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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Quality of life in patients undergoing repetitive TACE for the treatment of intermediate stage HCC

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Abstract

Purpose With a limited overall survival (OS) of 20 months in patients diagnosed with intermediate stage hepatocellular carcinoma (HCC), the preservation of quality of life (QoL) during transarterial chemoembolization (TACE) procedures remains a primary goal. The aim of our study was to evaluate the change in QoL amongst patients undergoing repetitive TACE and to identify specific risk factors that may predict change in QoL.

Methods QoL was assessed in 82 patients undergoing at least two TACE, before and 14 days after TACE, using validated EORTC QLQ-C30 and EORTC HCC18 questionnaires. Tumour response was assessed using established response criteria. Laboratory and clinical parameters were analysed.

Results Functional scores decreased due to first TACE treatment ($p < 0.01$), conversely symptom scores increased significantly ($p < 0.01$). During repetitive TACE no statistically significant changes were observed. Higher Global Health- and Physical Functioning scores at baseline were identified as independent prognostic factors for greater decrease in QoL. Tumour response did not alter QoL at all. Furthermore higher symptom scales including pain ($p = 0.00$), nausea and vomiting ($p = 0.00$) and fever ($p < 0.01$ for repetitive TACE) at baseline were predictive of a significantly lesser increase of symptom severity, and a greater reduction in pain during a course of TACE. Higher C-reactive protein (CRP) at baseline and female gender were associated with a greater decrease of functional scales and increase of symptom scales.

Conclusion QoL amongst patients receiving repetitive TACE showed neither significant nor clinically relevant changes over time. Pre-treatment assessment of QoL-scores, clinical and laboratory parameters can improve patient selection for TACE whilst optimizing QoL.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, representing the fifth most common cancer in men and eighth most common cancer in women (Bosch et al. 2004; El-Serag and Rudolph 2007;

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European Association For The Study Of The Liver et al. 2012). 70% of HCC are unresectable at diagnosis (Wang et al. 2007), corresponding with intermediate or higher stages of the Barcelona clinic liver cancer classification (BCLC), with fewer than 20% suitable for curative treatment (Salem et al. 2013). The median survival of patients suffering from untreated carcinoma in the intermediate stage amounts to 16 months (Llovet and Bruix 2003, 2008). Palliative treatments like transarterial chemoembolization (TACE) are a first-line therapeutic option (Bruix et al. 2011). Randomized controlled trials have shown that TACE can prolong median survival from 19 to 20 months (Llovet and Bruix 2003), with further prospective studies reporting up to 34 months (Takayasu et al. 2006). Considering the limited survival time of patients with advanced stage HCC, amongst those patients undergoing serial treatments, preservation of Quality of Life (QoL) is important. QoL in chronic or incurable diseases is often investigated in clinical trials (Heffernan et al. 2002), but few prospective studies have assessed QoL amongst patients undergoing TACE (Wang et al. 2007; Wible et al. 2010; Eltawil et al. 2012; Hinrichs et al. 2017; Aliberti et al. 2017). Many of these investigated QoL in small cohorts (Toro et al. 2012; Kaiser et al. 2014; Kolligs et al. 2015; Anota et al. 2016; Aliberti et al. 2017). Often QoL was observed only for a short period of time (Wang et al. 2007; Shun et al. 2012; Aliberti et al. 2017). As Ahmed et al. reported in their meta-analysis of six randomized controlled trials, the TACE QoL literature is heterogeneous. Comparability between the studies is, therefore, limited with regard to assessment-tool and time of reporting the QoL (Ahmed et al. 2016). Wang et al. used the Functional Assessment of Cancer Therapy-General questionnaire (Wang et al. 2007), Eltawil et al. the World Health Organization QOL questionnaire (WHOQOL-BREF) (Eltawil et al. 2012), and Aliberti et al. the Palliative Performance Scale (Aliberti et al. 2017). Thus while general trends in QoL can be ascertained, comparing different questionnaires which assess differing variables remains a limitation. One study showed effects on QoL for only one TACE in a limited patient collective, using the validated EORTC QLQ-C30 and EORTC HCC18 questionnaires as in a previous study (Hinrichs et al. 2017). Nonetheless it remains unclear how QoL changes over a course of several treatments, over a longer period of time. Furthermore, little is known about patient-specific factors that predict effects on QoL over a cycle of repetitive TACE. A greater awareness for such factors may help to select patients whose QoL is likely to benefit from TACE, and patients in whom QoL is unlikely to improve. Moreover, QoL measures are receiving increasing attention in times of financial scrutiny in healthcare. Quality adjusted life years (QALY) can measure the utility of TACE, and is included as an outcome measurement in many cost-effectiveness analyses (Cucchetti et al. 2016).

