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Clinical Trial

Geriatric factors analyses from FFCD 2001-02 phase III study of first-line chemotherapy for elderly metastatic colorectal cancer patients☆

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Abstract ***Aim:*** Several predictors of metastatic colorectal cancer (mCRC) outcomes have been described. Specific geriatric characteristics could be of interest to determine prognosis.
Method: Elderly patients (75+) with previously untreated mCRC were randomly assigned to receive infusional 5-fluorouracil-based chemotherapy, either alone (FU) or in combination with irinotecan (IRI). Geriatric evaluations were included as an optional procedure. The predictive value of geriatric parameters was determined for the objective response rate (ORR), progression-free survival (PFS) and overall survival (OS).
Results: From June 2003 to May 2010, the FFCD 2001-02 randomised trial enrolled 282 patients. A baseline geriatric evaluation was done in 123 patients; 62 allocated to the FU arm and 61 to the IRI arm. The baseline Charlson index was ≤1 in 75%, Mini-Mental State Examination was ≤27/30 in 31%, Geriatric Depression Scale was >2 in 10% and Instrumental Activities of Daily Living (IADL) was impaired in 34% of the patients. Multivariate analyses revealed that no geriatric parameter was predictive for ORR or PFS. Normal IADL was independently associated with better OS.

The benefit of doublet chemotherapy on PFS differed in subgroups of patients ≤80 years, with unresected primary tumour, leucocytes >11,000 mm^3 and carcinoembryonic antigen >2N. There was a trend towards better OS in patients with normal IADL.
Conclusion: The autonomy score was an independent predictor for OS. A trend toward a better efficacy of doublet chemotherapy in some subgroups of patients was reported and should be further explored.

1. Introduction

Colorectal cancer mainly occurs in elderly patients. Recent estimations showed that in France 45% of patients diagnosed with colorectal cancer are 75-years-old or older (http://www.invs.sante.fr/applications/cancers/projections2010). Specific data for the treatment of metastatic colorectal cancer (mCRC) in elderly patients are scarce and a number of issues remain unresolved [1]. Until recently, elderly patients were underrepresented in clinical trials [2]. Concerning mCRC, several prospective trials were specific for elderly patients but none of them planned a geriatric evaluation [3–7].

Elderly patients constitute a heterogeneous population. Comorbidities and disabilities become increasingly prevalent with advancing age and are associated with treatment-related side-effects and poor outcomes [8–10]. Older patients less frequently receive the recommended treatment compared with younger patients [11,12]. The choice of the best treatment strategy is an important challenge in elderly patients. Geriatric assessments (GA) evaluate the patient's functional status, mobility, comorbidities, polypharmacy, nutritional status, cognitive function, emotional status and social support [13] based on validated geriatric scales and tests. The International Society for Geriatric Oncology (SIOG) recommends a GA before cancer treatment decisions [14].

The FFCD 2001-02 trial was a randomised phase III study to evaluate chemotherapy with the classic bimonthly leucovorine + 5-fluorouracil (LV5FU2) regimen or a simplified LV5FU2 regimen with or without irinotecan in patients with mCRC aged 75 or older. A preliminary analysis of the geriatric factors revealed that cognitive and functional impairments were predictive of severe toxicity or unexpected

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hospitalisation [15]. The overall results for the patients enrolled in the trial revealed that in this elderly population, adding irinotecan to infusional 5-fluorouracil-based CT did not significantly increase either progression-free survival (PFS) or overall survival (OS) [16]. The analysis of the survival end-points in the subgroup of patients who had a GA before enrolment in the trial is presented here.

2. Materials and methods

2.1. Patient selection

The main eligibility criteria were histologically confirmed unresectable mCRC, elderly patients (age ≥75 years), Karnofsky index ≥60, life expectancy >6 months, ≥1 bi-dimensionally measurable lesion (Response Evaluation Criteria in Solid Tumours [RECIST]), no previous chemotherapy for metastatic disease, adjuvant therapy was allowed if stopped at least 6 months before randomisation, adequate organ and bone marrow function, creatinine clearance ≥45 ml/min (Cockroft–Gault; protocol in Supplementary File).

Written informed consent was obtained for each patient. The study was approved by the Ethics Committee (CPPRB Boulogne Billancourt no 020946 on September 26, 2002) and registered in clinicaltrials.gov with the number NCT00303771.

2.2. Study design

This phase III trial was a 2 × 2 factorial design (four arms) combining 5-fluorouracil-based CT, either alone (FU arms: LV5FU2 or simplified LV5FU2 + irinotecan (FOFIRI)) or in combination with irinotecan (IRI arms: LV5FU2-irinotecan or FOLFIRI). A second analysis was CLASSIC arms (LV5FU2 or LV5FU2-irinotecan) versus SIMPLIFIED arms (simplified LV5FU2 or FOLFIRI'). In the IRI arm, the first two cycles were performed with 150 mg/m^2 of irinotecan and, in the absence of toxicity, the dose of irinotecan was increased to 180 mg/m^2 for the following cycles [16]. Patients were randomly assigned to one arm and the randomisation was stratified according to centre, Charlson index (0 versus 1–2 versus 3+), Karnofsky index (60–70 versus 80–90 versus 100), previous adjuvant CT, sex, age (<80 versus ≥ 80 years) and alkaline phosphatases (≤2 limit of normal [LN] versus > 2 LN). Radiological assessments were performed every 8 weeks (abdominal and thoracic computed tomography scan or magnetic resonance imaging) and tumour response was classified according to RECIST 1.0 criteria.

