Health related quality of life in non-fit older patients with solid tumors and prognostic factors for decline

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**ABSTRACT**

Objectives:

This study aims to investigate health-related quality of life (HRQOL) at baseline and at follow-up in non-fit older patients with cancer and to determine prognostic factors for HRQOL decline.

Methods:

A prospective Belgian multicentre (n=22) study was performed. Patients ≥70 years with a malignant tumor and abnormal G8 (≤14/17) screening tool were included. Patients underwent geriatric assessment (GA) and HRQOL evaluation with follow up at three months. Uni- and multivariate regression models were performed to determine factors associated (p<0.05) with baseline HRQOL and HRQOL decline at follow-up.

Results:

In 3673 included patients, multivariate analysis showed a lower baseline HRQOL in patients with younger age, poor Eastern Cooperative Oncology Group – Performance Status (ECOG-PS), specific tumors types (gastrointestinal, gynaecological and thorax), higher stage, worse functional status and presence of pain, fatigue, depression and malnutrition.

During treatment (n=2972), improvement in HRQOL was observed in 1037 patients (35%) and a decline in 838 patients (28.2%). In multivariate analysis, stage and presence of baseline comorbidities, pain, fatigue or malnutrition were associated with HRQOL evolution.

Conclusion

Baseline HRQOL in non-fit older cancer patients depends on tumor and age related parameters. During follow-up, HRQOL improved in one third of patients, indicating that they may benefit from cancer treatment while one quarter demonstrated a HRQOL decline for which prognostic factors were identified.

KEYWORDS: older patients, cancer, health-related quality of life, geriatric domains, prognostic factors

**BODY TEXT**

Introduction

Health-related quality of life (HRQOL) is an important parameter for patients with cancer, because it is influenced by the disease and by its treatment.1

Evaluation of baseline and follow-up HRQOL provides knowledge of the effects of the disease and treatment on the patient’s sense of well-being and may stimulate physician-patient communication, resulting in a better shared decision making.2-5 In addition baseline HRQOL may be prognostic for chemotherapy response and for survival.6-8

HRQOL is an even more important endpoint for older patients with cancer.9,10 Older patients with cancer often give preference to maintenance or improvement of HRQOL rather than an increase in survival.11-12 As a consequence, older patients are less willing to accept severe toxicity and reduced HRQOL. In non-fit older patients with cancer this may complicate treatment decisions even more because HRQOL decreases with increased frailty 13

Knowledge of baseline HRQOL and its evolution (i.e. improvement, maintenance, deterioration) during treatment as well as of factors influencing HRQOL is therefore essential for treatment decisions in (non-fit) older patients with cancer and may guide appropriate interventions and care. In addition baseline HRQOL may be a possible stratification factor in studies specific for older patients with cancer in order to reduce imbalance between treatment arms.

For these reasons, the present study aims to investigate baseline and follow-up HRQOL in non-fit older patients with solid tumors and to identify prognostic clinical and age-related characteristics for HRQOL decline.

Patients and methods

Patient population

A prospective, multicenter, observational cohort study with the main goal to investigate the adherence to geriatric recommendations based on a geriatric assessment (GA), was performed in 22 hospitals (8 academic, 14 non-academic) in Belgium from November 2012 until February 2015.14 Patients 70 years and older with a solid tumor (including breast cancer, central nervous system tumors, carcinoma of unknown primary, digestive system tumors, gynaecologic tumors, head and neck tumors, musculoskeletal tumors, skin tumors, thorax tumors and genitourinary tumors) or hematologic malignancy were included at the time a treatment decision (surgery, systemic therapy, radiotherapy, hormonal therapy, other therapy or a combination) had to be made. The study was approved by the ethical committee of all participating centers (B322201215495). Here we present a substudy focusing on HRQOL at baseline and during follow-up in this large cohort.

Baseline assessment

At baseline, all patients were screened using the G8 screening tool.15,16

In the present analysis only non-fit patients with an abnormal G8 screening (score ≤14/17) were included, since fit patients with a normal G8 were not referred for baseline GA or HRQOL assessment.

