

# APPLICATION STUDY OF THE EQ-5D-5L IN ONCOLOGY: LINKING SELF-REPORTED QUALITY OF LIFE OF PATIENTS WITH ADVANCED OR METASTATIC COLORECTAL CANCER TO CLINICAL DATA FROM A GERMAN TUMOR REGISTRY - RESULTS FROM A TOBIT REGRESSION

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## BACKGROUND

- In Germany, colorectal cancer (CRC) is the second most frequent cancer among women and the third most frequent cancer among men. During their lifetime, one out of 18 women and one out of 15 men is diagnosed with colorectal cancer. Overall, approximately one out of eight cancers affects the bowel.<sup>1</sup>
- Affected patients suffer from a high psychological and physical burden of disease and have a reduced quality of life due to various problems in social functioning and disease-specific symptoms.<sup>2,3</sup>
- The EuroQoL five-dimension questionnaire with five answer levels (EQ-5D-5L) is widely used and well-accepted in oncology to generate health-related quality of life (hrQoL) weights and corresponding health states.<sup>4</sup>
- However, for patients with advanced or metastatic CRC, there are no data available reporting the influence of certain comorbidities or health states on the hrQoL.

## OBJECTIVE

- The aim of this study was to explore the relationship between demographic and clinical characteristics and hrQoL among patients with advanced or metastatic CRC by linking clinical data of a German CRC registry to self-reported hrQoL measures from the EQ-5D-5L.

## METHODS

- The study sample included patients with advanced or metastatic CRC who had been recruited into the German Tumor Registry Colorectal Cancer since March 2014.
- Data collection and methodology of the registry have been described previously.<sup>5</sup>
- Inclusion criteria for the registry were age  $\geq 18$  years, histologically confirmed CRC, and signed informed consent no longer than four weeks after the start of systemic neoadjuvant/adjuvant treatment for nonmetastatic or first-line treatment for metastatic/inoperable disease.
- Registered patients who had declared willingness to participate in patient-reported outcomes (PRO) surveys routinely received a PRO questionnaire including the Quality of Life Questionnaire Core 30 version 3.0 of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30). For our study, the EQ-5D-5L was added.
- The EQ-5D-5L was delivered once per patient by postal mail as part of the next round of PRO questionnaire delivery between November 2016 and May 2017. At the time of questioning, patients were at the beginning or at later stages of palliative treatment (0 to 24 months after first-line palliative therapy).
- Data from the EQ-5D-5L and EORTC QLQ-C30 was linked to pseudonymized clinical data from the registry.
- Patient, clinical, and treatment characteristics with the potential to influence hrQoL were defined by literature review and by medical experts.
- Utility scores from the EQ-5D-5L were calculated using a Germany-specific value set leading to scores from -0.661 (worst possible health state) to 1 (best possible health state).<sup>6</sup> VAS scores were recorded directly from the scale.
- Scores from the EORTC QLQ-C30 were calculated following the scoring manual published by the EORTC. The score spans from 0 to 100, with a higher score indicating a better level of functioning (functional scale) and a higher QoL (global health status/QoL scale), but a worse level of symptoms (symptom scale).<sup>7</sup>
- A tobit regression analysis was performed to explore the impact of patient, clinical, and treatment characteristics on the EQ-5D-5L utility score. Marginal effects were computed at the sample mean.
- Ordinary least squares (OLS) regression analyses were conducted to explore the impact of patient, clinical, and treatment characteristics on the EQ-5D-5L VAS score as well as the EORTC global health status/QoL score.
- Significant impacts on the quality of life were determined at a level of significance at  $p < 0.05$ .

## RESULTS

### PATIENT SELECTION

- The PRO questionnaire was sent to N=758 patients with advanced or metastatic CRC in Germany between November 2016 and May 2017. More than two thirds of the patients returned the questionnaire (n=535 patients).
- Patients were excluded if they withdrew their consent or returned a blank or incomplete EQ-5D-5L questionnaire. The final study population consisted of n=433 advanced or metastatic CRC patients for whom both an EQ-5D-5L utility as well as an EQ-5D-5L VAS score could be computed.

### PATIENT CHARACTERISTICS

- At the time of PRO questioning, the patients were on average 66.3 years ( $\pm 9.5$  years) old.
- The majority of patients (n=265, 61.2%) were male.