2.3. Geriatric assessment

The ancillary geriatric study was planned in the FFCD 2001-02 trial but was not mandatory. Only voluntary hospital teams participated in the geriatric study. Sites completed a visual analogue scale (VAS) of quality of life (QoL) scored on a 100-mm scale [17] at inclusion and the following geriatric questionnaires: Mini-Mental State Examination (MMSE) [18], instrumental activity of daily living (IADL) [19] and Geriatric Depression Scale (GDS) [20] to assess cognitive function, dependence and depression, respectively. The associated scores were calculated as the average of items that contributed to the scale. Scores were considered missing when more than half of the items were missing. A GA was done before randomisation and every 8 weeks thereafter until progression as assessed by physicians.

2.4. Statistical analyses

PFS was defined as the time from randomisation to the first progression (defined by RECIST 1.0 criteria) or death (all causes). Alive patients without progression were censored at the last follow-up date. OS was defined as the time between randomisation and death (all causes). The time to the deterioration in IADL and QoL scores was defined as the time from randomisation to the first loss of 20 points on the QoL VAS and to a 20% reduction in IADL. The time to deterioration was evaluated according to the treatment arm in patients who had at least one evaluation after baseline.

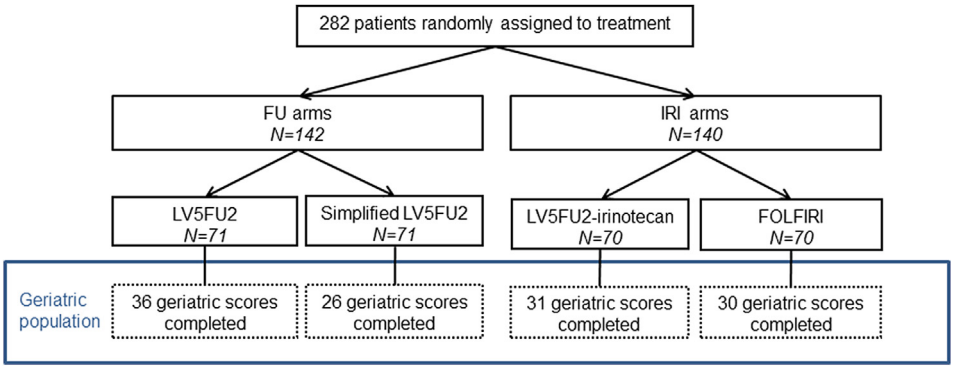

Fig. 1. Flow chart.

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Table 1
Patients' characteristics at randomisation.

