Research Article

Deterioration of Health-Related Quality of Life Scores under Treatment Predicts Longer Survival

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1. Introduction

Great scientific progress has been achieved in the fields of medicine, hygiene, and health care in recent decades, resulting in prolonged survival times for patients [1]. However, the number of cancer patients will further increase due to demographic change [2]. Both aspects together have already resulted in a dramatically increased number of long-term survivors of cancer and it will continue to rise [3, 4]. Another factor influencing this is increasingly specialized therapy options [5, 6].

Statistics from the USA prove that cancer plays an important role; in 2016, cancer was the second most frequent cause of death in the United States and one in four deaths could be attributed to cancer [7]. Important influencing and risk factors in recent decades such as smoking have also led to cancer cases becoming more frequent and therapy becoming increasingly important. In the last several years, scientists have discovered that successful therapy and survival are closely related to quality of life.

Cancer patients experience a wide variety of symptoms and reach their limits when trying to manage them. Their symptoms directly influence their quality of life. Therefore, symptom management improves QoL [8, 9]. Although more research has been done in recent years regarding these topics, this is not yet sufficient. As the number of cancer survivors continues to rise, not only the pure survival time but also the late effects of radiochemotherapy and the health-related quality of life (HRQoL) are crucial for patients. Radiochemotherapy in particular has a major influence on HRQoL [10]. HRQoL is highly relevant for patient care; it directly influences therapy, satisfaction, and compliance. Since patients themselves are the best source for measuring HRQoL, various questionnaires are used in clinical trials worldwide. HRQoL is important for making treatment decisions; especially, the questionnaire QLQ-C30 of the EORTC...
is recommended as a measuring instrument [11]. In particular, there is too little research on whether a poor HRQoL consequently means shorter survival time.

Some studies already indicated that the baseline score predicts overall survival (OS), both for a heterogeneous group of cancer types [12–16] and for certain tumor types, e.g., for lung cancer [17–21], head and neck cancer [22–24] and colorectal cancer [25, 26]. In addition, it has been suggested that older patients are less affected by radiochemotherapeutic treatment than younger patients [27].

However, it is important to know whether one can deduce survival from a certain factor. Furthermore, only few studies have addressed whether a change in HRQoL between before and after therapy is decisive for survival [21, 25, 28]. The general assumption is that patients who tolerate therapy better or recover faster will survive longer. But is this the case? For this reason, our aim was to investigate how HRQoL before therapy, after therapy, and the changes in between those two points in time affect survival.

2. Patients and Methods

2.1. Study Population. This clinical trial included 400 consecutive patients who met the inclusion criteria. These were a clinically diagnosed cancer treated with radiochemotherapy in our clinic and the ability to understand and complete the EORTC QLQ-C30 questionnaire. Patients were surveyed in their first week of in-patient therapy at the time of inclusion. The sex of the 400 patients was male in 272 (68%) patients and female in 128 (32%) patients. Furthermore, 162 (40.5%) patients were under 60 years of age and 238 (59.5%) were over 60 years of age (Table 1). The largest diagnostic groups include 138 (34.5%) patients with head and neck cancer, 98 (24.5%) patients with rectal cancer, and 52 (13.0%) patients with lung cancer. For further information on diagnostic groups and TNM staging, see Table 1.

2.2. Design. At the beginning of the therapy, the patients who fulfilled the inclusion criteria were informed about the study in a personal conversation and gave their written consent. The Ethics Review Committee of the University Hospital Erlangen approved the study including the use of patients’ individual data. Thus, the questionnaires could be completed directly on site and remaining questions of the patients were clarified. For the first time, the patients were interviewed during their first in-patient stay; these values determine the baseline score. For the following questionnaires, the patients were either interviewed personally at follow-up appointments or the questionnaire was sent to them by mail. They were then interviewed after six weeks, i.e., after completion of therapy, and then after each completed year after the start of therapy up to a maximum of six years or until their drop out from the study for any reason.

2.3. EORTC QLQ-C30 Questionnaire. The first version of the EORTC QLQ-C30 questionnaire was first published in 1987 and has been updated ever since, until the current version 3.0 was released in 1997. Since then, the questionnaire has been used in various studies around the world, giving a whole new meaning to quality of life in cancer therapy. The QLQ-C30 consists of 30 questions divided into functional scales, symptom scales, and global health status/quality of life. Functional scales are 5 multi-item scales containing physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. Higher scores represent better quality of life. Symptom scales are 3 multi-item scales, namely, fatigue, pain, nausea and vomiting, and 6 single items such as dyspnoea, appetite loss, insomnia, constipation, diarrhoea, and financial issues. Higher scores stand for higher symptom burden causing poorer quality of life. Functional and symptom scales include the first 28 questions; answer options on a four-point scale are from 1 (not at all) to 4 (very much). The last two questions offer answer options from 1 (very poor) to 7 (excellent), resulting in the global health status and the quality of life. This questionnaire has been extensively tested for reliability and validity, making it an important instrument for measuring HRQoL of cancer patients in clinical research [29–32].