### CLINICAL CHARACTERISTICS

#### Tumor history and metastases

- More than half of the primary tumors were in the colon (56.4%), whereas 43.4% were located in the rectum. Primary tumors were classified as inoperable in 19.9% of the patients.
- About one-fifth of the patients (21.0%) had experienced at least one progression prior to questioning.
- Most of the patients (83.8%) had one or more metastases when filling in the PRO questionnaire with 61.4% of patients having liver metastases, 23.8% lung metastases, 14.6% peritoneal metastases, and 3.0% bone metastases.

#### Comorbidities

- At the time of inclusion in the registry, 61.7% of patients had at least one of the pre-defined comorbidities including for example cardiovascular and metabolic diseases.
- The most frequent comorbidity among the patients was hypertension (41.3%), followed by diabetes (14.6%) and thyroid disease (9.0%).

### TREATMENT CHARACTERISTICS

#### Treatment status

- More than half of the patients were in first-line palliative therapy (55.2%) when filling in the PRO questionnaire. Another 23.3% were at break after first-line therapy, 15.5% were in second-line or at break after second-line therapy, and 5.1% in third-line therapy or in later treatment lines.
- The most current chemotherapy at the time of questioning was based on irinotecan (44.8%), oxaliplatin (37.4%), or both irinotecan and oxaliplatin (4.9%). Another 10.4% of the patients were treated with fluoropyrimidine monotherapy.
- VEGF-inhibitors in addition to chemotherapy were prescribed in 49.7% of patients, 26.1% received EGFR-inhibitors, and 22.6% of patients did not receive any monoclonal antibodies.

### Disease or treatment-related symptoms

- The mean EORTC QLQ-C30 fatigue score of the interviewed patients with advanced or metastatic CRC was calculated to be 47.2 at the time of questioning.
- The EORTC QLQ-C30 pain score was 26.6 and the EORTC QLQ-C30 nausea and vomiting score was 12.7 on average.
- Table 1 gives an overview of the patient, clinical, and treatment characteristics of the study population.

**Table 1. Summary of patient, clinical, and treatment characteristics of the included patients with advanced or metastatic CRC (n=433)**