Characteristics	FU arm N = 62	IRI arm N = 61	Total N = 123
Age (years)			
≤80	34 (54.8%)	37 (60.7%)	71 (57.7%)
>80	28 (45.2%)	24 (39.3%)	52 (42.3%)
Mean age (years) ± SD	80.3 ± 3.9	80.5 ± 3.5	80.4 ± 3.7
Sex			
Male	33 (53.2%)	33 (54.1%)	66 (53.7%)
Female	29 (46.8%)	28 (45.9%)	57 (46.3%)
Body mass index (kg/m^2)		***n = 60***	***n = 122***
≤20	3 (4.8%)	5 (8.3%)	8 (6.6%)
20–30	54 (87.1%)	48 (80.0%)	102 (83.6%)
>30	5 (8.1%)	7 (11.7%)	12 (9.8%)
Mean body mass index (kg/m^2) ± SD	24.8 ± 3.6	25.4 ± 4.0	25.1 ± 3.8
Number of metastatic sites		***n = 60***	***n = 122***
1	29 (46.8%)	29 (48.3%)	58 (47.5%)
2	26 (41.9%)	15 (25.0%)	41 (33.6%)
>2	7 (11.3%)	16 (26.7%)	23 (18.9%)
Primary tumour resected		***n = 60***	***n = 122***
No	20 (32.3%)	19 (31.7%)	39 (32.0%)
Yes	42 (67.7%)	41 (68.3%)	83 (68.0%)
Previous adjuvant chemotherapy		***n = 59***	***n = 121***
No	50 (80.6%)	54 (91.5%)	104 (86.0%)
Yes	12 (19.4%)	5 (8.5%)	17 (14.0%)
Alkaline phosphatases	***n = 59***	***n = 59***	***n = 118***
≤2 LN	44 (74.6%)	48 (81.4%)	92 (78.0%)
>2 LN	15 (25.4%)	11 (18.6%)	26 (22.0%)
Leucocytes		***n = 60***	***n = 122***
≤11,000/mm^3	52 (83.9%)	51 (85.0%)	103 (84.4%)
>11,000/mm^3	10 (16.1%)	9 (15.0%)	19 (15.6%)
Haemoglobin (g/dL)		***n = 60***	***n = 122***
<10 (female), <11 (male)	54 (87.1%)	53 (88.3%)	107 (87.7%)
≥10 (female), ≥11 (male)	8 (12.9%)	7 (11.7%)	15 (12.3%)
CEA	***n = 58***	***n = 56***	***n = 114***
≤2 LN	16 (27.6%)	21 (37.5%)	37 (32.5%)
>2 LN	42 (72.4%)	35 (62.5%)	77 (67.5%)
CA 19-9	***n = 54***	***n = 54***	***n = 108***
≤2 LN	27 (50.0%)	27 (50.0%)	54 (50.0%)
>2 LN	27 (50.0%)	27 (50.0%)	54 (50.0%)
Karnofsky index	***n = 61***	***n = 60***	***n = 121***
60–70	21 (34.4%)	18 (30.0%)	39 (32.2%)
80–90	32 (52.5%)	30 (50.0%)	62 (51.2%)
100	8 (13.1%)	12 (20.0%)	20 (16.5%)
Charlson index	***n = 61***	***n = 60***	***n = 121***
0	34 (55.7%)	26 (43.3%)	60 (49.6%)
1	17 (27.9%)	15 (25.0%)	32 (26.4%)
2+	10 (16.4%)	19 (31.7%)	29 (24.0%)
QoL VAS (mm)	***n = 59***	***n = 58***	***n = 117***
≤70	37 (62.7%)	36 (62.1%)	73 (62.4%)
>70	22 (37.3%)	22 (37.9%)	44 (37.6%)
Mean score of QoL VAS (mm) ± SD	57.9 ± 24.2	63.3 ± 21.4	60.5 ± 22.9
MMSE	***n = 45***	***n = 46***	***n = 91***
>27/30	27 (60.0%)	20 (43.5%)	53 (58.2%)
≤27/30	18 (40.0%)	26 (56.5%)	38 (41.8%)
Not evaluated	17	15	32
GDS	***n = 43***	***n = 47***	***n = 90***
>2	9 (20.9%)	4 (8.5%)	13 (14.4%)
≤2	34 (79.1%)	43 (91.5%)	77 (85.6%)
Not evaluated	19	14	33
IADL	***n = 44***	***n = 43***	***n = 87***
Impaired	22 (50.0%)	20 (46.5%)	42 (48.3%)
Normal	22 (50.0%)	23 (53.5%)	45 (51.7%)
Not evaluated	18	18	36

MMSE, Mini-Mental State Examination; CEA, carcinoembryonic antigen; LN, limit of normal; QoL, quality of life; VAS, visual analogue scale; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living.

Qualitative and continuous variables were described using usual descriptive statistics.

The median follow-up was calculated according to reverse Kaplan–Meier estimates. Survival analyses were done using the Kaplan–Meier method and described using medians with 95% confidence intervals (95% CIs). Comparisons between subgroups were made with the log-rank tests. The univariate Cox model was used to estimate the hazard ratio (HR) with à 95% CI. Multivariate Cox models were used to explore potential prognostic factors of PFS and OS. Logistic regressions were performed for objective response rate (ORR). All baseline variables significant at 15% in univariate analyses were included in the multivariate analyses. The cut-off of 15% was chosen due to the less patients' number.

3. Results

3.1. Baseline characteristics

The FFCD 2001-02 trial enrolled 282 patients from 2003 to 2010. Fifty centres participated in the study, among which 32 (64%) participated in the geriatric study. Geriatric scores were calculated in 123 (44%) patients of the 282 patients randomised in the study (Fig. 1). The characteristics of these 123 patients are described in Table 1. Patients and centre characteristics are comparable between the subgroup of patients that have a geriatric evaluation and the subgroup of patients that did not benefit from geriatric evaluation (Supplementary Table 1).

Tumour and geriatric parameters were comparable in the FU and IRI arms except for a higher proportion of patients with >2 metastatic sites in the IRI arm (27% versus 11%, p = 0.04) and a slightly higher proportion of patients with comorbidities assessed by a Charlson index >1 in the IRI arm (32% versus 16%, p = 0.06, marginally significant).

MMSE, GDS and IADL were not available for analysis (totally missing or more than half of the items missing) for 29% of the patients. Altogether, 31% of patients had at least one questionnaire missing or not exploitable.

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3.2. Efficacy results

3.2.1. Progression-free survival

The median PFS was 7.4 months (6.1–8.6). Univariate analyses revealed that alkaline phosphatases ≤2 LN and carcinoembryonic antigen (CEA) ≤2 LN were associated with a prolonged PFS (Table 2). No factor was associated with prolonged PFS in multivariate Cox analysis (Table 3). The baseline characteristics of patients with all questionnaire available included in multivariate analysis were similar to those of patients with missing questionnaires except for tumour marker level (Supplementary Table 2).