The aim of our study was to assess changes of QoL in patients undergoing multiple (at least two) TACE treatments for intermediate stage HCC, and to investigate possible predictive factors that may determine QoL changes. Understanding how QoL changes over time, and correlating with clinical symptoms may help refine TACE indications and technique with regard to the optimizing patient quality of life.

Methods

Study design

The institution's Human Subjects Research Review Board approved our prospective single-centre study. Each patient receiving a TACE procedure in our department was asked for study inclusion. Written informed consent for both the study and the TACE procedure was obtained for all patients. One to three days before each treatment QoL was assessed using the validated EORTC questionnaires version QlQ-C30 version 3.0 and QLQ-HCC18 (Aaronson et al. 1993; Blazeby et al. 2004; Chie et al. 2012). A medical student or a radiologist not performing the procedure consented for participation in the study. Every patient was asked to repeat the questionnaires two weeks after TACE, to measure change in QoL following treatment. An interval of 14 days was chosen to prevent interference with post-embolization syndrome, which typically has resolved by this time (Mason et al. 2015). Changes in QoL were measured before and after first TACE, and over a course of serial TACE procedures.

Exclusion criteria for the study were poor vernacular (German) language skills, inability to understand and fill out the questionnaire without help, and patient refusal to partake in the study.

Patients

Between July 2012 and February 2015, QoL assessment for TACE was conducted at a single tertiary referral centre following treatment decision by an interdisciplinary tumourboard in accordance with modified BCLC criteria (Bruix et al. 2011; European Association For The Study Of The et al. 2012). If suitable patients were scheduled for TACE procedure every 3 months.

148 patients agreed to complete the QoL-questionnaires pre- and post-treatment. Of these 82 patients received repetitive TACE (4 TACE procedures $n=21$, 3 TACE procedures $n=27$, 2 TACE procedures $n=34$), allowing change in QoL over time to be measured. A total of 299 TACE procedures were included of which 295 could be analysed.

Table 1 Patient characteristics before first TACE treatment (baseline)

Patients' baseline characteristics	Value
Number of patients	148
Age at first TACE [years]	
Mean (SD)	66. 2 (± 10.6)
Min	36.6
Max	85.5
Sex	
Male	115 (77.7%)
Female	33 (22.3%)
Child	
A	107 (72.3%)
B	37 (25.0%)
MELD	
Mean (SD)	9.3 (± 2.5)
Min	6.0
Max	20.0
CRP [mg/L]	
Mean (SD)	12.3 (± 22.4)
Min	1.0
Max	166.0
BMI	
Mean (SD)	27.4 (± 4.9)
Min	17.4
Max	47.8
Risk factors for cirrhosis	
Alcoholic	51 (34.5%)
Infectious	
Hepatitis B	26 (17.6%)
Hepatitis C	45 (30.4%)
NASH	8 (5.4%)
Autoimmune	4 (2.7%)
Other	4 (2.7%)
Cryptogenic	29 (19.6%)

SD (standard deviation), min (minimum), max (maximum). Numbers exceeding 100% are due to possible multiple selections

Patient characteristics (Table 1) including age, gender, Child-Pugh status and risk factors for cirrhosis were documented before first TACE. Laboratory parameters were typically obtained on the day prior to TACE, and included coagulation status, inflammatory markers, liver and kidney function tests. Moreover, procedural data like such as use of microcatheters and imaging parameters were registered for each TACE.