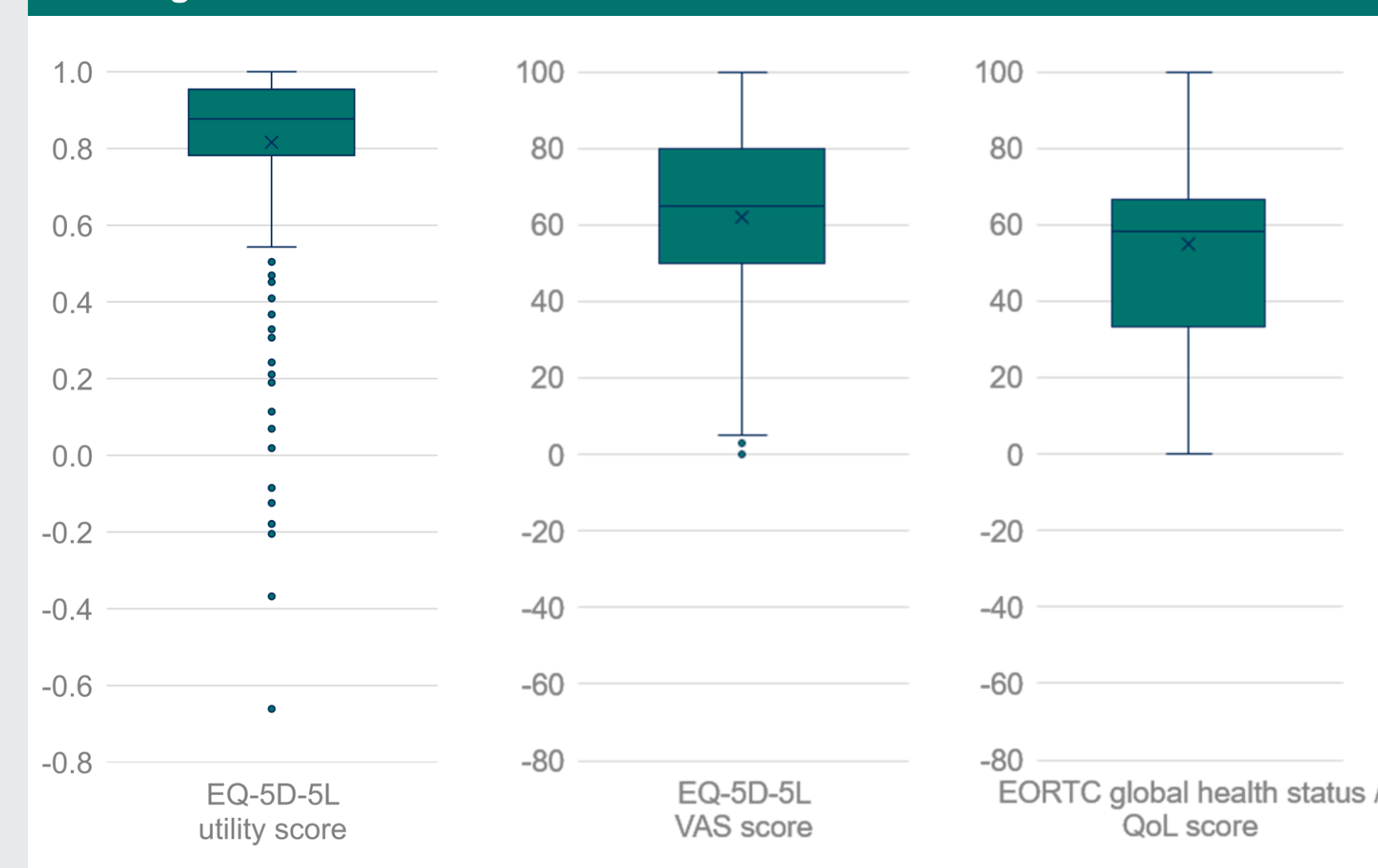
Variable	Definition	% or Mean (SD)
<b>Patient characteristics</b>		
Age	Years	66.33 ( $\pm 9.50$ )
Gender	Male	38.80%
	Female	61.20%
<b>Clinical characteristics</b>		
Localization of tumor	Colon	56.35%
	Rectum	43.42%
Inoperable primary tumor	Yes	19.86%
Number of progressions experienced prior to questioning	0	75.29%
	1	16.63%
	$\geq 2$	4.39%
	$\geq 3$	7.62%
Liver metastases	Yes	61.43%
Lung metastases	Yes	23.79%
Peritoneal metastases	Yes	14.55%
Bone metastases	Yes	3.00%
Number of metastatic localizations	0	10.85%
	1	51.27%
	2	24.94%
	$\geq 3$	7.62%
Hypertension	Yes	41.34%
Diabetes without impairment of organs	Yes	14.55%
Thyroid disease	Yes	9.01%
Coronary heart disease	Yes	8.31%
Tumor other than colorectal, lymphoma or leukemia	Yes	7.85%
Chronic gastric or bowel disease	Yes	6.70%
Adiposity	Yes	6.47%
Chronic pulmonary disease	Yes	5.77%
Anemia	Yes	4.39%
Heart failure	Yes	4.16%
Moderate or severe kidney disease	Yes	3.46%
<b>Treatment characteristics</b>		
Palliative treatment line	First-line	55.19%
	Break after first-line	23.33%
	Second-line or break afterwards	15.48%
	Third-line or later	5.08%
Antibodies	EGFR-inhibitor	26.10%
	VEGF-inhibitor	49.65%
	None	22.63%
EORTC QLQ-C30 symptom scales	Fatigue	47.24 ( $\pm 26.56$ )
	Pain	26.62 ( $\pm 30.42$ )
	Nausea and vomiting	12.71 ( $\pm 20.28$ )

\*Note: Missing values are not shown and therefore the single characteristics of each variable may not sum up to 100%.

## DESCRIPTIVE HRQOL SCORES

- The mean time until PRO questioning was 8.2 months after first-line palliative treatment initiation.
- The mean EQ-5D-5L utility score of the advanced or metastatic CRC patients reached 0.82 ( $\pm 0.23$ ).
- In comparison, the overall EQ-5D-5L VAS score and the overall EORTC global health status/QoL score were lower with a mean of 62.05 ( $\pm 22.23$ ) and 56.66 ( $\pm 21.66$ ), respectively.
- Figure 1 demonstrates the distribution of the three different scores.

