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Quality of life after brachytherapy in patients with glioblastoma multiforme

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Abstract

As quality of life (QoL) is perhaps the most important outcome for patients treated for glioblastoma multiforme (GBM), we measured QoL in GBM patients after brachytherapy. QoL was assessed by questionnaires for both patients and partners before brachytherapy and at various times during follow-up in 21 GBM patients by an extension of the Rotterdam Symptom Checklist (e-RSCL), consisting of four subscales. The Karnofsky Performance Scale (KPS) was also measured. Analysis of variance was done to evaluate the direct effect of brachytherapy (visit 1–2, short-term) and during follow up (visit 1–4, longer-term). Significant short-term effects were found for two subscales of the e-RSCL. Longer-term effects were found for all four subscales and for the KPS. A high correlation between partner and patient's QoL assessment was found. QoL in GBM patients after brachytherapy can therefore be carefully monitored with a subjective instrument such as the e-RSCL. Patients and partners experience QoL equally.

Keywords: Quality of life; Glioblastoma multiforme; Brachytherapy

1. Introduction

As the median survival of patients with glioblastoma multiforme (GBM) is less than one year, quality of life (QoL) is perhaps the most important outcome for patients and (palliative) treatment should therefore not interfere with this.

Brachytherapy or interstitial radiotherapy has been developed as an additional internal boost of radiation to improve local tumour control in patients with malignant astrocytoma. However, brachytherapy for malignant glioma has shown only moderate or no benefit at all in length of survival [1–3]. As brachytherapy is an invasive therapy, it may have a large impact on the patient and relatives. Treatment evaluation will finally become more balanced if social, mental and physical functioning as an outcome is incorporated into studies and if these items are combined with other items such as length of survival, morbidity and mortality.

The aim of the present study was to measure and follow prospectively the QoL in GBM patients treated with brachytherapy as an adjunct to standard treatment. Secondary research questions concerned the agreement between patients and their partners, and the relation between subjective QoL measurements such as the Rotterdam Symptom Checklist (e-RSCL) and more observer-rated measurements such as, for example, performance measured by the Karnofsky Performance Scale (KPS).

2. Patients and methods

2.1. Patients and partners

This study included 22 patients with a primary GBM according to criteria of Daumas–Duport (astrocytoma grade 4 according to the World Health Organisation) who underwent a brachytherapy boost (40 Gy) after

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cytoreductive surgery and external-beam radiotherapy (EBRT; 60 Gy in 6 weeks) between 1994 and 1999. Eligibility criteria for brachytherapy were (1) supratentorial, well-demarcated GBM with a maximal diameter of 5 cm after EBRT; (2) age >30 years (increased survival for young patients); (3) KPS at least 70; (4) non-midline tumour (3). Patients agreed to complete the QoL questionnaires during this study. The partners or relatives of all included patients were requested to participate in the study and to complete the partner QoL questionnaires. These questions concerned the patient's condition. The partner or relative who completed the questionnaire had to be the same person during the whole study. The partner was usually the husband, wife or child. Occasionally a very close relative completed the questionnaires.

2.2. Methods

2.2.1. Brachytherapy

Brachytherapy usually took place 8–10 weeks after cytoreductive surgery and has been described elsewhere [3]. In summary, parallel-unloaded catheters were placed stereotactically under general anaesthesia. After verification of the position, the catheters were loaded with ^{192}Ir; the patient was kept in a shielded room for approximately 4 days until the end of the radiation. Catheters were thereafter simply removed on the neurosurgical ward. Total hospitalisation time was approximately 10 days. Corticosteroids were given for up to 2 weeks after treatment to suppress acute effects of the brachytherapy. Patient and implant characteristics are summarised in Table 1.

2.2.2. Measurements

2.2.2.1. RSCL questionnaire. The original Rotterdam Symptom Checklist (o-RSCL), a well-validated QoL instrument [4], was the core instrument for measuring QoL in this study. This is a patient and partner, 4-point Likert-type questionnaire covering four domains (subscales): physical symptom distress, psychological distress, activity level and overall evaluation of life quality. To evaluate more specifically the QoL for brain tumour patients, a brain tumour module consisting of 17 disease-related items, developed for our brachytherapy patients and their partners, was added. The generation and selection of disease-related items was based on extensive pilot interviews with GBM patients who had undergone brachytherapy before this study started, administered by the senior author (JCJMH), who also developed the o-RSCL [4]. These disease-related items were tested by internal-consistency analysis to see whether they could be added to the domain of physical symptom distress or psychological distress (see statistics and Appendix). Items not belonging to either of these domains were omitted. The new extended instrument (e-RSCL) was validated and used for this study. A lower (e)-RSCL-score corresponds to better function or fewer complaints.