2.4. Statistics. The analysis was divided into three parts. First, the relationship between baseline HRQoL and OS was studied for all patients who had valid baseline values. In the second step, the relationship between HRQoL scores after therapy and OS was assessed for the same patient cohort. The third step included assessing the relationship between the change in HRQoL scores from baseline to after therapy and OS. These so-called change scores were calculated by

| Table 1: Patient demographics. |
|-------------------------------|
| Gender | n | (%) |
| Male | 272 | (68) |
| Female | 128 | (32) |
| Age (yrs) | | |
| <60 | 162 | (40.5) |
| >60 | 238 | (59.5) |
| Diagnostic group | | |
| Head and neck | 138 | (34.5) |
| Rectal | 98 | (24.5) |
| Lung | 52 | (13) |
| Gastrointestinal | 34 | (8.5) |
| Gynaecological | 21 | (5.3) |
| Others | 57 | (14.2) |
| TNM staging | | |
| T | | |
| 0 | 16 | (4.0) |
| 1 | 51 | (12.7) |
| 2 | 92 | (23.0) |
| 3 | 136 | (34.0) |
| 4 | 105 | (26.3) |
| N | | |
| 0 | 147 | (36.7) |
| 1 | 253 | (63.3) |
| M | | |
| 0 | 322 | (80.5) |
| 1 | 78 | (19.5) |
Table 2: Analysis of QoL scores. Figures quoted in parts i-v describe baseline scores. First value: group favourable HRQoL (higher QOL)/second value: group adverse HRQoL (lower QOL). The median scores were used as cut-off-points. Figures quoted in parts vi-x describe change scores. First value: group favourable HRQoL (better scores after therapy than baseline)/second value: group adverse HRQoL (equal or worse scores after therapy than baseline).

| i | ii | iii | iv | v | vi | vii | viii | ix | x |
|---|----|-----|----|---|----|-----|------|----|---|
| Functional scales | | | | | | | | | |
| Physical functioning | 93.3/60.0 | 168/232 | <80/63 | 71.4/54.9 | <0.001 | 73.3/86.7 | 100/143 | <76/- | 67.5/65 | 0.400 |
| Role functioning | 100/33.3 | 135/262 | <76/<84 | 60.6/63.6 | 0.690 | 50.0/66.7 | 113/123 | <70/80 | >59.1/74.2 | 0.027 |
| Emotional functioning | 83.3/41.7 | 189/208 | 70-310/64 | 67.0/57.7 | 0.122 | 58.3/75.0 | 138/86 | -70 | >61/66.5 | 0.700 |
| Cognitive functioning | 100/66.7 | 178/219 | 76/70 | 64.9/60.2 | 0.560 | 83.3/83.3 | 161/79 | 76/52-310 | 70.1/64.9 | 0.820 |
| Social functioning | 100/50.0 | 130/267 | -76 | 63.2/62.1 | 0.900 | 50.0/66.7 | 131/92 | 70/-80 | 65.2/62.8 | 0.600 |
| Global health status | 66.67/33.3 | 190/206 | 80-310/63 | 68.9/55.6 | <0.003 | 50.0/66.7 | 121/117 | <70/-310 | 60.7/75.5 | 0.018 |