All included patients underwent a baseline GA, as previously described.14,17 This GA included following geriatric domains: functional status by activities of daily living (ADL)18 and instrumental activities of daily living (iADL)19, the presence of falls in the past year, the presence of pain and fatigue using a visual analogue score (VAS), cognition by mini mental state examination (MMSE)20, mental status using the geriatric depression scale (GDS-15)21, nutritional status using the mini nutritional assessment – short form (MNA-SF)22, comorbidities using the Charlson Comorbidity index23 and polypharmacy by the number of drugs taken the week before inclusion.24

In addition a HRQOL evaluation was performed using the European Organization for Research and Treatment Quality of Life Questionnaire core 30 (EORTC QLQ-C30) Global Health Status Scale (GHS). For the present study, the 2 general questions 29 and 30 were selected: “How would you rate your overall health during the past week?” and “How would you rate your overall quality of life during the past week?”. Patients answer these two questions by means of 7-point Likert scales and the two scores are combined to define the GHS. The GHS score is linearly transformed to a 0-100 score to facilitate statistical interpretation. A higher HRQOL is reported by a higher GHS score. The GHS scale is one of the most frequently used QLQ-C30 subscales and administration of this instrument has been used as the primary endpoint in various trials.25,26

Classical patient characteristics such as age and gender as well as oncologic parameters such as Eastern Cooperative Oncology Group - Performance Status (ECOG-PS), tumor characteristics (type and stage), and treatment details (surgery / systemic therapy/ radiotherapy / hormonal therapy / other therapy/ combination) were recorded.

Follow-up evaluation

Three months (+/- two weeks) after the baseline assessment, HRQOL was reassessed using the same questions.

Statistical analysis

Unadjusted median scores and inter quartiles (75th and 25th percentiles) of the baseline HRQOL score were plotted by tumor group.

To assess statistically the association between baseline HRQOL score and different patient, tumor and age-related characteristics, uni- and multivariate normal regression models were applied. The final multivariate model was achieved in two steps. First, at univariate level, the association between baseline HRQOL and patient, tumor and age-related characteristics was assessed for each patient. With regards to treatment, patients receiving chemotherapy alone were compared to patients not receiving chemotherapy treatment or receiving a combination of treatments. Those variables statistically significantly at univariate level were included in the final multivariate model. Results were reported with the least mean square difference (ß), its 95% confidence interval (CI) and the p-value. A HRQOL difference of ten points or more between different subgroups was considered clinical significant.27

HRQOL change was defined as the difference between follow-up and baseline HRQOL score and categorized in three groups; HRQOL decline (<-10), HRQOL improvement (>10) and no HRQOL change over time (≥-10 and ≤10). Osoba et al. defined a threshold of 10 points to categorise patients as clinically improved or deteriorated on any of the EORTC HRQOL scales.27 A dummy variable was created to categorize patients that reported a HRQOL decline versus those patients that did not report a HRQOL decline; i.e. improvement and no change.

To assess statistically the association between HRQOL decline versus no HRQOL decline (improvement and no change) and patient, tumor and age-related characteristics, uni- and multivariate logistic regression models were applied. The final multivariate model was achieved in two steps. First, at univariate model, HRQOL decline versus no decline was assessed for each patient characteristic separately. Those variables statistically significant at univariate level were included in the final multivariate model. Results were reported with the odds ratio (OR), its 95% confidence interval (CI) and the p-value. OR determine whether a particular exposure is a risk factor for an outcome (i.e. QOL decline or not).28 If an OR=1 then exposure does not affect odds of outcome; OR>1 then exposure associated with higher odds of outcome; OR<1 then exposure associated with lower odds of outcome. The level of significance was set at p=0.05.

For the regression modeling, missing patient values were imputed using chained equations (MICE).29 This method is based on fully conditional specification (FCS) where each incomplete variable is imputed by a separate model. All analysis were performed with Stata.

