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A Prospective Evaluation of Health-related Quality of Life After Skull Base Re-Irradiation

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ABSTRACT

Purpose: To report cancer control outcomes and health-related quality of life (HRQoL) outcomes after highly conformal skull based re-irradiation (re-RT).

Methods: Patients planned for curative intent re-RT to a recurrent or new skull base tumor were enrolled. HRQoL were assessed using the MD Anderson Symptom Inventory Brain Tumor (MDASI-BT) and the anterior skull base surgery quality of life (ASBQ) questionnaires.

Results: 39 patients were treated with stereotactic body RT or intensity modulated RT. Median follow-up was 14 months. Progression free survival was 71% at 1-year. There was mild clinically significant worsening of fatigue, lack of appetite and drowsiness (MDASI-BT), and physical function (ASBQ) at the end of RT, followed by recovery to baseline on subsequent follow-ups. Subjective emotions were clinically improved at 12 months, with patients reporting feeling less tense/nervous.

Conclusion: Conformal skull base re-RT is associated with mild immediate deterioration in physical function followed by rapid and sustained recovery.

1. INTRODUCTION

Local recurrence of malignant skull base tumors (SBT) poses a significant treatment challenge due to the proximity to vital structures and the high rates of morbidity and mortality associated to tumor progression (1, 2). Thus, *aggressive* local treatment is warranted for durable disease control as well as symptom palliation. Five-year disease-free survival rate of 40% have been reported for recurrent SBT treated aggressively (3). Treatment options for malignant recurrent or second primary SBT include surgery, radiotherapy, systemic therapy, or a combination of these modalities. Re-irradiation (re-RT) is traditionally considered a last resort option because of the risks of severe morbidity associated with

overdosing adjacent critical structures that often have received maximally tolerated doses. Advances in radiotherapy including intensity modulated radiotherapy (IMRT) (4, 5), proton therapy (6) and stereotactic body radiotherapy (SBRT) (7), combined with improved image guided radiotherapy (IGRT) techniques, allow for increased precision of dose delivery and hold the promise to expand the therapeutic index for skull base re-RT. In fact, emerging literature suggests that re-RT of SBT with curative doses is feasible, safe and can achieve durable local control (LC) (6, 8, 9).

In addition to disease control and physician rated toxicity outcomes, health-related quality of life (HRQoL) is a critical component of assessing head and neck cancer treatment, providing critical insight into the patient's symptoms and function (10, 11), with a focus on the patient's perspective. In this prospective study, we report cancer control outcomes (LC and progression free survival) as well as HRQoL outcomes after modern re-RT of malignant recurrent or second primary SBT.

2. METHODS

a) Patients characteristics

Patients were enrolled in a prospective institutional registry of head and neck re-RT at MD Anderson Cancer Center between December 2014 and October 2017. Inclusion criteria were as follows: (1) patients > 18 years-old, (2) recurrent or second primary tumor of the skull base, (3) documented history of skull base radiotherapy, (4) planned for curative intent re-RT, and (5) with at least 6 months follow-up. Patients treated with induction chemotherapy or concurrent systemic therapy were included. This study was approved by the institutional review board and all enrolled patients provided informed consent.

b) Radiotherapy treatment planning

The radiotherapy planning details for patients undergoing head and neck re-RT at our institution has been previously described (8). In summary, patients were treated with one of the following approaches: conventional fractionation using either IMRT/volumetric arc therapy (VMAT) or proton beam therapy (PBT), or with hypofractionated stereotactic body radiotherapy. PBT was delivered using passive scatter or active scanning intensity-modulated proton therapy. All patients had a 1-2 mm slice-thickness (1 mm for SBRT) planning computed tomography (CT) scan in treatment position using a previously described custom head and neck mask and bite block immobilization device (12). When possible, the planning CT scan was co-registered with a planning magnetic resonance, contrast-enhanced dual-energy CT, and/or positron emission tomography imaging. Multi-fraction SBRT was delivered every other day, while conventional radiotherapy was delivered using 1.8 to 2 Gy per fraction, 5 fractions per week, over 6 to 7 weeks.