Symptom scales

| i | ii | iii | iv | v | vi | vii | viii | ix | x |
|---|----|-----|----|---|----|-----|------|----|---|
| Fatigue | 22.2/66.7 | 237/163 | 76/<63 | 68.5/52.8 | <0.0001 | 44.4/33.3 | 110/132 | 70/<310 | 62.5/70.7 | 0.137 |
| Pain | 0/50.0 | 212/186 | <76/63 | 69.6/54.4 | <0.018 | 33.3/0 | 136/105 | <70/- | 57.3/83.5 | <0.0001 |
| Appetite loss | 0/66.7 | 224/174 | <70/<76 | 66.9/55.7 | 0.102 | 0.0 | 138/98 | <70/76-310 | 63.5/74.3 | 0.113 |
| Insomnia | 0/66.7 | 265/130 | 80/63 | 66.4/52.8 | 0.103 | 33.3/0 | 167/70 | <76/-310 | 65.5/76.3 | 0.142 |
| Nausea and vomiting | 0/33.3 | 300/98 | <76/63 | 64.3/54.8 | 0.198 | 0.0 | 137/87 | 76/62 | 68.2/55.9 | 0.189 |
| Dyspnoea | 0/33.3 | 209/186 | -1/<70 | 62.0/>60.7 | 0.450 | 0.0 | 170/53 | <76/62-80 | 67.2/51.9 | 0.290 |
| Constipation | 0/33.3 | 264/133 | <80/<76 | 64.1/>56.7 | 0.090 | 0.0 | 141/82 | 76/- | 65.3/>58.8 | 0.420 |
| Diarrhoea | 0/33.3 | 267/128 | <76/70 | 58.1/>68.5 | 0.140 | 0.0 | 160/78 | <76/- | 67.4/70.2 | 0.220 |
| Financial difficulties | 0/66.7 | 221/172 | <70/<310 | 61.1/64.5 | 0.114 | 0.0 | 185/36 | 76/- | 65.9/71.6 | 0.560 |
subtracting the baseline score from the corresponding score after therapy.

The outcome variable was OS, calculated using the Kaplan-Meier method and calculated from the day of inclusion in the study until the date of death due to any cause. Univariate cox proportional hazards models (CPHM) were used to evaluate the prognostic significance of sociodemographic, clinical, and HRQoL variables [33]. In the following step, all variables that were univariate and prognostically significant were examined by multivariate CPHM for their common prognostic significance. \( p \text{ values} < 0.05 \) were considered significant.

Osoba et al. [34] described the minimum clinically meaningful important difference on the QLQ-C30 scales is at least 10 points as determined in the study. CPHM was used with a minimum of 10 events per variable (EPV) to increase accuracy and precision of regression coefficients and their tests of statistical significance [35, 36]. Microsoft Excel and IBM SPSS Statistics 25 were used for all calculations.

3. Results

The 400 participating patients were divided into two groups for each score and each time of interview according to their answers. These groups were created on the basis of the corresponding median score of all patients: group favourable HRQoL comprises the patients who in their answers reflected the better QOL, i.e., higher values on functional scales and lower values on symptom scales. The other group, also called group adverse HRQoL, represents accordingly the lower QOL, i.e., lower values on functional scales and higher values on symptom scales. The groups differ in size for each score, since one patient naturally does not receive good or bad scores throughout and not every patient answered every question (Table 2).

3.1. Scores prior to and after Therapy. In order to get an initial overview of how the scores generally change in the course of therapy, box plots were created. Only coherent data were used, meaning data of patients with valid scores for both the pretreatment and posttreatment interviews. This provides a more valid representation of the changes in quality of life caused by the therapy. Role functioning and global health status are given as examples of the functional scales and pain as a representation of the symptom scales. In these box plots, the scores on functional scales decrease in the course (Figures 1(a) and 1(b)), while they increase on symptom scales (Figure 1(c)), i.e., the quality of life deteriorates overall during treatment. This applies to the median score as well as to the first and third quartiles. The median score of role functioning deteriorated from 66.7 prior to therapy to 50 after therapy with \( p < 0.0001 \) (Figure 1(a)), and global health status changed from 58 to 50 with \( p < 0.0001 \) (Figure 1(b)). Pain also deteriorated; the median score rose from 16.7 to 33.3 with \( p = 0.0001 \) (Figure 1(c)). This trend
was also clearly associated with favourable survival, p < 0.001 – 0.0005).

Figure 2: (a–c) QoL scores after therapy and OS for (a) role functioning, (b) global health status, and (c) pain. (d–f) Change scores and OS for (d) role functioning, (e) global health status, and (f) pain.

3.2. Baseline HRQoL and Overall Survival (OS). The two groups were then screened for their overall survival depending on their baseline score. It was observed that group favourable HRQoL survived longer than group adverse HRQoL regarding various quality of life scores. Table 2, i–v provides the results of this analysis. Role functioning showed no relevant difference between the two groups (Figure 1(d)), whereas favourable global health status was a significant predictor of longer survival time, p < 0.003 (Figure 1(e)). Minor pain was also clearly associated with favourable survival, p < 0.018 (Figure 1(f)). Substantial differences were also observed in physical functioning (p < 0.001) and fatigue (p < 0.0005) (supplementary figure 4b and 5b). A trend was observed for emotional functioning, nausea and vomiting, appetite loss, insomnia, and obstipation, meaning the p value was below 0.2.

