

Quality of life priorities in patients with thyroid cancer - a multi-national EORTC phase I study

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Abstract

Background

The objectives of this study were to determine quality of life (QoL) issues that are relevant to thyroid cancer patients cross-culturally and to identify those with highest relevance to them in addition to the more general issues covered by the core QoL questionnaire EORTC QLQ-C30.

Methods

A systematic literature search provided a list of potentially relevant QoL issues to supplement the core questionnaire EORTC QLQ-C30 which is widely used in research and in care and that addresses QoL issues relevant to all groups of cancer patients. A panel of experts revised this list, and thyroid cancer patients rated the issues regarding their relevance for QoL by selecting the 25 issues they would include in a thyroid cancer specific QoL module.

Results

The literature search and expert discussion provided a list of 71 QoL issues which was rated by thyroid cancer patients (n=110) from seven countries. All issues were of high priority to at least some of the patients. The most frequently selected issues were sudden attacks of tiredness, exhaustion, quality of sleep, employment, social support, fear of cancer progression, fear of second operation, difficulties swallowing, and globus sensation.

Conclusions

Thyroid cancer patients cross-culturally rate fatigue related issues as highly important for their QoL, calling for increased efforts to find successful treatments for this problem. Vocational rehabilitation is also highly relevant for them and should therefore be an important aim of multi-disciplinary care. The third important area of concern is psychological issues, especially fear of progression and of additional treatments.

Introduction

Clinicians aim to achieve the best outcomes for their patients. But what is that - the “best outcome”? Of course, most people consider death as an outcome to be avoided and longevity as something to strive for. When it comes to quality of life (QoL), however, things become more complicated as individual values come into play [1]. For example, a 30 year old teacher who is passionate about her work and who is diagnosed with thyroid cancer perhaps finds it most important to keep a good voice so that she can pursue her work. For another person with the same diagnosis but with different priorities in life, say a 68 year old pensioner, the quality of the voice may be less important. Such differences in opinion exist not only between patients but also between an individual patient and his physician, between a doctor and her hospital manager, or between a hospital manager and the insurance company.

Value-based medicine sets out to address such disagreements [2]. It is a method of integrating the different values by one common metric, namely money spent per quality adjusted life year gained [2, 3]. In the United States, health care is already paid according to this value-based system [4]. The aim of this new system is to enable societies to apply new (often costly) medical treatments despite limited financial resources. Consequently, more and more clinical trials include value-based criteria when defining their outcomes of interest. To this end, researchers need to know what quality of life issues are most important for the majority of patients with a certain disease. However, value-based medicine should not only be understood as a method to ensure cost-effectiveness of a medical treatment but as an approach trying to address the complexity of different values in clinical decision making. The importance of this has been underlined by the U.S. Food and Drug Administration in their guidance for industry to use patient-reported outcomes for medical product development [5].

In the treatment of patients with thyroid cancer, QoL plays a major role as their prognosis is usually very good [6, 7]. In addition, thyroid cancer tends to affect patients of a younger age

compared to other malignancies [8, 9]. There is evidence that young age at diagnosis may be a risk factor for decreased QoL [10].

Whilst some studies reported that individuals with thyroid cancer generally have a QoL that is comparable to those in the general population [11, 12], most have found an impaired quality of life [13-21], comparable to patients from other tumor sites [21, 22].

The management of thyroid cancer is multi-disciplinary – requiring active consultation and intervention using surgery, nuclear medicine, and medical treatment. This can have profound effects on the patients' physical, social and psychological well-being. Some of the QoL issues specific to thyroid cancer are related to temporary hormone-withdrawal resulting in severe fatigue, neurological deficiencies and problems associated with appetite, memory, depression, motor skills and the bowel. Damage to laryngeal nerves during thyroid surgery can result in voice issues as well. With the use of recombinant human thyroid-stimulating hormone (rhTSH) for ablation of post-surgical thyroid remnants after low-dose radioactive iodine therapy, compared with conventional thyroid hormone withdrawal, fewer symptoms occur and patients feel more vital and energetic at the time of application [23, 24]. However, QoL deficits remain a problem, not only during treatment but also in the long-term [19, 25, 26].

For the planning of clinical trials, it is important to know what QoL issues are of highest priority to the patients. In the Netherlands, Husson et al. identified the following issues as most important to thyroid cancer survivors (n=18): stressfulness of diagnosis (82%), attention problems, decreased concentration, sudden attacks of fatigue (each 76%), problems with memory, problems with thinking, and stressfulness of radioactive iodine treatment (each 71%) [27]. From a multi-national perspective, we now aimed to identify the prioritised quality of life issues in patients from different cultural and societal backgrounds in addition to the more general issues covered by the EORTC QoL core questionnaire EORTC QLQ-C30. The

objective of this study was to determine the thyroid cancer specific QoL issues that are most relevant to thyroid cancer patients cross-culturally.

Methods

Identification of issues

To prepare a provisional list of QoL issues to be evaluated by patients, a systematic review was performed. It identified QoL questionnaires that are already in use with thyroid cancer patients and studies investigating QoL in thyroid cancer patients. For this review, we could build on previous work [28]. We updated this search to make sure that it was comprehensive, including the years 2010 to 2013, because this work only included studies up to February 2010.