3.2.2. Overall survival

The median OS was 17.7 months (13.3–19.4). Univariate analyses revealed that alkaline phosphatases ≤2 LN, leucocytes ≤11,000, primary tumour resected and the CLASSIC treatment arm were associated with a prolonged OS (Table 4). The multivariate Cox analysis revealed that the CLASSIC treatment arm and a normal IADL score (Fig. 2) were associated with better OS (Table 3).

3.2.3. Response rate

No geriatric factors were significantly associated with better or poor ORR. Only the CLASSIC treatment arm significantly improved the ORR in multivariate analysis (Supplementary File Tables 3 and 4).

3.2.4. Subgroup analysis

Subgroup analysis was performed according to the IRI or FU arm. A significant interaction was observed between age, primary tumour resected, leucocytes, CEA and the treatment effect on PFS (Fig. 3). There was a trend toward better OS in the subgroup of patients with normal IADL treated with IRI (Fig. 4).

3.2.5. Time to a deterioration in QoL and autonomy

Among the 123 patients with a geriatric score at inclusion, 85 had at least one QoL evaluation after baseline: 45 in FU and 40 in IRI. The median time before deterioration in QoL was 11.9 months (95% CI: 3.6–not reached (NR)) in FU versus 17.7 months (95% CI: 10.8–22.0) in IRI (p = 0.46). The Charlson index was an independent predictor for QoL deterioration (Table 5).

Sixty-four patients had at least one IADL evaluation after baseline: 34 in FU and 30 in IRI. The median time before deterioration in IADL for these patients was 18.9 months (95% CI: 7.1–NR) in FU. The median time was not reached in IRI (p = 0.24). In multivariate analysis, no factors remained associated with IADL deterioration (Supplementary File Table 5).

Table 2
Univariate analyses for PFS.

Univariate analysis	N	HR	95% CI	P
Age (years)				
≤80	123	1.19	0.83–1.72	0.34
>80		–	–	
Sex				
Female	123	1.01	0.70–1.44	0.98
Male		–	–	
Treatment arm				
IRI	123	0.98	0.69–1.41	0.93
FU		–	–	
Treatment arm				
CLASSIC	123	0.84	0.59–1.21	0.36
SIMPLIFIED		–	–	
Body mass index (kg/m^2)				
≤20	122	0.62	0.25–1.52	0.35
20–30		0.64	0.35–1.18	
>30		–	–	
Number of metastatic sites				
1	122	0.59	0.36–0.98	0.12
2		0.74	0.44–1.24	
>2		–	–	
Primary tumour resected				
No	122	1.45	0.97–2.17	0.07
Yes		–	–	
Previous adjuvant chemotherapy				
No	121	0.94	0.56–1.57	0.81
Yes		–	–	
Alkaline phosphatases				
≤2N	118	0.56	0.36–0.88	0.01
>2N		–	–	
Leucocytes				
≤11,000/mm^3	122	0.61	0.36–1.01	0.06
>11,000/mm^3		–	–	
Haemoglobin (g/dL)				
<10 (female), <11 (male)	122	0.88	0.51–1.52	0.65
≥10 (female), ≥11 (male)		–	–	
CEA				
≤2N	114	0.59	0.39–0.88	0.01
>2N		–	–	
CA 19-9				
≤2N	108	0.74	0.50–1.09	0.13
>2N		–	–	
Karnofsky index				
60–70%	121	1.35	0.78–2.34	0.48
80–90%		1.10	0.66–1.82	
100%		–	–	
Charlson index				
0	121	0.99	0.69–1.42	0.97
1+		–	–	
QoL VAS (mm)				
≤70	117	0.94	0.64–1.37	0.73
>70		–	–	
MMSE				
≤27/30	91	0.73	0.48–1.12	0.15
>27/30		–	–	
IADL				
Impaired	87	0.92	0.60–1.42	0.70
Normal		–	–	–

MMSE, Mini-Mental State Examination; CEA, carcinoembryonic antigen; LN, limit of normal; QoL, quality of life; VAS, visual analogue scale; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; CI, confidence intervals; PFS, progression-free survival.

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Table 3
Multivariate analyses for PFS and OS.

Multivariate analysis	PFS N = 80 (79 with event)				OS N = 79 (73 with event)			
	HR	95% CI		p	HR	95% CI		p
Treatment arm								
CLASSIC versus SIMPLIFIED					0.50	0.30	0.84	0.01
Number of metastatic sites								
1 versus > 2	0.72	0.36	1.45	0.64	0.61	0.30	1.24	0.35
2 versus > 2	0.76	0.37	1.56		0.80	0.38	1.68	
Primary tumour resected								
No versus yes	1.34	0.76	2.38	0.32	1.13	0.64	1.97	0.68
Alkaline phosphatases								
≤2N versus >2N	0.79	0.40	1.55	0.49	0.80	0.39	1.62	0.53
Leucocytes								
≤11,000/mm^3 versus >11,000/mm^3	1.16	0.52	2.60	0.72	0.58	0.28	1.18	0.13
CEA								
≤2N >2N	0.65	0.37	1.14	0.13	0.58	0.32	1.05	0.07
CA 19-9								
≤2N >2N	1.12	0.64	1.96	0.69				
IADL								
Impaired versus normal					1.99	1.12	3.55	0.02
MMSE								
≤27/30 versus >27/30	0.81	0.47	1.37	0.43				

MMSE, Mini-Mental State Examination; CEA, carcinoembryonic antigen; IADL, Instrumental Activities of Daily Living; CI, confidence intervals; PFS, progression-free survival; OS, overall survival.