3.3. HRQoL Scores after Therapy and OS. Six weeks after starting therapy, there were no significant differences between the two groups, which were also separated according to the median score (Figures 2(a)–2(c)). None of the selected HRQoL scores after therapy were predictive of survival. However, there is a trend for the adverse HRQoL group to have a shorter overall survival compared to the favourable HRQoL group. But these scores are not sufficient to make a general statement. For this reason, the change scores were further studied.

3.4. Change in HRQoL from Baseline and OS. The absolute difference between before and after therapy was calculated, and in a first step, two groups were formed based on the median score. The score of each patient after therapy was compared to his or her own pretreatment value. Table 2, vi–x describes the analysis of change scores. Role functioning (p = 0.027), global health status (p < 0.018), and pain (p < 0.0001) were predictive of survival (Figures 2(d)–2(f)). Patients whose global health status and role functioning scores after therapy were worse than prior to therapy or who had more pain survived clearly longer than the other
In the categories fatigue, appetite loss, and insomnia, the adverse HRQoL groups tended to a better outcome (supplementary Figures 5–6).

In a second step, three groups were created: the “no change” group contains patients whose scores did not change in the course of therapy, “adverse” group contains those patients whose scores after therapy were worse than before, and “improved” group comprises patients whose scores improved compared to prior to therapy (Figure 3). Regarding role functioning, the adverse group survived clearly longer than the other two groups, \( p = 0.031 \). Adverse global health status and pain were also distinct predictors of improved survival with \( p = 0.044 \) and \( p < 0.0001 \), respectively.

3.5. Univariate and Multivariate Analyses of Baseline Scores and Prognostic Factors for OS. To rule out any potential confounding, baseline QoL scores were added to the univariate and multivariate analyses. Well-known prognostic factors such as TNM classification, age, or gender were compared to different baseline QoL scores. The QoL scores were previously selected by significant Kaplan-Meier estimates. QoL scores then included global health status, functional scores, such as physical functioning and role functioning, and symptom scores such as fatigue, pain, and appetite loss. Table 3 describes the univariate and multivariate analyses of the baseline scores.

The univariate analysis reveals that M status and age were significant predictors of survival. Pain was borderline significant (\( p = 0.054 \)). Multivariate analysis indicates that high global health status (\( p = 0.005 \)) and mild pain (\( p = 0.04 \)) were favourable for survival. Young age and M0 category were also beneficial. Patients with low global health status at baseline have a 1.76 times higher risk of dying (HR = 1.758). Moreover, patients who experienced more pain prior to therapy had a 1.5 times higher risk of dying (HR = 1.489).

3.6. Univariate and Multivariate Analyses of Change Scores and Prognostic Factors for OS. Change scores were also subjected to univariate and multivariate analyses in order to account for confounding. Table 4 describes the changes in QoL scores from baseline to after therapy. TNM staging, age, and gender were compared to physical functioning, role functioning, global health status, fatigue, pain, and appetite loss. Regarding univariate analysis of all analysed QoL scores, only mild pain was beneficial for survival (\( p = 0.002 \)). Another favourable predictor of survival was young patient
Our aim was to find out whether these patients really do survive better than those who showed self-reported improvement in quality of life during the course of therapy. We were able to demonstrate significance for physical functioning, global health status, fatigue, and pain at baseline. In addition, the change score is also appropriate to make a statement about the survival of cancer patients. Various studies have already shown that an improvement in HRQoL in the course of therapy leads to longer survival [24, 37, 38].

We could prove the existence of other studies that the baseline score is a meaningful predictor of survival. We were able to demonstrate prognostic relevance for physical functioning, global health status, fatigue, and pain at baseline. In addition, the change score is also appropriate to make a statement about the survival of cancer patients. Various studies have already shown that an improvement in HRQoL in the course of therapy leads to longer survival [24, 37, 38].

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4. Discussion

It is generally assumed that patients whose quality of life deteriorates in the course of cancer therapy compared to the past have a worse outcome and thus a lower survival rate. Our aim was to find out whether these patients really do survive better than those who showed self-reported improvement in quality of life during the course of therapy. Therefore, we analysed the scores prior to therapy, after therapy, and the difference between these two points in time, creating 2 and 3 groups.

Our data confirm other studies that the baseline score is a meaningful predictor of survival. We were able to demonstrate prognostic relevance for physical functioning, global health status, fatigue, and pain at baseline. In addition, the change score is also appropriate to make a statement about the survival of cancer patients. Various studies have already shown that an improvement in HRQoL in the course of therapy leads to longer survival [24, 37, 38].

