Review

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Systematic review of health-related quality of life following thyroid cancer

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Abstract

This systematic review provides a summary of all studies published between 2000 and 2019 using a health-related quality of life (HRQOL) patient-completed questionnaire to report outcomes following diagnosis and treatment of thyroid cancer. The search terms were "thyroid cancer" or "thyroid carcinoma," "quality of life" or "health related quality of life," and "questionnaire" or "patient reported outcome." EMBASE, PubMed, Medline, PsycINFO, CINAHL, and HaNDLE-On-QOL search engines were searched between 2 February and 23 February 2020. A total of 811 identified articles were reduced to 314 when duplicates were removed. After exclusion criteria (not thyroid specific, no quality of life questionnaires, and conference abstracts) were applied, 92 remained. Hand searching identified a further 2 articles. Of the 94 included, 16 had a surgical, 26 a primarily medical, and 52 a general focus. There were articles from 27 countries. A total of 49 articles were published from 2015 through 2019 inclusive. A total of 72 questionnaires were used among the articles and a range of 7 to 2215 participants were included within each article. This review demonstrated an increasing number of publications annually. The scope of enquiry into aspects of HRQOL following thyroid cancer is broad, with relatively few addressing surgical aspects and many focusing on the impact of radio-iodine. More research is required into shared decision-making in initial management decisions and HRQOL and interventions aimed specifically at addressing long-term HRQOL difficulties.

Keywords

Thyroid cancer, quality of life, questionnaire, review, patient-reported outcomes

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Introduction

The diagnosis of thyroid cancer (TC) is increasing globally[1,2]: in the United States, it accounts for 3.4% of all new cancers annually,[3] and through earlier diagnosis and improvement in treatments,[2] TC mortality is falling and the survivor population rising. TC diagnosis and management can have a detrimental impact on the health-related quality of life (HRQOL) of patients and their carers, not only during initial management but also in the long term, given that survival is increasing. The overdiagnosis of TC, particularly papillary TC, in the last 3 decades due to incidental findings on medical imaging or ultrasonography-based population screening has been described as a major global public health challenge. The potential repercussions of unnecessary treatment exposures and the impact on HRQOL are of great concern to clinicians globally, considering the relatively low morbidity of the clinical diagnosis.[4–6]

TC prognosis is variable and depends on the combined effect of diagnostic stage, patient factors, such as age, and geographic variation in treatment protocols.[4–8] The

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HRQOL outcomes associated with surgery or medical treatment are varied and influenced by the consequence of cancer diagnosis, its treatment, and individual patient characteristics.[9,10] The effect on functional, emotional, and social aspects of a patient's life has previously been underappreciated, but with the more frequent use of patient-reported outcomes more data have emerged concerning HRQOL. This information aids improved treatment protocol, enhances care pathways, and drives new areas for intervention.

Published HRQOL outcomes focus on the effects of hormonal balance, surgery, radioiodine ablation (RIA), demographics, psychosomatic interventions, and behavioral help; the evidence base for these HRQOL concerns is growing with increasing numbers of studies published annually. However, there is a paucity of systematic reviews on HRQOL and TC. Husson et al.[9] reported 27 studies published from 1997 to 2010 and Bărbuş et al.[11] reported 16 studies published from 2008 to 2016. As optimal treatment strategies and patient/carer support continue to evolve, the aim of this systematic review is to provide a summary of all studies published from 2000 to 2019 that have used HRQOL patient-completed questionnaires following TC. This time period was chosen as it includes the most up-to-date publications and captures the surge of quality of life (QOL) articles published in recent decades.

Methods

Search strategy

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed in the reporting of this systematic review.[12] Six search engines were used: EMBASE, PubMed, Medline, PsycINFO, CINAHL, and HaNDLE-On-QOL. Searches were assisted by Leeds Teaching Hospitals NHS Trust and Liverpool University Hospitals NHS Foundation Trust between 2 February and 23 February 2020. To avoid missing relevant articles, one author (M.S.) hand searched the reference lists of a random 10% of articles.

The search terms used were "thyroid cancer," "quality of life," and "questionnaire"; however, these terms were expanded to achieve the most thorough results possible:

1. "thyroid cancer" or "thyroid carcinoma"
2. "quality of life" or "health-related quality of life"
3. "questionnaire" or "patient reported outcome"

No ethical approval was required to complete this review.

Study selection

We looked at TC articles between January 2000 and December 2019 inclusive involving humans of any age where full text was available in English, including those with nonvalidated, study-specific questionnaires. Studies where TC was part of a larger cancer cohort were included if the proportion of TC was at least 20% of the sample. Review articles, conference abstracts, and opinion articles were excluded. Qualitative research was included in this review. All forms of study design were included.

The research team included all the authors. Results of the literature search were downloaded into an Excel spreadsheet and screened by two independent reviewers (E.W., M.S.) who separately analyzed search results. Each article was categorized by year of publication, title, authors, cohort, design of study, theme and type of questionnaire, and then documented as included, excluded, or unable to decide from the abstract/title information, with inclusion disagreements resolved by the four remaining authors (A.K., S.N.R., J.W., D.K.).

Hand searching of a random 10% of articles (9) was completed by a single author (M.S.). Following the initial screening phase, full article consideration was undertaken by two independent reviewers (E.W., M.S.), and again escalated to the remaining four authors (A.K., S.N.R., J.W., D.K.) if inclusion disagreements occurred.

Data extraction and quality assessment

All authors were involved in data extraction from the selected articles, including recording the publication title, authors, cohort, design of study, theme, type of questionnaire, and summary of article conclusions and key findings.

Quality appraisal and assessment of risk of bias was performed on all included articles by a single author (E.W.). Quality appraisal was guided by the Joanna Briggs Institute critical appraisal checklists.[13,14]

Results

Following removal of duplicates, 314 articles were identified, of which 222 were excluded (99 not thyroid-specific, 28 no QOL questionnaires, 58 conference abstracts, 13 not written in English, 2 qualitative, 1 protocol, 12 benign thyroid lesions, 2 clinician-focused questionnaires, 2 literature reviews, and 5 could not be located). Hand-searching of articles identified two further eligible articles, resulting in 94 total articles. Figure 1 demonstrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for this selection process.

The articles were subcategorized into having a surgical (16), medical (26), or general (52) focus, which aided descriptive analysis and enabled development of key themes relating to HRQOL. Subcategorization was completed during the full article review phase and agreed between all authors. For articles to qualify as being in the surgical category, the primary focus of the article must

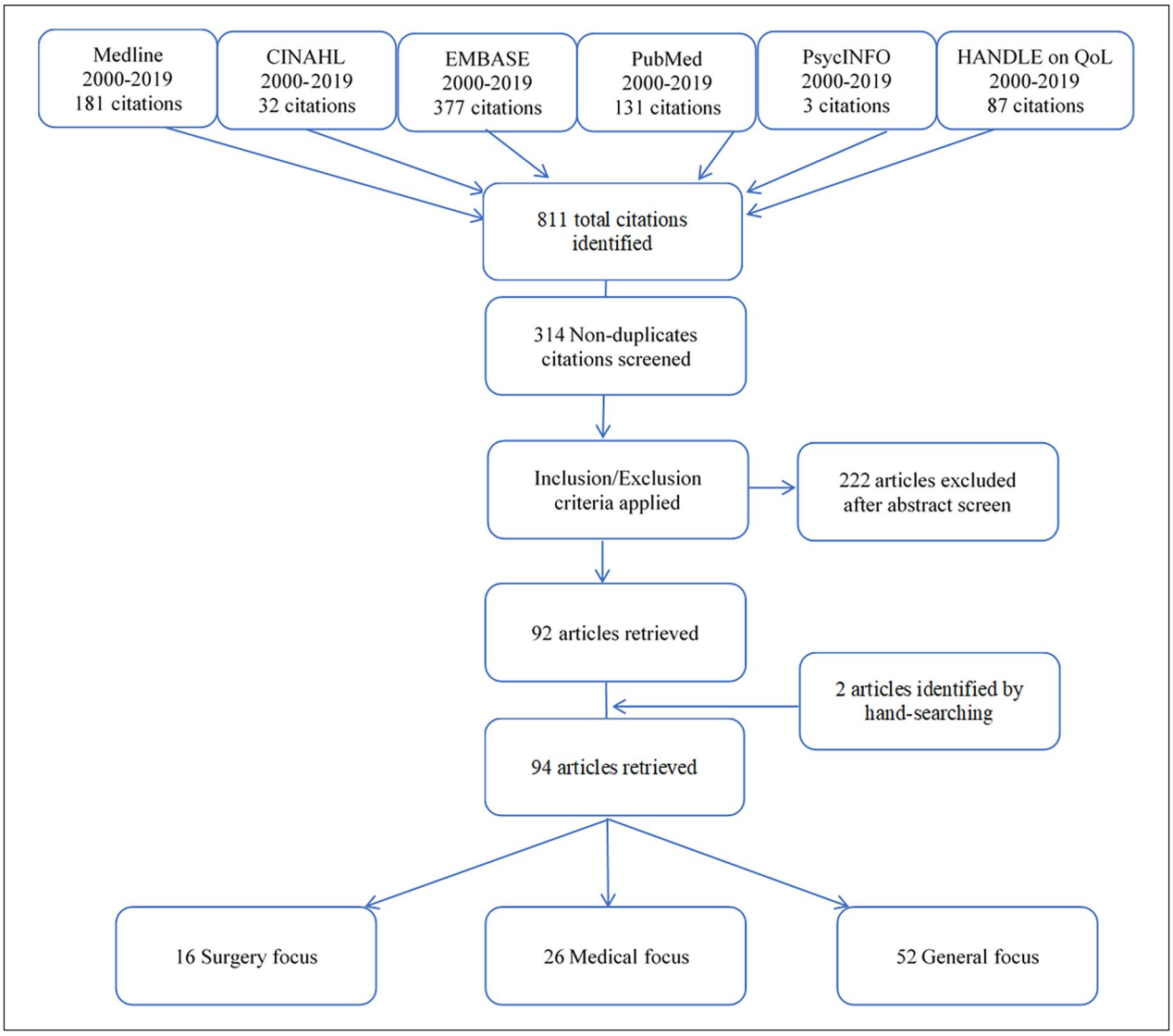

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart demonstrating the search and selection pathway for articles.

have been on HRQOL following surgical management of TC. Those articles categorized as being medical were focused on endocrinologic and nuclear medicine treatments of TC. In comparison, the general category encompassed articles whose focus was on the impact of TC on HRQOL as a broader construct, including functional, emotional, social, and existential considerations such as self-esteem and purpose.

The number of articles published annually shows a general trend towards increased volume with time (Table 1). A large variety of validated and nonvalidated patient-reported questionnaires (including study-specific) were utilized (total 72, range of 1–8 per article) (Table 2). The most commonly used was the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), followed by Short Form–36 (SF-36). Articles were published from 27 countries (Table 3), with no clear geographic pattern, although Korea had more surgical articles (7 of 11) and the Netherlands a tendency to general HRQOL (9 of 12).

The number of participants included within these studies varied significantly, between 7[15] and 2215.[16] Study design was variable, but the majority of studies were cross-sectional in nature (78 of 94 [83%]).

The majority of articles focused on the HRQOL of participants with differentiated TC. A total of 12 articles did not specify histologic diagnosis of TC for included participants, and only 14 included medullary TC. Further presentation of the results have been divided into the three subcategories and are presented narratively in Tables 4, 5, and 6.

Table 1. Articles published by year that were included in this systematic review.

Year of publication	Number of studies
2000	0
2001	0
2002	0
2003	3
2004	2
2005	1
2006	6
2007	1
2008	2
2009	4
2010	5
2011	3
2012	2
2013	11
2014	5
2015	6
2016	12
2017	9
2018	11
2019	11

Surgical

Sixteen articles had a surgical emphasis (Table 4). The most frequently utilized questionnaires were EORTC-QLQ-C30 (3), Thyroid Cancer–Specific Quality of Life Questionnaire (THYCA-QoL) (3), and University of Washington QOL (UW-QOL) (3). HRQOL issues focused around the following themes, in order of decreasing frequency:

1. Robotic and endoscopic surgical approaches (versus conventional technique)
2. Surveillance vs surgical management
3. Total thyroidectomy (TT) vs hemithyroidectomy (HT)
4. Other

Robotic and endoscopic surgical approaches. Up to 2013, five studies explored the effects of thyroid surgery on HRQOL. These varied in scope with no consistent findings. They reported lower HRQOL in TC than other cancers[17] and negative scar perception[18] was associated with long-term reduced HRQOL. However, there was no clear relationship between HRQOL and the extent of surgery.[17–21] Since 2013, there have been increased publication rates exploring thyroid surgery and HRQOL, mainly driven by the advent of novel endoscopic and robotic-assisted techniques aimed at minimizing surgical scars. Seven studies from Korea (where remote-access techniques have been most rapidly adopted) demonstrate the importance of scarring after thyroidectomy and the HRQOL conferred by its reduced visibility with minimally invasive procedures.[22–28] Conversely, a US study found scar visibility to have only mild negative HRQOL influence, returning to normal after 2 years.[29]

Song et al.[24] found that patients were more satisfied with their scar after robotic surgery, although no significant difference in overall HRQOL was found between robotic and conventional surgical approaches to papillary TC resection. They observed that despite surgical approach, the most important issues relating to ultimate HRQOL scores were baseline anxiety and humor. Reduced paresthesia to the neck (i.e. reduced hyperesthesia or paresthesia), better swallow function, and scar satisfaction resulted in better HRQOL following endoscopic/robotic thyroidectomy and neck dissection in patients with metastatic TC, in comparison to open approach.[22] The duration of surveillance, differences in patient groups, and bias of preselection due to patient preference into comparative groups are highlighted by all the studies to likely influence the study findings. Prospective randomized trials are needed to resolve these issues.

