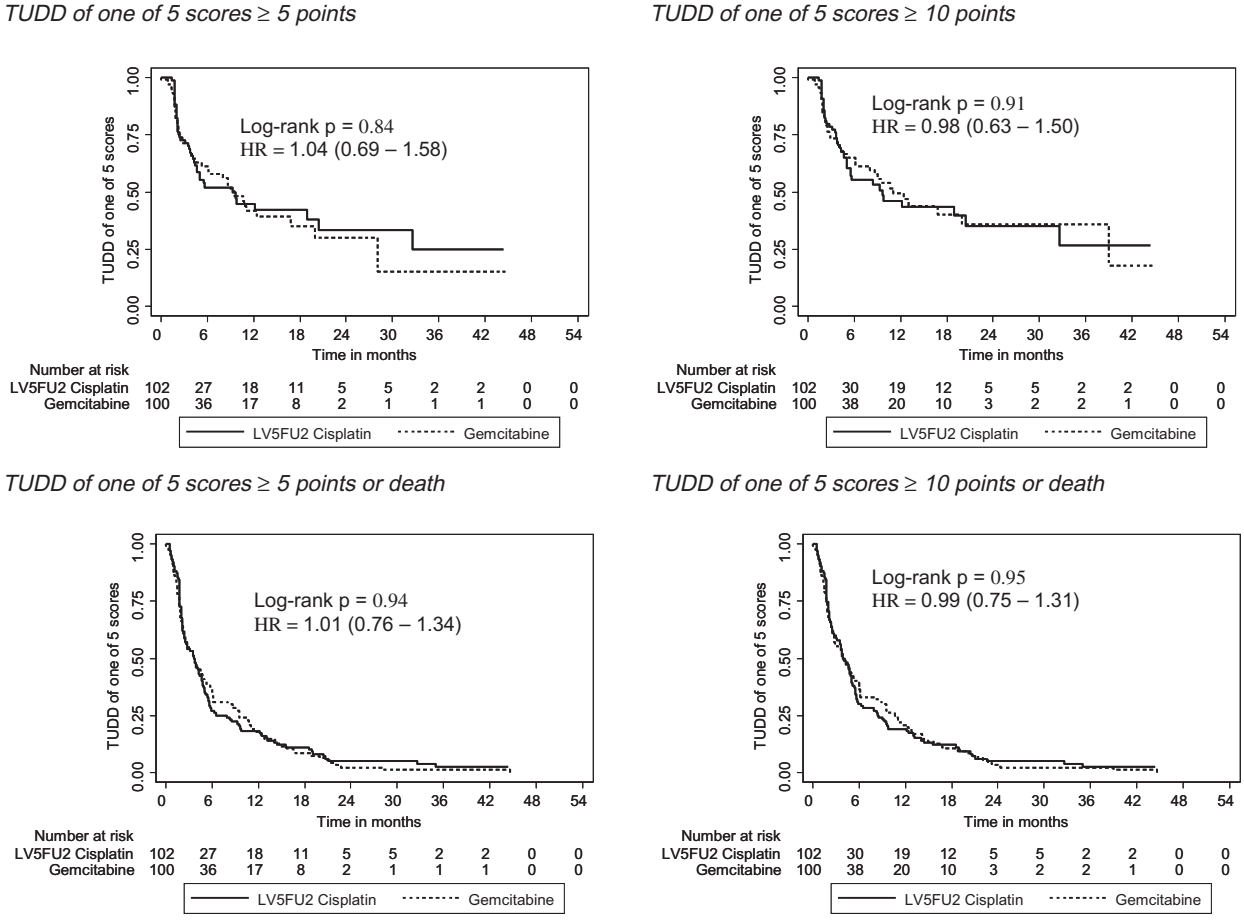
3.7. *TUDD of fatigue score*

3.7.1. *MCID ⩾5 points (or ⩾10 points)*

In Arms A and B, respectively, 25 patients experienced a definitive deterioration of FA score ⩾5 points (or ⩾10 points), while the median TUDD was not reached (log-rank $p = 0.81$) and an HR of 0.93 (0.54–1.63).