We could prove exactly the opposite, i.e., that patients who deteriorate in their quality of life during the course of therapy survive longer than those who showed self-reported improvement in quality of life. We were able to demonstrate significant prognostic relevance for the change scores of role functioning, pain, and global health. These counterintuitive findings have also been found in other clinical trials. Oskam et al. reported that age, \( p = 0.023 \). Concerning multivariate analysis, pain remained significant \( (p = 0.001) \). Further significant variables were the patient age and M category with \( p = 0.009 \) and \( p = 0.029 \), respectively. Pain was the superior predictor of survival of all variables and QoL scores studied. A deterioration in pain was associated with a 2.8 times higher change of longer survival (HR 0.36).

### Table 3: Univariate and multivariate analyses according to Cox’s proportional hazards model for sociodemographic and clinical variables and HRQoL scores at baseline.

| Variable                        | Univariate analysis | Multivariate analysis |
|---------------------------------|---------------------|-----------------------|
|                                | Hazard ratio | 95% C.I. | \( p \) | Hazard ratio | 95% C.I. | \( p \) |
| T category (T1/T2 (\( n = 137 \)) vs. T3/T4 (\( n = 223 \))) | 1.141       | 0.743–1.753 | 0.547 | —           | —       | —       |
| N category (N0 (\( n = 131 \)) vs. N+ (\( n = 229 \))) | 1.351       | 0.857–2.13 | 0.195 | 1.415       | 0.918–2.182 | 0.116 |
| M category (M0 (\( n = 103 \)) vs. M+ (\( n = 57 \))) | 2.334       | 1.471–3.703 | 0.0003 | 2.743       | 1.829–4.144 | <0.0001 |
| Gender (male (\( n = 249 \)) vs. female (\( n = 111 \))) | 1.096       | 0.724–1.661 | 0.665 | —           | —       | —       |
| Age (\(<60 \) years (\( n = 149 \)) vs. \( >60 \) years (\( n = 211 \))) | 1.887       | 1.248–2.853 | 0.003 | 2.059       | 1.379–3.072 | 0.0004 |
| Physical functioning (above (\( n = 161 \)) vs. below median (\( n = 199 \))) | 1.533       | 0.932–2.521 | 0.093 | 1.299       | 0.835–2.019 | 0.246 |
| Role functioning (above (\( n = 125 \)) vs. below median (\( n = 235 \))) | 0.774       | 0.497–1.206 | 0.258 | —           | —       | —       |
| Global health status/QoL (above (\( n = 176 \)) vs. below median (\( n = 184 \))) | 1.481       | 0.947–2.315 | 0.085 | 1.758       | 1.184–2.613 | 0.005 |
| Fatigue (below (\( n = 221 \)) vs. above median (\( n = 139 \))) | 1.091       | 0.676–1.762 | 0.722 | —           | —       | —       |
| Pain (below (\( n = 193 \)) vs. above median (\( n = 167 \))) | 1.518       | 0.993–2.323 | 0.054 | 1.489       | 1.018–2.178 | 0.040 |
| Appetite loss (below (\( n = 205 \)) vs. above median (\( n = 155 \))) | 0.855       | 0.55–1.328  | 0.485 | —           | —       | —       |

| Variable                        | Univariate analysis | Multivariate analysis |
|---------------------------------|---------------------|-----------------------|
|                                | Hazard ratio | 95% C.I. | \( p \) | Hazard ratio | 95% C.I. | \( p \) |
| T category (T1/T2 (\( n = 78 \)) vs. T3/T4 (\( n = 138 \))) | 1.144       | 0.629–2.081 | 0.660 | —           | —       | —       |
| N category (N0 (\( n = 77 \)) vs. N+ (\( n = 139 \))) | 1.290       | 0.694–2.397 | 0.421 | —           | —       | —       |
| M category (M0 (\( n = 183 \)) vs. M+ (\( n = 33 \))) | 1.745       | 0.956–3.187 | 0.070 | 1.895       | 1.069–3.359 | 0.029 |
| Gender (male (\( n = 148 \)) vs. female (\( n = 68 \))) | 1.068       | 0.607–1.879 | 0.820 | —           | —       | —       |
| Age (\(<60 \) years (\( n = 93 \)) vs. \( >60 \) years (\( n = 123 \))) | 1.954       | 1.095–3.454 | 0.023 | 2.113       | 1.209–3.695 | 0.009 |
| Physical functioning (above (\( n = 92 \)) vs. below median (\( n = 124 \))) | 1.742       | 0.904–3.355 | 0.097 | 1.487       | 0.832–2.657 | 0.180 |
| Role functioning (below (\( n = 103 \)) vs. above median (\( n = 113 \))) | 0.712       | 0.391–1.297 | 0.267 | 0.61        | 0.359–1.039 | 0.069 |
| Global health status (above (\( n = 113 \)) vs. below median (\( n = 103 \))) | 0.555       | 0.298–1.034 | 0.064 | —           | —       | —       |
| Fatigue (above (\( n = 100 \)) vs. below median (\( n = 116 \))) | 0.927       | 0.489–1.757 | 0.816 | —           | —       | —       |
| Pain (below (\( n = 119 \)) vs. above median (\( n = 97 \))) | 0.356       | 0.184–0.688 | 0.002 | 0.36        | 0.193–0.67  | 0.001 |
| Appetite loss (below (\( n = 125 \)) vs. above median (\( n = 91 \))) | 0.783       | 0.431–1.424 | 0.423 | —           | —       | —       |
a deterioration of global quality of life after treatment is a predictor of survival in patients with oral or oropharyngeal cancer [28]. Braun et al. showed that an improvement in social function at 3 months is associated with worse survival [25]. Ediebah et al. reported a higher risk of death for patients with a self-reported improvement over time for functional scales and global health status [21]. A deterioration of the quality of life could be responsible for an increased response to the therapy, especially in normal tissue. The cause could be an increased sensitivity of the patients to radiation [39], which leads to increased side effects and at the same time to an enhanced effect on the tumour cells.