The search strategy was as follows:

- published from 2010 to 14th January 2013 (= day of the search)
- Search engine: Web of Science (including MEDLINE, SciELO Citation Index, Science Citation Index Expanded, and Social Sciences Citation Index)
- Search terms: thyroid AND cancer or oncol* or neoplasm* or tumor* or tumour* AND "quality of life"
- Inclusion criteria:
 - study investigated QoL of patients with thyroid cancer
 - original article
- Exclusion criteria:
 - objective was to describe the relation of QoL with other variables such as mood states, without the description of QoL itself

All issues mentioned in the studies were listed, duplicates were removed and issues with similar content were grouped. All issues that are covered by the EORTC QLQ-C30 (e.g., nausea, vomiting) or that are not quality of life issues (e.g., high blood pressure) were excluded. This list was discussed within the thyroid module developing group of the EORTC QoL Group and the group of experts decided to keep, remove or change the issues. The following professions were represented in the group of experts: nuclear medicine, radiation oncology, medical oncology, laryngo-rhino-otology, general surgery, psychology, epidemiology, rehabilitation, dentist, nurse, and nutritionist. The final list of issues was translated following the guidelines of the EORTC Quality of Life Group [29, 30].

Data collection

The consolidated list of QoL issues was completed by thyroid cancer patients together with the QLQ-C30. In a debriefing semi-structured interview with pre-defined questions, we asked them to pick the 25 most important issues they would like to have included in a questionnaire, and to indicate relevant issues missing from this list. Missing issues mentioned by the patients were written down using the patients' wording.

Socio-demographic (age, sex, education) and clinical characteristics (histology, TNM stage, time since diagnosis, treatment) were documented on case report forms by the interviewer. All clinical data were obtained from the patients' medical charts.

Sampling

Male and female patients, aged 18 years or older and with all types and stages of thyroid cancer (International Classification of Diseases, version 10, code C73) were eligible for this study. Given the epidemiology of thyroid cancer types, we intended to include more patients with follicular and papillary cancer than patients with medullary and anaplastic types.

However, we also wanted to make sure that the rarer disease types were represented as well. The target sample size was therefore: at least n=25 for patients with follicular cancer, n=25 for patients with papillary, n=15 for medullary, and n=15 for patients with anaplastic cancer to ensure that sufficient patients were in each group to represent their priorities reliably, in accordance with the EORTC module development guidelines [30]. Consecutive patients attending the collaborating institutions were screened for eligibility and asked to participate. The enrolment was monitored monthly by the principal investigator and fed back to the collaborators to ensure that the sampling complied with the pre-defined sampling matrix. We interviewed patients before, during, or after thyroid cancer treatment. Exclusion criteria were insufficient command of the local language and no written informed consent.

Statistical analysis

Data entry, cleaning, and analysis were conducted at Mainz University using STATA (StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP). During patient enrolment, regular analyses regarding the frequency of patients' treatment types, cancer histology, and geographical area were performed and fed back to the multi-national team of collaborators every month.

For the final analysis, the frequencies of issue priorities were calculated. Finally, a ranking of the issues was performed, starting from highest priority to lowest. This was done for the entire patient sample and for pre-defined subgroups (differentiated vs. medullary vs. anaplastic thyroid cancer; <50 vs. ≥50 years old; geographical area).

Ethics, data protection, and study registration

This investigation was approved by the ethical committee of Rhineland-Palatinate, Germany, functioning according to the 3rd edition of the Guidelines on the Practice of Ethical Committees in Medical Research issued by the Royal College of Physicians of London.

Ethical approval was also obtained from the local ethical committees in each country.

Confidentiality of the data was ensured by using pseudonyms (patient identification numbers) on each questionnaire and data form. No person-identifying information was stored together with the medical and patient reported outcome data. The study was registered at the EORTC Headquarters (# EORTC QLQ-THY_Phase I).

Results

Issues identified from the literature

In addition to the review performed by Husson et al., we identified 118 potentially relevant studies of which 109 were excluded according to the selection criteria based on abstract screening and 9 full articles were read. Two of them fulfilled the inclusion criteria, and one additional study was found in the reference lists which had not been included in previous searches, resulting in 3 new studies [15, 31-33]. The consolidated list of issues resulting from both reviews, with duplicates and non-eligible issues removed, containing 112 items was discussed with all collaborators at a personal meeting. As a result, 44 issues were removed, 38 issues were kept, 1 new issue created, and 30 issues were re-worded. Main reasons for removal were that the issue was already covered by the EORTC QLQ-C30 with one exception: because fatigue was such an important issue in all the papers reviewed, the group decided to include additional (and more specific) issues to complement those in the EORTC QLQ-C30. Other reasons for removal were that issues were too similar and it was discussed which of the issues in question would be most suitable for the patients. The results of this

discussion together with explanations as for why an issue was removed or changed are displayed in Supplementary Table 1.

Translations

While preparing the list of issues for translation, it became clear that some of the issues are difficult to translate or unclear regarding what they actually cover. For example, the question arose whether there is a difference between “being judged” (issue 6) and “social stigmatization” (issue 5). This was discussed with the EORTC Translation Unit and a revised list emerged containing 71 issues (Supplementary Table 2). This list was translated from English into Dutch, French, German, Greek, Hungarian, Italian, Japanese, Polish, and Portuguese following a standardised forward-backward procedure with the help of several collaborators and the EORTC Translation Unit. For Austria and Germany, we performed two independent translations into German and resolved differences by discussion.

