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Research Paper

Prognostic value of baseline functional status measures and geriatric screening in vulnerable older patients with metastatic colorectal cancer receiving palliative chemotherapy – The randomized NORDIC9-study

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ABSTRACT

Introduction: Appropriate patient selection based on functional status is crucial when considering older adults for palliative chemotherapy. This pre-planned analysis of the randomized NORDIC9-study explored the prognostic value of four functional status measures regarding progression-free survival (PFS) and overall survival (OS) in vulnerable older patients with metastatic colorectal cancer (mCRC) receiving first-line palliative chemotherapy.
Materials and methods: Patients ≥70 years of age with mCRC *not* candidates for standard full-dose combination chemotherapy were randomized to receive full-dose S1 or reduced-dose S1 + oxaliplatin. At baseline, functional status was assessed using ECOG performance status (ECOG PS), frailty phenotype, Geriatric 8 (G8), and Vulnerable Elderly Survey-13 (VES-13). Multivariable regression models were applied and C-statistics were estimated.
Results: In total, 160 patients with a median age of 78 years (IQR: 76–81) were included. While in univariate analyses, ECOG PS, frailty phenotype, and VES-13 were statistically significantly associated with differences in OS between subgroups, G8 was not (HR = 1.55, 95%CI: 0.99–2.41, $p = 0.050$). In multivariable analyses adjusted for age, sex, body mass index, and treatment allocation, we found significant differences between subgroups for all applied tools and with C-statistics in the moderate range for ECOG PS and VES-13.
Concerning PFS, statistically significant differences were observed between subgroups of ECOG PS, G8, and VES-13 both in uni- and multivariable analyses, but not for frailty phenotype.
Discussion: In this Nordic cohort of vulnerable older patients with mCRC, baseline ECOG PS, frailty phenotype, G8, and VES-13 showed prognostic value regarding overall survival, and moderate predictive value of models based on ECOG PS and VES-13 was demonstrated.

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1. Introduction

Cancer is a disease of aging; age is the strongest non-modifiable risk factor for developing cancer [1]. One of the most common cancer types is colorectal cancer [2]. Despite its incidence and mortality peak in adults ≥70 years [2], older adults are still under-represented in randomized clinical trials (RCTs) [3] and therapeutic decision-making in the clinical practice is based on data from RCTs conducted in younger and healthier cohorts [4]. The evidence cannot be directly extrapolated to most patients treated in clinical practice who often have comorbidities, impaired organ function, geriatric syndromes (fall tendency, incontinence, osteoporosis, cognitive impairment, polypharmacy), and are at risk of developing frailty. Frailty is a common clinical syndrome in older adults resulting in increased vulnerability to stressors [5]. Frail patients are at significant risk of being undertreated, having shorter survival, experiencing more toxicities, and worse quality-of-life (QoL) [6]. Being able to identify patients with frailty is crucial in terms of providing personalized care in older patients with cancer [7].

It has repeatedly been questioned how older vulnerable patients with metastatic colorectal cancer (mCRC) should optimally be treated. Yet, few RCTs have investigated different treatment approaches in this setting [8–10]. Neither consensus nor uniform practice has been achieved so far. The NORDIC9-study included 160 patients ≥70 years treated with either full-dose monotherapy (S1) or reduced-dose combination chemotherapy (S1 + oxaliplatin) and established a potential new standard of care in this population [10]. Reduced-dose doublet chemotherapy resulted in significantly prolonged progression-free survival (PFS), less toxicity, and preservation of physical functioning and QoL [10,11].

The gold standard method in identifying frailty is the comprehensive geriatric assessment (CGA) [12]. Oncologists usually use the Eastern Cooperative Oncology Group Performance Status (ECOG PS) in clinical practice, though it has poor correlation with the CGA, and its utility questioned in older adults with cancer [13]. The frailty phenotype is a well-established model in geriatric medicine, however, containing measurements not used in oncology routinely, like handgrip strength and gait speed [14]. A compromise might be the application of brief, simple geriatric screening tools fitting the daily oncology practice such as Geriatric 8 (G8) and Vulnerable Elderly Survey-13 (VES-13) [15,16], both recommended by the International Society of Geriatric Oncology and the American Society of Clinical Oncology [12,17]. Screening tools do not require competences in geriatric medicine and are freely available in both paper form, on-line, and as mobile application (Oncoassist®). Furthermore, they can be completed by the patient or caregivers in 5–10 min, and provide information about survival, functional decline, and chemotherapy toxicity [17].

The overarching aim of this current pre-planned analysis was to assess the prognostic performance of the different functional status measures conducted at baseline regarding OS and PFS.

2. Patients and Methods

2.1. Study design and Participants

The NORDIC9-study, a randomized multi-center study included patients ≥70 years with mCRC who were not candidates for standard full-dose combination chemotherapy (EudraCT reg.no. 2014–000394-39). The detailed study protocol, the primary and several secondary endpoints have been published [10,11,18]. The current manuscript was prepared according to Consolidated Standards of Reporting Trials (CONSORT) 2010 statement [19].