4. Discussion

This was the first randomised prospective study specifically conducted in mCRC patients aged 75 or over to evaluate geriatric parameters. The main result of the study is that the addition of irinotecan to fluorouracil in the first line did not significantly prolong PFS and had no effect on OS but improved ORR [16]. Moreover, a previous analysis of predictive geriatric parameters for toxicity revealed that impaired MMSE and IADL were predictive of severe toxicity, and that impaired MMSE was predictive of unexpected hospitalisation [15].

The selection of patients who could benefit from doublet chemotherapy is a major challenge. The purpose of this study was to explore whether geriatric parameters could be independent predictive factors for survival.

Our results showed that alkaline phosphatases ≤2 LN and CEA ≤2 LN were associated with better PFS in univariate analyses but no factor was identified in multivariate analysis. It should be pointed out that in the whole trial population, alkaline phosphatase ≤2 LN and CEA ≤2 LN were independent factors associated with prolonged PFS [16]. Multivariate analysis reduced the number of subjects with all data available. Thus, the multivariate analysis was done in a small number of patients in our study and should be taken with caution. The number of parameters introduced in the model for PFS and OS was close to the limit acceptable for multivariate analysis but the ratio of number of parameters/number of events remains close to 0.1.

With regard to OS, multivariate analysis revealed that the CLASSIC treatment arm and a normal IADL score were associated with better OS. The prognostic value of geriatric factors has been poorly studied in mCRC. In the FOCUS 2 trial, a comprehensive health assessment based partly on geriatric parameters was associated with overall treatment utility (composite measure) at 3 months but not reported as a predictor for OS [6]. In all cancer types, several geriatric parameters have been inconstant predictors of OS. In a large study on 348 patients treated with first-line chemotherapy, impaired mobility was associated with poor OS [10]. Abnormal GDS was a predictor of poor OS in a large study, whatever the primary cancer [21] and in a specific study on ovarian cancer [22]. Moreover, an impaired IADL was associated with poor OS in metastatic non-small-cell lung cancer [23]. Nevertheless a meta-analysis published in 2012 reported that although various geriatric conditions appear to be of some value in predicting outcomes in elderly patients with cancer, the results were too inconsistent to guide treatment decisions [24]. As the main limitation of our study is the small number of patients with GA assessed, it is important to explore geriatric parameters further in large studies on homogeneous groups of patients (e.g. mCRC).

In the subgroup analysis of our study, there was an overall survival trend in favour of 5-fluorouracil monotherapy in patients with impaired IADL. This result is concordant with our previous observation that impaired IADL and MMSE scores were associated with toxicity [15]. Moreover, a trend towards longer PFS with doublet chemotherapy appeared only in patients aged ≤80 years, with tumour inflammation reflected by a high leucocyte count and with an unresected primary tumour. Thus, it could be hypothesised that with regard to the results of this study and the previous study [15] 5-fluorouracil

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Table 4
Univariate analyses for OS.

Univariate analysis	N	HR	95% CI	p
Age (years)				
≤80	123	0.93	0.64–1.35	0.71
>80		–	–	
Sex				
Female	123	1.22	0.84–1.77	0.30
Male		–	–	
Treatment arm				
IRI	123	1.04	0.72–1.50	0.85
FU		–	–	
Treatment arm				
CLASSIC	123	0.60	0.41–0.89	0.01
SIMPLIFIED		–	–	
Body mass index (kg/m^2)				
≤20	122	0.77	0.30–1.97	0.48
20–30		0.69	0.38–1.27	
>30		–	–	
Number of metastatic sites				
1	122	0.61	0.40–1.01	0.15
2		0.74	0.44–1.25	
>2		–	–	
Primary tumour resected				
No	122	1.66	1.10–2.49	0.02
Yes		–	–	
Previous adjuvant chemotherapy				
No	121	0.91	0.54–1.53	0.72
Yes		–	–	
Alkaline phosphatases				
≤2N	118	0.40	0.25–0.64	0.0001
>2N		–	–	
Leucocytes				
≤11,000/mm^3	122	0.56	0.33–0.93	0.02
>11,000/mm^3		–	–	
Haemoglobin (g/dL)				
<10 (female), <11 (male)	122	0.78	0.44–1.37	0.39
≥10 (female), ≥11 (male)		–	–	
CEA				
≤2N	114	0.68	0.45–1.04	0.07
>2N		–	–	
CA 19–9				
≤2N	108	0.76	0.51–1.13	0.18
>2N		–	–	
Karnofsky index				
60–70%	121	1.38	0.79–2.42	0.42
80–90%		1.08	0.64–1.83	
100%		–	–	
Charlson index				
0	121	0.90	0.62–1.31	0.58
1+		–	–	
QoL VAS (mm)				
≤70	117	1.02	0.69–1.52	0.91
>70		–	–	
MMSE				
≤27/30	91	0.74	0.47–1.16	0.19
>27/30		–	–	–
IADL				
Impaired	87	1.53	0.99–2.38	0.06
Normal		–	–	–

MMSE, Mini-Mental State Examination; CEA, carcinoembryonic antigen; QoL, quality of life; VAS, visual analogue scale; IADL, Instrumental Activities of Daily Living; CI, confidence intervals; OS, overall survival.