5. Conclusion

The general assumption that patients whose quality of life and symptom burden worsens in the course of therapy ultimately die earlier than patients whose quality of life remains the same or improves must be reconsidered. The natural resilience and coping strategies of patients with poorer quality of life appear to be underestimated. Not only the baseline HrQoL is a predictor of survival but also the change due to therapy, more specifically the worsening. The decisive factor is not only the quality of life immediately after therapy but also the change compared to before. This is a new prognostic factor regarding the survival of patients receiving radiochemotherapy. These results naturally raise new questions that could decisively influence and change the therapy. For example, it should be investigated whether patients with a worsening condition under therapy receive higher doses of chemotherapy or more intensive radiation, or whether they respond more intensively to the therapy individually and thus take all side effects with them.

In conclusion, HrQoL should be recorded continuously in the course of therapy and the results of the surveys should be included in the therapy. It might be possible to find out which type of therapy is related to changes in quality of life and how. In addition, early deterioration of patients can be detected and interventions can be planned that potentially improve both HrQoL and outcome. Nevertheless, distortive effects should be considered and excluded, as change score analyses can be biased by floor and ceiling effects at baseline [21].

Abbreviations

CPHM: Cox proportional hazards models
EORTC: European Organisation for Research and Treatment of Cancer
HRQoL: Health-related quality of life
OS: Overall survival
QoL: Quality of life.

Data Availability

The datasets analysed in this study are available on request from the corresponding author.

Ethical Approval

The Ethics Review Committee of the University Hospital Erlangen approved the study including the use of patients’ individual data.

Disclosure

The present work was performed in fulfillment of the requirements for obtaining the degree “Dr. med.”

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Supplementary Materials

Additional figures showing the results of the analysis of other QoL scores and their correlation with OS. Supplementary Figure 4: physical functioning; scores prior to and after therapy (a), baseline scores and OS (b), scores after therapy and OS (c), change scores and OS in 3 groups (d), and change scores and OS in 2 groups (e). Supplementary Figure 5: fatigue; scores prior to and after therapy (a), baseline scores and OS (b), scores after therapy and OS (c), change scores and OS in 3 groups (d), and change scores and OS in 2 groups (e). Supplementary Figure 6: appetite loss; scores prior to and after therapy (a), baseline scores and OS (b), scores after therapy and OS (c), change scores and OS in 3 groups (d), and change scores and OS in 2 groups (e). (Supplementary Materials)