Table 1
Patient and implant characteristics

No. of patients	22
Mean age (years)	55 (36–72)
Patient's age >45 years	86%
M:F ratio	3.2:1
KPS ⩾90	17 (81%)
Localization:	
Frontal	7
Parietal	9
Temporal	3
Occipital	2
Mean volume (cm^3)	35 (13–63)
Mean no. of catheters	7 (4–11)
Mean initial dose rate (cGy/h)	60 (42–100)
Median survival[a], whole group (months)	15 (4–36)

KPS, Karnofsky Performance Scale. Figures in parentheses are ranges.

[a] From the time of the diagnosis (usually 8–10 weeks before the brachytherapy).

2.2.2.2. Observer-assessed variables. The KPS (score 0–100) [5], Mini Mental State Exam (MMSE; score 0–30) [6] and Barthel Index for Activities of Daily Living (Barthel–ADL; score 0–20) [7] were recorded, serving as observer-assessed variables to measure performance, cognition and activity. For the KPS, MMSE and Barthel–ADL a higher score corresponds to better function.

2.2.3. Study design

Patient and partner were asked to complete the e-RSCL a few days before the brachytherapy (baseline, visit 1), at discharge usually 1 week after the brachytherapy (visit 2), every 3 months during the first year (visits 3–6), and every 6 months thereafter. Patients and partners completed the forms (self-administration) separately on the neurosurgical ward (visit 1–2) and in the hospital during their outpatient visits in the presence of a trial nurse after the doctor's visit. The forms were thereafter blindly added to a database. If a focal deficit prevented the patient from completing the questionnaires, the trial nurse assisted. Partners were under no circumstances allowed to help patients. If a patient was unable to visit the outpatient clinic as scheduled, the doctor and the trial nurse visited him or her at home. Due to disease progression, most patients were unable to complete the questionnaire during the last period of their life. Under these circumstances, the partner was asked to continue completing the partner module until the patient died. The first author (RWK) followed all patients at all visits.

2.2.4. Statistical analysis

Analysis of variance (ANOVA) was performed to test for significant changes over time in all variables. Due to the large dropout of patients, we performed separate analyses for short-term (visits 1 and 2) and long-term (visit 1–4) effects. As the study was small, we chose the level of significance as 10% to keep sufficient power. In the ANOVA of the e-RSCL, a factor 'source of information' was added to test for significant differences between patients and partners. In case the sphericity assumption was not tenable (Mauchly's test), the Huynh–Feldt adjustment for degrees of freedom (df) was applied.

To validate the e-RSCL, all variables were transformed to a 0–100 scale. The internal consistency of the o-RSCL and e-RSCL scale were assessed with Cronbach's α, using the data from the second visit. We considered 0.70 as the minimal α-coefficient for a reliable scale [8].

QoL assessments by patients and partners were compared with Pearson's correlation coefficient (CC). Pearson's CC were also used to compare the observer-assessed variables with the e-RSCL at the second visit.

3. Results

3.1. Questionnaire response

21 patients (95%) and 19 partners (86%) completed the QoL questionnaires at the first visit (Fig. 1). The response rate for the questionnaires decreased during the follow up. At visit 4, 14 patients and partners completed the questionnaires (67%), at visit 5 only 9 patients (53%) and at visit 6 only 8 patients (67%).

3.2. Questionnaire reliability and validity

All 17 additional items could be allocated to the o-RSCL variables physical symptom distress or psychological distress, according to their content and correlation, thus increasing reliability. Compared to the o-RSCL, Cronbach's α for all scales increased in the e-RSCL. For patients, Cronbach's α for the psychological and physical scale of the o-RSCL versus the psychological and physical scale of the e-RSCL was 0.63, 0.60 versus 0.77 and 0.84, respectively, at the first visit ($n = 21$) and 0.85, 0.83 versus 0.86 and 0.91 at the second visit ($n = 20$). For partners, Cronbach's α was 0.75, 0.68 versus 0.87 and 0.88 at the first visit and 0.81, 0.75 vs. 0.86 and 0.89 at the second visit.