Patient sample

Patient interviews were conducted between 2013 and 2014 in 8 centers from seven countries, contributing altogether 110 patients. Patients came from the following countries: Germany (18 patients), Austria (5), The Netherlands (22), The United Kingdom (7), Poland (20), Italy (18), Portugal (6), and Japan (14).

Women represent 65.5% of the sample which is equivalent to the true distribution in thyroid cancer patients which occurs more often in women. Half of the patients had papillary disease (n=55), followed by follicular (n=30), medullary (n=17), anaplastic (n=4), and other cancer (n=4) (Table 1). Other histologies were Hürthle cell carcinoma (n=2), follicular oncocytic (n=1), and follicular differentiated papillary cancer (n=1).

The mean Karnofsky performance score was 91 (SD 11, range 30-100). Time since first diagnosis varied from 1 day to 37 years with a median of 4.7 years (mean 6 years). This distribution of time since diagnosis was similar across the majority of histology types, i.e.

papillary, follicular and medullary thyroid cancer, but distinctly shorter in patients with anaplastic cancer (mean 0.7 years, min 7 days, max 2 years).

Patients had received different types of treatment, depending on the histology and stage of their disease. The majority (85%) underwent total thyroidectomy (Table 2).

Many patients had received radio-active iodine (RAI) in the past, and the most frequent current treatment was tyrosine kinase inhibitors (TKI). Systemic therapy or chemotherapy is usually only considered in patients with M1 disease and in patients with non-differentiated thyroid tumors, therefore only 5 patients in our sample had received this in the past. About half of the patients (48%) were under hormone suppression at the time of the interview, and 19% received rhTSH.

Priority of issues

Of the 71 issues presented to the patients, 53 were chosen by at least 20% of the patients as high priority, i.e., they chose this issue as one of the 25 issues that should be part of a QoL questionnaire. Thirteen issues were chosen by at least 40% of the patients (see Figure 1 for the 25 top ranking issues). All issues were selected by at least 9 of the 110 patients (8%), thus each issue was of high priority to at least some patients.

Quality of life issues most frequently selected were (in descending order): being afraid of recurrence of disease, social support from family and friends, quality of sleep, sudden attacks of tiredness, social support from health care providers, physical exhaustion, employment, being afraid of second operation, globus sensation, and mental exhaustion.

Top priorities in different subgroups

Table 3 displays the top 15 ranking issues in pre-specified groups according to histology (patients with differentiated vs. medullary vs. anaplastic cancer), age (below 50 years vs. 50 years and more), and geographical area (Asia vs. Europe). In all groups, social support by

health care providers and by family and friends was highly ranked. In all groups except in patients with anaplastic cancer, being afraid of disease recurrence, employment and sudden attacks of tiredness were highly ranked. Physical exhaustion was selected by all groups but the medullary cancer patients.

Issues highly ranked in five of the seven groups were mental exhaustion and quality of sleep. Four of the groups prioritized: being afraid of a second operation, being a burden to others, difficulties swallowing, discomfort in the neck, globus sensation, and voice changes.

Issues that were highly ranked only in one of the groups were: fertility and problems with weight gain in younger patients only; dry mouth and joint pain in older patients; muscle pain, movement of arm or shoulder, problems with hair loss, and worries about lifelong medication only in Asian patients; chewing, facial swelling, pain in the throat, being slow, and swelling in the cheeks only in patients with anaplastic cancer.

Discussion

The aim of this study was to determine quality of life issues that are relevant to thyroid cancer patients cross-culturally and to identify the QoL issues with highest relevance to thyroid cancer patients. From the literature, we identified 71 QoL issues of potential relevance to patients in addition to the core issues covered by the EORTC QLQ-C30, and all of them were selected as highly relevant by at least some of the patients.

In all groups of patients, fatigue was a commonly prioritized QoL issue. Though fatigue is an important problem for cancer patients in general [34, 35] and one of the major components of QoL, together with pain [36], this issue seems particularly important in patients with thyroid cancer [11, 20, 37-39] due to its treatment and due to the affected hormonal regulation.

Fatigue is a common side effect of the new TKIs [40]. For example, in a recent trial comparing lenvatinib versus placebo in radioiodine-refractory thyroid cancer, fatigue

occurred in 60% of the patients under lenvatinib versus in only 28% of the patients with placebo [41].

Interestingly, our study participants frequently mentioned “sudden attacks of tiredness” as an important issue, along with “quality of sleep”. Both issues are not often recognized as relevant in QoL questionnaires for cancer patients. The specificity of these symptoms shows how different the universe of these patients is compared to other cancer patients. It may place them in a disadvantaged position as the clinics seem at times alienated from and insensitive to this reality.

Another frequently selected issue was employment. As thyroid cancer often affects patients at a relatively young age, the disease and its treatment may have an impact on their ability to work [42], hence successful vocational rehabilitation is an important aim of care. A study from the U.S.A. revealed that thyroid cancer patients are at higher risk of bankruptcy than other cancer patients whose disease is more aggressive [43]. In Israel, the income of thyroid cancer patients two and four years after diagnosis has recently been shown to be lower than in the general population, presumably because of part-time jobs and/or reduced physical functioning [44]. Interestingly, in our study, not only young patients had selected this issue as highly relevant but also participants older than 50 years. This may imply that patients do not like the idea of early retirement; instead they strive to stay in the workforce as long as possible.