TACE procedure

Conventional TACE (cTACE, 130 patients) or drug-eluting beads TACE (DEB-TACE, 18 patients) was performed according to tumour burden, distribution, and localization. The indication for TACE and the preferred technique were determined by the interdisciplinary tumor-board following the local standards at our hospital. DEB-TACE was preferred in patients with 1–3 nodules and feasible super-selective position. In every other case cTACE was performed.

Every patient received up to 50 mg of pethidine and 8 mg of ondansetron for periprocedural pain and nausea. Intravenous normal saline was administered for continuous hydration. For cTACE, a suspension of doxorubicin in varying doses according to calculated body surface was administered, along with up to 6 mg mitomycin C (depending on bone marrow function) and 10 ml of Lipidol (Guerbet, Roissy, France). It was administered in either a selective (with embolization of the right or left hepatic artery), or superselective position (with embolization of the tumour-feeding artery). Considerable reduced blood flow within the tumour feeding vessels and visible lipiodol uptake of the tumour was taken to indicate satisfactory embolization. If necessary, up to an additional 10 ml of lipiodol was administered. DEB-TACE was performed using a similar technique, with DC-Beads (BTG, London, Great Britain) loaded with 75 mg doxorubicin in an in-house pharmacy. The size of particles varied from 100 to 300 µm and 300–500 µm depending on tumour number and the pattern of distribution.

Postoperative analgesic medication on the ward was administered in accordance with the World Health Organization (WHO) analgesic ladder (World Health Organization 2017).

Quality of life questionnaire

QoL assessment was performed both1-3 days before, and 14 days after each treatment to reduce the impact of a possible post-embolization syndrome. Two separate questionnaires were used: version 3 of the core 30 item Quality of Life Questionnaire (QLQ-C30), and the Hepatocellular Carcinoma 18 item questionnaire (HCC18). Both questionnaires were developed and validated by the European Organisation for Research and Treatment of Cancer (EORTC) (Aaronson et al. 1993; Blazeby et al. 2004) for assessment of QoL in patients suffering from cancer (QLQ C 30 (Aaronson et al. 1993)) and for patients diagnosed with HCC [HCC18 (Blazeby et al. 2004; Chie et al. 2012)].

The QLQ-C30 contains a total of 30 questions divided into nine multi-item scales that include more than one question dealing with the same content. These can generally be divided into five functional scales (physical-, role-, cognitive-, social- and emotional functioning), three symptom scales (fatigue, pain, nausea and vomiting) and a Global Health and quality of life scale. Six additional questions investigate so called "single items", regarding additional specific symptoms (Aaronson et al. 1993).

The HCC18 includes 18 questions comprising six scales assessing fatigue, body image, jaundice, nutrition, pain and fever. Two single items address sexual interest and abdominal swelling (Blazeby et al. 2004). Scoring was performed in accordance with the EORTC QLQ-C30 Scoring Manual and HCC 18 module (Fayers et al. 2001; Kavadas et al. 2003; Chie et al. 2012).

Response criteria

Cross-sectional imaging using contrast-enhanced CT or MRI was acquired at baseline prior to TACE, and follow-up imaging was obtained to evaluate therapy response using Response Evaluation Criteria In Solid Tumours 1.1(RECIST 1.1) (Eisenhauer et al. 2009), modified RECIST (mRECIST) (Lencioni and Llovet 2010), World Health Organisation (WHO) (Miller et al. 1981) and European Association for the Study of the Liver- (EASL) (Bruix et al. 2001) criteria. Response was dichotomized according to the mRECIST criteria into stable disease (SD) and objective response (OR).

Statistical analysis

All data were analysed using the SPSS statistical software package (SPSS Inc., Chicago, USA; Version 22.0). Descriptive statistics were calculated for demographic characteristics, QoL and QoL-affecting factors. Where appropriate, data was dichotomised according to the median. Linear regression was performed to identify potential factors that may affect changes in QoL: multiple TACE procedures, changes in QoL following first TACE, functional scales and symptom scales before first TACE, cTACE vs. DEB-TACE, level of serum C-reactive protein (CRP), CRP higher or lower than 10 mg/L for means in overall survival (Zheng et al. 2013), MELD Score (Kamath et al. 2001), age, gender, tumour response, and unselective vs. selective TACE. All factors showing a significant association with change in QoL were analysed in a common multivariate linear regression model using Wald backward elimination. 95%-confidence intervals showed direction of influence on QoL. Significances were calculated according to Wilcoxon sign-rank test. The level of significance was set to $p < 0.05$.