Results

Patient and tumour characteristics

The patient flow is presented in figure 1.

Of the 8,451 patients included in this study, 5,907 had an abnormal G8 (≤14/17). For the present HRQOL analysis we excluded patients with a hematologic malignancy (n=498), patients with ophthalmologic tumors (n=2) and patients who were deceased or lost to follow-up after three months (n=1499).

Of the remaining 3,908 patients baseline HRQOL was available for 3,673 patients (94%) and both baseline and follow-up HRQOL were available for 2,972 (76%).

Patient characteristics and GA results are presented in table 1.

Baseline HRQOL

At baseline, the highest median HRQOL was observed in malignant tumors of the skin and the lowest in tumors of the thorax, the musculoskeletal system, the genitourinary system, the gynaecological system and carcinomas of unknown primary (CUP). Median HRQOL and interquartile range (25-75 percentages) as well as minimum and maximum by tumor type are presented in figure 2.

Table 2 presents the results of a uni- and multivariate analysis assessing the statistical significant correlation between baseline HRQOL and patient, tumor and age-related characteristics.

In the univariate analysis, statistical significant associations (p<0.05) were observed between baseline HRQOL and different baseline patient and tumor characteristics such as age, ECOG-PS, tumor type, time of inclusion (new diagnosis versus progression/relapse), stage and planned chemotherapy treatment, Moreover, all age-related characteristics except comorbidity were significantly associated with baseline HRQOL.

In the multivariate analysis assessing the baseline correlation, increasing age was associated with a higher HRQOL (p<0.001). Patients with a bad ECOG-PS (≥2) had a significantly worse HRQOL compared to patients with a good ECOG-PS (0 or 1) (p<0.001). Patients with gastrointestinal tumours, gynecological tumours and tumours of the thorax had significantly lower HRQOL compared to older patients with breast cancer (p-values 0.030; 0.017 and 0.017 respectively). In addition patients with higher stage had worse baseline HRQOL when compared to patients with stage I (p=0.004, 0.042 and 0.004 for stage II, III and IV respectively). Finally a significantly lower HRQOL was observed in patients with a dependency on IADL (p=0.006), with presence of pain (p<0.001), fatigue (p<0.001) or depression (<0.001) and with malnutrition (p<0.001). However, no clinical significant differences (>10 points) were observed for any of the tumor or age related parameters.

HRQOL at follow-up

At follow-up, HRQOL improved with ≥10 points in 1,037/2,972 patients (35%) with a mean improvement of 29.75 (CI 28.9;30.6). HRQOL declined with ≥10 points in 838/2,972 patients (28,2%) with a mean decline of 29.4 (CI -30.4;-28.4). Patients with tumors of the central nervous system (CNS) experienced most frequently a decline in HRQOL (40%). A HRQOL improvement was observed most frequently for older patients with musculoskeletal tumors (45.5%) and carcinoma of unknown primary (45%). HRQOL change per tumor type is listed in appendix A.

Table 3 describes the uni- and multivariate analysis to determine which patient, tumor and age-related characteristics are prognostic for HRQOL decline.

In the multivariate analysis, the odds of experiencing a HRQOL deterioration was higher for those patients who were diagnosed with stage III carcinoma patients (28%: p=0.025) compared to those patients who were diagnosed with stage I carcinoma at baseline, The odds of experiencing a HRQOL deterioration during treatment was lower for those patients who reported pain (22%; p=0.016), fatigue (38%: p=0.001), malnutrition (22%: p=0.044) at baseline compared to those patients who reported no pain, no fatigue or malnutrition at baseline. The odds of experiencing a HRQOL deterioration during treatment was higher for those patients who reported at baseline presence of comorbidity (17%; p=0.043) compared to those patients who did not experience comorbidities at baseline

Discussion

This Belgian prospective study is, to our knowledge, the largest to investigate HRQOL in older patients with solid tumors, who are considered unfit according to the G8 screening tool.