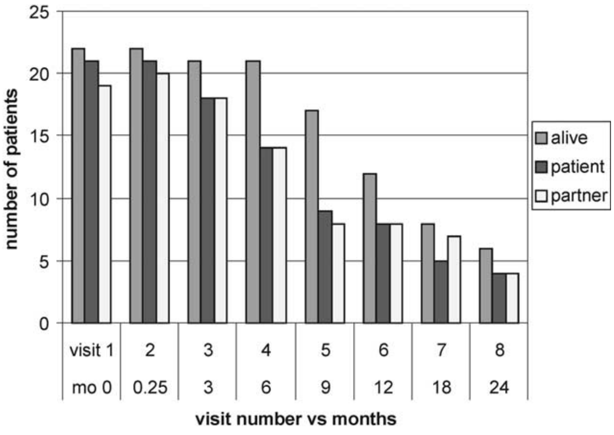

Fig. 1. Questionnaire response.

3.3. QoL before and immediately after the brachytherapy (short-term effects, visit 1–2)

Scores of 18 patients and partners who both completed the first two visits were available for the analysis of short-term effects. ANOVA showed a main effect for the factor 'time' (first versus second visit) on activity level (F = 8.38; df = 1; $P = 0.010$), and a main effect for the factor 'source of information' (patient versus partner) on the overall evaluation of life quality (F = 5.27; df = 1; $P = 0.035$). Main effects on other variables were not significant, and there were no significant 'time×source of information' interaction effects on any of the outcome variables. The Barthel–ADL showed no variance and had to be omitted from the statistical analysis.

3.4. QoL during follow-up (longer term effects, visit 1–4)

Average scores of patients and partners who both completed the first four visits are presented in Table 2. Main effects for the factor 'time' (i.e. the first to the fourth visit) were found on overall evaluation of life quality (F = 2.31; df = 3; $P = 0.078$, $n = 11$), activity level (Huynh-Feldt, F = 3.46; df = 1.455; $P = 0.069$, $n = 12$), psychological distress (F = 2.42; df = 3; $P = 0.084$, $n = 12$), physical symptom distress (Huynh-Feldt, F = 4.65; df = 2.139; $P = 0.018$, $n = 12$) and KPS (Huynh-Feldt, F = 10.40, df = 1.505, $P = 0.002$, $n = 13$). The time effect on MMSE (F = 1.82; df = 2.164; $P = 0.179$, $n = 14$) was not significant. From Table 2 it appears that the significant effects all indicated deterioration of health (with KPS and MMSE scores generally decreasing, and scores of other variables generally increasing).

Main effects for the factor 'source of information' were significant only on the overall evaluation of life quality (F = 11.23; df = 1; $P = 0.007$) and psychological distress (F = 4.87; df = 1; $P = 0.05$), with partners indicating poorer life quality and more distress. There were no significant 'time×source of information' interaction effects. Baseline visits (visit 1) of patients who completed the first 4 visits did not differ from those of patients who completed fewer visits.

3.5. Comparison of patient and partner

The CC for the self-reported tests (e-RSCL) between patient and partner in equal subscales for visit 2 were

Table 2
Quality-of-life scores of patients and partners who both completed all questionnaires during the first four visits

Overall evaluation of life quality	Visit	Patients Mean	Patients S.D.	Patients *n*	Partners Mean	Partners S.D.	Partners *n*
	1	22.73	17.12	11	28.79	16.82	11
Activity level		12.55	20.55	12	10.76	18.16	12
Psychological distress		21.99	8.82	12	23.34	15.13	12
Physical symptom distress		15.90	9.83	12	16.54	10.33	12
MMSE		28.71	3.00	14			
Barthel–ADL		20.00	0.00	14			
KPS		91.92	5.60	13			
	2	27.27	17.12	11	40.91	17.26	11
Activity level		19.91	22.59	12	21.76	24.70	12
Psychological distress		23.94	11.32	12	30.79	14.72	12
Physical symptom distress		16.34	10.90	12	17.55	10.85	12
MMSE		28.57	3.03	14			
Barthel–ADL		20.00	0.00	14			
KPS		91.15	6.18	13			
	3	37.88	19.85	11	39.39	20.10	11
Activity level		14.93	18.16	12	10.42	17.36	12
Psychological distress		30.09	15.75	12	30.74	14.04	12
Physical symptom distress		20.77	10.79	12	20.97	12.46	12
MMSE		26.21	6.45	14			
Barthel–ADL		20.00	1.57	14			
KPS		87.69	10.92	13			
	4	37.88	13.10	11	40.91	25.13	11
Activity level		25.97	26.38	12	29.17	29.57	12
Psychological distress		26.66	16.48	12	34.49	19.48	12
Physical symptom distress		23.18	12.36	12	23.03	13.07	12
MMSE		26.43	8.06	14			
Barthel–ADL		19.57	1.16	14			
KPS		80.77	14.27	13			