c) Symptom Burden Assessment

Patient reported outcomes were measured using the MD Anderson Symptom Inventory Brain Tumor (MDASI-BT) and the anterior skull base surgery quality of life (ASBQ) questionnaires. The MDASI-BT questionnaire includes 22 symptom items and 6 interference items (3 activity and 3 mood interference items), scored from 0 to 10, with a higher score indicating a worse outcome (13). The ASBQ questionnaire consists of 36 questions divided into the 6 following domains: performance, physical function, vitality, pain, specific symptoms and influence on emotions (14). For each question, ASBQ scores range from 0 to 5, with lower scores indicating worse outcome; mean scores are calculated for

each domain. Patients filled the HRQoL questionnaires before re-RT start (baseline), at the end of treatment (EoT), as well as at 3, 6, 9 and 12 months after re-RT. Clinical follow-ups were every 3 months for year 1, every 4 months for year 2, and every 6 months for years 3 to 5. At each follow-up visit, evaluation included history, physical examination and imaging (MRI, PET-CT scan, and/or CT).

d) Statistics

Follow-up duration was defined as time from the date of diagnosis to the date of last follow-up or death. A longitudinal data analysis of MDASI-BT and ASBQ scores consisting of repeated measures mixed-effects models was conducted. Using the Benjamini–Hochberg method (15) to correct for multiple statistical testing, adjusted p-values ≤ 0.05 were considered statistically significant. Statistically significant differences resulting in at least half a standard deviation of baseline score were deemed clinically significant, based on previously described distribution-based method (16, 17). HRQoL was compared between treatment regimens (SBRT vs. conventional fractionation) and between patients that recurred vs. those that did not during the follow-up period. Kaplan Meier analysis was used for secondary outcomes of local control and progression free survival (PFS). Local control (LC) was defined as no radiographic or clinical evidence of disease progression and/or recurrence within 2-cm of the reirradiation field. Progression free survival was defined from time of re-RT completion to time of local, regional or distant progression, or death. SPSS 24 (IBM, Armonk, NY) was used for statistical analysis.

3) RESULTS

a) Patients' population and clinical outcomes

Patients and treatments' characteristics are presented in **Table 1**. Thirty-nine patients with a median age of 58 year-old (range= 33-84) were enrolled. The majority of patients (95%) had an ECOG performance status of 0-1. Most common sites of recurrence were anterior and central skull base (38%), followed by nasopharynx and retropharynx (26%), lateral skull base (23%) and sinonasal cavity (13%). Median interval between previous radiotherapy and re-RT was 29 months (range).

Twenty patients (51%) had surgical resection of their recurrence followed by adjuvant re-RT, including 15 who had flap reconstruction. Twenty-four patients (62%) were treated with conventionally fractionated IMRT or PBT to a median dose of 60 Gy (range= 40-66) in 30 fractions (range= 20-33) while the remaining 15 (38%) were treated with SBRT to a median dose of 45 Gy (27-45) in 5 fractions (range= 3-5). Radiotherapy was administered concurrently with systemic therapy (cetuximab or platinum agent) in 20 patients (51%). Ten patients (26%) received induction chemotherapy.

Median follow-up was 14 months (range= 2-36 months). Actuarial LC at 1 and 2-year was 84% and 60%, respectively. PFS at 1 and 2-year was 71% and 37% respectively (Figure 1).

b) Patient-reported Outcomes

MDASI and ASBQ questionnaires were filled at baseline, EoT, 3, 6, 9 and 12 months post re-RT by 100%, 92%, 77%, 90%, 64% and 44% of patients, respectively. The minimal important difference was 0.3 for MDASI-BT and 0.2 for ASBQ questionnaires. At EoT, there was clinically and statistically significant mild worsening of the symptoms of fatigue (baseline mean score = 2.5 [SD 0.5] vs. EoT mean = 3.4 SD 0.5], $p=0.04$), lack of appetite (1.2 SD 0.4] vs. 2.8 [SD 0.4], $p=0.004$) and drowsiness (1.8 [SD

0.4] vs. 2.7 [SD 0.4], $p=0.04$) on MDASI-BT questionnaire (**Table 2**). This was followed by rapid recovery to baseline values at all subsequent follow-ups. There was no significant deterioration in all other MDASI-BT scores including activity and mood-related measures.