2.2. Interventions

In brief, participants were randomly allocated (1:1) to treatment with either full-dose S1 monotherapy (30 mg/m^2 orally twice-daily on days 1–14, every three weeks (q3w)) or with reduced-dose SOx (S1, 20 mg/m^2 orally twice daily + oxaliplatin 100 mg/m^2 intravenously on day 1, q3w), the addition of bevacizumab (7.5 mg/kg intravenously, q3w) was optional. Participants were treated until disease progression, unacceptable toxicity, or patient wish.

2.3. Key Variables of Interest

Four measurements of functional status were registered at baseline: ECOG PS, frailty phenotype, G8, and VES-13.

2.4. ECOG PS

The most commonly applied physician-reported measurement of functional status in oncology [20]. The physician chooses the one statement appropriately describing the patient's level of physical activity. Patients with ECOG PS ≥3 are usually not considered as candidates for anti-neoplastic treatment.

2.5. Frailty Phenotype

Frailty phenotype covers five domains: weight loss, exhaustion, low physical activity, weakness, and slow gait. Score ranges from zero to five. A score of 0–2 is categorized as non-frail, and a score of ≥3 as frail [14].

Domains were derived from our collected data as following: for weight loss, we used the patients' self-reported weight loss (>5% during the two months prior to inclusion). Exhaustion was derived from the patient-reported European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 version 3.0 (EORTC QLQ-C30) fatigue domain [21]. The questionnaire asks about the last one-week period and applies a four-point response format ranging from "not at all" to "very much". The raw score was linearly transformed to a score between 0 and 100 according to the EORTC scoring manual [22]. The higher value means larger symptom burden. We used the recommended threshold for clinical importance (TCI) predefined by the EORTC QoL expert panel (39 point) as cut-off (fatigue vs no fatigue) [23]. Low physical activity was also derived from EORTC QLQ-C30 using the physical functioning domain. We applied the same scoring procedure, as described above; though here, a higher score indicates better functioning. We applied the predefined TCI at 83 points [23]. Weakness was defined as reduced handgrip strength measured by handheld dynamometer; the lowest sex-adjusted 20% percentile was considered weak. Slow gait was considered as the lowest 20% percentile of the Timed Up and Go test.

2.6. G8

G8 is an eight-item questionnaire addressing geriatric domains with a maximum score of 17 [24]. The cut-off value is 14. Patients scoring 15–17 are considered fit, those with a score ≤ 14 vulnerable and candidates for CGA.

2.7. VES-13

VES-13 can identify older adults at increased risk for health deterioration [25]. It focuses on activities of daily living (ADL) and the instrumental activities of daily living (IADL). The maximum score is 10 and a score ≥ 3 indicates frailty.

2.7.1. Outcomes

The prognostic performance of ECOG PS, frailty phenotype, G8, and VES-13 according to OS and PFS in the NORDIC9-study.

2.7.2. Sample size

For this analysis, no formal sample size calculation was performed;

the current sample follows the sample size calculated for the PFS endpoint of the NORDIC9-study (intention-to-treat (ITT) population: $n = 160$) [10].

2.7.3. Statistical methods

For baseline demographical and clinical characteristics, we applied descriptive statistics. Depending on the number of observations, for categorical variables chi-squared-test or Fischer's exact test was used, for continuous numerical variables the Wilcoxon Mann-Whitney test was applied.

2.7.4. Survival analyses

The starting time point of follow-up for all included patients was the time point of inclusion when the patient signed the informed consent form. For OS and PFS, survival curves were estimated by the Kaplan-Meier method, the comparisons between sub-groups were performed by log-rank test. Hazard ratios (HR) and corresponding 95% confidence intervals (95%CI) were estimated by Cox proportional hazard regression and the proportional hazards assumptions were tested by Schoenfield residuals. All physical functioning measurements were analyzed separately.

2.7.5. Multivariable analyses

We constructed a multivariable regression model applying Cox proportional hazards regression for the survival outcomes. Clinically relevant covariates were identified and univariate analyses were conducted assessing the possible association between baseline characteristics and measurements of functional status. The co-variable was included in the model if the p-value was <0.1 or a co-variable was considered clinically relevant. The model hence was adjusted for age, sex, body mass index (BMI), and treatment allocation. We balanced the number of co-variables according to the number of observations to avoid over-fitting. The four measurements of functional status were tested one by one in the models for both OS and PFS; adding the co-variables one by one to the models allowed us to conduct sensitivity analyses. In these analyses, we also included the different functional status measures one by one being able to evaluate whether they improve the models.

Comparing the different models of functional status measurements beside HRs and statistical significance, we also applied C-statistics and calculated Harrell's C (area under the curve (AUC)) values from Cox proportional hazards regression models demonstrating the diagnostic ability of ECOG PS, frailty phenotype, G8, and VES-13. We included only the complete cases when estimating C-statistics to be able to provide a sensitivity analysis, hence, comparable Harrell's C values.