Surveillance vs surgical management. More recent studies exploring thyroid surgery impact on HRQOL have been driven by changes in practice and international guidelines in the management of low-risk TC.[4–7] Until 2015, almost all patients with TC underwent thyroidectomy. Those with macroscopic disease (>1 cm) were managed with TT and RIA. However, recent guidelines[7] have moved clinical practice towards offering patients with microcarcinoma surveillance only, and for those with small cancers (without high-risk features), HT. Two articles compared HRQOL in patients diagnosed with microcarcinoma offered surveillance versus thyroidectomy. Kong et al.[27] reported lower psychological and overall HRQOL after surgery. The study is significantly limited by a much smaller surgical cohort and higher proportion of females within the operated group and a short follow-up period (8 months median). Jeon et al.[28] reported lower HRQOL in the surgical group compared to the surveillance group. They observed that level of diagnosis-related anxiety and fear of recurrence were similar for both groups. The median follow-up was 6–7 months and there was clear selection bias into the comparative cohorts.

Total thyroidectomy vs hemithyroidectomy. Two studies compared HRQOL in patients undergoing HT versus TT. Nickel et al.[30] reported more prevalent HRQOL issues after TT whereas Bongers et al.[31] did not observe differences in the long term. Nickel et al.[30] reported only short-term follow-up, with a median <6 months in 60% of 1005 patients. Physical complaints were frequent, with fatigue and inconvenience of taking thyroxine being most common. However, the effects of RIA, which is used only after

Table 2. Questionnaires completed by patients with the articles included in this systematic review.

Questionnaire	Surgical	Medical	General	Total
15D			1	1
Assessment of Survivor Concerns (ASC)	1			1
Attentional Function Index (AFI)		1		1
Beck Anxiety Inventory[95]			2	2
Beck Depression Inventory (BDI)		3	2	5
Body Image Scale (BIS)	1			1
Brief Fatigue Inventory (BFI)			4	4
Center for Epidemiologic Studies Depression Scale[81]		1		1
Chalder Fatigue Questionnaire (CFQ 11)		1		1
Changes in Sexual Functioning Questionnaire (CSFQ-14)			1	1
Chinese version of Quality of Life Index (QLI)	1			1
Dermatology Life Quality Index (DLQI)	1			1
Distress Thermometer (DT)			1	1
Emotion Thermometers			1	1
European Organization for Research and Treatment of Cancer of Quality of Life for Thyroid Cancer Questionnaire (EORTC-QLQ-THY34)			1	1
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)	3		18	21
EuroQoL-5D		1	2	3
Fatigue Assessment Scale (FAS)			2	2
Fear of Progression (FoP)	1			1
FoR screening item			1	1
Functional Assessment of Cancer Therapy General (FACT-G)		1		1
Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F)		4	1	5
Goldberg Short Screening Scale for Anxiety and Depression (GSSSAD)			1	1
Hamilton Anxiety Rating Scale (HAM-A)			2	2
Hamilton Depression Rating Scale (HAM-D)		2	2	4
Head and Neck Companion Module			1	1
Health Utilities Index 2 (HUI2)			1	1
Health Utilities Index 3 (HUI3)			1	1
Hospital Anxiety and Depression Scale (HADS)		3	7	10
Illness Cognition Questionnaire (ICQ)			1	1
Illness Perception Questionnaire (IPQ-R)			1	1
Information, Support, and Care Delivery Needs			1	1
Kellner Symptoms Questionnaire (KSQ)		2	1	3
Kessler Psychological Distress Scale (K10)	1			1
Korean version of the Brief Encounter Psychosocial Instrument (BEPSI-K)			1	1
M.D. Anderson Symptom Inventory (MDASI)		2		2
M.D. Anderson Dysphagia Inventory (MDADI)		1		1
Multidimensional Fatigue Index–20 (MFI-20)		2	3	5
Neck Dissection Impairment Index (NDII)	1			1
Patient Health Questionnaire–9 (PHQ-9)			2	2
Patient-Reported Outcomes Measurement Information System (PROMIS)	1		3	4
Physical Self-Inventory (ISP25)			1	1
Pittsburgh Sleep Quality Index (PSQI)		1		1
Positive and Negative Affect Schedule			1	1
Post-Traumatic Growth Inventory (PTGI)			1	1
Problem List (PL)			1	1
Profile of Mood States (POMS)		1		1
QOL–Cancer Survivor Thyroid Instrument (QOL-CS Thyroid)			1	1
Quality of Life Thyroid Version (QOL-TV)	2	2	2	5
Quality of Life–Radiation Therapy Instrument (QOL-RTI)			1	1
RAND 36-item health survey (RAND 36)		1	1	2

(Continued)

Table 2. (Continued)

Questionnaire	Surgical	Medical	General	Total
Relationship Assessment Scale (RAS)			1	1
Ryff's Well Being Scale			1	1
Self-Assessed Wisdom Scale			1	1
Self-Rating Anxiety Scale (SAS)			2	2
Self-Rating Depression Scale (SDS)			2	2
Short Form–12 (SF-12)	1		3	4
Short Form–36 (SF-36)	2	9	11	22
Short Form–6 (SF-6D)			2	2
Single Item Question			2	2
State-Trait Anxiety Inventory (STAI)		1		1
Stress-Related Growth Scale (SRGS-R)			1	1
Study-specific	1	4	7	12
Three-Item Worry Index (TIWI)		1		1
ThyCAT			1	1
Thyroid Cancer–Specific Quality of Life Questionnaire (THYCA-QoL)	3		8	11
Thyroid-Related Patient-Reported Outcome (ThyPRO)		1	3	4
T-QoL			1	1
University of Washington QOL (UW-QOL)	3	1	1	5
Voice Handicap Index 10 (VHI 10)	1			1
WHO Quality of Life–BREF (WHOQOL-BREF)		2	2	4
Xerostomia-Related Quality of Life Scale (XeQOLS)		1		1

Table 3. Articles published by country included in systematic review.

Country	Surgical	Medical	General	Total
Australia	1		1	2
Austria		1	1	2
Brazil	1	2		3
Canada	2	2		4
China		1	4	5
Columbia	1			1
Croatia		1		1
Denmark		1	1	2
Finland			1	1
France		3	1	4
Germany		2	3	5
Iran		1		1
Israel	1		1	2
Italy		2	2	4
Korea	7	2	2	11
Morocco			1	1
Netherlands	1	2	9	12
Philippines			2	2
Puerto Rico			1	1
Romania		1	1	2
Singapore		1	0	1
South Korea			2	2
Sweden			4	4
Switzerland			2	2
Taiwan	1			1
United Kingdom			2	2
United States	1	4	11	16
Total	16	26	52	94

TT, may be responsible, and there were no data on adequacy of thyroxine replacement. The study design did not allow comparison of the relative impact of the psychological issues related to emotional distress of diagnosis and fear of recurrence. Bongers et al.[31] reported a long-term follow-up study of 529 patients[31] and no significant differences in HRQOL between HT and TT were observed. Their findings are supported by Shah et al.,[19] who reported comparable HRQOL in the short term (12 months) regardless of surgical extent. However, HT was associated with higher levels of recurrence anxiety. It is well known that worry about recurrence continues long-term and significantly affects HRQOL.[16,32] The importance of the relationship between surgery extent and recurrence concern should be explored further.

Other. The negative HRQOL repercussions of neck dissection was highlighted, in particular shoulder complaints, loss of neck sensation, swallowing discomfort, and reduced chewing ability.[17,20,22,33] Almeida et al.[20] found patients who had level II to VI neck dissections to have significantly worse chewing and shoulder scores relative to QOL, in comparison to those who underwent level VI alone. Lee et al.[22] reported the potential benefit from robotic surgery in patients undergoing neck dissection. They report better swallow function, less paresthesia of skin, and improved scar satisfaction.

The surgical risk of hypoparathyroidism following central compartment lymphadenectomy was acknowledged by numerous articles. The prevalence of permanent hypoparathyroidism varied significantly (0–18.5%),[19,22]

Table 4. Included studies within the surgical subcategory.

Author, year	Design	TC grade	Patients, n	Clinical characteristics	Questionnaire type	Critical appraisal	Main findings
Huang et al., 2004[18]	Cross-sectional	Differentiated TC (91.8%), anaplastic TC (0.7%), medullary TC (4.1%)	146	Age, sex, education status, employment, treatment received, postoperative symptoms, scar	QLI	Risk of selection bias (convenience sampling) and recall bias	Patients at 19–36 months postoperation had lower QOL compared with those within 18 months; fatigue, chills, and perceived higher impact of surgical scar were negatively associated with QOL; social support had positive QOL effects
Dagan et al., 2004[17]	Cross-sectional	Well-differentiated TC	20	Age, sex, surgical intervention, cancer staging, calcium replacement	UW-QOL	Risk for nonresponse bias (survey via mail); small sample size	QOL good although lower than expected compared with other cancers; no significant difference in QOL between advanced and early disease; better QOL in neck dissection patients <45 years old
Shah et al., 2006[19]	Prospective cohort study	Well-differentiated TC	76	Age, sex, symptoms, surgical treatment, RIA, postoperative complications	SF-36, QOL-TV	Limited discussion regarding recruitment and eligibility	Patients experienced a greater drop in QOL during the first 6 months following surgery when compared with patients with benign disease; QOL not significantly different in patients treated with TT vs HT
Almeida et al., 2009[20]	Cross-sectional	Differentiated TC	154	Age, sex, treatment received, ASA classification	UW-QOL	Recall bias likely and limited response rate (154/400)	Patients with RIT with doses higher than 150 mCi are at risk of poor QOL; the presence of comorbidities was the second predictor of worse QOL, following RIT
Gómez et al., 2010[21]	Cross-sectional	TC, not otherwise specified	75	Time since diagnosis, postoperative complications and symptoms	SF-36	Limited detail regarding recruitment and eligibility; no information regarding TC grade	A high, positive, and directly proportional correlation between time after thyroidectomy and the degree of psychological well-being and QOL reported by patients
Lee et al., 2013[22]	Cross-sectional	Papillary TC	128	Age, sex, BMI, TNM, surgical intervention, hospital stay, operation time	VHI 10, NDII	Risk of recall bias; ability to pay for treatment variant and potential confounding sociodemographic effects not explored	Robotic thyroidectomy with modified radical neck dissection resulted in better QOL outcomes and reduction in sensory changes and swallowing discomfort in comparison to open thyroidectomy; robotic thyroidectomy was a significantly longer operative time
Choi et al., 2014[23]	Prospective observational study	Differentiated TC	97	Age, sex, BMI, relationship status, education, smoker, type of scar, symptoms	DLQI	Two blinded dermatologist assessments of scars using validated scale; recall bias likely	Regardless of scar type, postthyroidectomy scars negatively affect QOL; patients with scar symptoms (e.g. pain, pruritis, and tightening sensations) showed the greatest QOL impairment
Song et al., 2014[24]	Cross-sectional	Papillary TC	111	Age, sex, marital status, education, religion, TNM, treatment received, postoperative complications	UW-QOL, QOL-TV	Limited detail regarding recruitment approach; confounding factors identified and accounted for	Patients who underwent robotic thyroidectomy reported higher satisfaction scores compared to patients receiving conventional thyroidectomy; no significant difference in postoperative complications between robotic and conventional surgical groups
Lee et al., 2014[25]	Prospective case series	Papillary TC	116	Age, sex, TNM, treatment received, hospital stay	BIS	High dropout rate (31%) with potential attrition bias; limited detail regarding recruitment approach	Robotic thyroidectomy provides better self-body image and improves QOL compared with conventional open thyroidectomy by avoiding a noticeable scar in female patients with papillary TC
Lee et al., 2016[26]	Cross-sectional	Differentiated microcarcinoma	308	Age, sex, tumor size, lymph nodes, surgical treatment received	EORTC-QLQ-C30	Confounding factors such as endoscopic approach and different surgeons were not accounted for; lack of covariate information and statistical investigation	Endoscopic thyroidectomy offers more rapid recovery of emotional and physical function than open thyroidectomy

(Continued)

Table 4. (Continued)