Results

Development of QoL for first and repetitive TACE

Differences between pre- and post-treatment scores, as well as differences between baseline values and values measured before last TACE, were calculated for QoL and QoL-affecting factors (Table 2).

From pre-TACE to post-first TACE, the Global Health Score and Physical Functioning significantly decreased, and symptom scales significantly increased. However, this only applied to initial TACE with neither mean Global Health Score nor Physical Functioning significantly changing with additional TACE. Symptom scales of fever and nausea and vomiting increased, but this change failed to reach significance. In contrast to the increase in pain scores following first TACE, pain scores in fact decreased with repetitive TACE. Development of QoL and influencing factors are depicted over the course of repetitive TACE in Fig. 1.

Prognostic factors for changes in QoL-scores

Factors evaluated for prognostic value were clinical and laboratory parameters, QLQ-C30 and HCC18 data, response assessment and periprocedural information (Table 3). If necessary, data was dichotomised.

Linear regression and backward elimination identified higher Global Health Score ($p < 0.01$) and Physical Functioning ($p < 0.01$) at baseline (dichotomised at median) according to QLQ-C30 as independent prognostic factors for a significantly greater decrease of these scores caused by first TACE, and with repetitive TACE. Conversely, higher symptom scales before first TACE (pain $p = 0.00$, nausea and vomiting $p = 0.00$) were predictive of a significantly smaller

Table 2 Differences for absolute mean values of Global Health Score, functional and symptom scales of QLQ-C30 and HCC18 questionnaires due to first TACE and over course from first to last TACE. P-values were calculated for absolute changes in QoL-scores

Difference in QoL and influence factors	First TACE ($n = 148$)					First to last TACE ($n = 82$)				
	Mean	SD	Min	Max	p	Mean	SD	Min	Max	p
Global health score	− 11.77	24.58	− 83.33	50.00	< 0.01*	0.00	25.46	− 83.33	58.33	0.75
Physical functioning	− 17.25	21.34	− 73.33	40.00	< 0.01*	− 3.58	19.52	− 73.33	46.67	0.06
Symptom scales										
Fever	12.57	23.73	− 33.33	83.33	< 0.01*	1.42	14.86	− 50.00	33.33	0.41
Pain	9.21	26.06	− 83.33	100.00	< 0.01*	− 2.44	22.99	− 10.00	50.00	0.41
Nausea and vomiting	10.09	20.15	− 33.33	83.33	< 0.01*	0.81	14.56	− 83.33	50.00	0.42

* Significant at $p < 0.05$

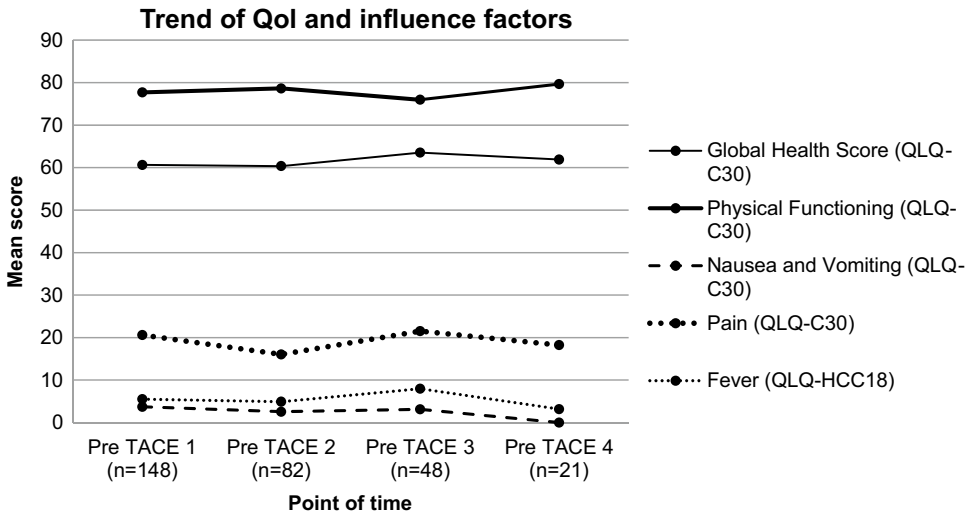

Fig. 1 Development of assessed mean absolute scores of Global Health, functional and symptom scales according to EORTC QLQ-C30 and EORTC HCC18 questionnaires. Scores were registered before each treatment. No significant change can be seen over time

