Patient-Reported Quality-of-Life Outcome Measures in the Thyroid Cancer Population

Eve M. Roth,¹ Carrie C. Lubitz,^{1–3} John Shannon Swan,^{1,3,4} and Benjamin C. James^{1,5}

Background: There is an escalating worldwide population of thyroid cancer (TC) survivors. In addition to conventional metrics of quality of care, quality-of-life (QoL) assessment in TC patients is imperative. TC survivors face unique impediments to health-related quality of life (HRQoL), including thyroid-specific symptoms and exposure to disease-related stressors—including fear of recurrence and financial toxicity—over a prolonged survival period. Survey instruments currently used to assess HRQoL in TC survivors may be insufficient to accurately capture the burden of disease in this population. We aimed to identify the HRQoL instruments in the literature, which have been applied in the TC survivor population, and to present the psychometric properties of the scales and indexes that have been used. We hypothesized that few instruments have shown evidence of validity in this population.

Summary: Of the 927 articles identified by search criteria, only 28 studies using 15 HRQoL instruments met inclusion criteria. Of the 15 HRQoL instruments identified, 9 were psychometric health status instruments and 6 were preference-based indexes, but none had been validated in the TC survivor population. While the majority of reviewed studies demonstrated impaired psychological and emotional well-being in TC survivors, these findings were not uniformly demonstrated across studies, and the longevity of the impact of TC on HRQoL was variably reported.

Conclusions: Discrepancies in the literature regarding the impact of TC survivorship on HRQoL emphasize the challenges of accurately assessing patient perspectives, reinforcing the importance of using well-constructed instruments to measure patient-reported outcomes in the target population. Care providers involved in the treatment of TC survivors should be aware of longitudinal effects on HRQoL, especially pertaining to chronic psychological debilitation. Further development and rigorous validation of TC-specific instruments will allow for better data gathering and understanding of the barriers to achieving high long-term HRQoL in TC survivors throughout their long postsurvival course.

Keywords: patient-reported outcomes, thyroid cancer, quality of life

Introduction

WITH THE INCREASING INCIDENCE of thyroid cancer (TC), young age at diagnosis, and comparatively low disease-specific mortality, there is an escalating worldwide population of TC survivors (1,2). Assessing survival alone as the key outcome for TC patients is inadequate. In addition to conventional metrics of quality of care, quality-of-life (QoL) assessment in TC patients is imperative. Health-related quality of life (HRQoL) comprised the physical, psychological, social, and spiritual impacts of a disease, as described by

Ferrell *et al.* in their defining qualitative studies of HRQoL in cancer survivors (3–7).

Assessment of HRQoL relies on information obtained directly from the patient and/or a proxy, termed a Patient-Reported Outcome Measure (PROM). PROMs enable communication of the needs and goals of patients beyond survival, including patient prioritization of QoL versus length of life (8–10). Measurement of HRQoL can both assess the effectiveness of an intervention and, in some reports, ultimately be correlated with improved survival (11–13). HRQoL is multidimensional, encompassing symptoms, functioning,

¹Harvard Medical School, Boston, Massachusetts, USA.

²Division of Surgical Oncology, Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts, USA.

³Institute for Technology Assessment, Massachusetts General Hospital, Boston, Massachusetts, USA.

⁴Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts, USA.

⁵Section of Endocrine Surgery, Division of Surgical Oncology, Department of Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA.

and general perceptions of well-being that are challenging to measure objectively (14). Moreover, HRQoL is subjective, personal, and may fluctuate over time and with progression of disease.

Two main methods are used in HRQoL measurement: psychometric health status measurement and utility/preference-based measurement (15). Psychometric measures (such as the short-form 36-item [SF-36]) are derived from patient-reported data regarding the presence, frequency, and intensity of symptoms, combined to generate functional summary scales for domains such as physical and psychological well-being (16).

Numerous psychometric surveys exist and can broadly be categorized as generic, disease-specific, and/or problem-specific. Utility- or preference-based instruments (such as the EuroQol Instrument, or EQ-5D-5L), designed as indexes, are derived from macroeconomics, psychological and decision theory, and are developed for economic analyses by design (17). These values or preferences for states of health, also called “utilities,” are usually generic in scope, meaning they generate health values comparable across different diseases. However, there has been recent interest in disease-specific utility indexes, due to the shortcomings in coverage in generic instruments.