References

[1] L. Ferrucci, F. Giallauria, and J. M. Guralnik, “Epidemiology of aging,” Radiologic Clinics of North America, vol. 46, no. 4, pp. 643–652, 2008.
[2] B. D. Smith, G. L. Smith, A. Hurria, G. N. Hortobagyi, and T. A. Buchholz, “Future of cancer incidence in the United States: burdens upon an aging, changing nation,” Journal of Clinical Oncology, vol. 27, no. 17, pp. 2758–2765, 2009.
[3] C. C. Gotay and M. Y. Muraoka, “Quality of life in long-term survivors of adult-onset cancers,” Journal of the National Cancer Institute, vol. 90, no. 9, pp. 656–667, 1998.
[4] C. Parry, E. E. Kent, A. B. Mariotto, C. M. Alfano, and J. H. Rowland, “Cancer survivors: a booming population,” Cancer Epidemiology, Biomarkers & Prevention, vol. 20, no. 10, pp. 1996–2005, 2011.
[5] L. Cozzi, C. Franzese, A. Fogliata et al., “Predicting survival and local control after radiochemotherapy in locally advanced head and neck cancer by means of computed tomography based radioimaging,” Strahlentherapie und Onkologie, vol. 195, no. 9, pp. 805–818, 2019.
[6] J. Haussmann, B. Tamaskovics, E. Bölk et al., “Addition of chemotherapy to hyperfractionated radiotherapy in advanced head and neck cancer—a meta-analysis,” Strahlentherapie und Onkologie, vol. 195, no. 12, pp. 1041–1049, 2019.
[7] US Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute: US Cancer Statistics Working Group, U.S. Cancer
Statistics Data Visualizations Tool, based on November 2018 submission data, pp. 1999–2016, US Cancer Statistics Working Group, 2019.

[8] M. Nayak, A. George, M. Vidyasagar et al., "Quality of life among cancer patients," *Indian Journal of Palliative Care*, vol. 23, no. 4, pp. 445–450, 2017.

[9] M. Nayak, A. George, M. Vidyasagar et al., "Symptoms experienced by cancer patients and barriers to symptom management," *Indian Journal of Palliative Care*, vol. 21, no. 3, pp. 349–354, 2015.

[10] B. Sunde, F. Klevebro, A. Johar et al., "Health-related quality of life in a randomized trial of neoadjuvant chemotherapy or chemoradiotherapy plus surgery in patients with oesophageal cancer (NeoRes trial)," *BJIS*, vol. 106, no. 11, pp. 1452–1463, 2019.

[11] E. Basch, A. P. Abernethy, C. D. Mullins et al., "Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology," *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, vol. 30, no. 34, pp. 4249–4255, 2012.

[12] G. I. Ringdal, K. G. Gøtestam, S. Kaasa, S. Kvinsland, and K. Ringdal, "Prognostic factors and survival in a heterogeneous sample of cancer patients," *British Journal of Cancer*, vol. 73, no. 12, pp. 1594–1599, 1996.

[13] A. Coates, F. Porzsolt, and D. Osoba, "Quality of life in oncology practice: prognostic value of EORTC QLQ-C30 scores in patients with advanced malignancy," *European Journal of Cancer*, vol. 33, no. 7, pp. 1025–1030, 1997.

[14] J. Dancey, B. Zee, D. Osoba et al., "Quality of life scores: an independent prognostic variable in a general population of cancer patients receiving chemotherapy," *Quality of Life Research*, vol. 6, no. 2, 1997.

[15] C. Quinten, C. Coens, M. Mauer et al., "Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials," *The Lancet Oncology*, vol. 10, no. 9, pp. 865–871, 2009.

[16] E. Wong, L. Rowbottom, M. Tsao et al., "Prognostic value of pre- and post-treatment health-related quality of life in predicting survival of patients with brain metastases," *CNS Oncol*, vol. 6, no. 2, pp. 119–129, 2017.

[17] P. A. Ganz, J. Jack Lee, and J. Siau, "Quality of life assessment. An independent prognostic variable for survival in lung cancer," *Cancer*, vol. 67, no. 12, pp. 3131–3135, 1991.

[18] J. E. Herndon, S. Fleshman, A. B. Kornblith, M. Kosty, M. R. Green, and J. Holland, "Is quality of life predictive of the survival of patients with advanced non-small cell lung carcinoma?" *Cancer*, vol. 85, no. 2, pp. 333–340, 1999.

[19] P. Maione, F. Perrone, C. Gallo et al., "Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly Study," *Journal of Clinical Oncology*, vol. 23, no. 28, pp. 6865–6872, 2005.

[20] J. A. Sloan, X. Zhao, P. J. Novotny et al., "Relationship between deficits in overall quality of life and non-small-cell lung cancer survival," *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, vol. 30, no. 13, pp. 1498–1504, 2012.

[21] D. E. Ediebah, on behalf of the Lung Cancer Cooperative Group, Quality of Life Department et al., "Does change in health-related quality of life score predict survival? Analysis of EORTC 08975 lung cancer trial," *British Journal of Cancer*, vol. 110, no. 10, pp. 2427–2433, 2014.

[22] F.-M. Fang, Y.-T. Liu, Y. Tang, C.-J. Wang, and S.-F. Ko, "Quality of life as a survival predictor for patients with advanced head and neck carcinoma treated with radiotherapy," *Cancer*, vol. 100, no. 2, pp. 425–432, 2004.