Table 3 Tested prognostic factors significant after linear regression and backward elimination for development of QoL over course from pre-first to pre-last TACE

Difference in QoL and influence factors	Prognostic factor significant after backward elimination	p-Level backward elimination	Confidence interval
Course from first to last TACE			
Global Health Score	Global Health Score at baseline	0.000*	− 0.960 to − 0.524
Physical functioning	Physical functioning at baseline	0.001*	− 0.558 to − 0.194
Fever	Fever at baseline	0.008*	− 0.845 to − 0.337
Pain	Pain at baseline	0.000*	− 0.894 to − 0.512
Nausea and vomiting	Nausea and vomiting at baseline	0.000*	− 0.843 to − 0.400
	Difference nausea and vomiting due to 1. TACE	0.006*	− 0.063 to 0.356

*Significant at $p < 0.05$

increase of symptom severity, and even predicted a greater reduction in pain over a course of TACE.

A high CRP at baseline (Median 4.0 mg/L/Mean 11.96 mg/L) was associated with greater decrease of Global Health Score ($p = 0.00$) and Physical Functioning ($p = 0.00$) as well as an increase of pain ($p = 0.00$), nausea and vomiting ($p < 0.01$) following first treatment.

Female gender was predictive for a greater decrease of Physical Functioning at first TACE ($p < 0.01$), as well as a greater increase in fever ($p = 0.02$) and nausea and vomiting ($p = 0.00$) amongst patients undergoing initial treatment. Amongst patients undergoing multiple TACE, observed loss of function and pain increase at first TACE were less for those undergoing a single treatment.

Tumour response dichotomised into stable disease and objective response according to mRECIST criteria did not alter QoL. No significant influence on Global Health Score ($p = 0.75$; 0.54), physical functioning ($p = 0.84$; 0.18), fever ($p = 0.90$; 0.49), pain ($p = 0.11$; 0.18), or nausea and vomiting ($p = 0.06$; 0.97) was found at initial TACE, or over the course of multiple TACE. Furthermore, type of TACE (cTACE or DEB-TACE) demonstrated no significant between-group differences.

Discussion

TACE is a first-line treatment for HCC diagnosed in intermediate stage according to BCLC classification (Bruix et al. 2011). Previous studies have investigated the safety, efficacy, survival benefit and adverse effects of TACE (Oliveri et al. 2011; Yu and Kim 2015; Zou et al. 2016; Lu et al. 2017), but QoL is rarely a primary study aim. Given the palliative role of TACE, preservation of an acceptable level of QoL may be as important as prolonging survival time (Heffernan et al. 2002; Llovet and Bruix 2003).

The use of QALY as an outcome measurement for TACE (Cucchetti et al. 2016) in cost-effectiveness analyses shows that sustaining an adequate QoL is relevant not only for patient comfort, but also permits the evaluation of treatment

success and cost-effectiveness in a time of limited healthcare resources. Nevertheless only few prospective studies to date have analysed QoL during repetitive TACE (Wang et al. 2007; Wible et al. 2010; Eltawil et al. 2012; Hinrichs et al. 2017; Aliberti et al. 2017).

A previous study used the validated EORTC QLQ-C30 and EORTC HCC18 questionnaires in patients undergoing a single TACE procedure to assess changes in QoL as well as prognostic factors that influence QoL (Hinrichs et al. 2017). Similar to our finding they indicated a greater decrease in Global Health Score during the first treatment in patients with a higher initial Global Health Score compared to patients with lowers initial scores. These patients also showed a higher increase of symptom scales.

The current study confirms this finding with statistical significance.