Two-sided p-values ≤ 0.05 were considered statistically significant and estimates were reported with 95%CI.

2.7.6. Missing data

Only 2–6% of observations were missing for variables in the dataset, so we concluded that excluding those observations from analysis was

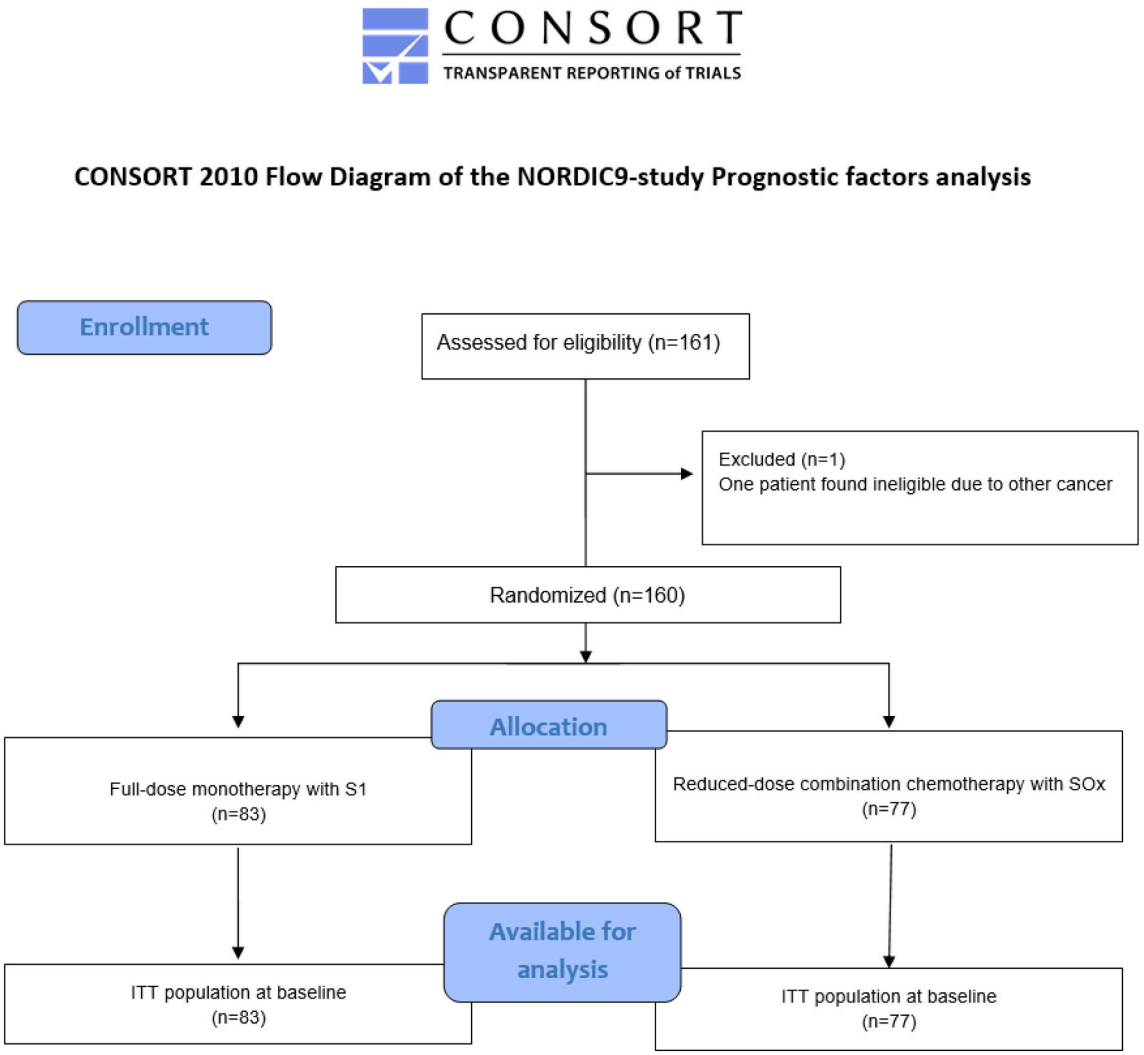

Fig. 1. Consort flow-chart.

reasonable.

2.7.7. Software

We performed data analysis in STATA v17 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Patient Population

Between March 2015 and October 2017, 160 patients were included in the NORDIC9-study and available for analysis [18]. The median follow-up was 23.8 months (interquartile range (IQR): 18.8–30.9). The participant flow is presented as a CONSORT 2010 diagram (Fig. 1**).** The inclusion was ended when the required number of patients was achieved.

The median age was 78 years (IQR: 76–81). Patient, disease, and clinical characteristics were well balanced between the treatment arms (**Table 1**).