Author, year	Design	TC grade	Patients, n	Clinical characteristics	Questionnaire type	Critical appraisal	Main findings
Roerink et al., 2017[33]	Cross-sectional	Differentiated TC (88.1%), medullary TC (2.8%)	190	Age, sex, TNM, treatment received, ASA, thyroid bloods, relationship status, education level	EORTC-QLQ-C30	Risk for nonresponse bias (survey via mail); patients recruited their own "health subject" comparator, introducing significant selection bias	QOL reduced in patients who have experienced TC, in comparison to healthy controls; shoulder complaints had a higher prevalence in patients who underwent level V neck dissection; shoulder complaints represent an underestimated problem and correlate with negative QOL scores
Nickel et al., 2019[30]	Content analysis	Differentiated TC	1005	Age, sex, residential area, education, time since diagnosis, treatment received, TNM	Study-specific, K10	Risk for interviewer bias due to nature of study-specific verbal questionnaire; reliant on nurse accuracy in recording patient responses and researcher's interpretation	HRQOL issues more prevalent among patients who have TT rather than HT
Bongers et al., 2020[31]	Cross-sectional	Differentiated TC	270	Age, sex, family history, income, time since diagnosis, treatment received, comorbidities	EORTC-QLQ-C30, THYCA-QoL, ASC	Low response rate (51%) with probable nonresponse bias; confounders identified and accounted for	Long-term QOL was not significantly different between patients with low-risk differentiated TC treated with TT compared with HT; worry about recurrence significantly varied between TT and HT groups, with those undergoing HT being more affected
Kurumety et al., 2019[29]	Cross-sectional	TC, not otherwise specified	1922	Age, sex, ethnicity, treatments received, time since surgery	PROMIS score	Response bias highly likely as patients asked to recall historic perceptions and self-reported data	The impact of postthyroidectomy neck appearance on QOL appears to be mild and transient and returns to preoperative levels after 2 years
Kong et al., 2019[27]	Cohort prospective study	Papillary thyroid microcarcinoma	395	Age, sex, tumor size, BMI, thyroid bloods, follow-up period, treatments received	THYCA-QoL	Self-selection bias likely due to nature of the study; short follow-up period (8 months)	QOL is different according to the type of treatment received: improved physical and psychological health at follow-up for patients in active surveillance rather than immediate surgery; QOL in relation to physical health had severe deterioration in immediate surgery group
Jeon et al., 2019[28]	Cross-sectional	Papillary thyroid microcarcinoma	191	Age, sex, marital status, education level, socioeconomic status, time since diagnosis, treatments received	THYCA-QoL, SF-12, FoP	Significant differences in baseline patient characteristics and time intervals between completing questionnaires	Patients who underwent lobectomy experienced more HRQOL problems than those managed by active surveillance

ASA: American Society of Anesthesiologists; ASC: Assessment of Survivor Concerns; BIS: Body Image Scale; BMI: body mass index; DLQI: Dermatology Life Quality Index; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FoP: Fear of Progression; HRQOL: health-related quality of life; HT: hemithyroidectomy; NDII: Neck Dissection Impairment Index; PROMIS: Patient-Reported Outcomes Measurement Information System; QOL: quality of life; QOL-TV: Quality of Life Thyroid Version; RIA: radioiodine ablation; RIT: radioactive iodine treatment; SF: Short Form; TC: thyroid cancer; THYCA-QoL: Thyroid Cancer–Specific Quality of Life Questionnaire; TNM: tumor/node/metastasis; TT: total thyroidectomy; UW-QOL: University of Washington QOL; VHI 10: Voice Handicap Index 10.

Table 5. Included studies within the medical subcategory.

Author, year	Design	Grade	Patients, n	Clinical characteristics	Questionnaire type	Critical appraisal	Main findings
Golger et al., 2003[43]	Cross-sectional	Well-differentiated TC	181	Sex, age, histology, stage well-differentiated TC, previous treatment, thyroid bloods	SF-36	Little information regarding recruitment process; risk of recruitment bias	Significant changes in HRQOL were obtained during T4 withdrawal; the degree of functional impairment was not severe and did not result in loss of employment time
Crevenna et al., 2003[51]	Cross-sectional	TC, not otherwise specified	150	Sex, age, treatment history, thyroid bloods, period since diagnosis, postoperative complications	SF-36	No information about TC diagnosis and histology; consecutive recruitment of patients with good follow-up period (5.5 years mean)	"Cured" patients taking levothyroxine therapy had a reduced HRQOL in mental health, physical, social functioning, and vitality within the first year of diagnosis; concomitant disease and age significantly negatively influenced HRQOL
Giusti et al., 2005[39]	Cross-sectional	Differentiated TC	61	Sex, age, time from diagnosis, TNM, thyroid bloods	KSQ, HAM-D	High dropout rate (30/61) between QOL evaluations; risk of recall bias	DTC thyroid hormone withdrawal induces slight but significant deterioration of QOL, which is tolerated well by the majority
Schroeder et al., 2006[34]	Cross-sectional	Differentiated TC	229	Age, sex, type of TC, thyroidectomy, time since surgery, RAI	SF-36	Low dropout rate (4/229) throughout study; limited information regarding recruitment process, selection bias risk	Short-term hypothyroidism after L-T4 withdrawal is associated with a significant decline in HRQOL, which is abrogated by rTSH use
Eustatia-Rutten et al., 2006[52]	Prospective single-blinded randomized study	Differentiated TC	24	Age, sex, TNM, histology, dose 1131, duration of TSH-suppressing treatment	HADS, MFI-20, SF-36	Small sample size; single-blind randomization; short follow-up period (6 months), risk of selection bias	L-thyroxine dose was replaced by study medication containing L-thyroxine or L-thyroxine plus placebo; HRQOL in patients with long-term subclinical hyperthyroidism in general is preserved; restoration of euthyroidism does not affect QOL
Chow et al., 2006[35]	Cross-sectional	Differentiated TC	58	Sex, histology, education, employment, job nature, marital status, smoker, alcoholic, finance	FACT-G	Risk of reporting bias given nature of patients recalling historic thoughts/feelings	HRQOL declines with time of T4 withdrawal in Chinese patients with DTC; a 4-week period of withdrawal adversely affects physical, social, emotional, and global aspects of HRQOL
Davids et al., 2006[44]	Cross-sectional	Well-differentiated TC	181	Sex, age, histology, stage well-differentiated TC, previous treatment, thyroid bloods	QOL-TV	Limited information regarding participant recruitment, risk of selection bias; no control group for comparison of results	QOL-TV is a more appropriate tool than SF-36 to assess the impact of an induced hypothyroid state on QOL; there was a statistically significant difference between QOL scores following resumption of T3/T4 combination therapy
Tagay et al., 2006[40]	Cross-sectional	Differentiated TC (98%); insular carcinoma (2%)	136	Age, sex, education, relationship status, employment, histology	SF-36, HADS, POMS, BDI, study-specific	Consecutive recruitment of participants and low dropout rate (24/160); short follow-up period, risk of bias	HRQOL was distinctly reduced in DTC patients undergoing thyroid hormone withdrawal; the high frequency of anxiety should be considered in the aftercare of patients with TC
Tan et al., 2007[45]	Cross-sectional	Differentiated TC	152	Age, sex, education, race, survey language	SF-36	Limited information about confounding factors, including thyroid hormone status and extent of disease	Patients experience lifelong stress from the diagnosis of cancer, associated with poorer HRQOL; elderly and poorer educated need more attention
Taïeb et al., 2009[47]	Prospective randomized clinical trial	Differentiated TC	68	Age, sex, education, number of children, marital status, professional activity, TNM, treatment received	FACIT-F (includes FACT-G and FS), CES-D, BDI, STAI	Clear inclusion and exclusion criteria; prospective randomization with open label, risk of reporting bias	rhTSH preserves QOL of patients undergoing RRA with similar rates of ablation success compared to hypothyroidism
Lee et al., 2010[46]	Randomized controlled, open-label trial	Differentiated TC	291	Age, sex, BMI, papillary/follicular carcinoma, TNM, urinary iodine concentration	Study-specific, HAM-D, KSQ	Clear inclusion and exclusion criteria; clear randomization process; short follow-up, risk of bias within results	QOL was best preserved in the rTSH group as opposed to T4-withdrawal and T3-withdrawal groups

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Table 5. (Continued)

Author, year	Design	Grade	Patients, n	Clinical characteristics	Questionnaire type	Critical appraisal	Main findings
Taïeb et al., 2011[50]	Longitudinal study	Differentiated TC	83	Age, sex, educational level, marital status, children, occupation, TNM	FACIT	Consecutive recruitment of participants; identification and accounting of confounding factors	Radioiodine ablation does not affect medium term QOL; medium term QOL is mainly determined by preablation QOL scores
de Oliveira Chachamovitz et al., 2013[36]	Cross-sectional	Differentiated TC	92	Age, sex, BMI, lifestyle disease duration, menopause, muscle function	SF-36, Chalder questionnaires	Low educational status excluded, risk of exclusion bias; single time measurement of fatigue, potential systematic bias included in patients and control results	SCH (induced by levothyroxine) in DTC patients had worse muscle function compared with EU group; SCH patients also have worse self-perception of fatigue by QOL
Dingle et al., 2013[55]	Cross-sectional	Differentiated TC	145	Age, sex, race, diagnosis, AJCC stage, neck dissection status	MDADI, UW-QOL, XeQOLS	Low response rate (145/379), possible nonresponse bias and recruitment bias	Patients with DTC treated with RAI exhibited an increased risk for sialadenitis as well as a reduction in swallowing-related and global head and neck QOL
Nygaard et al., 2013[48]	Double blinded crossover study	Differentiated TC	56	Age, sex, histology, T3 dosages	SF-36	Randomized double-blinded placebo-controlled crossover study; low risk of bias	Significant reduction in QOL for those treated with liothyronine (L-T3) in comparison to those treated with rTSH over 10 days
Valle et al., 2013[53]	Prospective longitudinal cohort study	Differentiated TC	47	Age, sex, pathology, TNM, duration of disease, treatment received	FACIT-F	Minimal information regarding recruitment, possible selection bias	FACIT-F correlated with TSH, but was not sensitive to detect mild hypothyroidism
Emmanouilidis et al., 2013[49]	Prospective randomized trial	Differentiated TC	44	Age, sex, histology, tumor size, TNM, UICC, risk category, sick leave	Study-specific	Nonvalidated HRQOL questionnaire; limited information regarding recruitment, possible selection bias	Radioablation in euthyroidism in quick succession after thyroidectomy did not lead to higher tumor recurrence rates and was advantageous with respect to QOL, sick leave time, and job performance
Vigário et al., 2014[41]	Cross-sectional, nonblinded randomized controlled trial	Differentiated TC	82	Age, sex, disease duration, thyroid function bloods, menopause, BMI	WHOQOL-BREF	Nonblinded trial, risk of reporting bias	TSH suppressive therapy with L-T4 patients have reduced QOL in comparison to euthyroid patients; this QOL reduction improved following a 3-month exercise program
Rubic et al., 2014[10]	Prospective case series	Differentiated TC	150	Age, sex, education level, follow-up, ablation, TSH	QOL-TV	Lack of control group and comparison of responses; limited information regarding histology and progression of disease; risk of missed confounder analysis	Patients undergoing thyroid hormone withdrawal underwent the greatest QOL changes in psychological (distress caused by initial diagnosis, surgery, ablation, fear of metastases) and social (distress in the family caused by illness) domains; females had more difficulties than males
Locati et al., 2014[57]	Prospective case series	Differentiated TC (87%), medullary TC (12%), oncocytic TC (2%)	52	Age, sex, race, histology, anthracycline refractory, prior thyroidectomy, sites of disease	MDASI	Small sample size; risk of sampling bias due to altering eligibility criteria during recruitment of the study to include further histologic TC types	QOL was maintained during treatment with axitinib, and no significant deterioration in symptoms or interference in daily life caused by symptoms was observed
Borget et al., 2015[37]	Randomized controlled trial	Differentiated TC	684	Not stated	SF-36, EuroQoL-5D	Limited information regarding recruitment, risk of selection bias	THW caused a clinically significant deterioration of HRQOL, whereas HRQOL remained stable with rhTSH; this deterioration was transient with no difference 3 months later

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Table 5. (Continued)

Author, year	Design	Grade	Patients, n	Clinical characteristics	Questionnaire type	Critical appraisal	Main findings
Dadu et al., 2015[15]	Cross-sectional	Medullary TC	7	Age, sex, race, distant metastases, calcitonin, treatment at enrollment	MDASI-THY	Small sample size; short follow-up period (3 weeks); risk of reporting bias	Diarrhea symptom scores improved with medication use; the worst MDASI-THY symptoms included fatigue, disturbed sleep, feeling sleepy during the day, distress, and sadness
Massolt et al., 2016[54]	Cross-sectional	Differentiated TC	143	Age, sex, BMI, time since diagnosis, number of drugs, treatment, thyroid bloods	RAND-36, ThyPRO, MFI-20	Clear inclusion and exclusion criteria; marked differences in characteristics between study sample and reference group; risk of bias	Subjects (on LT4 monotherapy) had lower HRQOL compared with reference groups, except for physical functioning and bodily pain; no evidence that increased dose improves symptoms
Badihian et al., 2016[38]	Cross-sectional	Differentiated TC	29	Age, sex, TNM, stress factors, immigration, spouse death, income, thyroid bloods	WHOQOL-BREF, BDI-II, HADS	Small sample size and lack of control group; limited detail about recruitment methods, risk of selection bias	DTC patients studied pre-levothyroxine withdrawal and 1-month post; decreased QOL after short-term hypothyroidism (especially physical health and psychological dimensions), also increased depression and anxiety after levothyroxine withdrawal
Jung et al., 2017[42]	Cross-sectional	Papillary TC	180	Age, education, marital status, employment, menstrual state, comorbid conditions, time since diagnosis, thyroidectomy	AFI, FACIT-F, PSQI, TIWI	Low risk of bias	Women receiving thyroid hormone replacement therapy after thyroidectomy are at risk for attention and working memory problems; coexisting symptoms and culture-related women's burden affected perceived cognitive dysfunction
Barbus et al., 2018[56]	Cross-sectional	Differentiated TC	54	Age, sex, histology, RAI, surgery	Study-specific	Limited information regarding potential confounders, including educational status and previous radioiodine treatment; risk of bias	Pre-RIT questionnaire reported strong confidence in the medical team, good and accurate information regarding treatment, and that >50% had anxiety before RIT; post-RIT questionnaire revealed no fear of isolation and most patients would undergo another treatment

AFI: Attentional Function Index; AJCC: American Joint Committee on Cancer; BDI: Beck Depression Inventory; BMI: body mass index; CES-D: Center for Epidemiological Studies-Depression; DTC: differentiated thyroid cancer; EU: euthyroid; FACIT: Functional Assessment of Chronic Illness Therapy; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-G: Functional Assessment of Cancer Therapy–General; HADS: Hospital Anxiety and Depression Scale; HAM-D: Hamilton Depression Rating Scale; HRQOL: health-related quality of life; KSQ: Kellner Symptoms Questionnaire; MDADI: M.D. Anderson Dysphagia Inventory; MDASI: M.D. Anderson Symptom Inventory; MDASI-THY: M.D. Anderson Symptom Inventory–thyroid cancer module; MFI-20: Multidimensional Fatigue Index–20; POMS: Profile of Mood States; PSQI: Pittsburgh Sleep Quality Index; QOL: quality of life; QOL-TV: Quality of Life Thyroid Version; RAI: radioactive iodine; RAND-36: RAND 36-item health survey; rhTSH: recombinant human thyroid-stimulating hormone; RIT: radioactive iodine treatment; RRA: radioiodine remnant ablation; rTSH: recombinant thyroid-stimulating hormone; SCH: subclinical hypothyroidism; SF: Short Form; STAI: State-Trait Anxiety Inventory; TC: thyroid cancer; THW: thyroid hormone withdrawal; ThyPRO: Thyroid-Related Patient-Reported Outcome; TIWI: Three-Item Worry Index; TNM: tumor/node/metastasis; TSH: thyroid-stimulating hormone; UICC: Union for International Cancer Control; UW-QOL: University of Washington QOL; XeQOLS: Xerostomia-Related Quality of Life Scale.