Similarly for ASBQ, there was worsening of domains of physical function at EoT (4.1 [SD 0.1] vs. 3.6 [SD 0.2], $p=0.02$) (**Table 3**). These scores returned to baseline on subsequent time points. In terms of specific individual ASBQ questions, there was a mild but significant worsening of appetite (3.6 [SD 0.2] vs. 3.0 [SD 0.2], $p=0.008$), ability to walk 100 metres (4.0 [SD 0.2] vs. 3.5 [SD 0.2], $p=0.02$), as well as an increased frequency of staying in bed during the day (4.5 [SD 0.1] vs. 4.0 [SD 0.1], $p=0.03$) and feeling tired (3.7 [SD 0.2] vs. 3.1 [SD 0.2], $p=0.02$). At EOT, patients reported decreased participation in social activities (3.4 [SD 0.2] vs. 3.0 [SD 0.2], $p=0.04$), and an increased feeling their health was affecting their accomplishments (3.6 [SD 0.2] vs. 3.0 [SD 0.2], $p=0.03$). Conversely, the domain of influence on emotion improved at 12 months post-treatment compared to baseline (3.7 [SD 0.1] vs. 4.1 [SD 0.2], $p=0.02$). More specifically, patients reported feeling less tense/nervous at EoT compared to baseline (3.9 [SD 0.2] vs. 4.3 [SD 0.2], $p=0.01$), which continued to improve up to 12 months after treatment, and remained significant compared to baseline (3.8 [SD 0.2] vs. 4.4 [SD 0.2], $p=0.003$).

There was no detectable difference in MDASI-BT and ASBQ scores between patients treated with conventionally fractionated RT and SBRT. Notably, no differences were observed between patients who developed local recurrence and those who did not. Figure 2 shows comparative MDASI-BT trajectory for selected scores between conventionally fractionated RT vs. SBRT, as well as between LR vs. no LR.

Figure 3 shows comparative MDASI-BT trajectory for selected scores between conventionally fractionated RT vs. SBRT, as well as between LR vs. no LR.

4) DISCUSSION

To our knowledge, this is the first prospective report dedicated to HRQoL after skull base re-RT. We report a mild but significant deterioration of patient-reported symptoms of appetite, taste and fatigue immediately following ultra-conformal skull base re-RT, followed by a return to baseline scores at 3 months post-treatment. In addition, there was an improvement in the emotional domain with patients feeling less nervous and less worried at 12 months after re-RT compared to the pre-treatment baseline.

The literature on HRQoL after management of skull base tumors is limited to primarily surgical series typically combining outcomes of new and recurrent skull base disease, as well as benign and malignant tumors (14, 18-22). In these surgical series, only a minority of patients has typically received radiotherapy. While the use of radiotherapy was generally associated with adverse quality of life of outcomes in these series, radiotherapy details, including technique and/or dose/fractionation, are not described (14, 18). Abergel et al. prospectively evaluated HRQoL in patients who underwent anterior skull base surgery (23), of which 41% received radiotherapy and only 36% were treated for recurrent disease. Adjuvant radiotherapy was associated with worse outcomes in 4 ASBQ domains (physical functioning, role of performance, vitality and specific symptoms) at 6 months post-operatively. These domains subsequently returned to baseline at 12 months post-operatively. This compares to a return to baseline values at 3 months in our cohort of patients in which all were treated with highly conformal radiotherapy. The extent to which surgery impacts recovery time is unclear since 51% of our patients

received surgery and no differences were found between the surgery and non-surgery groups. Interestingly, Abergel et al. also reported an overall improvement in the emotional domain at 6-12 months post-operatively compared to pre-operative values (23). In our cohort, the overall improvement in the emotional domain of ASBQ was associated with specific improvements in feeling less nervous/tense and feeling less worried. Overall, these findings, which present the first known evaluation dedicated to the assessment of HRQoL after skull base reirradiation, mirror surgical series showing no deterioration of HRQoL scores within 12 months after local therapy for recurrent skull base tumors.