3.7.2. *MCID ⩾5 points (or ⩾10 points) or death*

In Arms A and B, respectively, 96 and 98 patients experienced a definitive deterioration pf FA score ⩾5 points (or ⩾10 points) or death with median TUDD of 4.76 months (3.6–6.3)



LV5FU2 cisplatin: Arm A, LV5FU2-cisplatin followed by gemcitabine
Gemcitabine: Arm B, gemcitabine followed by LV5FU-cisplatin

Fig. 4 – Time until definitive deterioration (TUDD) of one of 5 scores (GH or PF or EF or PA or FA) according to treatment arm (Kaplan Meier estimation).

Table 2 – Multivariate Cox analyses of time until definitive deterioration (TUDD) of one of 5 scores.

	Multivariate Cox analyses					
	Hazard ratio (95% CI)	*p*	*N*	Hazard ratio (95% CI)	*p*	*N*
	TUDD ⩾5 points			TUDD ⩾5 points or death		
TUDD of one of 5 scores			157			157
Treatment Arm B versus Arm A	0.94 (0.60–1.45)	0.764		0.99 (0.71–1.38)	0.958	
WHO PS at baseline	0.99 (0.70–1.39)	0.951		1.15 (0.89–1.49)	0.283	
Age in years	0.99 (0.97–1.01)	0.378		0.99 (0.97–1.01)	0.360	
Gender: female versus male	1.30 (0.82–2.07)	0.272		1.10 (0.77–1.58)	0.589	
Localisation: others versus head	1.60 (1.02–2.52)	0.043		1.56 (1.11–2.20)	0.010	
Grade 3/4 toxicity: yes versus no	1.42 (0.73–2.76)	0.302		1.05 (0.67–1.65)	0.828	
Progression: yes versus no	2.74 (1.26–5.96)	0.011		1.97 (1.20–3.25)	0.008	
	TUDD ⩾10 points			TUDD ⩾10 points or death		
TUDD of one of 5 scores			157			157
Treatment Arm B versus Arm A	0.90 (0.57–1.41)	0.638		0.99 (0.71–1.37)	0.932	
WHO PS at baseline	1.04 (0.73–1.48)	0.845		1.19 (0.92–1.53)	0.190	
Age in years	1.00 (0.97–1.02)	0.911		1.00 (0.98–1.02)	0.919	
Gender: female versus male	0.95 (0.59–1.55)	0.846		0.90 (0.63–1.29)	0.569	
Localisation: others versus head	1.49 (0.93–2.38)	0.097		1.42 (1.01–2.00)	0.043	
Grade 3/4 toxicity: yes versus no	1.80 (0.86–3.77)	0.116		1.14 (0.72–1.79)	0.576	
Progression: yes versus no	2.34 (1.09–5.01)	0.029		1.79 (1.11–2.89)	0.017	

Arm A: 1st line LV5FU2-cisplatin; Arm B: 1st line gemcitabine.

Table 3 – Quality of time until definitive deterioration (TUDD) (⩾5 points or 10 points) definition according to surrogacy for OS.