Table 6. Included studies within the general subcategory.

Author, year	Design	Grade	Patients, n	Clinical characteristics	Questionnaire type	Critical appraisal	Main findings
Schultz et al., 2003[58]	Cross-sectional	TC, not otherwise specified	518	Sex, age at diagnosis, marital status, time from diagnosis, affected health, ethnicity	Study-specific	Limited information regarding histologic diagnosis, surgical treatment, and radiation modality; risk of missed confounder analysis	TC survivors generally report good health long term but describe distinct, lasting medical problems including symptoms of thyroid dysregulation
Hoftijzer et al., 2008[59]	Cross-sectional	Differentiated TC	153	Age, sex, educational level, marital status, cancer, treatment, thyroid bloods	SF-36, HADS, MFI-20	Limited information regarding recruitment, risk of selection bias	Despite cure, excellent prognosis, and moderate aggressive treatment, DTC patients have decreased QOL that may be restored only after years of follow-up
Roberts et al., 2008[79]	Cross-sectional	TC, not otherwise specified	62	Age, ethnicity, work, education, marital status, histology, time since diagnosis	EORTC-QLQ-C30, QOL-TV, Information support and care delivery needs	Small sample size, low response rate (43%); risk of nonresponse bias; potentially unrepresentative sample regarding educational status, risk of selection bias	Results indicate that QOL is generally high in this population and that most information needs are adequately addressed in the context of routine care
Pelttari et al., 2009[60]	Cross-sectional	Differentiated TC	341	Sex, tumor type; no table of characteristics	15D	Limited information regarding histology surgery, RIA and hormone replacement, and effects of these factors on HRQOL	After long-term follow-up, cured patients do not have overall impaired HRQOL; DTC patients with a long duration of cure demonstrate an age-related decline in HRQOL, which is comparable to that seen in the general population
Hirsch et al., 2009[80]	Cross-sectional	TC, not otherwise specified	110	Age, sex, family, education, employment, duration of disease, disease stage, treatment received, evidence of recurrence	IPQ-R	No information regarding histologic diagnosis, risk of selection bias	The number of iodine treatments significantly negatively affected illness identity, severity of consequences, and emotional representation; less-educated patients as well as patients who required repeated radioactive iodine treatments were most susceptible
Malterling et al., 2010[105]	Cross-sectional	Differentiated TC	130	Age, sex, type of cancer, metastases, clear margins, TNM	SF-36	Thorough discussion regarding recruitment; 10-year patient follow-up; clear statistical analysis	Small differences in HRQOL using SF-36 between TC groups and normative Swedish population
Lee et al., 2010[61]	Cross-sectional	Differentiated TC	316	Age, sex, marital status, education, employment status, religious state, finance	EORTC-QLQ-C30, HADS, BFI	Homogenous study population, risk of inapplicability to general population; selection bias risk due to socioeconomic demographics within study	Disease-free survivors of DTC experience significantly decreased HRQOL; anxiety, depression, and fatigue were the major determinants of decreased HRQOL
Watt et al., 2010[85]	Longitudinal	TC, not otherwise specified	907	Age, sex, diagnosis, time since diagnosis, mode of treatment, current thyroid function, thyroid volume	ThyPRO	Risk of selection bias, as limited information regarding recruitment; unable to compare validity between TC groups	ThyPRO had good clinical validity and good test–retest reliability; recommended for use in clinical studies of patients with thyroid diseases
Giusti et al., 2011[73]	Longitudinal	Differentiated TC	128	Age, sex, MBMI, time since surgery, thyroid bloods, second cancer	study-specific, HAM-A, HAM-D, KSQ	Nonvalidated study-specific questionnaire; comparatively sound control group utilized	A wide variation in illness perception in DTC subjects, which is generally unrelated to the favorable clinical follow-up; increased age and severity of staging need particular attention
Singer et al., 2012[62]	Cross-sectional	TC, not otherwise specified	121	Age, sex, histology, TNM	EORTC-QLQ-C30	Response bias risk due to recruitment via inpatient rehabilitation postoperatively	Patients with TC at the beginning of inpatient rehabilitation experience more QOL problems; clinicians should be aware that QOL is not directly related to cancer prognosis
Costa et al., 2012[106]	Cross-sectional	TC, not otherwise specified	154	Age, sex, time since diagnosis, marital status, education, employment, income, disease present, stage, treatment	SRGS-R, PTGI, HADS, Ryff's well-being scale, FACIT, positive and negative affect schedule, self-assessed wisdom scale, single item question	Low response rate of patients (154/300) and partners (32/121), risk of nonresponse bias; limited information regarding TC histology	Benefit finding evidenced associations with greater positive affect, wisdom, spiritual well-being, and lifestyle changes

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Table 6. (Continued)

Author, year	Design	Grade	Patients, n	Clinical characteristics	Questionnaire type	Critical appraisal	Main findings
Roerink et al., 2013[91]	Cross-sectional	Differentiated TC	159	Age, sex time since diagnosis, pathology, TNM, treatment received, complications	DT, PL, HADS, ICQ	Retrospective opinions of patients sort, risk of response bias	The prevalence of distress is high in patients with DTC even after long-term remission; physical and emotional problems were the main sources of distress
Husson et al., 2013[64]	Cross-sectional	Differentiated TC (94%), medullary TC (6%)	306	Age, sex, type, treatment, stage, comorbidity, partner, education level, employment status	FAS, THYCA-QoL, HADS	Risk of selection bias, as age of short- and long-term TC survivors did not differ; limited information regarding hormonal treatment, risk of missing this confounding factor	40% of survivors report a high level of fatigue up to 20 years after diagnosis; short- and long-term survivors report higher levels of fatigue; HRQOL and psychological distress were highly associated with fatigue
Husson et al., 2013[63]	Retrospective questionnaire	Differentiated TC (96%), medullary TC (4%)	306	Age, sex, type, treatment, stage, comorbidity, partner, education level, employment status	EORTC-QLQ-C30, THYCA-QoL	Lack of long-term follow-up; risk of nonresponse bias as younger patients with stage I papillary TC were unable to be contacted more frequently (unverified addresses)	Survivors have worse HRQOL compared to the normative population; specific neuromuscular, sympathetic, concentration, and psychological problems last long after diagnosis and are more strongly associated with HRQOL than sociodemographic and clinical factors alone
Husson et al., 2013[86]	Retrospective series	Differentiated TC	306	Age, sex, type, treatment, stage, comorbidity, partner, education level, employment status	EORTC-QLQ-C30	Lower reliability observed for some aspects of scale, possibly due to limited variability of scores; risk of recruitment bias (45% patients diagnosed >10 years ago)	THYCA-QoL is the first TC-specific HRQOL questionnaire developed using standard methodologically proven guidelines
Gal et al., 2013[68]	Cross-sectional	Well-differentiated TC	34	Age, sex, diagnosis, time since surgery, treatment	QOL-RTI, H+N companion module	Small sample population	There is measurable impact on QOL measures with adjuvant therapy; patients with advanced disease requiring external beam radiation demonstrate additional QOL decrement in the areas of pain and swallowing
Vega-Vázquez et al., 2015[81]	Cross-sectional	Differentiated TC	75	Age, sex, histology, TNM, size, cancer remission, treatment, thyroid bloods	UW-QOL	Risk of information and response bias, as questionnaire performed in face to face setting	Despite its good clinical prognosis, QOL domains can be affected by TC treatment and its side effects
Jeong et al., 2015[87]	Cross-sectional	Differentiated TC	227	Age, sex, marital status, education level, financial status, stage, thyroid bloods, histology, treatment	THYCA-QoL, EORTC-QLQ-C30, BFI, BEPSI-K, PHQ-9, GSSSAD	Risk of recruitment bias as sample unrepresentative of entire TC population, as most participants were female, with early-stage DTC	THYCA-QoL was found to be reliable, valid, and suitable for use in primary care settings for measuring the HRQOL of Korean-speaking TC survivors
Gamper et al., 2015[107]	Longitudinal	Differentiated TC	241	Age, sex, histology, stage, general population	EORTC-QLQ-C30	Overrepresentation of follicular TC in sample population; risk of nonresponse bias, as number of participants in monitoring program decreased through time	Psychosocial distress, persistent problems with fatigue, and the resulting difficulties at work and during leisure time are frequently overlooked in clinical practice and often falsely attributed to hypothyroidism
Hedman et al., 2016[32]	Cross-sectional	Differentiated TC	279	Age, sex, education level, comorbidity, primary treatment, patient reported recurrence	SF-36, study-specific	Study-specific nonvalidated questionnaire utilized	HRQOL in those with a recurrence was significantly lower than in those without concerns of a recurrence
Li et al., 2016[108]	Cross-sectional	Differentiated TC	231	Age, sex, education, civil status, employment, years since diagnosis, histology, stage of cancer, comorbidities, treatment received	EORTC-QLQ-C30	Limited information regarding recruitment, risk of selection bias	EORTC-QLQ-C30 has been developed and validated for Filipino adults
Metallo et al., 2016[93]	Cross-sectional	Differentiated TC	45	Age, sex, age at diagnosis, time since diagnosis, histology, TNM, radioiodine treatment, marital status, education, profession, smoking, BMI	SF-36, ISP25	Risk of nonresponse and selection bias (12/90 nonrespondents and 29/90 unable to be contacted or refusal)	Long-term HRQOL, self-esteem, and pregnancy outcomes are not affected in young female survivors of DTC

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Table 6. (Continued)