The stability of HRQoL and symptom-function scores after skull base reirradiation is notable in that it demonstrates that the delivery of curative doses to treat patients with larger skull base tumors and tumors deemed unresectable is feasible and well tolerated. The delivery of high dose to the skull base without exceeding nearby critical structures tolerance is made possible by the advent of highly conformal radiotherapy techniques such as IMRT, SBRT and proton therapy coupled with advancements in IGRT (24). In our experience, each conformal radiotherapy approach offers distinct advantages and has unique clinical applications. IMRT and VMAT are photon-based techniques that can achieve steep dose gradients towards adjacent critical structures such as the brainstem and are well suited to treat irregularly shaped skull base tumors (4, 5). SBRT further capitalizes on IMRT/VMAT by utilizing precise image guidance to deliver very high and ablative doses in fewer treatments to smaller skull base lesions (7, 25, 26). In centers with access to heavy ion accelerators, PBT is considered an attractive option to treat skull base tumors because the unique physical beam characteristics of protons produces a sharp dose drop off at the edge of the target and minimal exit dose beyond the tumor thereby minimizing low dose radiation exposure (6). We previously demonstrated the use of these highly conformal approaches in patients with

retropharyngeal node recurrences provided excellent local control and was safe and well tolerated (7). Similarly, Krengli et al, evaluated patients with recurrent benign and malignant skull base tumors amenable to single session and/or multi-fraction stereotactic radiosurgery and demonstrated that treatment was tolerated and effective (8). The current cohort differs from prior studies in that the majority of patients reported here have larger tumors (median 23.7 cc vs. 8.1 cc from Pollard et al.) involving the anterior, central and postero-lateral skull base locations. Although we did not identify detectable differences in HRQoL measures among techniques or between conventionally fractionated (IMRT & PBT) and hypofractionated (SBRT) regimens, a direct comparison is limited by the small sample size of this study. Literature on clinical outcomes of skull base re-RT remains embryonic and future studies focusing on comparison of outcomes and optimal selection of treatment strategy are needed.

HRQoL has become an essential part of the assessment of head and neck cancer treatment strategies (27, 28). The recovery of patient function and return to normal activities are recognized as crucial outcomes of survivorship. While the prognosis of locally recurrent or second-primary tumors in previously irradiated fields has been poor historically, the emergence of potentially curative re-RT strategies offers the possibility of durable local control with reduced toxicity risk. Coupled with innovations in surgical techniques (29) and tailored systemic therapy options (30), long-term disease control and survival in these patients are expected to improve significantly in the future, making HRQoL a valuable tool to compare the effectiveness of therapeutic options, select the optimal treatment strategy, and guide treatment individualization.

Our study is limited by its small sample size and thus subject to inherent selection bias; however, given the relative rarity of skull base re-RT and scant literature, the study is among the largest reports of skull base reRT. Pre-operative HRQoL for those who received surgery was not assessed in this study. Although this data would have been informative to assess the impact of combined modality therapy, the lack of difference in baseline scores between surgery and non-surgery patients and the low symptom and function burden scores at baseline suggest a mild impact, if any, of the surgery on the HRQoL measures. In addition, results of HRQoL outcomes in this study were evaluated at the group level using a mixed linear model; while this is the most frequently used method for assessed of longitudinal changes in HRQoL, this method has the limitation of potentially masking individual deteriorations of HRQoL. Furthermore, while the use induction or concurrent systemic treatment likely contributed to the heterogeneity of scores in our cohorts, this treatment intensification is expected to further deteriorate HRQoL in comparison to re-RT alone. This is all the more reassuring, given that the observed HRQoL trajectory shows excellent treatment tolerability.

In conclusion, this study suggests overall excellent tolerance of patients to highly conformal skull base re-RT. Both conventionally fractionated and SBRT radiation techniques were associated with minimal, immediate post-RT deterioration in specific symptoms and physical function followed by rapid recovery at 3 months post-treatment. The influence of emotions (feeling nervous, or feeling worried) was significantly improved post-treatment compared to baseline. These findings will need to be confirmed in subsequent, larger studies.

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Table 1. Baseline patients and treatments characteristic