Global health	Physical functioning	Emotional functioning	Pain	Fatigue
Hazard ratio [95% CI] (*p* value)				
TUDD ⩾5 points				
Effect of treatment on TUDD				
HR(trt) = 0.74 [0.40; 1.38] (*p* = 0.35)	HR(trt) = 1.03 [0.62; 1.72] (*p* = 0.90)	HR(trt) = 1.49 [0.81; 2.74] (*p* = 0.20)	HR(trt) = 1.50 [0.78; 2.89] (*p* = 0.22)	HR(trt) = 0.94 [0.54; 1.63] (*p* = 0.81)
Effect of TUDD on OS				
HR(TUDD) = 2.15 [1.48; 3.12] (*p* < 0.0001)	HR(TUDD) = 1.81 [1.30; 2.50] (*p* = 0.0004)	HR(TUDD) = 1.97 [1.37; 2.83] (*p* = 0.0003)	HR(TUDD) = 2.79 [1.92; 4.06] (*p* < 0.0001)	HR(TUDD) = 1.91 [1.35; 2.71] (*p* = 0.0003)
Effect of TUDD on OS adjusted on treatment				
HR(trt) = 1.03 [0.77; 1.37] (*p* = 0.84)	HR(trt) = 0.95 [0.71; 1.26] (*p* = 0.71)	HR(trt) = 0.94 [0.70; 1.25] (*p* = 0.65)	HR(trt) = 0.96 [0.72; 1.28] (*p* = 0.78)	HR(trt) = 0.97 [0.73; 1.29] (*p* = 0.83)
HR(TUDD) = 2.16 [1.48; 3.15] (*p* < 0.0001)	HR(TUDD) = 1.81 [1.31; 2.51] (*p* = 0.0004)	HR(TUDD) = 1.98 [1.38; 2.86] (*p* = 0.0002)	HR(TUDD) = 2.79 [1.92; 4.07] (*p* < 0.0001)	HR(TUDD) = 1.91 [1.35; 2.71] (*p* = 0.0003)
Freedman's proportion explained PTE				
2.00	−0.80	−1.72	−0.37	−0.003
TUDD ⩾10 points				
Effect of treatment on TUDD				
HR(trt) = 0.64 [0.31; 1.35] (*p* = 0.24)	HR(trt) = 1.12 [0.63; 1.99] (*p* = 0.70)	HR(trt) = 1.48 [0.74; 2.92] (*p* = 0.27)	HR(trt) = 1.50 [0.78; 2.89] (*p* = 0.22)	HR(trt) = 0.94 [0.54; 1.63] (*p* = 0.81)
Effect of TUDD on OS				
HR(TUDD) = 2.72 [1.79; 4.14] (*p* < 0.0001)	HR(TUDD) = 2.13 [1.50; 3.01] (*p* < 0.0001)	HR(TUDD) = 3.00 [2.02; 4.46] (*p* < 0.0001)	HR(TUDD) = 2.79 [1.92; 4.06] (*p* < 0.0001)	HR(TUDD) = 1.91 [1.35; 2.71] (p = 0.0003)
Effect of TUDD on OS adjusted on treatment				
HR(trt) = 1.05 [0.78; 1.39] (*p* = 0.76)	HR(trt) = 0.96 [0.73; 1.28] (*p* = 0.80)	HR(trt) = 0.92 [0.69; 1.22] (*p* = 0.54)	HR(trt) = 0.96 [0.72; 1.28] (*p* = 0.78)	HR(trt) = 0.97 [0.73; 1.29] (*p* = 0.83)
HR(TUDD) = 2.75 [1.80; 4.20] (*p* < 0.0001)	HR(TUDD) = 2.13 [1.50; 3.02] (*p* < 0.0001)	HR(TUDD) = 3.04 [2.05; 4.53] (*p* < 0.0001)	HR(TUDD) = 2.79 [1.92; 4.07] (*p* < 0.0001)	HR(TUDD) = 1.91 [1.35; 2.71] (*p* = 0.0003)
Freedman's proportion explained PTE				
2.46	−0.24	−1.92	−0.37	−0.003

and 5.61 months (4.2–7.7) (log-rank $p = 0.76$) and an HR of 0.96 (0.72–1.27).

3.8. *TUDD of one of 5 scores (GH, PF, EF, PA or FA) (Fig. 4)*

3.8.1. *MCID ⩾5 points*

In Arms A and B, respectively, 44 and 45 patients experienced a definitive deterioration of ⩾5 points in one of 5 scores with a median TUDD of 9.33 months (4.3–20.4) and 9.59 months (5.3–16.8).

3.8.2. *MCID ⩾5 points or death*

In Arms A and B, respectively, 98 and 99 patients experienced a definitive deterioration of ⩾5 points or death in one of 5 scores with a median TUDD of 3.71 months (2.4–4.7) and 3.68 months (2.5–5.1).

3.8.3. *MCID ⩾10 points*

In Arms A and B, respectively, 42 and 41 patients experienced a definitive deterioration of ⩾10 points in one of 5 scores with a median TUDD of 9.72 months (5.0–20.4) and 11.0 months (6.2–39.0).

3.8.4. *MCID ⩾10 points or death*

In Arms A and B, respectively, 98 and 99 patients experienced a definitive deterioration ⩾10 points in one of 5 scores or death with a median TUDD of 3.94 months (2.8–5.0) and 3.84 months (2.6–5.3).

Multivariate Cox analysis (Table 2) showed that other than head tumour localisation and progression were independently associated with shorter TUDD whatever the definition of the events.

3.9. *Quality of TUDD definition according to surrogacy of OS*

Exploratory analysis for the surrogacy of OS showed that the four conditions of the Prentice criteria were not fulfilled (Table 3). Although TUDD has a significant prognostic value for OS (HR > 1 and $p < 0.001$ whatever the TUDD definition) there

was no downward trend from the effect of treatment. Because treatment has no significant effect on TUDD and OS, the Freedman's proportion of treatment effect explained (PTE) cannot be interpreted.