While the accuracy of HRQoL measurement is imperative, the challenges of accurately measuring HRQoL in TC survivors are manifold: TC patients are distinct from survivors of most other cancers in that many patients are relatively younger, otherwise healthy, and most will live with their cancer diagnosis for many years. TC survivors face unique impediments to QoL, including thyroid-specific symptoms and exposure to disease-related stressors—including fear of recurrence and financial toxicity—over a prolonged survival period (18,19). For these reasons, survey instruments currently used to assess HRQoL in TC survivors may be insufficient to accurately capture the burden of disease in this population. Therefore, we aim to identify the HRQoL instruments in the literature, which have been applied in the TC survivor population, and to present the psychometric properties of the scales and indexes that have been used. We hypothesized that few instruments have shown evidence of validity in this population.

Literature Review

A systematic review of the literature was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) method for all peer-reviewed literature published between 1990 and 2018 in both PubMed and Embase. The aim of the search was to identify all studies over the time period, which either used existing instruments or developed HRQoL instruments in TC survivors older than 17 years. Search terms included: *thyroid cancer, thyroid carcinoma, thyroid cancer survivors, quality of life, health-related quality of life, thyroid surgery, thyroidectomy, radioactive iodine, post-thyroid surgery, post-radioactive iodine*.

Studies were included if they evaluated TC QoL within the adult population (defined as age >17 years) using validated HRQoL instruments. In addition, only instruments that were validated in the language used, and had a description of their development and reported specific psychometric properties, were included. *A priori* exclusion criteria included previ-

ously developed instruments used in a language other than English, and those that did not use all components of a previously validated instrument. Studies that evaluated only specific aspects of TC treatment (i.e., thyroid hormone withdrawal, radioactive iodine treatment, robotic thyroidectomy) or specific aspects of QoL (salivary function, body image) were also excluded. In addition, we excluded all review articles, abstracts, perspectives, and nonpeer-reviewed articles.

Review of all studies was conducted independently by two authors (E.M.R., B.C.J.) and compared for consistency of application of inclusion and exclusion criteria. There was no major disagreement between reviewers regarding application of inclusion and exclusion criteria, and no arbitration was required.

Instruments included in the analysis were categorized as generic HRQoL instruments, cancer-specific instruments, or TC-specific instruments. Instrument characteristics were cataloged in detail, including number of items, domains, domain description, incorporation of Ferrell's QoL domains (physical, psychological, social, spiritual), scaling, scoring, and description of administration instructions (3–7).

Information on psychometric properties of each instrument was extracted from each study reporting the instrument's use, as well as from studies referenced by the included study. Reliability was reported as poor, moderate, or strong based on Cronbach's alpha (α) measuring internal consistency. We also looked for any evidence of use of Item Response Theory (IRT) calibration of items. Validity was reported as degree of correlation with established QoL metrics. Convergent, divergent, and discriminant validity was noted if reported in original validation studies. Responsiveness was reported as specific changes in health status over which it was observed. Additional collected information included sample size, patient population, reported objectives, study conclusions, instruments used as well as implementation appropriateness, and Ferrell's QoL domains collectively assessed by instruments used in the study.

Results

Studies and instruments

An initial query identified 927 articles based on the search criteria. Of these, 791 articles were excluded by title as they did not concern TC survivorship. Of the remaining 136 articles, 91 were excluded based on the inclusion and exclusion criteria (Fig. 1). Forty-five articles remained for review of their QoL instruments. Five instruments were excluded as they were not validated in the language used in the study, and 12 were excluded due to lack of documented validation. The remaining 28 studies (18,20–45) utilized 15 QoL instruments for analysis (Table 1). The primary findings of the 28 studies are summarized in Table 2.

Of these 15 HRQoL instruments identified, 9 were psychometric health status instruments and 6 were preference-based indexes. Importantly, while each of these instruments has been utilized in other cancer types and numerous other disease states, none of them has been validated in TC survivors. The majority of studies (18/28) reported the use of a single HRQoL instrument. Eight studies used two or more instruments, and two studies used three instruments. Half (14) of the studies used cancer-specific instruments, including 9 studies that used TC-specific instruments. Of the four TC-specific instruments identified, only two—COH-QoL

FIG. 1. Schematic presentation of methodology used and selection criteria.

and THYCA-QoL—had undergone phase IV testing. Notably, 5 of the 28 reviewed studies made alterations in instrument scaling or administration at the discretion of the investigators, using the instrument in an alternate manner other than that in which it was intended to be used.

QoL in TC survivors

Of the 28 included studies, 17 demonstrated impaired HRQoL in TC survivors compared with age- and sex-matched controls (40), the general population (21,30,34,36,43), or survivors of other types of cancer (34,36,38). Only three studies reported no decrease in HRQoL in TC survivors (41,42,44). Again, none of the instruments used had undergone thorough psychometric testing in TC survivors.