Age (median, range); y	58	33-84
Gender (N; %)		
Female	16	41%
Male	23	59%
Performance status (N; %)		
0	20	51%
1	17	44%
2	2	5%
Initial site of disease (N; %)		
Skull base/Sinonasal/periorbital	12	31%
Nasopharynx/retropharynx	9	23%
Skin	7	18%
Parotid	5	13%
Oropharynx/Larynx/Oral cavity	4	10%
Neck	2	5%
Histology (N; %)		
SCC	21	54%
Adenoid cystic	4	10%
SNUC	2	5%
Olfactory neuroblastoma	2	5%
Carcinoma ex-pleomorphic adenoma	2	5%
Other	8	21%
Site of recurrence (N; %)		
Anterior/Central skull base	15	38%
Nasopharynx/retropharynx	10	26%
Lateral skull base	9	23%
Sinonasal	5	13%
Surgery at recurrence (N; %)	20	51%
Surgical flap at recurrence (N; %)	15	38%
Interval time between RT (median; range)	29	4-491
ReRT technique (N; %)		
IMRT	14	36%
Proton	10	26%
SBRT	15	38%
Dose (median, range); Gy		
Conventional	60	40-66
SBRT	45	27-45
Fractions (median, range)		
Conventional	30	20-33
SBRT	5	3-5
Concurrent systemic therapy (N; %)	20	51%

Skull base recurrent sites were classified according to the epicenter of the recurrence: Anterior and central skull base: orbit, nasolacrimal duct, cavernous sinus, clivus, Meckel's cave, sphenoid sinus; Nasopharynx/retropharyngeal: nasopharyngeal mucosa, retropharyngeal node and mucosa; Lateral skull base: temporal bone, parotid; Sinonasal cavity: maxillary sinus, ethmoid sinus, nasal cavity.

Table 2. Mixed model analysis of MDASI-BT scores at baseline and at each subsequent time point

	Baseline		End of Tx			3 m			6 m			9 m			12 m		
	M	SD	M	S D	Sig P- value	M	S D	Sig P- value	M	S D	Sig P- value	M	S D	Sig P- value	M	S D	Sig P- value
SYMPTOMS																	
<i>Pain</i>	2.2	0.5	2.8	0.5		1.8	0.5		2.2	0.5		2.5	0.5		2.0	0.6	
<i>Fatigue</i>	2.5	0.5	3.4	0.5	0.04	2.9	0.5		2.5	0.5		2.7	0.5		2.2	0.6	
<i>Nausea</i>	0.8	0.2	0.6	0.2		0.4	0.3		0.1	0.2		0.04	0.3		0.1	0.3	
<i>Disturbed Sleep</i>	1.7	0.3	2.0	0.4		1.7	0.4		1.3	0.4		1.4	0.4		0.9	0.5	
<i>Distress</i>	1.6	0.4	1.4	0.4		1.5	0.4		1.4	0.4		1.7	0.4		1.2	0.5	
<i>Shortness of breath</i>	0.6	0.3	0.6	0.3		0.9	0.3		0.7	0.3		0.5	0.3		0.4	0.4	
<i>Memory</i>	1.6	0.4	1.3	0.4		1.6	0.4		1.4	0.4		1.8	0.4		1.1	0.5	
<i>Lack of Appetite</i>	1.2	0.4	2.8	0.4	0.004	1.3	0.4		1.6	0.4		1.3	0.5		0.7	0.6	
<i>Drowsy</i>	1.8	0.4	2.7	0.4	0.04	1.9	0.4		1.8	0.4		1.8	0.5		1.7	0.5	
<i>Dry Mouth</i>	2.8	0.5	3.6	0.5		3.1	0.5		3.4	0.5		3.1	0.6		3.3	0.6	
<i>Sad</i>	1.5	0.3	1.1	0.3		1.4	0.3		1.4	0.3		1.5	0.4		1.4	0.4	
<i>Vomiting</i>	0.3	0.1	0.1	0.1		0.0	0.1		0.0	0.1		0.0	0.2		0.0	0.2	
<i>Numbness</i>	1.6	0.4	1.3	0.4		1.5	0.4		1.3	0.4		1.7	0.4		0.8	0.5	
<i>Weakness on one side</i>	1.1	0.3	1.2	0.4		1.2	0.4		1.5	0.4		1.1	0.4		0.6	0.5	
<i>Difficulty Understanding</i>	0.7	0.2	0.5	0.2		0.6	0.2		0.6	0.2		0.5	0.3		0.3	0.3	
<i>Difficulty Speaking</i>	1.0	0.4	1.2	0.4		1.4	0.4		1.7	0.4		1.3	0.4		1.8	0.5	
<i>Seizures</i>	0.2	0.1	0.0	0.1		0.0	0.2		0.1	0.2		0.0	0.2		0.0	0.2	
<i>Difficulty Concentrating</i>	0.7	0.3	0.9	0.3		1.0	0.3		0.9	0.3		0.8	0.3		0.8	0.4	
<i>Vision</i>	1.4	0.4	1.4	0.4		1.2	0.4		1.7	0.4		2.0	0.4		2.1	0.5	
<i>Appearance</i>	1.5	0.4	1.7	0.4		1.3	0.4		1.9	0.4		2.1	0.5		1.9	0.6	
<i>Bowel Pattern</i>	1.3	0.4	1.5	0.4		1.0	0.4		0.9	0.3		1.7	0.4		1.4	0.5	
<i>Irritability</i>	1.4	0.4	1.4	0.4		1.6	0.4		1.4	0.4		1.8	0.4		1.5	0.5	
ACTIVITY																	
<i>General Activity</i>	1.7	0.4	2.6	0.5		2.7	0.5		2.0	0.5		2.6	0.5		1.7	0.6	
<i>Work</i>	1.7	0.5	2.5	0.5		2.6	0.5		2.0	0.5		2.6	0.5		1.6	0.6	
<i>Walking</i>	1.2	0.4	2.1	0.4		1.5	0.4		1.0	0.4		1.3	0.4		1.3	0.5	
MOOD RELATED																	
<i>Relations</i>	0.9	0.3	1.3	0.4		1.1	0.4		1.3	0.4		1.9	0.4		1.3	0.5	
<i>Mood</i>	1.4	0.4	1.6	0.4		1.9	0.4		1.3	0.4		1.9	0.5		1.9	0.6	
<i>Enjoyment of Life</i>	1.4	0.4	2.1	0.4		1.7	0.5		1.7	0.4		2.3	0.5		2.1	0.6	