3.1.1. Outcomes

In univariate analyses, both ECOG PS 1 and 2 resulted in statistically significantly shorter OS compared to ECOG PS 0: 21.4 months for ECOG PS 0, 13.1 months for ECOG PS 1, and 10.3 months for ECOG PS 2, respectively (Table 2, Fig. 2**).** In addition, a significant difference was found between ECOG PS 0 and 2 regarding PFS (8.3 (95%CI: 5.9–10.2) vs 3.9 months (95%CI 3.1–5.5), HR = 1.96 (1.24–3.08), $p = 0.004$) (Table 2**,** Fig. 3).

In univariate analyses, patient stratification based on frailty phenotype found a significant difference in OS between the non-frail and frail group: 14.2 (95%CI: 11.3–19.6) vs 12.9 months (95%CI: 5.6–14.4), HR = 1.63, (95%CI: 1.04–2.55), $p = 0.031$) (Fig. 2**,** Table 2**.**). The significance was maintained in multivariable analysis adjusted for age, sex, BMI, and treatment allocation (HR: 1.68 (95%CI: 1.07–2.65), $p = 0.025$).

Regarding PFS, no statistically significant differences between subgroups of frailty phenotype were observed in univariate analyses (Fig. 3**,** Table 2, and Table 3).

Applying G8, OS tended to be statistically significant in favor of those with a score > 14: 18.6 (95%CI: 12.3–27.6) vs 11.5 (95% CI: 10.3–14.4) months (HR = 1.55 (95%CI: 0.99–2.41), $p = 0.050$). The PFS difference was 8.3 vs 5.3 months (HR = 1.63, $p = 0.009$).

Stratification based on VES-13 resulted in statistically significant OS and PFS differences (OS: 15.9 (95%CI: 12.3–21.2) vs 6.5 months (95% CI: 5.3–13.4), HR = 2.12 (95%CI: 1.38–3.24), $p = 0.001$), PFS: 6.5 (95% CI: 5.5–8.1) vs 3.4 months (95%CI: 2.3–4.6), HR = 1.86 (95%CI: 1.27–2.74), $p = 0.002$).

We created a table (Supplementary Table 1) showing failure rates in different time points during follow-up according to survival outcomes in subgroups of functional status measures and geriatric screening tools; our data are consistent regarding OS and PFS in the subgroups, such as for OS at 1-, 2-, and 3-year follow-up.

Applying multivariable analyses, we found statistically significant differences in all models for OS; the highest HRs were observed between ECOG PS (for ECOG PS: 1: HR: 1.99 (95%CI: 1.26–3.16), $p = 0.003$; for ECOG PS: 2: HR: 3.32 (95%CI: 1.89–5.83), $p < 0.001$) and VES-13 subgroups (for VES-13 ≥ 3: HR: 2.29 (95%CI: 1.48–3.56), p < 0.001) (Table 3). While C-statistics showed a moderate prediction for these two models with an AUC above 0.6; for frailty phenotype and G8 the predictive ability was below 0.60, (0.58 and 0.59, respectively) (Table 3).

3.2. Sensitivity analyses

Our sensitivity analysis applying stepwise addition of variables showed improved sensitivity when age, sex, BMI, and treatment allocation were included in the models, though, further adjustments for ECOG PS, frailty phenotype, G8, and VES-13 did not enhance the sensitivity (Supplementary Table 2).

Table 1
Demographic and baseline clinical characteristics of the intention-to-treat population in the NORDIC9-study and statistical comparison of the treatment arms.

Baseline characteristics Data presented as median (IQR) or n (%) as appropriate.	NORDIC9-study Intention-to-treat population $n = 160$	NORDIC9-study treatment arms		Comparison of Arm A and B
		Full-dose monotherapy (S1) Arm A $n = 83$	Reduced-dose doublet (SOx) Arm B $n = 77$	*p*-value
Age				0.5631
Median age in years (IQR)	78 (75–81)	78 (76–81)	78 (75–80)	
70–74 years	35 (22%)	16 (19%)	19 (25%)	
75–79 years	74 (46%)	38 (46%)	36 (47%)	
≥ 80 years	51 (32%)	29 (35%)	22 (29%)	
Sex				0.8840
Female	78 (49%)	40 (48%)	38 (49%)	
Male	82 (51%)	43 (52%)	39 (51%)	
Location of primary tumor				0.9930
Left sided	97 (61%)	50 (60%)	47 (61%)	
Right sided	62 (39%)	32 (39%)	30 (39%)	
Surgery for primary tumor				0.7000
No	69 (43%)	37 (45%)	32 (42%)	
Yes	91 (57%)	46 (55%)	45 (58%)	
Prior adjuvant chemotherapy				0.2250
Yes	29 (18%)	18 (22%)	11 (14%)	
No	131 (82%)	65 (78%)	66 (86%)	
Presentation at diagnosis				0.1750
Synchronous	96 (60%)	54 (65%)	42 (55%)	
Metachronous	64 (40%)	29 (35%)	35 (45%)	
Number of metastatic sites				0.9630
1–2	127 (79%)	66 (80%)	61 (79%)	
≥3	33 (21%)	17 (20%)	16 (21%)	
Sites of metastatic disease				
Liver	102 (64%)	58 (70%)	44 (57%)	0.0940
Lung	65 (41%)	34 (41%)	31 (40%)	0.9280
Lymph nodes	69 (43%)	41 (52%)	28 (39%)	0.1390
Peritoneum	40 (25%)	12 (14%)	28 (36%)	**0.0010**
Bone	6 (4%)	3 (4%)	3 (4%)	0.7750
Other	25 (16%)	12 (14%)	13 (17%)	0.8830
Self-reported weight-loss > 5% within the last 2 months				0.0710
No	123 (77%)	59 (71%)	64 (83%)	
Yes	37 (23%)	24 (29%)	13 (17%)	
ECOG Performance status				0.4875
0	53 (33%)	30 (36%)	23 (30%)	
1	75 (47%)	37 (45%)	38 (49%)	
2	32 (20%)	16 (19%)	16 (21%)	
Frailty phenotype				0.5259
Non-frail	131 (82%)	70 (84%)	61 (79%)	
Frail	29 (18%)	13 (16%)	16 (21%)	
Geriatric 8				0.0380
>14	44 (28%)	21 (25%)	23 (30%)	
≤14	110 (69%)	60 (72%)	50 (65%)	
Unknown	6 (3%)	2 (3%)	4 (5%)	
Vulnerable Elderly Survey-13				0.9530
0–2	113 (71%)	59 (71%)	54 (70%)	
≥3	36 (23%)	19 (23%)	17 (22%)	
Unknown	11 (6%)	5 (6%)	6 (8%)	