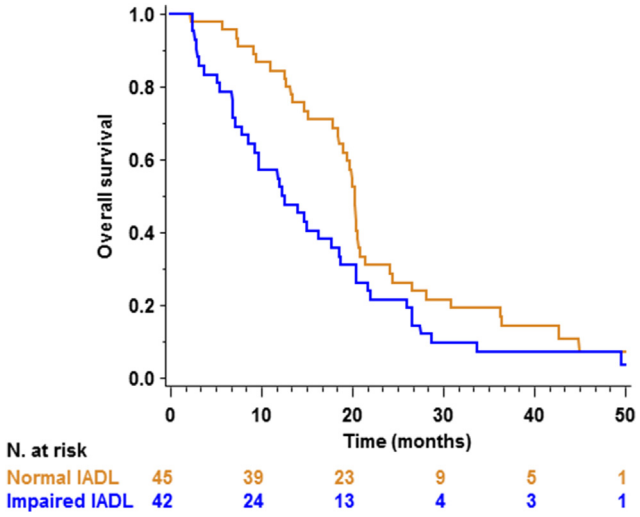

Fig. 2. Kaplan–Meier curves for overall survival according to instrumental activity of daily living (IADL).

monotherapy is preferable in patients with impaired geriatric parameters while doublet chemotherapy should be considered in patients with a good general status, a high leucocyte count and an unresected primary tumour. It must be pointed out that among the results for the whole study population, no subgroup of patients showed any benefit with doublet chemotherapy [16]. The geriatric evaluation thus appears to add value to subgroup analyses. Nevertheless, these findings need to be interpreted with caution given the small number of patients. Since this study was performed, two phase III studies have demonstrated a significant improvement in PFS using a combination of bevacizumab + capecitabine compared with capecitabine alone in elderly patients with mCRC [3,25]. No geriatric parameters were reported in these studies. Nevertheless, another randomised phase II study that evaluated different chemotherapy regimens ± bevacizumab revealed that normal IADL was associated with a composite end-point that combined efficacy and safety criteria [26].

Altogether, our study and other studies advocate GA for elderly patients with mCRC. It has already been demonstrated that GA modify care in around 20% of patients [27]. One recent study demonstrated that GA and geriatric interventions were associated with better outcomes for older people undergoing chemotherapy [28]. However, GA and geriatric interventions are time consuming. Several screening tools are therefore used to identify frail elderly patients with cancer who are most likely to benefit from geriatric interventions [29]. The use of a screening tool is recommended by the SIOG especially Geriatric 8 screening tool (G-8), Flemish version of the Triage Risk Screening Tool or Vulnerable Elders Survey-13 [30]. Among these, the G-8 may be the most sensitive to select patients for GA [31]. Another study reported significant differences in the accuracy of the G-8 to detect frailty according to tumour site. In