The third area of concern for most patient groups was fear of progression. Again, this is a factor that is known to be relevant for cancer patients in general [45, 46], but it is striking to see that this issue was on the first rank in four of the seven groups under study. Similarly, support from health care professionals and from relatives and friends was mentioned by all patient groups as one of the top priorities for QoL questionnaires. Interestingly, three quarter of the patients with anaplastic and medullary cancer selected support from health care

providers as highly important compared to half of the patients with differentiated thyroid tumors, probably also reflecting a higher need for support in this group. Both issues, fear of recurrence and social support, are not specific to thyroid cancer patients, but to cancer patients and survivors in general [47, 48]. It should be noted though that the thyroid cancer patients prioritized it highly. It is possible that they find it especially important, probably even more than other cancer patients, as they often experience devaluation of their anxieties by health care professionals who sometimes consider thyroid cancer to be the “good cancer” because of its usually good prognosis [19]. However, for a patient, cancer is cancer, and this feels threatening [25, 49].

The results of this study should be seen in the light of its limitations. The differences found between the patient groups are interesting but should be interpreted with caution. As we compared rankings, we could not adjust for relevant covariates when comparing groups. For example, 86% of the patients in Japan selected “unanswered questions about disease or treatment” as an important issue. This could imply that Japanese patients receive less information about the disease and its treatment than European patients. Another explanation would be that they find it more important to get all their questions answered compared to Europeans. The Japanese experts in our group reported that, in their experience, Japanese patients want to know everything, but when they are in front of their doctors, they hesitate to ask their doctors about their disease because they do not want to bother them about their disease or questions, even when the doctors encourages them to ask questions. This clinical observation is supported by a number of studies [50-53]. However, the group of Japanese patients might also differ from the European patients in terms of other socio-demographic or disease characteristics, creating a “false” correlation between cultural area and issue priority, attributable purely to confounding. For example, the Japanese patients reported more concerns about life-long medication which could be explained by the fact that most of them were

treated with TKIs. As we were not able to control for these factors statistically, as explained above, we suggest focusing on the shared QoL priorities, not on the differences between groups.

Another limitation is that we could not include many patients with anaplastic thyroid cancer due to its low incidence and poor prognosis. After discussion within our expert group we decided to calculate separate priority rankings also for this group of patients instead of combining medullary and anaplastic cancer patients to one group of non-differentiated thyroid cancer. Given the different prognosis and treatment of those patients this combination would have been arbitrary. It seemed preferable to have separate rankings, however as the number of patients with anaplastic cancer was low, they may be not representative for the entire group of patients with this histology.

Keeping these limitations in mind, we think our data provide insight into the values of thyroid cancer patients regarding their quality of life. The rankings can be used for developing a thyroid cancer specific questionnaire to assess quality of life, for clinical trials and for daily practice when trying to base decisions on patient priorities [54]. The interest of our work was to objectify issues related to the QoL of patients with thyroid cancer that in clinical practice we sometimes devalue and even deny [25]. The British Thyroid Association has acknowledged this problem and focuses now more on patient needs and QoL in their new guidelines [55] in order to improve patient care. In order to do so, site-specific questionnaires are needed to sensitively detect clinically relevant differences in QoL between groups or treatment arms. Generic tools are often not able to do so as they do not cover all relevant aspects of QoL in this group of patients [56, 57]. The results of our study can be the basis for developing such questionnaires.

Author Disclosure Statement

Conflict of interest: All authors declare that they have no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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

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Table 1 Socio-demographic and clinical characteristics of the study participants (n=110)

		Frequency	Percent
Sex	male	38	34.6%
	female	72	65.5%
Age (years)	<40	22	20.0%
	40-49	19	17.3%
	50-59	29	26.4%
	60-69	18	16.4%
	70-79	17	15.5%
	80+	4	3.6%
	unknown	1	0.9%
Education	compulsory or less	19	17.3%
	post compulsory	56	50.9%
	university level	31	28.2%
	unknown	4	3.6%
Histology	follicular	30	27.3%
	papillary	55	50.0%
	medullary	17	15.5%
	anaplastic	4	3.6%
	other	4	3.6%
T	T1	26	23.6%
	T2	22	20.0%
	T3	38	34.6%
	T4a	5	4.6%
	T4b	1	0.9%

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	Tx	2	1.8%
	missing	16	14.6%
N	N0	55	50.0%
	N1a	13	11.8%
	N1b	23	20.9%
	Nx	3	2.7%
	missing	16	14.6%
M	M0	70	63.6%
	M1	25	22.7%
	Mx	11	10.0%
	missing	4	3.6%

Table 2 Treatment of the study participants (n=110)