4. Discussion

4.1. Summary of the Results

We found that functional status by ECOG PS, frailty phenotype, G8, and VES-13 was significantly associated with OS in multivariable

Table 2
Summary of progression-free survival and overall survival in univariate models according to the Eastern Cooperative Oncology Group Performance Status (ECOG PS), Frailty phenotype, Geriatric 8, and Vulnerable Elderly Survey-13.

Progression-Free and Overall Survival according to functional status measurements Univariate analyses							
Physical functioning measurements	Progression-free Survival				Overall Survival		
	n	Months (95% CI)	Hazard ratio (95%CI)	*p*-value	months (95% CI)	Hazard ratio (95%CI)	p-value
ECOG PS							
0	53	8.3 (5.9–10.2)	1.00		21.4 (14.2–27.6)	1.00	
1	75	5.4 (4.1–6.7)	1.38 (0.96–1.98)	0.085	13.1 (10.6–15.1)	1.87 (1.19–2.94)	**0.006**
2	32	3.9 (3.1–5.5)	1.96 (1.24–3.08)	**0.004**	10.3 (6.1–13.9)	2.42 (1.42–4.11)	**0.001**
Frailty phenotype							
Non-frail	131	6.2 (5.3–7.4)	1.29 (0.86–1.96)	0.216	14.2 (11.3–19.6)	1.63 (1.04–2.55)	**0.031**
Frail	29	4.1 (2.6–6.1)			12.9 (5.6–14.4)		
Geriatric 8							
>14	44	8.3 (5.3–10.5)	1.63 (1.13–2.37)	**0.009**	18.6 (12.3–27.6)	1.55 (0.99–2.41)	0.050
≤14	110	5.3 (4.1–6.2)			11.5 (10.3–14.4)		
Vulnerable Elderly Survey-13							
0–2	113	6.5 (5.5–8.1)	1.86 (1.27–2.74)	**0.002**	15.9 (12.3–21.2)	2.12 (1.38–3.24)	**0.001**
≥3	36	3.4 (2.3–4.6)			6.5 (5.3–13.4)		

analyses, thus, all applied tools demonstrated prognostic value. Moderate prediction of the models ECOG PS and VES-13 was shown in the NORDIC9 cohort.

4.2. Perspective/Clinical Context

Using the well-established ECOG PS in daily oncology practice provides important prognostic information. The addition of geriatric screening tools may add important details on the challenges older vulnerable patients face, such as weight-loss, mobility issues, medication use, cognitive issues, and help needed for ADL and IADL (housekeeping, assisting with self-care, shopping). This information may contribute to more proper prognostic understanding, help to explore patient and caregiver preferences, provide more details for shared decision-making, guide personalized interventions, and improve QoL [26].

4.3. Comparison to Other Studies

A systematic review assessing the sensitivity and specificity of seven geriatric screening tools in older patients with cancer, including frailty phenotype, G8, and VES-13 found the lowest median sensitivity (31%) for frailty phenotype with a high specificity(91%), while the sensitivity of G8 and VES-13 were 87% and 68%, and the specificity 61% and 78%, respectively [16]. This is in line with our findings.

The prognostic value of ECOG PS in older patients with cancer has been questioned several times, especially when compared to CGA [13,27]. Some studies found its prognostic value appropriate compared to geriatric screening [28]. Despite ECOG PS provides a shallow assessment of physical function, in our cohort it demonstrated comparable prognostic approximation to VES-13. A possible explanation may be that both tools assess ADL, though, ECOG PS only is considered as a shallow description of these activities. Of note, ECOG PS is the tool oncologists use most often and are most familiar with, patient stratification based on ECOG PS, thus, reflects to their treatment pattern, habits, and experience.