Conversely higher pre-existing levels of pain, nausea and vomiting appear beneficial against the development of new symptoms. This suggests that patients suffering from severe pain and nausea before initial procedure may have adapted or developed tolerance to their symptoms. Alternatively, previously started medical treatment such as analgesia and antiemetics may account for this trend. Based on these results, we recommend that peri- and post-procedural antiemetic, antipyretic and analgesic medication needs to be given to all patients, even to those with lesser clinical symptoms. This could be an appropriate step to reduce symptom severity and improve comfort.

Whereas Hinrichs et al. previously demonstrated no significant difference in loss of Physical Function following first TACE we did observe such an effect in the current study. A higher than average Physical Functioning score at baseline is an independent risk factor for a decrease in Physical Function.

Summarizing, changes following first TACE in different QoL-domains of our patients can be categorised as "a little" or "moderate" as classified by Osoba et al. (Osoba et al. 1998). All determinations did not lead to an unacceptable decrease in QoL, and therefore, would not be a cause to prohibit further TACE.

Furthermore, the change of QoL in patients undergoing repetitive TACE was assessed. Eltawil et al. and Wible et al. described no significant decline of QoL in first 12 months after TACE in 48 and 73 patients respectively (Wible et al. 2010; Eltawil et al. 2012). Our study confirmed these results in a larger cohort. No significant changes in QoL were observed in Global Health, Physical Functioning, fever, pain, nausea and vomiting throughout a course of several treatments. According to the grading reported by Osoba et al. the changes in QoL-domains can be categorized as "no change" over the course (Osoba et al. 1998).

QoL deterioration at 14 days seemed not to be sustainable as no change can be seen over a longer course in contradistinction to for example treatment with sorafenib (Chow et al. 2018).

In order to make TACE still more tolerable and to preserve current QoL in different patient groups we investigated potential prognostic factors. Zheng et al. reported on the prognostic relevance of CRP for poor overall survival (OS) and recurrence free survival (RFS) in HCC patients (Zheng et al. 2013). In the current study, a higher-than-average CRP at baseline was predictive of a greater decrease of functional scales, and an increase in pain, nausea and vomiting at first TACE. Over repetitive treatments however, we observed no persisting effect. Nonetheless, an elevated CRP should be considered a factor, which may result in reduced patient benefit from first TACE.

In addition, female gender predicts a greater decrease of Physical Functioning as well as greater increase in fever and in nausea and vomiting following first TACE. This may support extended antiemetic, antipyretic, and analgesic medication, to improve QoL. Similar gender specific effects have not yet been described in other studies. On the contrary, Shun et al. described male gender as a risk factor for lower mental QoL in Asian population (Shun et al. 2012).

Elevated symptom scales at baseline, including pain, are associated with a significantly lesser increase of symptom severity from first TACE, and even predict a higher reduction of pain over a course of several TACE treatments. Hinrichs et al. showed similar effects for one TACE (Hinrichs et al. 2017). This suggests the most symptomatic patients may actually benefit most from TACE in terms of pain. Even though high symptom scales before treatment appear protective of QoL, the addition to the existing antiemetic and analgesic medication may be appropriate to further reduce symptoms. As this was not part of the present work, further studies should investigate correlation between different types of medication and QoL.

As the correlation of mRECIST and OS is well acknowledged in literature (Vincenzi et al. 2015; Lencioni et al. 2017), aggressive TACE aiming for maximum treatment effect is, therefore, preferred. In our study, radiological response showed no significant influence on QoL over time. This suggests that more aggressive TACE regimes to improve tumour response do not appear to sacrifice QoL. This conclusion may be biased however, as patients with progressive disease were excluded for further TACE therapy by our tumor-board, and therefore, excluded from further analysis.

DEB-TACE is an effective treatment, reducing adverse effects due to lower peak systemic concentrations of the chemotherapeutic agent (Varela et al. 2007; Xie et al. 2015). In the current study, no statistically significant difference in QoL between cTACE or DEB-TACE was detected. This suggests that the lower systemic

doxorubicin blood levels experienced with DEB-TACE are of questionable clinical relevance.