Overall evaluation of life quality, activity level, psychological distress and physical symptom distress belong to the Extended Rotterdam Symptom Checklist. Mini Mental State Exam (MMSE), Barthel-Activities of Daily Living (ADL) and Karnofsky Performance Score (KPS) belong to the observer-assessed variables.

highly significant in all cases. For overall evaluation of life quality, physical symptom distress, psychological distress and activity level, the CC were 0.72, 0.81, 0.63 and 0.83, respectively.

3.6. Comparison of self-reported tests (e-RSCL) with observer-assessed variables

Physical symptom distress was the only subscale of the e-RSCL that correlated significantly with the KPS (CC = 0.49; $P = 0.030$, $n = 21$). Subscale of the e-RSCL that correlated significantly with the MMSE (CC = 0.48; $P = 0.033$; $n = 21$). There were no other significant correlations between self-reported tests and observer-assessed variables. During the study the observer-assessed variables remained stable for longer than did the self-reported tests.

4. Discussion

We investigated prospectively and longitudinally the QoL as assessed by patients and partners of GBM patients who underwent brachytherapy. There are several brain tumour studies in which QoL is not only expressed as performance, measured by the physician-related KPS, but also by a self-reported, multi-dimensional QoL instrument [9–21]. However, most of these studies use one single time assessment in the follow up for their analysis. For brain tumour patients treated with brachytherapy the study of Bampoe [22] is the only longitudinal and multidimensional study in a prospective randomised trial as far as we know. The only other study using more follow-up time points concerns low-grade glioma [12]. Our study not only considers QoL prospectively in GBM patients treated with brachytherapy but also takes into account the partner's view and may thus provide useful extra information, especially when the validity of patients' judgement is in question, as may be seen in those with brain tumours.

4.1. Questionnaire response

We consider a major weakness of our study to be the small sample size ($n = 22$) and a compliance of only 53%

at 9 months (visit 5), although the response rate in Bampoe's study (66%) [22] was not much higher and that of Choucair (40%) [15] was even worse. The e-RSCL is easy to complete within 10 min for healthy patients, but may take considerably more time for patients who are mentally and/or physically ill. After the doctor's visit, patients were asked to fill in the questionnaires in the presence of the trial nurse. Some patients who were in a moderate condition refused to stay any longer to fill in the questionnaires. This may explain the low compliance in particular at visit 5 (9 patients died between visit 4 and 6). Sending the questionnaires to the patient's address would have adversely influenced the results, as the separate completion of the forms was not guaranteed. Therefore we decided to accept a higher dropout at these visits. Filling in the forms before or during the doctor's visit or visiting at home by the trial nurse could have increased compliance.

One of the objectives of this study was to follow the QoL of the patients in the last phase of their life via their partners, who still completed the questionnaires. This objective was, however, not realised, as most partners did not return the forms, even after repeated calls. Apparently, they gave low priority to completing questionnaires in the last phase of their partners' life.

For short-term follow up we analysed the first two visits; for longer-term follow up we chose to analyse only the first four visits because of the still acceptable number of patients and the reasonable follow-up period. Although 14 patients and partners answered the questionnaires at the fourth visit (Fig. 1), there were only 11 of 14 couples that completed all questionnaires during the first four visits (Table 2).

As the brachytherapy study was not randomised and consisted of highly selected patients (81% of the patients with a KPS of 90–100), a control group of GBM patients with evenly matched baseline performance could not be recruited. This is another weak point of this study.