Table 3. Mixed model analysis of ASBQ scores for 6 relevant domains as well as for the 35 individual questions, at baseline and at each subsequent time point.

	Baseline		End of Tx			3 m			6 m			9 m			12 m		
	M	SD	M	SD	Sig P-value	M	SD	Sig P-value	M	SD	Sig P-value	M	SD	Sig P-value	M	SD	Sig P-value
6 DOMAINS																	
<i>Performance</i>	3.7	0.2	3.4	0.2		3.5	0.2		3.6	0.2		3.5	0.2		3.7	0.2	
<i>Vitality</i>	3.6	0.2	3.3	0.2		3.5	0.2		3.6	0.1		3.5	0.2		3.6	0.2	
<i>Specific Symptoms</i>	3.2	0.2	2.9	0.2		3.2	0.2		3.1	0.2		2.9	0.2		3.2	0.2	
Physical Function	4.1	0.1	3.6	0.2	0.02	3.8	0.2		4.0	0.1		3.9	0.2		4.0	0.2	
<i>Pain</i>	3.8	0.2	3.9	0.2		4.1	0.2		4.1	0.2		3.8	0.2		4.1	0.2	
Influence on emotions	3.7	0.1	3.8	0.1		3.9	0.1		3.9	0.1		3.7	0.1		4.1	0.2	0.02
35 QUESTIONS																	
<i>Gen. Performance</i>	3.7	0.2	3.4	0.2		3.4	0.2		3.6	0.2		3.6	0.2		3.7	0.2	
<i>Performance at Work</i>	3.5	0.2	3.2	0.2		3.2	0.2		3.6	0.2		3.5	0.2		3.6	0.3	
<i>Performance at Home</i>	3.6	0.2	3.4	0.2		3.4	0.2		3.5	0.2		3.5	0.2		3.6	0.2	
<i>Communication with people</i>	3.8	0.2	3.8	0.2		3.7	0.2		3.6	0.2		3.6	0.2		3.5	0.2	
Ability to carry out routine activities	4.0	0.2	3.3	0.2		3.5	0.2		3.7	0.2		3.5	0.2		3.8	0.2	
<i>Motivation to perform activities</i>	3.7	0.2	3.2	0.2		3.3	0.2		3.5	0.2		3.4	0.3		3.6	0.3	
<i>Relations with your partner</i>	4.0	0.2	3.7	0.2		3.7	0.2		4.1	0.2		3.8	0.2		3.8	0.2	
<i>Financial/ economic status</i>	3.7	0.2	3.4	0.2		3.4	0.2		3.6	0.2		3.5	0.2		3.5	0.3	
Appetite	3.6	0.2	3.0	0.2	0.008	3.6	0.2		3.8	0.2		3.5	0.2		4.0	0.3	
Sense of taste	3.3	0.2	2.5	0.2		2.9	0.2		2.9	0.2		2.8	0.3		3.1	0.3	
<i>Sense of smell</i>	3.2	0.3	3.0	0.3		3.2	0.3		3.1	0.2		2.8	0.3		3.1	0.3	
<i>Appearance</i>	3.5	0.2	3.1	0.2		3.2	0.2		3.3	0.2		3.2	0.2		3.4	0.2	