Author, year	Design	Grade	Patients, n	Clinical characteristics	Questionnaire type	Critical appraisal	Main findings
Singer et al., 2016[82]	Cross-sectional	Differentiated TC (77.3%) medullary TC (15.5%), anaplastic TC (3.6%)	110	Sex, age, education, histology, TNM, treatment received	EORTC-QLQ-C30, study-specific	Difficulty adjusting for covariates; as such, risk of bias within comparative statistics; low number of anaplastic TC participants, risk of being unrepresentative of this population	In all groups except in patients with anaplastic cancer, being afraid of disease recurrence, employment, and sudden attacks of tiredness reduced HRQOL
Goldfarb et al., 2016[67]	Cross-sectional	Differentiated TC (97.5%), medullary TC (2.5%)	277	Age, age at diagnosis, sex, ethnicity, relationship, insurance, education, employment, histology, treatment	THYCA-QoL, SF-12, SF-6D	Risk of selection bias during recruitment, as participants had to be within TC survivor group THYCA during enrollment	In young adult survivors, neuromuscular, concentration, and anxiety complaints, along with the presence of a comorbidity, had the greatest impact on HRQOL
Tamminga et al., 2016[94]	Cross-sectional	Differentiated TC	257	Age, sex, marital status, education, treatment received, comorbidities, financial difficulties	EORTC-QLQ-C30, HADS-A, HADS-D, THYCA-QoL, FAS, SF-12	Unable to assess certain confounding factors, such as type of occupation; risk of missing these in response analysis	TC survivors face problems when obtaining life insurance, and older, fatigued, and lower educated TC survivors may be at risk of not having employment
Applewhite et al., 2016[76]	Cross-sectional	Differentiated TC	1174	Age, sex, marital status, education, recruitment source, time since diagnosis, stage, treatment	QOL-CS Thyroid	Risk of response bias, depending on whether participants completed the questionnaire face to face or at home/ in private	Survivors report an overall similar QOL to other cancers; many patients feel they have a lack of support from families and physicians; they are frequently given the impression that TC is the "good kind of cancer"; patients feel such comments trivialize the diagnosis and decreases their QOL
Wu et al., 2016[77]	Cross-sectional	Differentiated TC	60	Histologic type	EORTC-QLQ-C30, SDS, SAS	Limited information regarding recruitment, risk of selection bias; not registered with any trial registry	After 1 year of a consistent psychological and behavioral intervention, patients with DTC demonstrated improved QOL and mental health outcomes
Shin et al., 2016[109]	Cross-sectional	TC, not otherwise specified	21	Age, sex, weight, blood pressure, thyroid bloods	SF-12, PHQ-9	Small sample size	Local brain functional connectivity is increased in the acute hypothyroid state; higher FC correlates with a poorer mental QOL and increased depression in the hypothyroid state
Drabe et al., 2016[110]	Cross-sectional	Differentiated TC	71	Age, sex, education, employment, partnership duration, number of children, living arrangement, time since diagnosis, treatment	BAI, BDI, BFI, WHOQOL-BREF, EORTC-QLQ-C30	Retrospective nature of treatment burden, risk of response bias; risk of nonresponse bias	Patients had significantly higher mean anxiety scores than the norm; female partners expressed the highest burden, associated with fatigue levels in male patients and with anxiety, depression, and fatigue levels in female patients
Nies et al., 2017[92]	Cross-sectional	Differentiated TC	67	Sex, age at evaluation, age at diagnosis, follow-up duration, nationality, marital status, education, employment	SF-36, MFI-20, HADS, THYCA-QoL	Small sample size; non-normally distributed data limited ability for multivariable regression and analysis	Long-term QOL in survivors of pediatric DTC was normal; survivors experienced mild impairment in physical problems, mental fatigue, and various TC-specific complaints
Rogers et al., 2017[84]	Cross-sectional	Differentiated TC	169	Age, sex, histologic type, TNM, time from first treatment	EORTC-QLQ-C30, THYCA-QoL, Emotion Thermometers, FoR screening item, single-item question	Risk of nonresponse bias, as reduced response rates from different age categories	HRQOL was generally good; global health status and emotional function were the functional domains most adversely affected; voice problems had a low impact on QOL, despite recurrent injury to the laryngeal nerve being a recognized complication after thyroidectomy
Singer et al., 2017[89]	Cross-sectional	Differentiated TC (80%), medullary TC (12%), anaplastic TC (3%)	182	Age, sex, education, histology, TNM, treatment received, time and help required for completing the questionnaire	EORTC-QLQ-C30, EORTC-QLQ-THY34	Small number of patients with anaplastic TC, potentially unrepresentative of this sample	EORTC-QLQ-THY34 moves onto next stage of validation; patients mentioned issues including shoulder dysfunction, face/neck sensitivity, and menstruation problems
Hedman et al., 2017[65]	Cross-sectional	Differentiated TC	279	Sex, education level, comorbidity, menopause, primary treatment, patient reported recurrence	SF-36	Risk of selection bias, considering method of recruitment via retrospective methodology	Patients with a single symptom, e.g. fatigue, sleeping disorder, and irritability, had significantly lower HRQOL compared with those without any specific symptoms

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Table 6. (Continued)

Author, year	Design	Grade	Patients, n	Clinical characteristics	Questionnaire type	Critical appraisal	Main findings
Lubitz et al., 2017[111]	Cross-sectional	Papillary TC	117	Age, sex, ethnicity, education level, marital status, number of children, family history, treatment received, complications, histology	SF-6D, EuroQoL-5D, HUI2, HUI3	Risk of sampling bias, as unrepresentative sample of TC patients regarding ethnicity and socioeconomic status	HRQOL scores declined at 2 weeks postoperatively and returned to pretreatment levels at 6 months
Gou et al., 2017[112]	Prospective observational	Papillary TC	186	Age, sex, ethnicity, education, marital status, employment, income, comorbidities, smoking, alcohol	SF-36	Risk of selection bias, limited information regarding recruitment methods	Decreased SF-36 scores, even 2 years after surgery
Bernardo et al., 2018[88]	Cross-sectional	Differentiated TC	104	Age, sex, marital status, education, employment, comorbidities, treatment received	EORTC-QLQ-C30, SF-36	Risk of selection bias, as participants recruited from outpatient setting; potentially not representative of whole DTC group	EORTC-QLQ-C30 Tagalog had acceptable convergent and discriminant validity and internal consistent reliability for the scales of global health, role, social and emotional functioning and nausea/vomiting when applied among adult Filipinos
Barbus et al., 2018[83]	Cross-sectional	TC, not otherwise specified	135	Age, sex, physical issues, psychological issues, social concerns and spiritual aspects	QOL-TV	Risk of selection bias, recruitment from in-patient facilities; limited investigation into TNM stage and tumor markers, which could be confounding factors	Initial diagnosis and surgery had a large impact on psychological well-being; TC had a large impact on family and religious activities may help patients restore spiritual well-being
Goswami et al., 2018[113]	Comparative study	Differentiated TC (91.3%), medullary TC (4.8%), anaplastic TC (0.5%)	1743	Sex, race, age, age at diagnosis, disease stage, histologic type, treatment history	PROMIS score	Risk of selection bias as participants were required to have Internet access; participants were also part of a voluntary support network	Survivors may be encumbered with greater psychological and social burdens than survivors of cancers that have a worse prognosis
Hedman et al., 2018[114]	Cross-sectional	Differentiated TC	349	Sex, age, education, comorbidities, marital status, menopause, histology, TNM, treatment received, recurrence	SF-36, study-specific	Limited information regarding recruitment methods, risk of selection bias	HRQOL was substantially affected at the time of diagnosis, with some improvements after 1 year
Wang et al., 2018[69]	Cross-sectional	Differentiated TC (94%), undifferentiated TC (6%)	970	Sex, education, marital status, employment, income, activity, age, histology, diet, TNM, treatment received, time since diagnosis	SF-36, EORTC-QLQ-C30	Exclusion of medullary TC patients as authors felt sample size was too small, risk of selection bias; no information regarding stage of TC disease, potentially lost confounder consideration	Sex, education, marital status, employment status, weight status, per capita disposable income, number of surgeries, type of surgery, physical activity per week, fruit and levothyroxine intake per day are important correlates of HRQOL
Büel-Drabe et al., 2018[78]	Cross-sectional	TC, not otherwise specified	71	Age, sex, education, employment, partnership duration, number of children, living arrangement, time since diagnosis	BAI, BDI, BFI, WHOQOL-BREF, RAS, CSFQ-14, study-specific	Low response rate (43.2% of patients and 35% of partners); risk of nonresponse bias	Compared to other cancer sites, TC had a relatively small impact on patient–partner relationships and levels of intimacy
Ryu et al., 2018[90]	Cross-sectional	Differentiated TC	272	Age, sex, TNM, type of surgery	KT-QoL	Limited information about recruitment methodology; risk of selection bias	KT-QoL is a valid instrument for evaluating QoL of Korean patients with TC
McIntyre et al., 2018[66]	Cross-sectional	Differentiated TC	82	Age, time since diagnosis, age at time of diagnosis, sex	EuroQoL-5D	Risk of sample bias as patients recruited from a patient: doctor thyroid conference	QOL is lower than that of the UK population, and lower than in patients with breast, colorectal and prostate cancer; patients may have fatigue and depression requiring antidepressants and/or counseling
Aschebrook-Kilfoy et al., 2018[115]	Cross-sectional	Differentiated TC (73.1%), medullary TC (3.4%)	1077	Sex, race, age, education, annual household income, histology, stage, time since diagnosis	ThyCAT	Difficult to assess bias, as limited information regarding recruitment and data collection reported	ThyCAT can be administered on a smartphone app
Mols et al., 2018[71]	Cross-sectional	Well-differentiated TC	293	Age, time since diagnosis, age at diagnosis, sex, marital status, education level, occupation, comorbidity, TNM	EORTC-QLQ-C30, THYCA-QoL	Excluded medullary TC, risk of selection bias	TC has a greater long-term impact on young survivors; the lower HRQOL in older survivors is probably caused mostly by their age and not the cancer

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Table 6. (Continued)

Author, year	Design	Grade	Patients, n	Clinical characteristics	Questionnaire type	Critical appraisal	Main findings
Papaleontiou et al., 2019[16]	Cross-sectional	Differentiated TC	2215	Age, sex, race, education, TNM, comorbidities, prior depression	Study-specific	Risk of recall bias as patients asked to report outcomes during a historic time period (1 month)	Participants worried about death, harms from treatment, impaired QOL, family risk, and disease recurrence; there was more worry in patients with lower education and in Hispanic and Asian participants; older age and male sex were associated with less worry
van Velsen et al., 2019[116]	Cohort prospective	Differentiated TC	185	Age, sex, histology, ATA risk stratification, TNM, treatment received, hypoparathyroidism, recurrent nerve paralysis	MFI-20, RAND-36, ThyPRO	Risk of selection bias, as patients treated in the tertiary recruitment center may have more aggressive disease	QOL before initial therapy is lower than that in the general population; QOL develops nonlinearly over time in general, with the lowest QOL around RAI therapy, while 2 to 3 years later, it approximates baseline values
Goswami et al., 2019[70]	Cross-sectional	Differentiated TC (91.3%), medullary TC (4.7%), anaplastic TC (0.5%)	1743	Sex, race, age, age at diagnosis, disease stage, histologic type, treatment history	PROMIS score	Risk of selection bias as participants were required to have Internet access; participants were also part of a voluntary support network	The factors associated with significantly worse HRQOL scores across multiple PROMIS domains for TC survivors included patient age and RAI complications
Haraj et al., 2019[75]	Cross-sectional	Differentiated TC	128	Age, sex, antecedents, profession, marital status, recurrence markers, histology, response to treatment, metastases	SF-36, HAM-A, HAM-D	No longitudinal assessment of HRQOL	Alterations of QOL were most significant with radioiodine therapy, its dose, multifocality, and the presence of microcarcinoma
Mongelli et al., 2020[74]	Cross-sectional	Differentiated TC (91.3%), medullary TC (4.7%), anaplastic TC (0.5%)	1743	Age, years since diagnosis, household, sex, ethnicity, treatments, disability, financial characteristics	PROMIS score	Risk of recruitment bias as recruitment from a support network; risk of underrepresentation of lower socioeconomic status participants	Financial distress and negative financial events were common among TC survivors and were associated with poorer HRQOL
Giusti et al., 2020[72]	Longitudinal	Differentiated TC	123	Age, sex, BMI, time since surgery, treatment received	ThyPRO	No collection of socioeconomic data, possible missed confounding variables for analysis	Illness perception is similar after thyroidectomy for malignant or benign pathology; marginal improvement in QOL was noted in DTC subjects over the 5-year study period; In both groups, females showed a greater perception of illness than males
Liu et al., 2019[95]	Randomized control trial (2-arm)	Differentiated TC	120	Sex, age, marital status, residence, educational level, employment status, religion, TNM stage, RAI dose	EORTC-QLQ-C30, SDS, SAS	Moderate sample size; no long-term follow-up after 3-month mindfulness program	8-week mindfulness program significantly improved a wide range of scales in HRQOL and reduced depression/anxiety among DTC patients receiving RIT

ATA: American Thyroid Association; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BEPSI-K: Korean version of the Brief Encounter Psychosocial Instrument; BFI: Brief Fatigue Inventory; BMI: body mass index; CSFQ-14: Changes in Sexual Functioning Questionnaire; DT: Distress Thermometer; DTC: differentiated thyroid cancer; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC-QLQ-THY34: European Organization for Research and Treatment of Cancer of Quality of Life for Thyroid Cancer Questionnaire; FACIT: Functional Assessment of Chronic Illness Therapy; FAS: Fatigue Assessment Scale; FC: functional connectivity; GSSSAD: Goldberg Short Screening Scale for Anxiety and Depression; H+N: Head and Neck; HADS: Hospital Anxiety and Depression Scale; HADS-A: Hospital Anxiety and Depression Scale–Anxiety; HADS-D: Hospital Anxiety and Depression Scale–Depression; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; HRQOL: health-related quality of life; HUI2: Health Utilities Index 2; HUI3: Health Utilities Index 3; ICQ: Illness Cognition Questionnaire; IPQ-R: Illness Perception Questionnaire; ISP25: Physical Self-Inventory; KSQ: Kellner Symptoms Questionnaire; KT-QoL: Korean version of the self-reported thyroid-specific quality of life questionnaire for thyroid cancer patients; MBMI: modified body mass index; MFI-20: Multidimensional Fatigue Index–20; PHQ-9: Patient Health Questionnaire–9; PL: Problem List; PROMIS: Patient-Reported Outcomes Measurement Information System; PTGI: Post-Traumatic Growth Inventory; QOL: quality of life; QOL-CS: QOL–Cancer Survivor; QOL-RTI: Quality of Life–Radiation Therapy Instrument; QOL-TV: Quality of Life Thyroid Version; RAI: radioactive iodine; RAS: Relationship Assessment Scale; RIA: radioiodine ablation; SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; SF: Short Form; SRGS-R: Stress-Related Growth Scale; TC: thyroid cancer; THYCA-QoL: Thyroid Cancer–Specific Quality of Life Questionnaire; ThyPRO: Thyroid-Related Patient-Reported Outcome; TNM: tumor/node/metastasis; UW-QOL: University of Washington QOL.

but no study reported any specific HRQOL changes due to this altered hormonal state.