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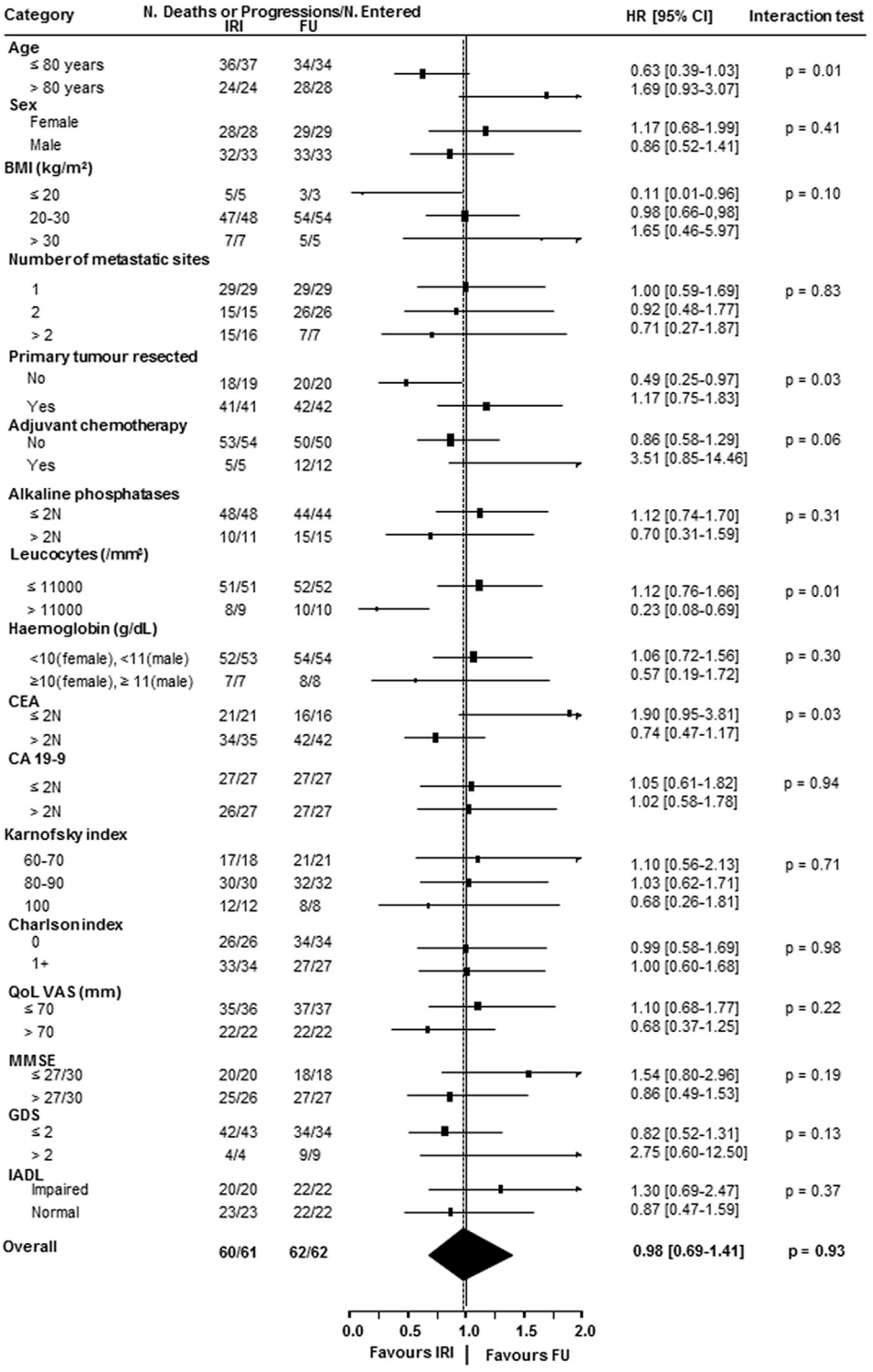

Fig. 3. Forest plots of progression-free survival by subgroups—IRI versus FU.

colorectal cancer, the G-8 screening tool identified frail elderly patients with high sensitivity (90%) but low specificity (23%) [32]. This relevant screening tool to access frailty and predict morbidity may therefore need to be adapted to the cancer stage, the primary cancer and treatment toxicities. A recent study has validated a simple prediction tool of 11 questions for chemotherapy toxicity in elderly patients with cancer [9]. Nevertheless this tool should be validated in specific tumour type as mCRC.

In conclusion, our data suggest that IADL is an independent prognostic factor following first-line treatment for mCRC. Subgroup analysis according to the geriatric evaluation suggests that doublet chemotherapy

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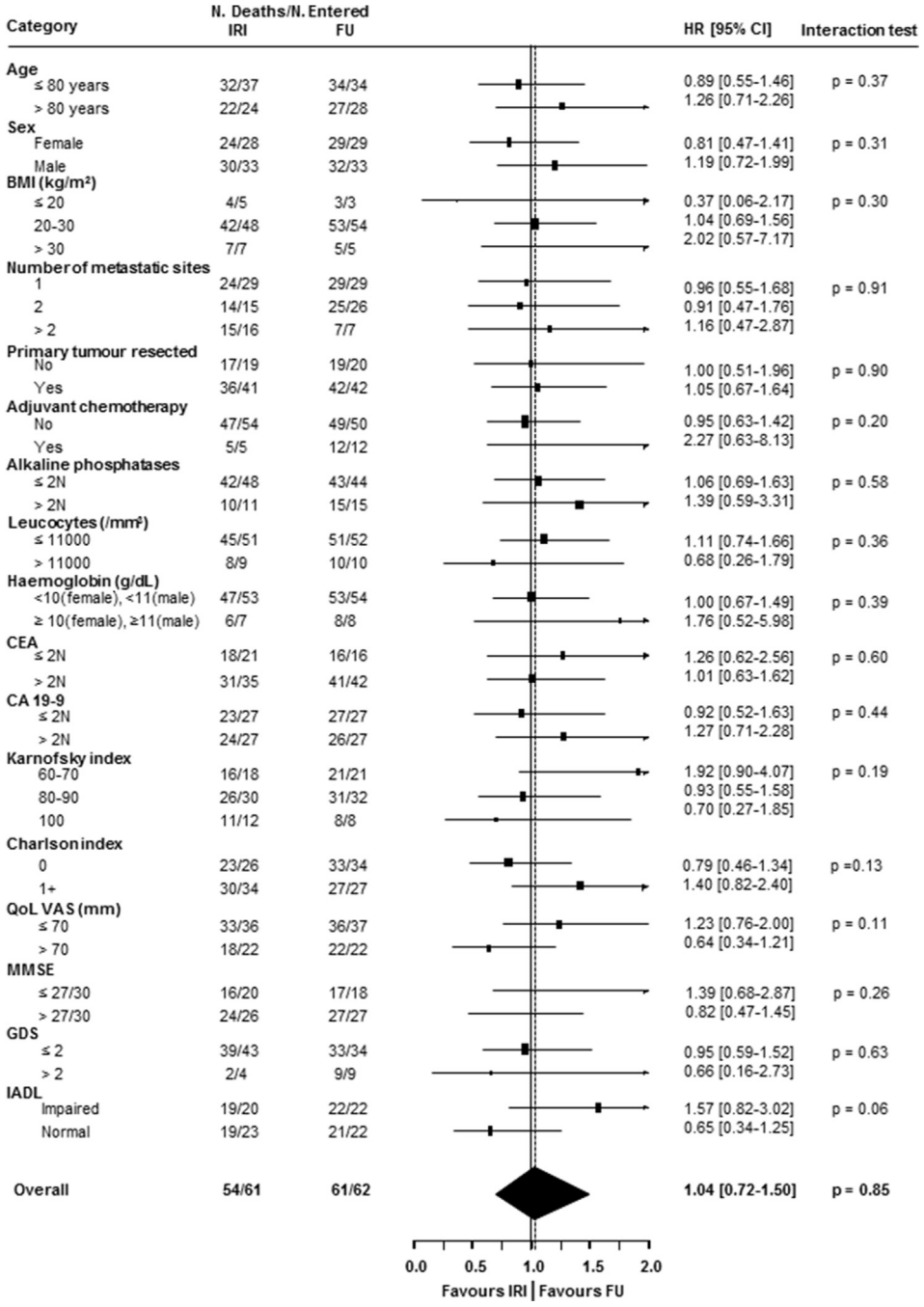