<i>Nasal secretion</i>	2.7	0.2	2.4	0.2		3.1	0.2		2.8	0.2		2.7	0.2		2.9	0.3	
<i>Eye secretion/ tears</i>	3.1	0.2	2.9	0.2		3.0	0.2		2.7	0.2		2.8	0.2		3.0	0.3	
<i>Eyesight</i>	3.2	0.2	3.0	0.2		3.6	0.2		3.1	0.2		2.8	0.2		2.9	0.3	
<i>Climb stairs</i>	3.7	0.2	3.3	0.2		3.3	0.2		3.7	0.2		3.6	0.2		3.7	0.2	
<i>Lean/ stand</i>	4.0	0.2	3.6	0.2		3.7	0.2		4.0	0.2		3.9	0.2		4.0	0.2	
Walk 100 meters	4.0	0.2	3.5	0.2	0.02	3.7	0.2		3.9	0.2		3.8	0.2		4.0	0.3	
<i>Walk 10 meters</i>	4.3	0.2	3.9	0.2		4.1	0.2		4.1	0.2		4.1	0.2		4.1	0.2	
In bed during the day	4.5	0.1	4.0	0.1	0.03	4.3	0.1		4.5	0.1		4.6	0.2		4.5	0.2	
Feel Tired	3.7	0.2	3.1	0.2	0.02	3.5	0.2		3.6	0.2		3.5	0.2		3.7	0.2	
<i>Feel Energetic</i>	3.4	0.2	3.0	0.2		3.2	0.2		3.3	0.2		3.3	0.2		3.2	0.3	
<i>Experience Pain</i>	3.6	0.2	3.8	0.2		3.7	0.2		3.9	0.2		3.6	0.2		4.0	0.3	
<i>Take Painkillers</i>	3.8	0.2	4.0	0.2		4.1	0.2		4.2	0.2		3.9	0.3		4.1	0.3	
Feel Tense/ Nervous	3.9	0.2	4.3	0.2	0.01	4.2	0.2		4.2	0.2	0.004	3.9	0.2		4.6	0.2	0.003
<i>Problem Falling Asleep</i>	3.8	0.2	4.1	0.2		4.0	0.2		4.0	0.2	NS	3.8	0.2		3.9	0.3	
Feel Worried	3.8	0.2	3.9	0.2		3.9	0.2		4.1	0.2		3.7	0.2		4.4	0.2	0.008
<i>Feel Relaxed/ Calm</i>	3.5	0.2	3.7	0.2		3.8	0.2		3.5	0.2		3.6	0.2		3.8	0.2	

<i>Participate in Social Activities</i>	3.4	0.2	3.0	0.2	0.04	3.5	0.2	3.2	0.2	3.3	0.2	3.6	0.3
<i>Performance</i>	4.1	0.2	3.6	0.2		3.8	0.2	3.9	0.2	3.8	0.2	3.9	0.3
<i>Activity</i>	4.0	0.2	3.4	0.2		3.7	0.2	3.7	0.2	3.9	0.2	4.0	0.3
<i>Accomplishment</i>	3.6	0.2	3.0	0.2	0.03	3.4	0.2	3.4	0.2	3.5	0.2	3.7	0.3
<i>Pain Interferes with Performance</i>	4.1	0.2	4.0	0.2		4.4	0.2	4.1	0.2	4.0	0.2	4.3	0.3
<i>Strong or Weak</i>	3.4	0.2	3.1	0.2		3.4	0.2	3.5	0.2	3.5	0.2	3.3	0.2
<i>Depressed or Happy</i>	3.5	0.2	3.7	0.2		3.7	0.2	3.8	0.2	3.9	0.2	4.0	0.3

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