**Figure 1. Distribution of the EQ-5D-5L utility score, EQ-5D-5L VAS score, and EORTC global health status/QoL score**



## TOBIT AND OLS REGRESSION

- Overall, the results from the tobit and OLS regressions indicated that none of the patient demographic characteristics and only few of the clinical and treatment characteristics had an effect on hrQoL.
- In the tobit regression, hypertension, fatigue, and pain had a negative effect on the EQ-5D-5L utility score. The marginal effects showed that concomitant hypertension reduced the utility score by 0.052, each one-unit increase in the fatigue symptom scale by 0.003, and each one-unit increase in the pain symptom scale by 0.002.
- In the OLS regression on the EQ-5D-5L VAS score, having completed the PRO questionnaire 12 or 24 months after enrollment into the registry and one prior progression had a positive effect on the score. However, treatment in second-line or later, chronic gastric or bowel disease, fatigue, and pain had a negative effect on the score.
- In the OLS regression of the EORTC global health status/QoL score, chronic pulmonary diseases positively affected the score, but fatigue and pain had a negative effect.
- In summary, the symptoms fatigue and pain had a negative effect in all three performed regression analyses (see Table 2).

**Table 2. Results from tobit and OLS regression analyses of the relationship between health state utilities (EQ-5D-5L utility score, EQ-5D-5L VAS score, EORTC global health status/QoL score) and patient, clinical and treatment characteristics**

	EQ-5D-5L Utility		EQ-5D-5L VAS		EORTC QoL	
	$\beta_{\text{tobit}}$	SE	$\beta_{\text{OLS}}$	SE	$\beta_{\text{OLS}}$	SE
Intercept	1.092	0.101**	83.911	9.531**	74.268	8.717**
Time of PRO questioning after enrollment into the registry						
0 months	ref	ref	ref	ref	ref	ref
2 months	-0.017	0.033	4.349	3.120	-0.270	2.847
4 months	-0.001	0.039	1.538	3.699	1.773	3.347
8 months	-0.029	0.036	0.704	3.278	-4.164	2.961
12 months	-0.027	0.037	8.225	3.497*	-0.533	3.216
16 months	0.004	0.040	6.400	3.714	6.568	3.384
20 months	-0.009	0.045	1.183	4.180	2.669	3.894
24 months	0.059	0.051	12.543	4.625**	7.240	4.268
Age	0.001	0.001	-0.079	0.102	0.070	0.092
Male	0.018	0.021	1.719	1.947	-1.069	1.791
BMI	0.001	0.002	0.200	0.207	0.127	0.197
Primary tumor localization						
Colon	ref	ref	ref	ref	ref	ref
Rectum	-0.006	0.021	0.189	1.916	0.201	1.750
Inoperable primary tumor	0.007	0.025	2.245	2.283	0.657	2.063
Number of progressions						
0	ref	ref	ref	ref	ref	ref
1	0.034	0.038	7.763	3.615*	-1.686	3.333
$\geq 2$	0.002	0.059	10.871	5.654	-5.621	5.151
Number of metastatic localizations						
0	ref	ref	ref	ref	ref	ref
1	-0.023	0.034	0.656	3.143	-1.168	2.894
2	-0.043	0.038	0.080	3.519	0.225	3.231
$\geq 3$	-0.053	0.049	0.522	4.539	1.627	4.131
Palliative treatment line						
First-line	ref	ref	ref	ref	ref	ref
Break after first-line	-0.047	0.029	-4.536	2.657	0.399	2.418
Second-line or later	-0.053	0.042	-11.939	4.000**	-1.377	3.725
Antibodies						
None	ref	ref	ref	ref	ref	ref
EGFR	0.012	0.029	-2.900	2.699	0.766	2.468
VEGF	0.022	0.025	-2.343	2.358	3.732	2.153
Comorbidities						
Adiposity	-0.010	0.043	1.318	4.063	0.577	3.707
Anemia	-0.055	0.045	-0.436	4.394	1.463	4.061
Chronic gastric or bowel disease	-0.015	0.039	-7.434	3.742*	-4.851	3.378
Coronary heart disease	0.022	0.039	-3.193	3.578	-4.569	3.235
Heart failure	0.029	0.051	-1.782	4.688	-2.827	4.245
Hypertension	-0.072	0.022**	-3.202	2.074	-2.377	1.904
Moderate or severe kidney disease	-0.026	0.056	-0.262	5.268	1.763	5.082
Diabetes mellitus†	0.031	0.029	1.637	2.746	2.521	2.502
Chronic pulmonary disease	-0.074	0.041	0.388	3.924	7.996	3.709**
Thyroid disease	-0.041	0.036	1.108	3.385	1.788	3.108
Tumor††	0.010	0.036	4.215	3.435	-4.265	3.134
Disease and treatment-related symptoms (EORTC QLQ-C30 symptom scales)						
Nausea and vomiting	0.000	0.001	-0.011	0.051	-0.058	0.047
Fatigue	-0.004	0.000**	-0.384	0.044**	-0.472	0.040**
Pain	-0.003	0.000**	-0.170	0.036**	-0.121	0.033**
$\sigma$	0.177	0.007**	--	--	--	--
Pseudo- $R^2$		0.035		--		--
Adjusted $R^2$		--		0.386		0.485