		Frequency	Percent
Thyroidectomy	none	2	1.8%
	hemithyroidectomy	12	10.9%
	partial thyroidectomy	2	1.8%
	total thyroidectomy	93	84.6%
	missing	1	0.9%
Neck dissection	none	44	40.0%
	unilateral	18	16.4%
	bilateral	29	26.4%

	central	5	4.6%
	missing	14	12.7%
Radio-active iodine therapy	never/not yet	30	27.3%
	last therapy >6 months before interview	61	55.5%
	last therapy <6 months before interview	14	12.7%
	currently receiving treatment	5	4.6%
Tyrosine kinase inhibitors	never/not yet	86	78.2%
	last therapy >6 months before interview	1	0.9%
	last therapy <6 months before interview	2	1.8%
	currently receiving treatment	21	19.1%
Chemotherapy	never/not yet	105	95.5%
	last therapy >6 months before interview	3	2.7%
	last therapy <6 months before interview	1	0.9%
	currently receiving treatment	1	0.9%
Radiotherapy	never/not yet	85	77.3%
	last therapy >6 months before interview	13	11.8%
	last therapy <6 months before interview	2	1.8%
	currently receiving treatment	3	2.7%
	missing	7	6.4%

Table 3 Top 15 quality of life issues in different groups of thyroid cancer patients

Rank	Histology				Age				Region					
	DTC (n=89)		Medullary (n=17)		Anaplastic (n=4)		<50 years (n=41)		≥50 years (n=68)		Europe (n=96)		Asia (n=14)	
1	being afraid of recurrence of disease	67%	discomfort in the neck	82%	discomfort in the neck	100%	being afraid of recurrence of disease	80%	being afraid of recurrence of disease	55%	being afraid of recurrence of disease	64%	unanswered questions about disease or treatment	86%
2	social support from family and friends	58%	social support from families and friends	76%	speech problems	100%	social support from family and friends	76%	social support from HCP	53%	social support from family and friends	61%	being a burden to others	71%
3	physically exhausted	53%	social support from HCP	76%	weak voice	100%	quality of sleep	73%	social support from family and friends	51%	quality of sleep	59%	social support from HCP	71%
4	sudden attacks of tiredness	52%	quality of sleep decreased	76%	facial swelling	100%	employment	63%	sudden attacks of tiredness	48%	sudden attacks of tiredness	48%	sudden attacks of tiredness	71%
5	quality of sleep	52%	difficulty breathing	71%	being a burden to others	75%	physically exhausted	61%	quality of sleep	46%	employment	47%	physically exhausted	71%
6	employment	48%	voice changes	71%	social support from families and friends	75%	sudden attacks of tiredness	58%	physically exhausted	44%	social support from HCP	47%	muscle pain	71%
7	being afraid of second operation	45%	globus sensation	71%	social support from HCP	75%	being afraid of second operation	56%	mentally exhausted	43%	physically exhausted	47%	being afraid of recurrence of disease	71%
8	social support from HCP	44%	restlessness	69%	mentally exhausted	75%	globus sensation	54%	speech problems	41%	globus sensation	45%	movement of arm or shoulder	64%
9	mentally exhausted	43%	weak voice	65%	pain in the throat	75%	fertility	51%	employment	40%	difficulties swallowing	43%	being afraid of second operation	64%
10	unanswered questions about disease or treatment	41%	difficulties swallowing	65%	chewing	75%	problems with weight gain	51%	discomfort in the neck	39%	restlessness	42%	worried about lifelong medication	64%
11	globus sensation	38%	tolerance to cold or heat	65%	hoarseness	75%	tolerance to cold or heat	49%	difficulties swallowing	38%	discomfort in the neck	42%	employment	57%
12	palpitation	37%	employment	59%	voice changes	75%	voice changes	46%	dry mouth	38%	mentally exhausted	41%	social support from family and friends	57%
13	being a burden to others	37%	sudden attacks of tiredness	59%	swelling in the cheeks	75%	restlessness	46%	pain in the joints	37%	being afraid of second operation	40%	mentally exhausted	57%
14	difficulties swallowing	36%	palpitation	59%	being slow	75%	social support from HCP	45%	difficulty breathing	37%	difficulty breathing	39%	speech problems	57%
15	hoarseness	35%	been afraid of recurrence of disease	59%	physically exhausted	50%	being a burden to others	44%	palpitation	36%	voice changes	39%	problems with hair loss	57%

Thyroid

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Notes

DTC
HCP

Differentiated thyroid cancer
Health-care provider

The percentages represent the proportion of respondents choosing the particular issue as one of the 25 most important issues.