In a multivariate analysis of this study, baseline HRQOL was influenced by patient characteristics such as age and ECOG-PS, tumor characteristics such as type and stage and age related characteristics such as functional status, pain, fatigue, mental status and nutritional status. The findings of our study confirm previous findings in smaller studies where performance status, tumor type, functional status, pain, fatigue and depression were prognostic for baseline HRQOL.30-36 The association between nutritional status and HRQOL has also been reported in the general older population and in a non small cell lung cancer population.37,38 Interestingly, in our large study

HRQOL increased with increasing age, which can be explained by some of the oldest patients reporting an extremely good HRQOL. The phenomenon of older patients reporting very good HRQOL has been observed previously in a non-cancer population39 and could be explained by adaptation which leads to a change of the personal goals and standards.40 Additionally our study could not confirm the relationship between comorbidity and baseline HRQOL which was reported previously in two smaller studies.33,34

At three months follow-up, our study observed a clinical improvement (>10) in HRQOL in one third of older patients with cancer, which was consistent with the observations of Puts et al at 12 months follow-up.41 In addition Ronning et al observed significant improvement in HRQOL at three months after surgery for colorectal cancer, also in the subgroup of frail patients according to GA.42 We can therefore conclude that a substantial proportion of older patients with cancer demonstrate an improvement in HRQOL during cancer treatment. This is an important observation both for treating physicians and for older patients with cancer when discussing treatment options. Even if the survival benefit is low for certain older patients, an improvement in HRQOL can be considered as a reason to propose a certain treatment modality.

On the other hand, one quarter of older patients with cancer demonstrate a decline in HRQOL during cancer treatment in our study and in the studies of Puts et al and Esbensen et al.41,43 In order to identify patients at risk for such a HRQOL decline it is important to identify prognostic factors.

In the study by Puts et al, none of the sociodemographic, health or functional status variables were associated with decline in QOL during the first year after diagnosis.41 In our study patients experiencing pain, fatigue or malnutrition at baseline demonstrated a significant lower risk of HRQOL decline in multivariate analysis. This is certainly reassuring since these patients have a lower baseline HRQOL. A possible explanation for this observation, may be that pain and malnutrition at baseline were more frequently observed in patients treated with surgery, which may have resulted in a resolution of these complaints.44 Ebensen et al identified functional status by means of ‘contact with district nurse at baseline’ and ‘need more help in daily living at baseline and mental status by means of ‘low level at hope’ as prognostic for HRQOL decline at six months.42 In our larger study, functional status by means of ADL and iADL and mental status by means of GDS-15 were not prognostic for HRQOL decline at three months.

Finally, our study demonstrated that patient comorbidities at baseline had a higher risk of HRQOL decline than patients with no comorbidities, although there was no significant difference at baseline between these two groups. This observation indicates that patients with comorbidities should be followed with extreme caution during follow-up.

Our study has several limitations. First of all we included only patients considered unfit according to the G8, which is not a perfect screening tool with a sensitivity of 65-92%.16 In addition the G8 on itself has shown to be predictive for quality-adjusted survival in older head and neck cancer patients.45 Secondly, we excluded patients with hematologic malignancies because they were considered as a different entity. In addition we excluded patients who had died or were lost to follow-up at three months. These may have been some of the frailest patients, but on the other hand a life expectancy of three months is often regarded necessary to consider treatment for cancer. Thirdly, the population in this study is heterogeneous, but this may also be a strength since our results are applicable to a large population of older patients with cancer. Finally the follow-up of three months is quite short and HRQOL studies with longer follow-up in older patients with cancer are needed.

In conclusion, the results of this large Belgian study demonstrate that baseline HRQOL is influenced by different tumor, patient and geriatric characteristics and may therefore be an interesting stratification factor for further studies in older patients with cancer. An important subset of non-fit older patients with cancer reported an improvement of HRQOL at follow-up. Since this is an important end point for older patients with cancer, treatment decisions should not be based on age or the presence of an abnormal screening tool. We also identified the presence of comorbidities as a prognostic factor for HRQOL decline at follow-up, which should be included in the treatment discussion with these patients.

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