Combining screening tools, such as G8 and VES-13 showed increased sensitivity and specificity in terms of identifying frailty [16]. Using a modified cut-off value, e.g., 11 instead of 14 when G8 is used has also been investigated, though the results are conflicting [10,33,34], which could be explained by different populations, study design, and methodology.

Of note, the details obtained by CGA may provide more precise prognostic and predictive information than screening tools, ECOG PS, and frailty phenotype. CGA may predict chemotherapy toxicity, surgical complications, mortality, and QoL as highlighted in recent publications, hence, CGA should be considered as the standard of care in the multidisciplinary management of older patients with cancer [29–32].

4.4. Interpretation, Explanation, and Methodological Considerations

In the NORDIC9-study, all applied tools measuring functional status provided prognostic information on OS; however, considering the AUC values, only ECOG PS and VES-13 showed moderate prediction. It is though important to note that patient stratification was primarily based on ECOG PS at inclusion; G8 and VES-13 were applied and frailty phenotype was estimated after the patients entered the study. This might have influenced the outcomes.

Despite the statistically significant OS difference, the prediction of frailty phenotype was low. A possible explanation is that frailty phenotype has been developed and applied in geriatric medicine, thus, patients considered frail according to frailty phenotype are “more“frail than those usually considered for anti-neoplastic treatment. The patients usually managed by geriatricians are therefore not included in clinical trials and often receive best supportive care exclusively. Moreover, given the design of our study and the collected dataset, we could not apply the original measurements used by Fried [14]. However, we considered our surrogate measures as an appropriate approximation of