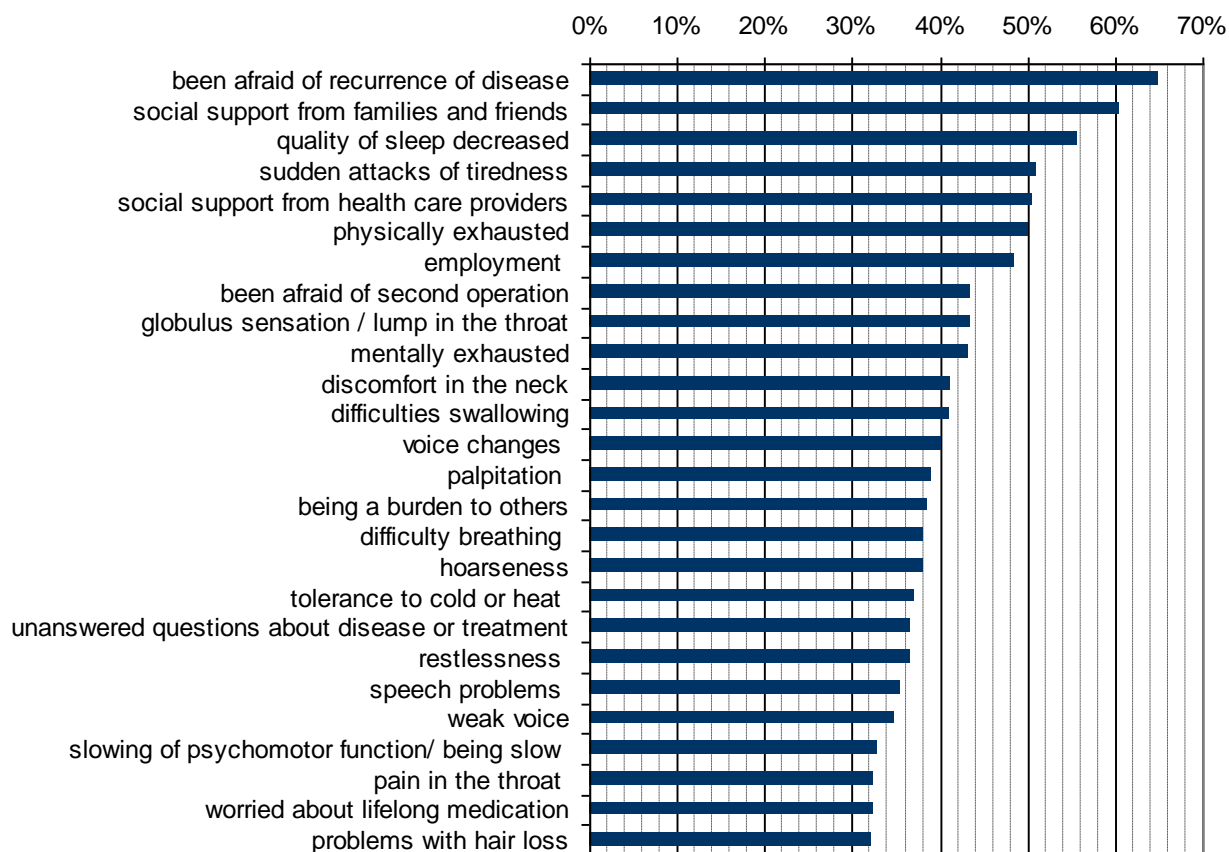


Figure 1 Quality of life issues with highest priority ranking in thyroid cancer patients. Displayed is the percentage of respondents choosing the particular issue as one of the 25 most important issues.

Online supplementary material

Suppl. Table 1. Issues derived from the literature and decision by the expert group to keep, change, or remove them

#	Issues	Decision	Remarks / change into ... (if change)
1	Employment	keep	
2	Environment	remove	too vague
3	To be unable to resume daily activities or work	remove	covered by C30
4	Unable to participate in social activities	remove	covered by C30
5	social stigmatization	keep	
6	Being judged	keep	
7	Being a burden to others	keep	
8	Social support from families and friends	keep	
9	Social support from health care providers	keep	
10	Weakness	change	abrupt attacks of tiredness
11	Fatigue	change	mentally exhausted
12	Apathy	change	physically exhausted
13	Malaise	remove	similar to issue 11
14	Activity	remove	too vague
15	Insomnia	remove	covered by C30
16	Tiredness	remove	covered by C30
17	Recreation	remove	covered by C30
18	General anesthesia	remove	covered by C30
19	Weight gain	change	problems with weight gain
20	Weight gain of more than 6 months duration	remove	similar to issue 19
21	Pain in the throat	keep	
22	Pain/discomfort postoperatively	change	discomfort in the neck
23	Aches or pain	remove	covered by C30

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24	Migraine headaches	change	headaches
25	Headaches	remove	see 24
26	Muscle pain	keep	
27	Pain	change	pain in the joints
28	Brown-Sequard syndrome (sensibility problems, muscles weakness)	change	bone pain
29	Coughing	keep	
30	Difficulty breathing	keep	
31	Dyspnea	remove	better is issue 30
32	Altered taste, changes in taste, taste disturbance	change	altered taste
33	Loss of appetite	remove	covered by C30
34	Appetite changes	keep	
35	Chewing	keep	
36	Decay	remove	not QoL
37	Gum or dental problems	change	problems with gum / problems with teeth
38	Speech problems	keep	
39	Temporary/permanent hoarseness	change	hoarseness
40	Vocal cord palsy	remove	better is issue 39
41	Voice changes	keep	
42	Voice problems/ weak voice	change	weak voice
43	Dry eyes	keep	
44	Dry skin	keep	
45	Sicca syndrome	remove	not QoL
46	Hair loss	remove	same as issue 47
47	Hair loss or thin hair/ hair problems	change	problems with hair loss
48	Impaired endothelial function/ skin problems	remove	better is issue 44
49	Nail problems	keep	
50	Swallowing	change	difficulties swallowing
51	Swallowing changes/ dysphagia	remove	see 50