Certain limitations must be noted. TACE differs, not only between centres, but also between interventionalists. Eltawil et al. used drug-eluting beads loaded with doxorubicin or a mixture of doxorubicin and lipiodol. If necessary polyvinyl alcohol particles were administered subsequently until stagnant flow was observed (Eltawil et al. 2012). Wible et al. described a combination of cisplatin, doxorubicin, and mitomycin C in emulsion with ethiodol followed by polyvinyl alcohol particles (Wible et al. 2010). To account for the variability, we compared DEB TACE and cTACE and did not show significant differences.

Furthermore QoL-questionnaires varied as well. World Health Organization QoL questionnaire (WHOQOL-BREF) (1998) (Eltawil), Short Form-36 (SF-36) Health Survey Forms (Ware 2000) (Wible), and EORTC QlQ-C30/HCC18 have all been used. While some differences exist with the questionnaires used, the results are comparable with a general trend in QoL across all three studies.

In our study the analysis of QoL after the first TACE was only performed in patients receiving several TACE treatments. Of course, in case of disease progression TACE was discontinued. Patients that experienced significant side effects following a single TACE may be less likely to be rescheduled for repetitive TACE, particularly where response was limited.

The study was limited to patients suitable for TACE treatment according to the modified BCLC criteria; therefore, a comparison of QoL in patients undergoing different HCC treatments is not provided and remains subject of further investigation.

Nonetheless it has to be considered that another treatment option implies a different stage of the disease. Even though we cannot prove that effects seen in our study were caused by TACE treatment and are not HCC-related, literature shows that QoL worsens with progress of the disease and TNM stage (Qiao et al. 2012).

QoL after surgical treatment was investigated using the EORTC questionnaires QLQ-C30 and HCC18 and a significant deterioration in pain after treatment could be found (Blazeby et al. 2004; Chie et al. 2015). In a literature review consisting of 45 studies and four meta-analyses of the years 2001–2013 Gandhi et al. described a negative short-term impact of surgery and liver-directed therapies on QoL as well as beneficial long-term outcomes (Gandhi et al. 2014). We observed this trend even in our study.

Ablation caused higher odds of deterioration in QoL compared to surgery (Chie et al. 2015).

SIRT showed significantly better QoL data (GHS) in comparison with sorafenib in the SARAH trial (Vilgrain et al. 2017). Moreover, QoL was comparable in patients undergoing SIRT therapy or TACE in a study performed at our hospital which is not yet published.

Furthermore, while a medical student or radiologist was present to assist patients in the completion of the QoL questionnaire before each TACE, the 2-week post-TACE follow-up questionnaire was self-administered in the patient's home. It is, therefore, possible that the presence (and subsequent absence) of a healthcare professional could influence answers provided in either a positive or negative direction, and bias is possible.

Another limitation is the applicability of these results, performed in a single centre where TACE technique was standardized in accordance with a predefined protocol, to other centres where TACE technique (including dosages and arterial selectivity) may vary.

In Conclusion TACE is a palliative treatment option, and quality of life (QoL) does not significantly change even with multiple treatments.

Tumour response is not correlated with QoL, this suggests aggressive TACE treatment is reasonable to optimize treatment response without sacrificing QoL.

Patients with higher QoL before treatment demonstrate the greatest decrease in QoL, although levels remain acceptable. Conversely, patients with a lower pre-TACE QoL benefit especially regarding pain.

An elevated pre-procedural CRP level before initial TACE is associated with a reduction in QoL. Although this effect does not persist for repetitive treatments, elevated CRP should alert clinicians as to an increased risk of worsening symptoms.

Extension of antiemetic, antipyretic and pain medication should be a particular consideration for female patients.

Compliance with ethical standards

Conflict of interest Kyana Hartrumpf declares that she has no conflict of interest. Thomas Werncke declares that he has no conflict of interest. Timothy E. Murray declares that he has no conflict of interest. Thomas Rodt declares that he has no conflict of interest. Martha M. Kirstein was supported by the Ellen Schmidt program from Hannover Medical School. Arndt Vogel and Steffen Marquardt have received honoraria from Delcath Systems Inc for Advisory Boards and speaker's activities, outside the submitted work. Frank Wacker reports grants and personal fees from Delcath Systems, Inc., grants from Siemens Healthineers, Promedicus Ltd., and personal fees from Novartis Pharma GmbH, outside the submitted work.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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