4. Discussion

Studies have shown that most oncologists or patients are unwilling to prolong survival at the expense of worsening QoL.[25,26] From this point of view, the results of QoL as a secondary end-point in the FFCD trial[10] are important to analyse the impact of sequence line administration. Our study shows that LV5FU2-P followed by gemcitabine or the opposite sequence did not significantly influence longitudinal QoL in patients with MPA. Progression and tumour localisation other than in the head of the pancreas were independently associated with a shorter TUDD.

There are very few trials reporting QoL results in metastatic or advanced cancer patients. One recent trial concluded that there was no significant difference in QoL but analysis was not extensively detailed.[27] Bernhard et al.[28] have shown that QoL was similar whatever the treatment but worsened one to 2 months before treatment failure in primary inoperable or MPA patients. In that study, an in-depth 6 month assessment schedule was used to avoid missing QoL data.[28] In many studies in advanced cancer patients completion of QoL fails due to drop out.[29,30] Patients are often unable to complete QoL questionnaires because of deteriorating health or early death.[31] Our results confirm that the QoL of patients with progressive disease deteriorated more rapidly with only 57 patients in our study completing the QoL questionnaire at the 3rd follow-up; moreover these healthy patients may not represent the target population.[32] We used time to definitive deterioration of QoL as a conservative approach which took into account non-ignorable missing scores in advanced-stage trials.[31] Some trials on advanced hepatocellular carcinoma (HCC) have already used this approach; timeto symptomatic progression is defined as either a decrease of 4 or more points from the baseline QoL score (change confirmed 3 weeks later) or a deterioration in ECOG performance status to 4 or death has been proposed.[33] The MCID cut-off for the decrease in QoL was not justified[21] and the end-point seems too composite to interpret results. Other trials in advanced HCC have used different definitions.[34,35] These analytic modalities have also been applied in other cancer trials with several definitions using different MCID cut-offs for the decrease in QoL or using death as event.[36] The necessity of rationalising the terminology related to survival or time to event end-points has been emphasised when comparing trial results.[37] Thus, in this study we investigated different TUDD definitions. TUDD definitions could be used by stating that most of the missing data after an observed deterioration probably correspond to a continuous deterioration of QoL. This assumption is supported by the setting of this study in patients with short survival. To our knowledge there are no formal statistical tests to select the best definition of time to event end-points. Surrogacy could constitute an alternative statistical method to check the quality of investigated definitions. Although we showed that all TUDD definitions were correlated to OS, we failed to validate TUDD as a surrogate of OS. The PTE was not interpretable because treatment did not have a significant effect on TUDD and OS.

Based on our results we suggest that the 5 point MCID is a more clinically meaningful event definition that would improve power.[21] With a 6.7 month median OS for Arm A and 8.0 months for Arm B,[10] reported results of TUDD including death as an event seem to be more clinically relevant since the median TUDD occurred before the median OS. When the TUDD definitions were used without including death as an event, the median was not reached or it was too long to be clinically relevant. In relation to the 3 month median delay between last available QoL assessment and last follow-up it could be argued that most of the QoL questionnaires were not completed by patients in case of severe health deterioration. In this case our data do not include all definitive deteriorations in QoL as a result we suggest that the estimation of TUDD including death should be used whatever the MCID cut-off.

One of the benefits of this modality of analysis is to propose meaningful longitudinal QoL results for clinicians. To improve QoL results, in future trials QoL completion should be required independent from patient health status. Help in completing questionnaires should be provided. There should be an in-depth QoL assessment schedule in this setting to avoid missing QoL data[28] and to prevent overestimating TUDD by increasing real time data on QoL deterioration.[38] These preliminary approaches to TUDD definitions should be developed by evaluating other definitions and could help to assess therapeutic strategies by optimising the balance between QoL and OS in metastatic pancreatic adenocarcinoma.

Contributorship statement

Study concepts: F. Bonnetain, L. Dahan, J.F. Seitz, L. Bedenne, J.L. Legoux, P. Rougier, P. Hammel, M. Ychou, E. Mitry, B. Chauffert & L. Bedenne.

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Manuscript editing: F. Bonnetain & L. Dahan.

Manuscript review: F. Bonnetain, L. Dahan, E. Maillard, J.F. Seitz, L. Bedenne, J.L. Legoux, P. Rougier, P. Hammel, M. Ychou, E. Mitry, B. Chauffert & L. Bedenne.

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Conflict of interest statement

None declared.

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