4.2. Questionnaire reliability and validity

As the internal consistency of all subscales of the o-RSCL was improved, the e-RSCL seems to be a reliable and well-validated instrument. As the e-RSCL was specially developed for this study, no earlier reliability and validity data were available, but we believe that the e-RSCL, with its addition of a brain tumour module, should be used preferentially for QoL measurements in patients with brain tumours, instead of the o-RSCL.

4.3. Short-term effects on QoL

Between visit 1 and 2, significant changes were found for activity level. Although the brachytherapy procedure was well tolerated, the deterioration in activity level means that the patients felt more dependent. The significant factor 'source of information' for the overall evaluation of life quality means that the partner experienced the impact of the brachytherapy on QoL more seriously than did the patient.

4.4. Longer-term effects on QoL

Between visit 1 and 4, significant changes were found in the overall evaluation of life quality, activity level, psychological distress, physical symptom distress and KPS. This means that within 6 months of brachytherapy both QoL and performance were seriously impaired. Although the partners had more pessimistic or more critical views about the QoL in general, the differences between patients and partners were only significant for the overall evaluation of life quality and psychological distress. It is interesting that the patients experienced the serious deterioration after the brachytherapy (between visit 2 and 3) whereas the partners experienced this deterioration around the brachytherapy itself (visit 1 and 2).

The timing of the QoL assessment (1 week after treatment and then not for 3 months) does not tease out the acute effects of the brachytherapy followed by recovery by 3 months, since the questionnaire covers only the last week before the visit. Even though the patients did not complete the forms, they were seen 6 weeks after the brachytherapy in the out patient clinic. None of the patients who completed the first four visits showed acute effects.

4.5. Comparison of patients and partners

Differences in QoL experience between patients and partners were also found in other studies on diseases not affecting cognition as well in studies on brain tumours patients [13]. Patients in general rate QoL higher than partners. In our study the differences between patient and partner did not increase during the first four visits and in fact the correlation between patient and partner was highly significant. Reasons for discrepancy between this and other studies may be the selection of patients with an initially very high performance and the fact that the assumed cognitive impairment only slightly interferes with an adequate interpretation of the patient's situation. Another reason may be the fact that brain tumour patients suffer less than those with other malignancies and therefore their partners are less biased when filling in the forms, leading to higher scores. The significant correlation between patient and partner means that during the progression of the disease, when the patient may finally no longer be able to complete the forms, the partner can give a reliable impression of the patient's QoL. Moderate to high patient-proxy agreement was also reported in a recently published review of 23 health-related QoL studies [23].

4.6. Comparison of self-report questionnaires (e-RSCL) and observer-assessed variables

Several studies stress the fact that KPS and Barthel–ADL are insufficient measures for the assessment of health-related QoL [21]. They fall short of the criteria required by the World Health Organisation's definition of health: '… a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.'

During the follow up the discrepancy between the observer-assessed variables and the self-reported questionnaires increased, which is in our opinion not surprising in patients with brain tumours. This discrepancy was due to a ceiling effect for the observer-assessed variables, in particular the KPS [24], which has been noted by other investigators who used a multidimensional instrument [25]. It means that performance is preserved longer than QoL, which is in general the rule unless the tumour is directly affecting motor activities by its location.

4.7. The effect of treatment

There are different opinions about the effects of radiotherapy on cognition and QoL in general. Some reports stress the damage caused by radiotherapy on cognitive function in patients with (low-grade) tumours [11,12,26,27]. Other studies found no effect of radiotherapy on cognitive function in (low-grade) tumours [9,12,16]. In a study of long-term survivors of high-grade glioma after treatment with chemotherapy and radiotherapy, most had severe cognitive impairment. However, since this impairment was measured at least 5 years after the diagnosis was made, it was impossible to determine whether it could be attributed to 'progression of the disease' or to late side-effects of either the radiotherapy or the chemotherapy [5]. In our study, the survival was too short to reach a conclusion about cognitive function.

In the study of Bampoe [22] there were no significant differences in QoL between the implant and non-implant groups. Compared to samples from a normal population and to samples from studies with tumours at different locations not in the brain [4], the psychological distress in our study was relatively high. This finding is in agreement with the published reports of generally high levels of psychological distress in brain tumour patients [11,13,28]. Whether this is a tendency in general in such patients or in brachytherapy patients in particular cannot be answered by the current study as a control group was not investigated. We believe, however, that the psychological impact of brachytherapy, which has no proven benefit in high-grade glioma, is considerable, as indicated by the patients' partners. Brachytherapy should therefore be used only cautiously.