\* $P < 0.05$ ; \*\* $P < 0.01$ ; †without organ impairment; ††other than colorectal, lymphoma, or leukemia

## CONCLUSIONS

- This study linking clinical registry data to hrQoL data illustrated a feasible opportunity for a cross-sectional study design.
- The regression analyses revealed that none of the patient demographic and only few of the clinical and treatment characteristics, especially fatigue and pain, had a significant impact on the hrQoL of patients with CRC.
- Our findings are in line with a review by Marventano and colleagues which showed that gender was not a significant determinant of CRC patients' hrQoL. Furthermore, the review revealed that results on age were controversial and that symptoms induced by cancer or its treatment such as fatigue had a significant negative impact on hrQoL. On the contrary, the review depicted that heart disease had a significant effect on hrQoL which was not confirmed in our study.<sup>8</sup>
- One explanation for the few significant determinants of hrQoL might be that seriously ill patients have accepted their fate (coping) and recognize their disease, treatment, and comorbidities as part of their daily life.
- Another reason could be that the investigated comorbidities are under control and not relevant when compared to the symptoms associated with the cancer and its treatment.
- Furthermore, data on patients with severely reduced hrQoL might be under-represented in our study because these patients are less likely to return the questionnaires.

## LIMITATIONS

- The patient characteristics were documented at different points in time prior to questioning leading to possible unobserved changes at the time of PRO questioning.
- Moreover, confounding by unmeasured variables cannot be ruled out.

## REFERENCES

- Robert Koch Institut und Gesellschaft der epidemiologischen Krebsregister in Deutschland (2017) Krebs in Deutschland 2013/2014. 11. Ausgabe. [http://www.gkidl.de/Doc/krebs\\_in\\_deutschland\\_2015.pdf](http://www.gkidl.de/Doc/krebs_in_deutschland_2015.pdf).
- Emmert M, Pohl-Derrick K, Wein A, Dorje F, Merkel S, Boxberger F, Mannlein G, Joost R, Harich HD, Thiemann R, Lambert C, Neurauf MF, Hohenberger W, Schoffski O (2013) Palliative treatment of colorectal cancer in Germany: cost of care and quality of life. The European journal of health economics : HEPAC : health economics in prevention and care 14 (4):629-638. doi:10.1007/s10198-012-0408-5
- Engel J, Kerr J, Schlesinger-Raab A, Eckel R, Sauer H, Holzel D (2003) Quality of life in rectal cancer patients: a four-year prospective study. Annals of surgery 238 (2):203-213. doi:10.1097/01.sla.0000080823.38569.b0
- Schwenkglens M, Matter-Walstra K (2016) Is the EQ-5D suitable for use in oncology? An overview of the literature and recent developments. Expert Review of Pharmacoeconomics & Outcomes Research 16 (2):207-219. doi:10.1586/14737167.2016.1146594
- Marschner N, Arnold D, Engel E, Hutzschenreuter U, Rauh J, Freier U, Hartmann H, Frank M, Jänicke M (2015) Oxaliplatin-based first-line chemotherapy is associated with improved overall survival compared to first-line treatment with irinotecan-based chemotherapy in patients with metastatic colorectal cancer - Results from a prospective cohort study. Clinical epidemiology 7:295-303. doi:10.2147/CELEP.S73857
- Ludwig K, von der Schulenburg JM, Geiner W (2018) German Value Set for the EQ-5D-5L. Pharmacoeconomics 36 (6):863-874. doi:10.1007/s40273-018-0615-8
- Fayers PM, Bjorndal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. (2001) EORTC QLQ-C30 Scoring Manual (Third Edition).
- Marventano S, Forjaz MJ, Grosso G, Misrretta A, Giorgianni G, Platania A, Gangi S, Basile F, Biondi A (2013) Health related quality of life in colorectal cancer patients: state of the art. BMC Surgery 13 (Suppl 2):S15