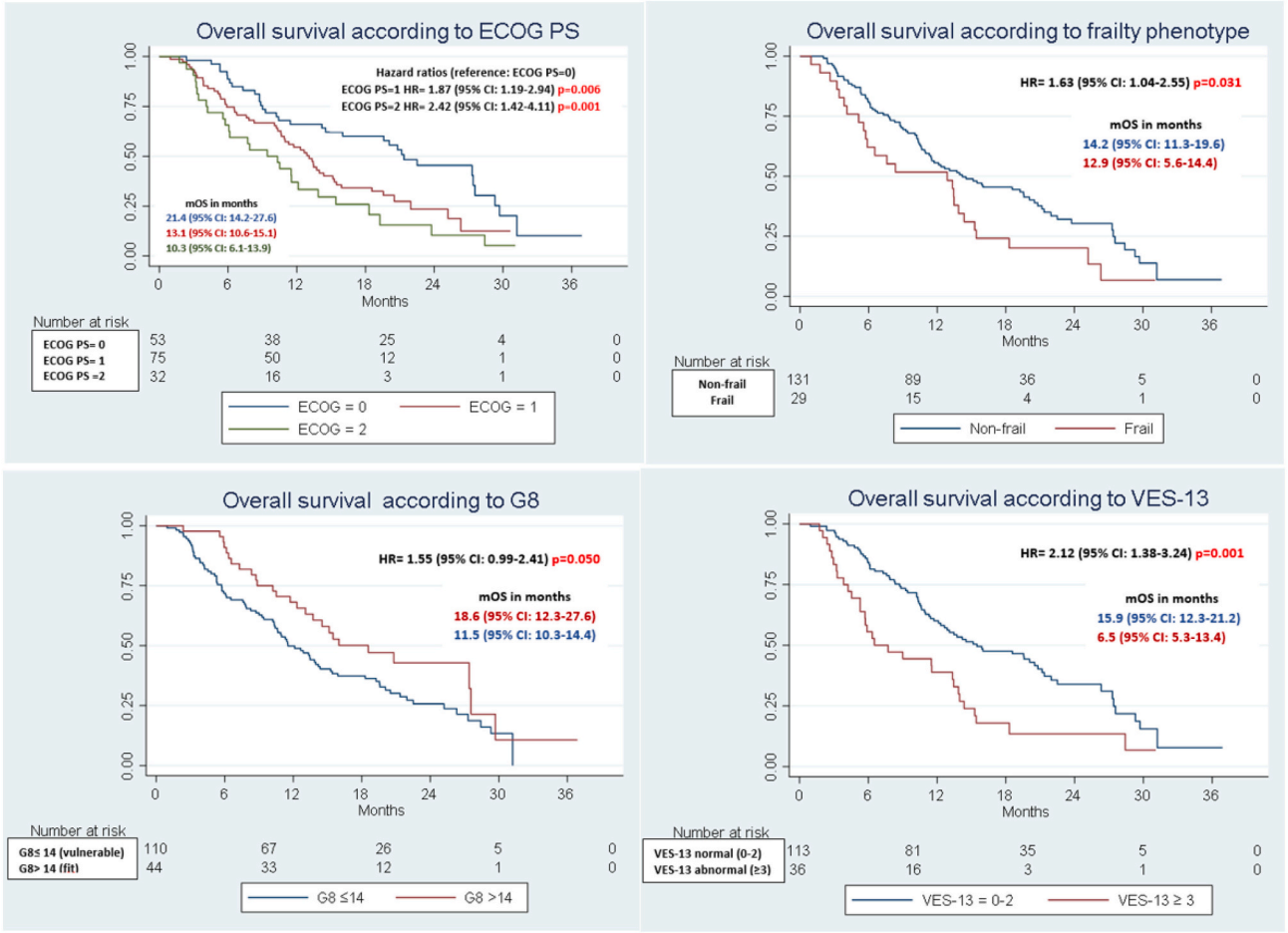

Fig. 2. Univariate Kaplan-Meier survival estimates of overall survival (OS) according to Eastern Cooperative Oncology Group Performance Status (ECOG PS), Frailty phenotype, Geriatric 8 (G8), and Vulnerable Elderly Survey-13 (VES-13).

the original measures.

We applied derived variables for fatigue and physical functioning, using the EORTC QLQ-C30 questionnaire and the TCIs recommended by the EORTC expert panel. These TCI values were developed in younger and less comorbid cohorts of patients with different types of malignancies, not in vulnerable older patients with mCRC. Equivalent TCIs are not available in these patients yet. We also considered applying thresholds available from a general healthy older Danish population, though it may not reflect our vulnerable older population appropriately. Specific TCIs developed in this particular population might have improved our frailty phenotype model.

We evaluated four different functional status measurements in a prospective randomized multicenter setting in a homogenous cohort of vulnerable older patients with mCRC. To the best of our knowledge, the utility of frailty phenotype has not previously been assessed in this setting.

Our study has limitations. As mentioned above, we used surrogate values derived from EORTC QLQ-C30; using the original frailty phenotype criteria might have shown different results. The application of TCI developed in a specific cohort of vulnerable older patients with mCRC might have contributed to improved sensitivity and specificity of our frailty phenotype model.

5. Conclusions

We established that ECOG PS, frailty phenotype, G8, and VES-13 were associated with OS and moderate prediction of ECOG PS and VES-13 was demonstrated in vulnerable older patients with mCRC receiving palliative chemotherapy. ECOG PS is already an established tool in daily oncology practice. The addition of VES-13 systematically in daily oncology practice may add important information about IADL and lead to personalized interventions, thus potentially improving the decision-making and outcomes in this population.

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Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Regional Scientific Ethical Committee (project ID: S-20140020, date of approval: 08.05.2014), the Danish Health and Medicines Authority (journal nr.: 2014023387), and the Danish Data Protection Agency (number of approval: 2008-58-0035). EudraCT-number: 2014–000394-39. Finland: Operatiivinen eettinen toimikunta at Helsinki University Hospital (357/13/03/02/14, the date of approval: 21.10.2015). Norway: Regional Committee for Medical and Health Research Ethics, REC West, Norway (2014/598, the date of approval: 22.05.2014). Sweden: Regionala Etikprovningsnämnden, Uppsala (2014/288, the date of approval: 19.11.2014).