52	Acute sialoadenitis	change	swelling in the cheeks
53	Chronic xerostomia	change	dry mouth
54	Acute xerostomia	remove	see 53
55	Slowing of psychomotor function/ being slow	keep	
56	Motor skills/coordination	keep	
57	Felt giddy or dizzy	keep	
58	Tolerance to cold or heat	keep	
59	Cold intolerance	remove	see 58
60	Chills, cold intolerance/ felt colder than other people	remove	see 58
61	urinary incontinence	keep	
62	Fecal incontinence because sensory loss	change	fecal incontinence
63	Constipation	remove	covered by C30
64	Unanswered questions	change	unanswered questions about disease or treatment
65	Tension	remove	covered by C30
66	Stress	remove	covered by C30
67	Concern	remove	covered by C30
68	Anxiety	remove	covered by C30
69	Depression	remove	covered by C30
70	Negative mood	remove	covered by C30
71	Psychological problems	remove	covered by C30
72	Feeling embarrassed	keep	
73	Attention problems	keep	
74	Decreased concentration	keep	
75	Confusion	keep	
76	Difficulty planning	keep	
77	Difficulty understanding complex words	keep	
78	Learning difficulties	keep	
79	Memory loss, forgetfulness/memory problems	keep	

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80	Slow or unclear thinking	keep	
81	Worries about the scar	keep	
82	Appearance	keep	
83	Intimacy	keep	
84	Sleep changes	change	quality of sleep decreased
85	Sleep disorders	remove	covered by C30
86	Restlessness	keep	
87	Palpitation	keep	
88	Nausea, vomiting	remove	covered by C30
89	Facial swelling	keep	
90	Swelling in front of the neck	remove	too similar to 89
91	Swelling/fluid retention	change	whole body swelling / fluid retention
92	Swollen hands or feet	remove	better 92
93	Numbness and tingling in hands, feet or around mouth	change	numbness or tingling in hands or feet AND numbness or tingling around mouth
94	Temporary/permanent tetany and tingling around the mouth	remove	better 93
95	Menstrual changes or fertility	change	menstrual changes AND fertility
96	Impaired systolic and diastolic functioning during activity	remove	not QoL
97	Hearing problems	keep	
98	One shoulder may be lower than the other	change	movement of arm or shoulder
99	Shoulder	change	shoulder pain
100	Calcium problems	remove	not QoL
101	Transitory and permanent hypocalcemia	remove	not QoL
102	Globus sensation	change	globus sensation / lump in the throat
103	Elevated levels of cholesterol	remove	not QoL

104	Epigastralgia	change	pain in the stomach
105	Second operation	change	being afraid of second operation
106	Complications following surgery	remove	too broad
107	Waiting time for surgery	remove	
108	Whole body scanning	change	being afraid of recurrence of disease
109	Withdrawal from thyroid hormone	change	being afraid of withdrawal from thyroid hormone
110	Thyroglobulin testing	remove	better 108
111	Time since my treatment was completed	remove	unclear
112	Lifelong medication	change	worried about lifelong medication
113	weight loss	new	

Suppl. Table 2. Consolidated list of issues for patient interviews

s31	employment
s32	being judged
s33	being a burden to others
s34	social support from families and friends
s35	social support from health care providers
s36	sudden attacks of tiredness
s37	mentally exhausted
s38	physically exhausted
s39	problems with weight gain
s40	problems with weight loss
s41	pain in the throat
s42	discomfort in the neck
s43	headaches
s44	muscle pain
s45	pain in the joints
s46	bone pain
s47	coughing
s48	difficulty breathing

Thyroid
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s49	altered taste
s50	appetite changes
s51	chewing
s52	problems with gum
s53	problems with teeth
s54	speech problems
s55	hoarseness
s56	voice changes
s57	weak voice
s58	dry eyes
s59	dry skin
s60	problems with hair loss
s61	nail problems
s62	difficulties swallowing
s63	swelling in the cheeks
s64	dry mouth
s65	slowing of psychomotor function/ being slow
s66	motor skills/coordination
s67	felt giddy or dizzy

s68	tolerance to cold or heat
s69	urinary incontinence
s70	faecal incontinence
s71	unanswered questions about disease or treatment
s72	feeling embarrassed
s73	attention problems
s74	decreased concentration
s75	confusion
s76	difficulty planning
s77	difficulty understanding complex words
s78	learning difficulties
s79	memory loss, forgetfulness/memory problems
s80	slow or unclear thinking
s81	worries about the scar
s82	appearance
s83	intimacy
s84	quality of sleep decreased
s85	restlessness
s86	palpitation

Thyroid

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s87	facial swelling
s88	whole body swelling / fluid retention
s89	numbness or tingling in hands or feet
s90	numbness or tingling around mouth
s91	menstrual changes
s92	fertility
s93	hearing problems
s94	movement of arm or shoulder
s95	shoulder pain
s96	globus sensation / lump in the throat
s97	pain in the stomach
s98	being afraid of second operation
s99	being afraid of recurrence of disease
s100	being afraid of withdrawal from thyroid hormone
s101	worried about lifelong medication

Suppl. Table 3. Top 15 quality of life issues in thyroid cancer patients according to time since diagnosis