Fig. 4. Forest plots of overall survival by subgroups—IRI versus FU.

may be beneficial in some patients. This needs to be confirmed in future studies.

Contributors

TA, PR, OB, LB and EMi contributed to the study concept and design. TA, SL-D, J-MP, J-LJ, DG, MG, CL, XA, PM, AK, TL, JP, GB, J-LL, PR, JCh, JCr, LC, AA, OB, IS, LB and EMi contributed to data collection. TA, EMa and EMi contributed to data analysis. TA, EMa, J-LJ, OB and EMi contributed to manuscript writing. The final version of the manuscript has been approved by all authors and the study sponsor.

Conflict of interest statement

TA has received grants from Roche and Amgen and honoraria for presentations or advisory boards from Roche, Sanofi, Novartis and Merck Sereno. CL has received honoraria for presentations or advisory boards from Roche, Merck Sereno, Sanofi and Novartis. OBouc has received honoraria from Roche, Merck Sereno,

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Table 5
Univariate and multivariate analyses for QoL deterioration.

Univariate analysis	N	HR	95% CI	p
Age (years)				
≤80	84	1.16	0.50–2.68	0.73
>80		–	–	
Sex				
Female	84	1.38	0.60–3.17	0.45
Male		–	–	
Treatment arm				
IRI	84	0.73	0.32–1.69	0.46
FU		–	–	
Treatment arm				
CLASSIC	84	0.67	0.29–1.54	0.35
SIMPLIFIED		–	–	
Body mass index (kg/m^2)				
≤20	84	2.31	0.21–25.57	0.72
20–30		2.30	0.31–17.21	
>30		–	–	
Number of metastatic sites				
1	84	1.66	0.52–5.30	0.31
2		0.82	0.24–2.85	
>2		–	–	
Primary tumour resected				
No	84	0.54	0.21–1.40	0.21
Yes		–	–	
Previous adjuvant chemotherapy				
No	83	0.44	0.18–1.08	0.07
Yes		–	–	
Alkaline phosphatases				
≤2N	81	1.23	0.41–3.65	0.71
>2N		–	–	
Leucocytes				
≤11,000/mm^3	84	1.10	0.32–3.80	0.88
>11,000/mm^3		–	–	
Haemoglobin (g/dL)				
<10 (female), <11 (male)	84	1.73	0.23–12.96	0.59
≥10 (female), ≥11 (male)		–	–	
CEA				
≤2N	80	0.80	0.34–1.88	0.60
>2N		–	–	
CA 19-9				
≤2N	75	1.05	0.44–2.53	0.91
>2N		–	–	
Karnofsky index				
60–70%	83	1.14	0.36–3.62	0.93
80–90%		1.24	0.41–3.70	
100%		–	–	
Charlson index				
0	83	0.33	0.14–0.81	0.02
1+		–	–	
MMSE				
≤27/30	65	0.69	0.26–1.85	0.46
>27/30		–	–	
Multivariate analysis (N = 82)				
Previous adjuvant chemotherapy				
No	82	0.43	0.17–1.06	0.07
Yes		–	–	
Charlson index				
0	82	0.36	0.15–0.87	0.02
1+			–	

MMSE, Mini-Mental State Examination; CEA, carcinoembryonic antigen; QoL, quality of life; CI, confidence intervals.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.09.029.

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