Medical

The 26 medically focused articles are summarized in Table 5. The most common questionnaire was SF-36 (9). The main HRQOL aspects pertained to the following themes in decreasing frequency:

1. Thyroid hormone withdrawal (THW) prior to radioiodine therapy or imaging
2. Chronic subclinical hyperthyroidism (thyroid-stimulating hormone [TSH] suppression)
3. RIA therapy
4. Therapies for advanced disease
5. Other

Thyroid hormone withdrawal. A significant decrease in HRQOL following the onset of hypothyroid symptoms after THW in preparation for therapy or imaging was frequently reported.[10,34–45] The cross-sectional study by Tagay et al.[40] demonstrated overall anxiety and depression prevalence of 63% and 17%, respectively, in patients undergoing THW. Rubic et al.[10] found significant negative determinants of HRQOL at the time of diagnosis: fear of metastases, family distress, and the need for surgery/RIA. Females had significantly more concerns. Tan et al.[45] found patients of a lower education level and increased age had the most significant HRQOL decrease. Interestingly, they did not find a negative HRQOL impact (as measured by SF-36) for those patients who had ceased thyroxine in the preceding 6 weeks, despite the expectation that it would. Recommencement of thyroid hormone supplementation was shown to improve HRQOL (particularly fatigue) within patients who had experienced a 6-week hypothyroid state following THW.[44]

The relatively positive HRQOL of those patients who were provided with recombinant TSH (rTSH) as opposed to THW was reported.[34,37,39,43,46–50] These positive HRQOL implications further support recent changes to clinical guidance, advising routine use of rTSH prior to imaging or RIA.

Chronic subclinical hyperthyroidism (TSH suppression). The impact of chronic TSH suppression on HRQOL was explored.[41,42,51–54] HRQOL was negatively affected by TSH suppression when compared with euthyroid reference groups with no history of thyroid disease.[41,42,51–54] Jung et al.[42] found women receiving thyroxine following thyroidectomy were at increased risk for attention and memory problems, and those with TC had greater reported fatigue and sleep problems. However, a blinded randomized control study in which L-thyroxine was titrated to continue TSH suppression or establish euthyroidism demonstrated no HRQOL benefit to restoring euthyroidism.[52] These findings were reinforced by Massolt et al.,[54] who found no improvement in HRQOL relating to fatigue and well-being with increased L-thyroxine dosages. Vigário et al.[41] found a supervised exercise program improved relatively low HRQOL of TSH-suppressed patients.

RIA therapy. The potential toxicities of RIA were highlighted, as the increased risk of sialadenitis and reduced swallowing capability negatively affected HRQOL.[55] Despite >50% of patients having anxiety and concerns prior to RIA, Barbus et al.[56] found most patients would undergo further courses if indicated, suggesting treatment burden has a relatively low HRQOL effect. This was supported by Taïeb et al.,[50] who reported RIA to have no significant effect on HRQOL in the medium term (9 months). They did find younger age, sex (male), and higher pre-RIA HRQOL scores to have significant positive effects on ultimate HRQOL.

Therapies for advanced disease. A small number of studies investigated the effect of drug treatments on the HRQOL of patients with advanced TC. The utilization of axitinib in patients with iodine refractory differentiated TC was shown to maintain HRQOL as well as improve progression-free survival.[57] There was a notable absence of HRQOL data relating to licensed treatments for advanced disease, such as Sorafenib and Lenvatinib.

Other. Medullary TC-related diarrhea reduces HRQOL in relation to fatigue, disturbed sleep, distress, and sadness; the use of calcium aluminosilicate antidiarrheal improved HRQOL.[15]

General

Fifty-two articles had a general focus (Table 6). EORTC-QLQ-C30 was the most frequently used questionnaire (n=18), followed by SF-36 (n=11). This category was broken down into the following categories in decreasing frequency:

1. HRQOL with and without comparison to normative data
2. Development of questionnaires and translations
3. Lifelong distress within at-risk groups
4. Other

HRQOL with and without comparison to normative data. The majority of articles found HRQOL to be good when compared to normative data. Most were published since 2013, and focused on anxiety, depression, fatigue, and recurrence concerns. Prior to 2013, four articles found HRQOL to normalize following a short-lived drop after diagnosis and treatment.[39,58–60] Lee et al.[61] and Singer et al.[62] both found HRQOL to be lower than comparative populations

and anxiety, depression, and levels of fatigue significantly impacted this. Following 2013, a large number of articles revealed specific areas that impacted a survivor's HRQOL. Fatigue,[63–66] concentration ability,[63,67] pain,[68] swallowing difficulties,[68] anxiety,[67] depression,[66] comorbidity,[65,67] increased age,[69,70] decreased age,[71] sex,[69,72,73] lower education status,[69] financial distress,[74] RIA requirement,[75] and fear of recurrence[32] significantly reduced HRQOL. TC survivors highlighted having their cancer referred to as the "good kind" trivialized their diagnosis and decreased HRQOL as they felt unsupported by physicians and family.[76] Wu et al.[77] found a 12-month psychological support program resulted in higher HRQOL compared to those who did not receive such support, although their sample size was small (60) and participant selection bias likely. Büel-Drab et al.[78] found TC to have very small impacts on patient–partner relationships and intimacy.

There is an equally large evidence base reporting good HRQOL that does not compare to reference populations. Roberts et al.[79] found high HRQOL and any patient-reported information needs were covered within routine follow-ups. However, multiple authors reported factors that reduced HRQOL, including the number of RIA treatments required,[80] treatment side effects,[81] fear of recurrence,[16,82] employment status,[82] sudden tiredness,[82,83] age,[84] nausea and vomiting,[84] and lower education level.[16] Surprisingly, HRQOL was not significantly impacted when patients experienced voice problems, despite the expectation that recurrent laryngeal nerve damage following thyroidectomy would result in decreased HRQOL.[84]

Development of questionnaires and translations. Six articles focused on developing and translating questionnaires.[85–90] THYCA-QoL was developed[86] and recommended for use in combination with EORTC-QLQ-C30. Jeong et al.[87] published their validation of THYCA-QoL for use in the Korean language, after determining strong Cronbach α coefficient scores in the majority of multi-items. The third phase of developing an EORTC QOL module for TC (EORTC-QLQ-THY34) was published.[89] The EORTC-QLQ-C30 was further analyzed by Bernardo et al.,[88] who found acceptable validity and internal consistent reliability with Filipino adults with differentiated TC. Watt et al.[85] found ThyPRO to have good clinical validity and reliability in a variety of thyroid diseases. Ryu et al.[90] found KT-QoL to be valid in evaluating QOL in Korean patients with TC.

Lifelong distress within high-risk groups. Three articles identified lifelong distress in groups considered to be at high risk of distress, as determined by the authors of this systematic review. Roerink et al.[91] found lower education levels correlated with worse HRQOL scores. Two articles looked at long-term HRQOL of young patients treated for TC and found generally comparable scores with normative data.[92,93] Metallo et al.[93] identified female survivors diagnosed <25 years old, and found no difference in HRQOL compared to the reference population. Pregnancy outcomes following historic I^{131} treatment and miscarriage rates were comparative and no birth defects observed. Nies et al.[92] included participants diagnosed <18 years old and found no significant HRQOL differences compared to controls.

Other. Two articles focused on areas not covered by the previous subcategories.[94,95] Employment and insurance factors were explored and found 62% of survivors struggled to obtain life insurance and increased age, level of fatigue, and lower educational obtainment were associated with unemployment. Employed TC survivors had improved HRQOL compared to unemployed survivors.[94] Liu et al.[95] described a mindfulness-based stress reduction program for those undertaking RIA. This randomized controlled trial found an 8-week program reduced depression and anxiety and improved emotional function. This effect was particularly evident in the first 4 weeks during THW but also 3 months following treatment.

Discussion

This is the first systematic literature review of studies using patient-reported questionnaires published from 2000 to 2019 on HRQOL and TC. The authors worked independently and in collaboration to ensure robustness of the review process.

Until 2013, only five studies examined effects of surgery on HRQOL in patients with TC. They varied in their design and aims. These early studies revealed low HRQOL in patients with TC after surgery and that the extent of surgery did not have a clear effect on HRQOL. These early studies also alluded to scar and its perception as an important factor for patients.[17–21] From 2013, driven by development of new endoscopic and robotic techniques to hide visible scarring, several studies examined the impact of endoscopic/robotic techniques compared to conventional open surgery and whether improved aesthetics affected HRQOL. The symptoms of surgical scars such as pruritus, tightening, and pain also lower HRQOL.[23,25] These studies, mainly arising from Korea, report improved swallow function, less scar-related symptoms, and improved HRQOL as a result of improved aesthetics from a hidden scar, particularly in setting of metastatic TC requiring additional neck dissection. In contrast, a US study showed little impact of scar visibility on HRQOL after thyroidectomy, which may be due to the cultural differences between the countries.[29] The confounding effects of disparate study groups, partly as a result of self-selection bias for those patients who underwent endoscopic versus open surgical approaches, was highlighted by multiple studies.[26,29]

Subsequent to changes in international guidelines (2014/2015) in the management of low-risk TC, more recent studies have explored the effect of HT versus TT, and compared HRQOL in patients with microcarcinomas undergoing surgery versus active surveillance. The HRQOL effects of TT versus HT were inconclusive, with disagreement between published articles.[30,31] However, the concern of recurrence within the HT population is considerable and worthy of future research. Postoperative hypocalcemia is an important issue that is central to the debate on the benefits of HT versus TT. However, no studies examining its effect on HRQOL were revealed in this systematic review. A randomized trial to address the question of TT vs HT is soon to open in the United Kingdom (HoT trial). The primary endpoint of this study will be recurrence-free survival, but the study will also address HRQOL aspects and provide more robust data.

Patients with microcarcinomas appear to have better HRQOL compared to those who undergo HT.[27,28] However, patients undergoing surveillance may have higher level of fear/anxiety of future disease recurrence. The main cause for the reported reduced HRQOL was related to physical health such as muscle discomfort, scar, and throat symptoms, which may be expected considering the short follow-up after surgery (6–8 months). The operation group had a larger cohort of females and much higher rate of ongoing thyroxine treatment.[28] There may be significant selection bias as the operated group showed lower baseline QOL scores, and there was self-selection into the surveillance group by patients with lower anxiety of recurrence.[27] Again, a prospective randomized study is required to resolve these important confounding factors.

The cost difference between endoscopic and open thyroid surgery was not explored within any included article. This important factor should be considered in future analysis of HRQOL following different surgical approaches, as the subconscious cost–benefit analysis applied by a patient may have significant implications on both short- and long-term HRQOL. This is particularly relevant to healthcare systems that financially supplement some surgical options and not others.

The effects of THW, TSH suppression, and RIA all reduce HRQOL. The negative implications on attention span, memory capability, fatigue, disturbed sleep, anxiety, depression, and distress have all been demonstrated. The use of rTSH instead of THW prior to RIA and imaging is supported by the relatively positive HRQOL. The randomized HiLo and ESTIMABL trials both support the findings from this systematic review that patients undergoing THW had significantly worse HRQOL than those receiving thyrotropin-α treatment.[96,97]

Rendering patients into chronic subclinical hyperthyroidism (TSH suppression) is a topic of debate, considering the potential negative implications on cardiac and bone health. This review found reports of mixed impact following TSH suppression, and that recovery of HRQOL depletion could occur with a supervised exercise routine.

We did not find any reliable evidence regarding the effect of RIA on long-term HRQOL. Any potential negative effects on HRQOL may be obviated considering the use of thyroglobulin monitoring and reassurance of all thyroid tissue being ablated could obviate these deleterious effects; however, we found no evidence to support or disprove this.

The consequences of systemic therapies on HRQOL have been poorly represented. Locati et al.[57] discuss the unlicensed use of axitinib, which maintained HRQOL. However, the use of licensed treatments (such as Sorafenib and Lenvatinib) and HRQOL has not been thoroughly explored and would be of interest. Singer et al.[89] found nine patients who had experienced tyrosine kinase inhibitor (TKI) treatment reported more frequent problems with thin or lifeless hair. Since our literature search was performed, a systematic review primarily focused on the objective response of medullary TC after TKI use has been published. This article did not include investigation into HRQOL but found moderate therapeutic benefit to their use.[98]

The 2020 QaLM study investigated HRQOL for patients diagnosed with medullary TC. This prospective multicenter randomized study utilized 4 patient-reported validated QOL questionnaires and found the least popular questionnaire focused on gastrointestinal symptoms, suggesting diarrhea was not a significant concern to the study participants.[99]

The review highlights diverse issues in respect to HRQOL that can be associated with detrimental outcomes following TC. There are physical, emotional, and social ramifications. The impact on HRQOL can be underestimated by professionals because, when compared to other head and neck cancers (HNCs), which might involve tracheostomy, free-tissue microvascular transfer, or chemoradiotherapy, the surgical and nonsurgical treatment of TC is less. However, from the patients' perspective, the diagnosis of cancer can have profound negative repercussions. Although the prognosis and treatment morbidity can be much better than for other HNCs, the HRQOL response might be worse than expected given the younger age of the patient group.[100] It seems that patients with TC have been compared to healthy populations and their HRQOL much more frequently than patients with other HNCs.[100] The inference might be that their outcomes are not that different from those of noncancer comparisons, but this assessment might belittle the true impact on HRQOL of TC. Given the potential for unmet needs and the difficulties that clinicians might have to identify these in routine practice, further research has potential value around the development of a prompt list approach[101] such the Patient Concerns Inventory (PCI).[102] Fear of recurrence is a common concern across all cancers and is evident in TC in spite of a favorable prognosis. Cancer fears can be raised by patients in their consultations through a PCI approach[103] and more research in TC is needed to assess this and also

the benefit of interventions such as the Mini-AFTER.[104] The other area where HRQOL information might inform future practice and clinical outcome research is around the issue of shared decision-making.