Rank	< 1 year (n=24)		1 to 5 years (n=31)		> 5 years (n=53)	
1	being afraid of recurrence of disease	78%	physically exhausted	74%	being afraid of recurrence of disease	63%
2	social support from families and friends	71%	social support from health care providers	72%	social support from families and friends	52%
3	globulus sensation / lump in the throat	59%	sudden attacks of tiredness	70%	sudden attacks of tiredness	51%
4	quality of sleep decreased	57%	quality of sleep decreased	70%	quality of sleep decreased	45%
5	difficulty breathing	54%	social support from families and friends	65%	social support from health care providers	44%
6	difficulties swallowing	54%	employment	61%	employment	43%
7	being a burden to others	52%	being afraid of recurrence of disease	55%	discomfort in the neck	42%
8	hoarseness	50%	being afraid of second operation	52%	weak voice	40%
9	voice changes	50%	mentally exhausted	48%	voice changes	40%
10	mentally exhausted	48%	discomfort in the neck	47%	difficulties swallowing	40%
11	restlessness	45%	headaches	47%	being afraid of second operation	38%
12	been afraid of second operation	43%	palpitation	45%	physically exhausted	38%
13	fertility	42%	globulus sensation / lump in the throat	45%	pain in the joints	38%
14	employment	42%	unanswered questions about disease or treatment	43%	difficulty breathing	38%
15	physically exhausted	42%	speech problems	42%	hoarseness	38%

Notes The percentages represent the proportion of respondents choosing the particular issue as one of the 25 most important issues.

1 **Suppl. Table 4. Top 15 quality of life issues in thyroid cancer patients according to gender**

Rank	female (n=72)		male (n=38)	
1	social support from families and friends	64%	being afraid of recurrence of disease	68%
2	being afraid of recurrence of disease	63%	sudden attacks of tiredness	66%
3	quality of sleep decreased	56%	physically exhausted	58%
4	social support from health care providers	54%	quality of sleep decreased	55%
5	physically exhausted	46%	employment	54%
6	employment	46%	social support from families and friends	54%
7	being afraid of second operation	45%	voice changes	53%
8	mentally exhausted	44%	difficulties swallowing	50%
9	sudden attacks of tiredness	43%	difficulty breathing	47%
10	discomfort in the neck	42%	speech problems	47%
11	globulus sensation / lump in the throat	42%	globulus sensation / lump in the throat	46%
12	palpitation	41%	weak voice	45%
13	problems with hair loss	41%	social support from health care providers	44%
14	unanswered questions about disease or treatment	39%	mentally exhausted	42%
15	hoarseness	39%	tolerance to cold or heat	41%

2
3
4
5
Notes *The percentages represent the proportion of respondents choosing the particular issue as one of the 25 most important issues.*

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Suppl. Table 5. Top 15 quality of life issues in thyroid cancer patients according to spread of disease

Rank	no metastases (n=51)		lymph node metastases (n=27)		distant metastases (n=25)	
1	being afraid of recurrence of disease	66%	quality of sleep decreased	59%	being afraid of recurrence of disease	72%
2	social support from families and friends	62%	social support from families and friends	56%	social support from health care providers	68%
3	quality of sleep decreased	60%	sudden attacks of tiredness	56%	being a burden to others	60%
4	sudden attacks of tiredness	47%	being afraid of recurrence of disease	56%	social support from families and friends	60%
5	physically exhausted	45%	globulus sensation / lump in the throat	54%	mentally exhausted	60%
6	globulus sensation / lump in the throat	45%	difficulty breathing	52%	physically exhausted	60%
7	employment	43%	social support from health care providers	50%	speech problems	60%
8	restlessness	42%	physically exhausted	48%	unanswered questions about disease or treatment	60%
9	discomfort in the neck	41%	employment	46%	employment	58%
10	difficulties swallowing	41%	difficulties swallowing	44%	sudden attacks of tiredness	56%
11	fertility	41%	restlessness	42%	being afraid of second operation	56%
12	palpitation	40%	headaches	41%	pain in the throat	54%
13	being afraid of second operation	40%	appetite changes	41%	discomfort in the neck	50%
14	social support from health care providers	39%	hoarseness	41%	muscle pain	48%
15	tolerance to cold or heat	39%	dry mouth	41%	voice changes	44%

Notes

The percentages represent the proportion of respondents choosing the particular issue as one of the 25 most important issues.

Suppl. Table 5. Top 15 quality of life issues in thyroid cancer patients according to treatment with tyrosine kinase inhibitors (TKI)

Rank	TKI (n=24)		no TKI (n=86)	
1	muscle pain	67%	being afraid of recurrence of disease	68%
2	social support from health care providers	65%	social support from families and friends	63%
3	speech problems	58%	quality of sleep decreased	61%
4	voice changes	58%	physically exhausted	52%
5	pain in the throat	57%	sudden attacks of tiredness	50%
6	altered taste	57%	employment	48%
7	unanswered questions about disease or treatment	57%	social support from health care providers	46%
8	sudden attacks of tiredness	54%	mentally exhausted	46%
9	difficulty breathing	54%	being afraid of second operation	45%
10	hoarseness	54%	globulus sensation / lump in the throat	44%
11	movement of arm or shoulder	54%	restlessness	43%
12	shoulder pain	54%	palpitation	40%
13	being afraid of recurrence of disease	54%	discomfort in the neck	38%
14	worried about lifelong medication	54%	difficulties swallowing	38%
15	employment	52%	being a burden to others	36%

Notes

The percentages represent the proportion of respondents choosing the particular issue as one of the 25 most important issues.

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