[23] M. Nordgren, M. Jannert, M. Boysen et al., "Health-related quality of life in patients with pharyngeal carcinoma: a five-year follow-up," *Head & Neck*, vol. 28, no. 4, pp. 339–349, 2006.

[24] F. Meyer, A. Fortin, M. Gélinas et al., "Health-related quality of life as a survival predictor for patients with localized head and neck cancer treated with radiation therapy," *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, vol. 27, no. 18, pp. 2970–2976, 2009.

[25] D. P. Braun, D. Gupta, J. F. Grutsch, and E. D. Staren, "Can changes in health related quality of life scores predict survival in stages III and IV colorectal cancer?" *Health and Quality of Life Outcomes*, vol. 9, no. 1, p. 62, 2011.

[26] N. R. Maisey, A. Norman, M. Watson, M. J. Allen, M. E. Hill, and D. Cunningham, "Baseline quality of life predicts survival in patients with advanced colorectal cancer," *European Journal of Cancer*, vol. 38, no. 10, pp. 1351–1357, 2002.

[27] M. J. Weiling, W. Losensky, K. Wächter et al., "Older patients are less affected by radiochemotherapeutic treatment than younger," *BioMed Research International*, vol. 2018, Article ID 5471054, 8 pages, 2018.

[28] I. M. Oskam, I. M. Verdonck-de Leeuw, N. K. Aaronson et al., "Quality of life as predictor of survival: a prospective study on patients treated with combined surgery and radiotherapy for advanced oral and oropharyngeal cancer," *Radiotherapy and Oncology*, vol. 97, no. 2, pp. 258–262, 2010.

[29] N. K. Aaronson, S. Ahmedzai, B. Bergman et al., "The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life instrument for use in international clinical trials in oncology," *JNCI Journal of the National Cancer Institute*, vol. 85, no. 5, pp. 365–376, 1993.

[30] B. Bergman, N. K. Aaronson, S. Ahmedzai, S. Kaasa, and M. Sullivan, "The EORTC QLQ-LC13: A modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials," *Lung Cancer*, vol. 12, no. 1-2, p. 139, 1995.

[31] D. Osoba, B. Zee, J. Pater, D. Warr, L. Kaizer, and J. Latreille, "Psychometric properties and responsiveness of the EORTC quality of life questionnaire (QLQ-C30) in patients with breast, ovarian and lung cancer," *Quality of Life Research*, vol. 3, no. 5, pp. 353–364, 1994.

[32] M. Groenvold, M. C. Klee, M. A. G. Sprangers, and N. K. Aaronson, "Validation of the EORTC QLC-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient–observer agreement," *Journal of Clinical Epidemiology*, vol. 50, no. 4, pp. 441–450, 1997.

[33] D. R. Cox, "Regression models and life-tables," *Journal of the Royal Statistical Society: Series B: Methodological*, vol. 34, pp. 187–220, 1972.

[34] D. Osoba, G. Rodrigues, J. Myles, B. Zee, and J. Pater, "Interpreting the significance of changes in health-related quality-of-life scores," *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, vol. 16, no. 1, pp. 139–144, 1998.
[35] J. Concato, P. Peduzzi, T. R. Holford, and A. R. Feinstein, “Importance of events per independent variable in proportional hazards analysis I. Background, goals, and general strategy,” *Journal of Clinical Epidemiology*, vol. 48, no. 12, pp. 1495–1501, 1995.

[36] P. Peduzzi, J. Concato, A. R. Feinstein, and T. R. Holford, “Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates,” *Journal of Clinical Epidemiology*, vol. 48, no. 12, pp. 1503–1510, 1995.

[37] D. T. Eton, D. L. Fairclough, D. Cella et al., “Early change in patient-reported health during lung cancer chemotherapy predicts clinical outcomes beyond those predicted by baseline report: results from Eastern Cooperative Oncology Group Study 5592,” *Journal of Clinical Oncology*, vol. 21, no. 8, pp. 1536–1543, 2003.

[38] T. M. Beer, K. Miller, B. Tombal et al., “The association between health-related quality-of-life scores and clinical outcomes in metastatic castration-resistant prostate cancer patients: exploratory analyses of AFFIRM and PREVAIL studies,” *European Journal of Cancer*, vol. 87, pp. 21–29, 2017.

[39] B. Schuster, A. Ellmann, T. Mayo et al., “Rate of individuals with clearly increased radiosensitivity rise with age both in healthy individuals and in cancer patients,” *BMC Geriatrics*, vol. 18, no. 1, p. 105, 2018.