Limitations

Meta-analysis was not possible from this literature search as there was such large variation in the range of clinical characteristics and questionnaires included. Uniformity in study designs, questionnaire choice, and clinical characteristics inclusion would aid future research analysis and may enable a future meta-analysis.

The nature of patient-reported questionnaires lends itself to risk of response bias. The majority of included articles within this review were cross-sectional and as such it is difficult to conclusively report causative relationships. These factors result in most articles within this review having significant risk of bias and therefore reported outcomes should be considered within this context.

The review has not uncovered a significant number of articles focused on less prevalent TC histology, including anaplastic and medullary TC. Many articles excluded these diagnoses based on the relatively small numbers of patients. Considering this, the applicability of the findings from this review on these less prevalent TCs should be recognized. The only article focused solely on medullary TC was the one by Dadu et al.,[15] in which HRQOL was a secondary outcome following the use of antidiarrheal medication.

There are a paucity of randomized controlled trials to guide TC management, and in those completed, very few use patient-reported HRQOL questionnaires. If further research expands into these domains, it would aid decision-making when clinical outcomes (e.g. recurrence risk and survival) are similar.

Conclusions

We identified, collated, and summarized a substantial number of articles published on HRQOL and TC. It can be a challenge for clinicians and researchers to find all the relevant articles and this structured review gives a synopsis for those published between 2000 and 2019. HRQOL is a crucial outcome following TC, even more so as the prognosis generally is favorable and survivorship is increasing. This review identifies areas for improved clinical care and research regarding TC, including uniformity in validated questionnaire use and the prospect of future randomized controlled trials encompassing HRQOL to enable holistic care of patients diagnosed with and treated for TC.

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E.G. Walshaw: Literature searching, analysis of literature, drafting of work, final approval. M. Smith: Literature searching, analysis of literature, drafting of work, final approval. D. Kim: Analysis of literature, drafting of work, final approval. J. Wadsley: Analysis of literature, drafting of work, final approval. A. Kanatas: Conception of work, literature searching, analysis of literature, drafting of work, final approval. S.N. Rogers: Conception of work, literature searching, analysis of literature, drafting of work, final approval.

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References

1. Horn-Ross PL, Lichtensztajn DY, Clarke CA, et al. Continued rapid increase in thyroid cancer incidence in California: trends by patient, tumor, and neighborhood characteristics. *Cancer Epidemiol Biomarkers Prev* 2014; 23: 1067–1079.
2. La Vecchia C, Malvezzi M, Bosetti C, et al. Thyroid cancer mortality and incidence: a global overview. *Int J Cancer* 2015; 136: 2187–2195.
3. Howlader NNA, Krapcho M, Miller D, et al. SEER Cancer Statistics Review 1975–2017, https://seer.cancer.gov/archive/csr/1975_2017/ (2017, accessed 25 Jun 2020).
4. Perros P, Colley S, Evans C, et al. British Thyroid Association guidelines for the management of thyroid cancer. *Clin Endocrinol* 2014; 81: 1–122.
5. Schlumberger M, Bastholt L, Dralle H, et al. 2012 European Thyroid Association guidelines for metastatic medullary thyroid cancer. *Eur Thyroid J* 2012; 1: 5–14.
6. Fugazzola L, Elisei R, Fuhrer D, et al. 2019 European Thyroid Association guidelines for the treatment and follow-up of advanced radioiodine-refractory thyroid cancer. *Eur Thyroid J* 2019; 8: 227–245.
7. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016; 26: 1–133.
8. Wells SA, Jr., Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 2015; 25: 567–610.
9. Husson O, Haak HR, Oranje WA, et al. Health-related quality of life among thyroid cancer survivors: a systematic review. *Clin Endocrinol* 2011; 75: 544–554.

10. Rubic M, Kuna SK, Tesic V, et al. The most common factors influencing on quality of life of thyroid cancer patients after thyroid hormone withdrawal. *Psychiatr Danubina* 2014; 26(Suppl 3): 520–527.
11. Bărbuş E, Peştean C, Larg MI, et al. Quality of life in thyroid cancer patients: a literature review. *Clujul Med (1957)* 2017; 90: 147–153.
12. Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. *PLOS Med* 2009; 6: e1000097.
13. Moola S, Munn Z, Tufanaru C, et al. Systematic reviews of etiology and risk. In: Aromataris E and Munn Z (Eds.). JBI Manual for Evidence Synthesis, https://synthesismanual.jbi.global (2020, accessed 15 November 2020).
14. Aromataris E and Munn Z (Eds.). JBI Manual for Evidence Synthesis, https://synthesismanual.jbi.global (2020, accessed 12 November 2020).
15. Dadu R, Hu MI, Cleeland C, et al. Efficacy of the natural clay, calcium aluminosilicate anti-diarrheal, in reducing medullary thyroid cancer-related diarrhea and its effects on quality of life: a pilot study. *Thyroid* 2015; 25: 1085–1090.
16. Papaleontiou M, Reyes-Gastelum D, Gay BL, et al. Worry in thyroid cancer survivors with a favorable prognosis. *Thyroid* 2019; 29: 1080–1088.
17. Dagan T, Bedrin L, Horowitz Z, et al. Quality of life of well-differentiated thyroid carcinoma patients. *J Laryngol Otol* 2004; 118: 537–542.
18. Huang SM, Lee CH, Chien LY, et al. Postoperative quality of life among patients with thyroid cancer. *J Adv Nurs* 2004; 47: 492–499.
19. Shah MD, Witterick IJ, Eski SJ, et al. Quality of life in patients undergoing thyroid surgery. *J Otolaryngol* 2006; 35: 209–215.
20. Almeida JP, Vartanian JG and Kowalski LP. Clinical predictors of quality of life in patients with initial differentiated thyroid cancers. *Arch Otolaryngol* 2009; 135: 342–346.
21. Gómez MMN, Gutierrez R, Castellanos S, et al. Psychological well-being and quality of life in patients treated for thyroid cancer after surgery. *Terapia Psicologica* 2010; 28: 69–84.
22. Lee J, Kwon IS, Bae EH, et al. Comparative analysis of oncological outcomes and quality of life after robotic versus conventional open thyroidectomy with modified radical neck dissection in patients with papillary thyroid carcinoma and lateral neck node metastases. *J Clin Endocrinol Metab* 2013; 98: 2701–2708.
23. Choi Y, Lee JH, Kim YH, et al. Impact of postthyroidectomy scar on the quality of life of thyroid cancer patients. *Ann Dermatol* 2014; 26: 693–699.
24. Song CM, Ji YB, Bang HS, et al. Quality of life after robotic thyroidectomy by a gasless unilateral axillary approach. *Ann Surg Oncol* 2014; 21: 4188–4194.
25. Lee S, Kim HY, Lee CR, et al. A prospective comparison of patient body image after robotic thyroidectomy and conventional open thyroidectomy in patients with papillary thyroid carcinoma. *Surgery* 2014; 156: 117–125.
26. Lee MC, Park H, Lee BC, et al. Comparison of quality of life between open and endoscopic thyroidectomy for papillary thyroid cancer. *Head Neck* 2016; 38(Suppl 1): E827–E831.
27. Kong SH, Ryu J, Kim MJ, et al. Longitudinal assessment of quality of life according to treatment options in low risk papillary thyroid microcarcinoma patients: active surveillance or immediate surgery (interim analysis of MAeSTro). *Thyroid* 2019; 29: 1089–1096.
28. Jeon MJ, Lee YM, Sung TY, et al. Quality of life in patients with papillary thyroid microcarcinoma managed by active surveillance or lobectomy: a cross-sectional study. *Thyroid* 2019; 29: 956–962.
29. Kurumety SK, Helenowski IB, Goswami S, et al. Postthyroidectomy neck appearance and impact on quality of life in thyroid cancer survivors. *Surgery* 2019; 165: 1217–1221.
30. Nickel B, Tan T, Cvejic E, et al. Health-related quality of life after diagnosis and treatment of differentiated thyroid cancer and association with type of surgical treatment. *JAMA Otolaryngol Head Neck Surg* 2019; 145: 231–238.
31. Bongers PJ, Greenberg CA, Hsiao R, et al. Differences in long-term quality of life between hemithyroidectomy and total thyroidectomy in patients treated for low-risk differentiated thyroid carcinoma. *Surgery* 2020; 167: 94–101.
32. Hedman C, Djärv T, Strang P, et al. Determinants of long-term quality of life in patients with differentiated thyroid carcinoma: a population-based cohort study in Sweden. *Acta Oncol* 2016; 55: 365–369.
33. Roerink SH, Coolen L, Schenning ME, et al. High prevalence of self-reported shoulder complaints after thyroid carcinoma surgery. *Head Neck* 2017; 39: 260–268.
34. Schroeder PR, Haugen BR, Pacini F, et al. A comparison of short-term changes in health-related quality of life in thyroid carcinoma patients undergoing diagnostic evaluation with recombinant human thyrotropin compared with thyroid hormone withdrawal. *J Clin Endocrinol Metab* 2006; 91: 878–884.
35. Chow SM, Au KH, Choy TS, et al. Health-related quality-of-life study in patients with carcinoma of the thyroid after thyroxine withdrawal for whole body scanning. *Laryngoscope* 2006; 116: 2060–2066.
36. de Oliveira Chachamovitz DS, dos Santos Vigário P, Nogueira Cordeiro MF, et al. Quality of life, muscle strength, and fatigue perception in patients on suppressive therapy with levothyroxine for differentiated thyroid carcinoma. *Am J Clin Oncol* 2013; 36: 354–361.
37. Borget I, Bonastre J, Catargi B, et al. Quality of life and cost-effectiveness assessment of radioiodine ablation strategies in patients with thyroid cancer: results from the randomized phase III ESTIMABL trial. *J Clin Oncol* 2015; 33: 2885–2892.
38. Badihian S, Jalalpour P, Mirdamadi M, et al. Quality of life, anxiety and depression in patients with differentiated thyroid cancer under short term hypothyroidism induced by levothyroxine withdrawal. *Klin Onkol* 2016; 29: 439–444.
39. Giusti M, Sibilla F, Cappi C, et al. A case-controlled study on the quality of life in a cohort of patients with history of differentiated thyroid carcinoma. *J Endocrinol Invest* 2005; 28: 599–608.
40. Tagay S, Herpertz S, Langkafel M, et al. Health-related quality of life, depression and anxiety in thyroid cancer patients. *Qual Life Res* 2006; 15: 695–703.
41. Vigário P dos S, Chachamovitz DS, Teixeira Pde F, et al. Exercise is associated with better quality of life in patients