Appendix. Extended Rotterdam Symptom Checklist (e-RSCL) for patients as used in this study

First part (not bold): original Rotterdam Symptom Checklist (o-RSCL); second part (bold): 17 additional disease-related items resulting in the e-RSCL. Partners received an identical questionnaire. Last column: domain attributed to; phys: physical symptom distress; psych: psychological distress; act level: activity level; overall eval: overall evaluation of life quality.

Date: During the last week, did you suffer from:	e-RSCL not at all	a little	pretty	very much	domain (not in hand-out)
lack of appetite	not at all	a little	pretty	very much	phys
irritability	not at all	a little	pretty	very much	psych
tiredness	not at all	a little	pretty	very much	phys
worrying	not at all	a little	pretty	very much	psych
sore muscles	not at all	a little	pretty	very much	phys
depressed mood	not at all	a little	pretty	very much	psych
lack of energy	not at all	a little	pretty	very much	phys
low back pain	not at all	a little	pretty	very much	phys
nervousness	not at all	a little	pretty	very much	psych
nausea	not at all	a little	pretty	very much	phys
despairing about the future	not at all	a little	pretty	very much	psych
difficulty sleeping	not at all	a little	pretty	very much	phys
headaches	not at all	a little	pretty	very much	phys

vomiting	not at all	a little	pretty	very much	phys
dizziness	not at all	a little	pretty	very much	phys
sore mouth/pain when swallowing	not at all	a little	pretty	very much	phys
anxiety	not at all	a little	pretty	very much	psych
decreased sexual interest	not at all	a little	pretty	very much	phys
heartburn/belching (acid indigestion)	not at all	a little	pretty	very much	phys
shivering	not at all	a little	pretty	very much	phys
tingling hands or feet	not at all	a little	pretty	very much	phys
abdominal aches	not at all	a little	pretty	very much	phys
tension	not at all	a little	pretty	very much	psych
loss of hair	not at all	a little	pretty	very much	phys
burning/sore eyes	not at all	a little	pretty	very much	phys
difficulty concentrating	not at all	a little	pretty	very much	phys
shortness of breath	not at all	a little	pretty	very much	phys
dry mouth	not at all	a little	pretty	very much	phys
diarrhoea	not at all	a little	pretty	very much	phys
constipation	not at all	a little	pretty	very much	phys
palpitations	not at all	a little	pretty	very much	phys
a tired feeling in the head	not at all	a little	pretty	very much	phys
sound intolerance	not at all	a little	pretty	very much	phys
light intolerance	not at all	a little	pretty	very much	phys
crying fits	not at all	a little	pretty	very much	psych
worries whether things will turn out OK	not at all	a little	pretty	very much	psych
sore skin	not at all	a little	pretty	very much	phys
the feeling that it is too much	not at all	a little	pretty	very much	psych
difficulty expressing yourself	not at all	a little	pretty	very much	phys
an unreal feeling	not at all	a little	pretty	very much	psych
an unsafe feeling	not at all	a little	pretty	very much	psych
difficulty writing	not at all	a little	pretty	very much	phys
difficulty reading	not at all	a little	pretty	very much	phys
not being able to keep your attention	not at all	a little	pretty	very much	phys
forgetfulness	not at all	a little	pretty	very much	phys
slowness	not at all	a little	pretty	very much	phys
incontinence	not at all	a little	pretty	very much	phys
difficulty seeing	not at all	a little	pretty	very much	phys

Please mark the situation that is most appropriate to you during the last week.

	not able	not able without help	able with difficulties	able without difficulties	
care for myself (wash etc.)	0	0	0	0	act level
walk about the house	0	0	0	0	act level
light housework/household jobs	0	0	0	0	act level
climb stairs	0	0	0	0	act level
heavy housework/household jobs	0	0	0	0	act level
walk out of doors	0	0	0	0	act level
go shopping	0	0	0	0	act level
go to work	0	0	0	0	act level

How did you generally feel during the last week:	0	very good	overall eval
	0	good	
	0	pretty good	
	0	not good, not bad	
	0	pretty bad	
	0	bad	
	0	very bad	

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