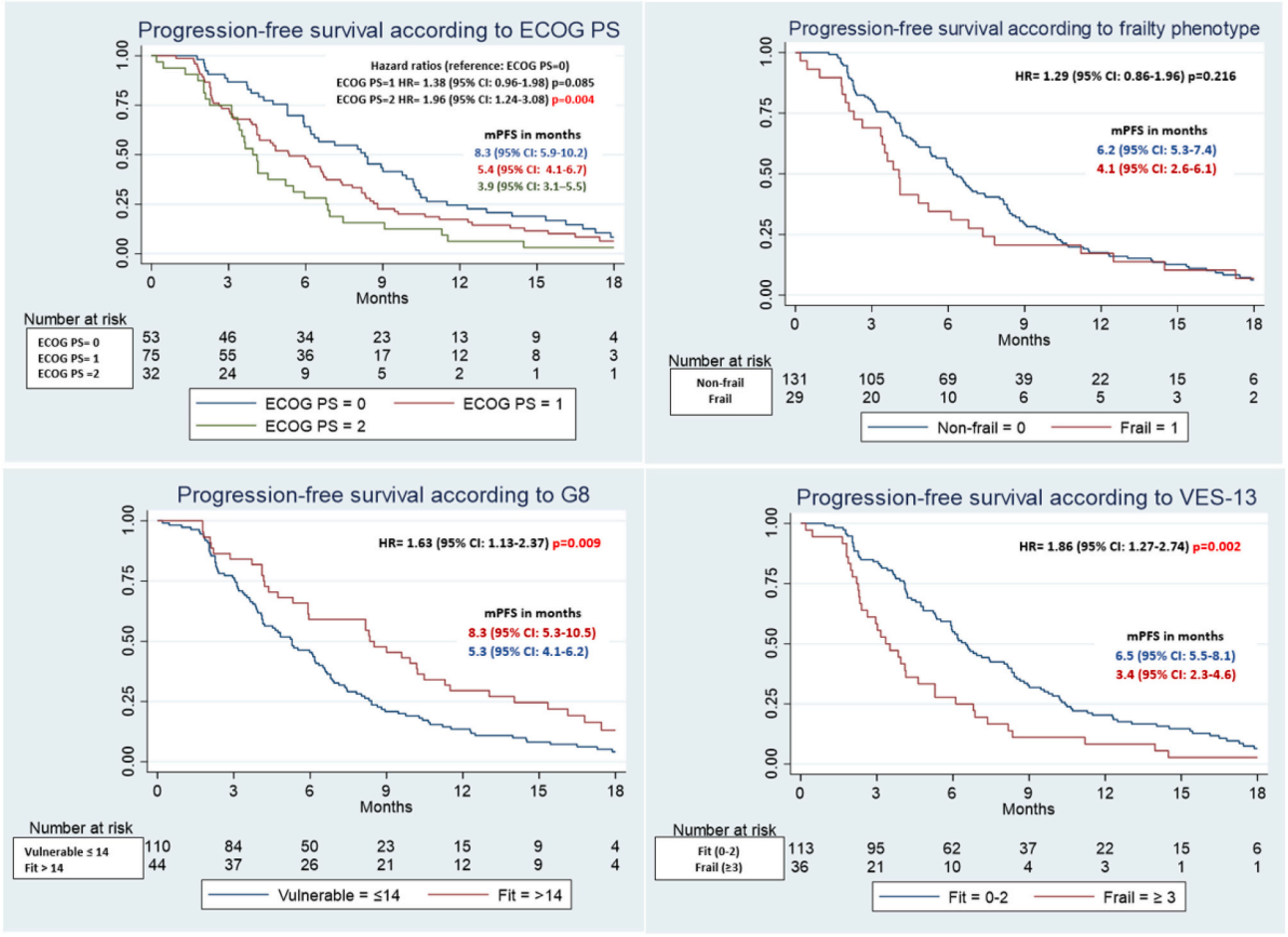

Fig. 3. Univariate Kaplan-Meier survival estimates of progression-free survival (PFS) according to Eastern Cooperative Oncology Group Performance Status (ECOG PS), Frailty phenotype, Geriatric 8 (G8), and Vulnerable Elderly Survey-13 (VES-13), follow-up time is censored at 18-month.

Table 3
The summary of progression-free survival and overall survival applying the Eastern Cooperative Oncology Group Performance Status (ECOG PS), Frailty phenotype, Geriatric 8, and Vulnerable Elderly Survey-13, using the main effects multivariable models.

Progression-free and overall survival according to functional status measurements Multivariable analyses									
Physical functioning measurements	n	Progression-free survival				Overall survival			
		HR	95% CI	p-value	Harrell's C (95% CI)	HR	95% CI	p-value	Harrell's C (95% CI)
ECOG PS									
0	53	1.00			0.63 (0.58–0.68)	1.00			0.64 (0.58–0.70)
1	75	**1.55**	1.05–2.29	**0.028**		**1.99**	1.26–3.16	**0.003**	
2	32	**2.47**	1.48–4.12	**0.001**		**3.32**	1.89–5.83	**<0.001**	
Frailty phenotype									
Non-frail	131	1.00		0.176	0.58 (0.52–0.63)	1.00		**0.025**	0.58 (0.52–0.64)
Frail	29	1.35	0.86–2.08			**1.68**	1.07–2.65		
Geriatric 8									
>14	44	1.00		**0.011**	0.57 (0.52–0.62)	1.00		**0.038**	0.59 (0.53–0.65)
≤14	110	**1.65**	1.12–2.42			**1.62**	1.03–2.55		
Vulnerable Elderly Survey-13									
0–2	113	1.00		**0.003**	0.60 (0.55–0.65)	1.00		**<0.001**	0.61 (0.54–0.67)
≥3	36	**1.81**	1.22–2.70			**2.29**	1.48–3.56		

The models for ECOG PS, frailty phenotype, and Vulnerable Elderly Survey-13 were adjusted for age, sex, body mass index, and treatment allocation. The model for Geriatric 8 was adjusted for age, sex, and treatment allocation but not body mass index to avoid multicollinearity.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Author Contributions

Gabor Liposits: Conceptualization, Methodology, Software, Writing – original draft, Writing – review & editing, Funding acquisition. **Jesper Ryg:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition. **Halla Skuladottir:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision. **Stine B. Winther:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Sören Möller:** Conceptualization, Methodology, Software, Writing – original draft, Writing – review & editing. **Eva Hofsli:** Writing – review & editing. **Carl-Henrik Shah:** Writing – review & editing. **Laurids Østergaard Poulsen:** Writing – review & editing. **Åke Berglund:** Writing – review & editing. **Camilla Qvortrup:** Writing – review & editing. **Pia Osterlund:** Writing – review & editing. **Bengt Glimelius:** Writing – review & editing, Supervision. **Halfdan Sorbye:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision. **Per Pfeiffer:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors have no competing interest to declare. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2022.11.007.

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