on TSH-suppressive therapy with levothyroxine for differentiated thyroid carcinoma. *Arq Brasil Endocrinol Metab* 2014; 58: 274–281.
42. Jung MS and Visovatti M. Post-treatment cognitive dysfunction in women treated with thyroidectomy for papillary thyroid carcinoma. *Support Care Cancer* 2017; 25: 915–923.
43. Golger A, Fridman TR, Eski S, et al. Three-week thyroxine withdrawal thyroglobulin stimulation screening test to detect low-risk residual/recurrent well-differentiated thyroid carcinoma. *J Endocrinol Invest* 2003; 26: 1023–1031.
44. Davids T, Witterick IJ, Eski S, et al. Three-week thyroxine withdrawal: a thyroid-specific quality of life study. *Laryngoscope* 2006; 116: 250–253.
45. Tan LG, Nan L, Thumboo J, et al. Health-related quality of life in thyroid cancer survivors. *Laryngoscope* 2007; 117: 507–510.
46. Lee J, Yun MJ, Nam KH, et al. Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. *Thyroid* 2010; 20: 173–179.
47. Taïeb D, Sebag F, Cherenko M, et al. Quality of life changes and clinical outcomes in thyroid cancer patients undergoing radioiodine remnant ablation (RRA) with recombinant human TSH (rhTSH): a randomized controlled study. *Clin Endocrinol* 2009; 71: 115–123.
48. Nygaard B, Bastholt L, Bennedbæk FN, et al. A placebo-controlled, blinded and randomised study on the effects of recombinant human thyrotropin on quality of life in the treatment of thyroid cancer. *Eur Thyroid J* 2013; 2: 195–202.
49. Emmanouilidis N, Schrem H, Winkler M, et al. Long-term results after treatment of very low-, low-, and high-risk thyroid cancers in a combined setting of thyroidectomy and radio ablation therapy in euthyroidism. *Int J Endocrinol* 2013; 2013: 769473.
50. Taïeb D, Baumstarck-Barrau K, Sebag F, et al. Heath-related quality of life in thyroid cancer patients following radioiodine ablation. *Health Qual Life Outcomes* 2011; 9: 33.
51. Crevenna R, Zettinig G, Keilani M, et al. Quality of life in patients with non-metastatic differentiated thyroid cancer under thyroxine supplementation therapy. *Support Care Cancer* 2003; 11: 597–603.
52. Eustatia-Rutten CF, Corssmit EP, Pereira AM, et al. Quality of life in longterm exogenous subclinical hyperthyroidism and the effects of restoration of euthyroidism, a randomized controlled trial. *Clin Endocrinol* 2006; 64: 284–291.
53. Valle LA, Gorodeski Baskin RL, Porter K, et al. In thyroidectomized patients with thyroid cancer, a serum thyrotropin of 30 μU/mL after thyroxine withdrawal is not always adequate for detecting an elevated stimulated serum thyroglobulin. *Thyroid* 2013; 23: 185–193.
54. Massolt ET, van der Windt M, Korevaar TI, et al. Thyroid hormone and its metabolites in relation to quality of life in patients treated for differentiated thyroid cancer. *Clin Endocrinol* 2016; 85: 781–788.
55. Dingle IF, Mishoe AE, Nguyen SA, et al. Salivary morbidity and quality of life following radioactive iodine for well-differentiated thyroid cancer. *Otolaryngol Head Neck Surg* 2013; 148: 746–752.
56. Barbus E, Pestean C, Larg MI, et al. Psychological impact of (131)I radioprotection measures on thyroid cancer patients. *Clujul Med (1957)* 2018; 91: 441–447.
57. Locati LD, Licitra L, Agate L, et al. Treatment of advanced thyroid cancer with axitinib: phase 2 study with pharmacokinetic/pharmacodynamic and quality-of-life assessments. *Cancer* 2014; 120: 2694–2703.
58. Schultz PN, Stava C and Vassilopoulou-Sellin R. Health profiles and quality of life of 518 survivors of thyroid cancer. *Head Neck* 2003; 25: 349–356.
59. Hoftijzer HC, Heemstra KA, Corssmit EP, et al. Quality of life in cured patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2008; 93: 200–203.
60. Pelttari H, Sintonen H, Schalin-Jäntti C, et al. Health-related quality of life in long-term follow-up of patients with cured TNM stage I or II differentiated thyroid carcinoma. *Clin Endocrinol* 2009; 70: 493–497.
61. Lee JI, Kim SH, Tan AH, et al. Decreased health-related quality of life in disease-free survivors of differentiated thyroid cancer in Korea. *Health Qual Life Outcomes* 2010; 8: 101.
62. Singer S, Lincke T, Gamper E, et al. Quality of life in patients with thyroid cancer compared with the general population. *Thyroid* 2012; 22: 117–124.
63. Husson O, Haak HR, Buffart LM, et al. Health-related quality of life and disease specific symptoms in long-term thyroid cancer survivors: a study from the population-based PROFILES registry. *Acta Oncol* 2013; 52: 249–258.
64. Husson O, Nieuwlaat WA, Oranje WA, et al. Fatigue among short- and long-term thyroid cancer survivors: results from the population-based PROFILES registry. *Thyroid* 2013; 23: 1247–1255.
65. Hedman C, Djärv T, Strang P, et al. Effect of thyroid-related symptoms on long-term quality of life in patients with differentiated thyroid carcinoma: a population-based study in Sweden. *Thyroid* 2017; 27: 1034–1042.
66. McIntyre C, Jacques T, Palazzo F, et al. Quality of life in differentiated thyroid cancer. *Int J Surg* 2018; 50: 133–136.
67. Goldfarb M and Casillas J. Thyroid cancer specific quality of life and health related quality of life in young adult thyroid cancer survivors. *Thyroid* 2016; 26: 923–932.
68. Gal TJ, Streeter M, Burris J, et al. Quality of life impact of external beam radiotherapy for advanced thyroid carcinoma. *Thyroid* 2013; 23: 64–69.
69. Wang T, Jiang M, Ren Y, et al. Health-related quality of life of community thyroid cancer survivors in Hangzhou, China. *Thyroid* 2018; 28: 1013–1023.
70. Goswami S, Peipert BJ, Mongelli MN, et al. Clinical factors associated with worse quality-of-life scores in United States thyroid cancer survivors. *Surgery* 2019; 166: 69–74.
71. Mols F, Schoormans D, Smit JWA, et al. Age-related differences in health-related quality of life among thyroid cancer survivors compared with a normative sample: results from the PROFILES Registry. *Head Neck* 2018; 40: 2235–2245.

72. Giusti M, Gay S, Conte L, et al. Evaluation of quality of life in patients with differentiated thyroid cancer by means of the thyroid-specific patient-reported outcome questionnaire: a 5-year longitudinal study. *Eur Thyroid J* 2020; 9: 247–255.
73. Giusti M, Melle G, Fenocchio M, et al. Five-year longitudinal evaluation of quality of life in a cohort of patients with differentiated thyroid carcinoma. *J Zhejiang U Sci B* 2011; 12: 163–173.
74. Mongelli MN, Giri S, Peipert BJ, et al. Financial burden and quality of life among thyroid cancer survivors. *Surgery* 2020; 167: 631–637.
75. Haraj NE, Bouri H, El Aziz S, et al. Evaluation of the quality of life in patients followed for differentiated cancer of the thyroid. *Ann Endocrinol* 2019; 80: 26–31.
76. Applewhite MK, James BC, Kaplan SP, et al. Quality of life in thyroid cancer is similar to that of other cancers with worse survival. *World J Surg* 2016; 40: 551–561.
77. Wu HX, Zhong H, Xu YD, et al. Psychological and behavioral intervention improves the quality of life and mental health of patients suffering from differentiated thyroid cancer treated with postoperative radioactive iodine–131. *Neuropsychiatr Dis Treat* 2016; 12: 1055–1060.
78. Büel-Drabe N, Steinert H, Moergeli H, et al. Thyroid cancer has a small impact on patient–partner relationships and their frequency of sexual activity. *Palliat Support Care* 2018; 16: 335–346.
79. Roberts KJ, Lepore SJ and Urken ML. Quality of life after thyroid cancer: an assessment of patient needs and preferences for information and support. *J Cancer Educ* 2008; 23: 186–191.
80. Hirsch D, Ginat M, Levy S, et al. Illness perception in patients with differentiated epithelial cell thyroid cancer. *Thyroid* 2009; 19: 459–465.
81. Vega-Vázquez MA, Gonzalez-Rodriguez L, Santiago-Rodríguez EJ, et al. Quality of life-in patients with differentiated thyroid cancer at the general endocrinology clinics of the University Hospital of Puerto Rico. *Bol Asoc Med Puerto Rico* 2015; 107: 25–31.
82. Singer S, Husson O, Tomaszewska IM, et al. Quality-of-life priorities in patients with thyroid cancer: a multinational European organisation for research and treatment of cancer phase I study. *Thyroid* 2016; 26: 1605–1613.
83. Barbus E, Pestean C, Larg M, et al. Quality of life in thyroid cancer: a questionnaire- based study. *J Evidence-Based Psychother* 2018; 18: 1–20.
84. Rogers SN, Mepani V, Jackson S, et al. Health-related quality of life, fear of recurrence, and emotional distress in patients treated for thyroid cancer. *Br J Oral Maxillofac Surg* 2017; 55: 666–673.
85. Watt T, Hegedüs L, Groenvold M, et al. Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO. *Eur J Endocrinol* 2010; 162: 161–167.
86. Husson O, Haak H, Mols F, et al. Development of a disease-specific health-related quality of life questionnaire (THYCA-QoL) for thyroid cancer survivors. *Acta Oncol* 2013; 52: 447–454.
87. Jeong Y, Choi J, Ahn AL, et al. Validation of the Korean version of the thyroid cancer-specific quality of life questionnaire. *Ann Surg Treat Res* 2015; 89: 287–294.
88. Bernardo D, Li R and Jimeno C. Validity and reliability of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30–Tagalog among adult Filipinos with differentiated thyroid cancer. *J ASEAN Fed Endocr Soc* 2018; 33: 174–180.
89. Singer S, Jordan S, Locati LD, et al. The EORTC module for quality of life in patients with thyroid cancer: phase III. *Endocr Relat Cancer* 2017; 24: 197–207.
90. Ryu CH, Park B, Ryu J, et al. Development and evaluation of a Korean version of a thyroid-specific quality-of-life questionnaire scale in thyroid cancer patients. *Cancer Res Treat* 2018; 50: 405–415.
91. Roerink SH, de Ridder M, Prins J, et al. High level of distress in long-term survivors of thyroid carcinoma: results of rapid screening using the distress thermometer. *Acta Oncol* 2013; 52: 128–137.
92. Nies M, Klein Hesselink MS, Huizinga GA, et al. Long-term quality of life in adult survivors of pediatric differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2017; 102: 1218–1226.
93. Metallo M, Groza L, Brunaud L, et al. Long-term quality of life and pregnancy outcomes of differentiated thyroid cancer survivors treated by total thyroidectomy and I(131) during adolescence and young adulthood. *Int J Endocrinol* 2016; 2016: 7586482.
94. Tamminga SJ, Bültmann U, Husson O, et al. Employment and insurance outcomes and factors associated with employment among long-term thyroid cancer survivors: a population-based study from the PROFILES registry. *Qual Life Res* 2016; 25: 997–1005.
95. Liu T, Zhang W, Xiao S, et al. Mindfulness-based stress reduction in patients with differentiated thyroid cancer receiving radioactive iodine therapy: a randomized controlled trial. *Cancer Manag Res* 2019; 11: 467–474.
96. Mallick U, Harmer C, Yap B, et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N Engl J Med* 2012; 366: 1674–1685.
97. Schlumberger M, Catargi B, Borget I, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *N Engl J Med* 2012; 366: 1663–1673.
98. Efstathiadou ZA, Tsentidis C, Bargiota A, et al. Benefits and limitations of TKIs in patients with medullary thyroid cancer: a systematic review and meta-analysis. *Eur Thyroid J* 2021; 10: 125–139.
99. Moss L, Cox C, Wadsley J, et al. Medullary thyroid cancer patient's assessment of quality of life tools: results from the QaLM study. *Eur Thyroid J* 2021; 10: 72–78.
100. Walshaw EG, Smith M, Kanatas A, et al. Handle-On-QOL: a dedicated quality of life resource following the diagnosis and treatment of head and neck cancer. *Br J Oral Maxillofac Surg* 2020; 58:e25–e32.
101. Miller N and Rogers SN. A review of question prompt lists used in the oncology setting with comparison to the Patient Concerns Inventory. *Eur J Cancer Care* 2018; 27: e12489.
102. Rogers SN, Allmark C, Bekiroglu F, et al. Improving quality of life through the routine use of the patient concerns inventory for head and neck cancer patients: baseline results in a cluster preference randomised controlled trial. *Eur Arch Oto-Rhino-Laryngol* 2020; 277: 3435–3447.

103. Ghazali N, Cadwallader E, Lowe D, et al. Fear of recurrence among head and neck cancer survivors: longitudinal trends. *Psychooncology* 2013; 22: 807–813.
104. Davidson J, Malloch M and Humphris G. A single-session intervention (the Mini-AFTERc) for fear of cancer recurrence: a feasibility study. *Psychooncology* 2018; 27: 2668–2670.
105. Malterling R, Andersson R, Falkmer S, et al. Differentiated thyroid cancer in a Swedish county: long-term results and quality of life. *Acta Oncol* 2010; 49: 454–459.
106. Costa RV and Pakenham KI. Associations between benefit finding and adjustment outcomes in thyroid cancer. *Psychooncology* 2012; 21: 737–744.
107. Gamper EM, Wintner LM, Rodrigues M, et al. Persistent quality of life impairments in differentiated thyroid cancer patients: results from a monitoring program. *Eur J Nucl Med Mol Imaging* 2015; 42: 1179–1188.
108. Li R, Jimeno C, Sandoval S, et al. Development and validation of a thyroid cancer-specific health-related quality of life questionnaire for adult Filipinos with differentiated thyroid cancer. *J ASEAN Fed Endocr Soc* 2016; 31: 87–96.
109. Shin YW, Choi YM, Kim HS, et al. Diminished quality of life and increased brain functional connectivity in patients with hypothyroidism after total thyroidectomy. *Thyroid* 2016; 26: 641–649.
110. Drabe N, Steinert H, Moergeli H, et al. Perception of treatment burden, psychological distress, and fatigue in thyroid cancer patients and their partners: effects of sex, role, and time since diagnosis. *Psychooncology* 2016; 25: 203–209.
111. Lubitz CC, De Gregorio L, Fingeret Al, et al. Measurement and variation in estimation of quality of life effects of patients undergoing treatment for papillary thyroid carcinoma. *Thyroid* 2017; 27: 197–206.
112. Gou J, Cheng W, Lei J, et al. Health-related quality-of-life assessment in surgical patients with papillary thyroid carcinoma: a single-center analysis from Mainland China. *Medicine* 2017; 96: e8070.
113. Goswami S, Mongelli M, Peipert BJ, et al. Benchmarking health-related quality of life in thyroid cancer versus other cancers and United States normative data. *Surgery* 2018; 164: 986–992.
114. Hedman C, Djärv T, Strang P, et al. Fear of recurrence and view of life affect health-related quality of life in patients with differentiated thyroid carcinoma: a prospective Swedish population-based study. *Thyroid*. Epub ahead of print Sep 25, 2018. DOI: 10.1089/thy.2018.0388
115. Aschebrook-Kilfoy B, Ferguson BA, Angelos P, et al. Development of the ThyCAT: a clinically useful computerized adaptive test to assess quality of life in thyroid cancer survivors. *Surgery* 2018; 163: 137–142.
116. van Velsen EFS, Massolt ET, Heersema H, et al. Longitudinal analysis of quality of life in patients treated for differentiated thyroid cancer. *Eur J Endocrinol* 2019; 181: 671–679.