The most frequently reported symptoms related to reduced HRQoL in TC survivors were anxiety (26,27,33,37,44), depression (35,37,44), and fatigue (26,28,33,35–37,44). Insomnia and sleep disturbances (32,35,36), memory issues, difficulty concentrating, and neuromuscular complaints (21,26,32) were also reported in several studies. Importantly, fear of recurrence was a significant contributor to reduced QoL reported in four studies (18,24,27,32), with one study reporting comparable effects of anticipated and actual disease recurrence on QoL in TC survivors over a decade after diagnosis (18).

Preference-based indexes and their properties

Six preference-based measures were used to assess HRQoL in TC survivors: HUI2, HUI3, EQ-5D-5L, EQ-5D-3L, 15D, and SF-6D. The number of items assessed ranged from 5 to 16. While EQ-5D-5L, EQ-5D-3L, and SF-6D evaluated the physical, psychological, and social domains

of HRQoL, HUI2 and HUI3 evaluated only the physical and psychological domains, which is often the case in utility indexes.

QoL evaluation using preference-based indexes

While one study found HRQoL in TC survivors to be comparable with that of the general population at long-term follow-up using 15D (42), all other studies using preference-based instruments found significant impairment in HRQoL in TC patients. Two studies used SF-6D to demonstrate impaired HRQoL in young female adult survivors and patients with advanced differentiated thyroid cancer (DTC), respectively (22,26). While EQ-5D-3L was used in multiple studies to demonstrate decreased HRQoL and increased anxiety and depression in patients with TC compared with other types of cancer (34,38), the ability of SF-6D to more comprehensively capture the HRQoL effects of DTC than other preference-based indexes has been demonstrated (22,28).

Psychometric instruments and their properties

Psychometric instruments used in the assessment of HRQoL in TC survivors demonstrated a variety of scoring metrics and assessed a range of symptoms and behaviors. The number of domains ranged from 4 to 10. The number of items assessed ranged from 12 to 58. All instruments were designed to be self-administered in a one-time sitting. Only two instruments evaluated all four of Ferrell's QoL domains (physical, psychological, social, and spiritual) (33,46). Five psychometric instruments evaluated three of the domains—SF-12, SF-36, PROMIS-29, EORTC QLQ-C30, and UW-QoL; each excluded the spiritual domain. Finally, two instruments evaluated two domains (physical

TABLE 1. DESCRIPTION OF QUALITY-OF-LIFE INSTRUMENTS USED IN THYROID CANCER SURVIVORS

Instruments	Domains (items)	Domain description	Ferrell's QoL domains				Scoring and administration
			Physical	Psychological	Social	Spiritual	
General HRQoL instruments—preference-based							
EuroQoL-5D-5 Level (EQ-5D-5L)	(5)	Mobility, self-care, usual activities, pain/discomfort, anxiety and depression	x	x	x		Lower scores reflect better health Self-administered, one-time survey
EuroQoL-5D-3 Level (EQ-5D-3L)	6 (16)						
15D	(15)	N/A	x	x			Higher scores reflect more symptoms Self-administered, one-time survey
Short-Form 6-Dimension (SF-6D)	6 (11)	Physical functioning, role limitations due to physical health, bodily pain, vitality, social functioning, and mental health	x	x	x		Higher scores reflect better health Self-administered, one-time survey
HUI2 HUI3	(6) (8)	Sensation, mobility, emotion, cognition, self-care, pain Vision, hearing, speech, ambulation, dexterity, emotion, cognition, self-care, pain	x	x			Higher scores reflect more symptoms Self-administered (15 question version) or interviewer-administered (40 question version); one-time survey
General HRQoL instruments—psychometric							
36-Item Short-Form Health Survey (SF-36)	7 (36)	Physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional health, and mental health	x	x	x		Higher scores reflect better health Self-administered, one-time survey
12-Item Short-Form Survey (SF-12)	7 (12)	Physical functioning, role limitations, bodily pain, health perception, energy level, social functioning, and psychological well-being	x	x	x		Higher scores reflect better health Self-administered, one-time survey
Patient-Reported Outcomes Measurement Information System (PROMIS-29)	7 (29)	Depression, anxiety, pain interference, physical function, fatigue, satisfaction with social role participation, sleep disturbance	x	x	x		Higher scores reflect more symptoms Self-administered, one-time survey
Cancer-specific instruments—psychometric							
European Organization for Research and Treatment of Cancer (EORTC QLQ-C30)	10 (30)	Functional: physical, role, emotional, cognitive, social, global Symptoms: fatigue, nausea/vomiting, pain Single-item: dyspnea, appetite loss, sleep disturbance, constipation, diarrhea	x	x	x		For physical and role function, higher scores reflect better health For other items, lower scores reflect better health Self-administered or interviewer-administered, one-time survey

(continued)

TABLE 1. (CONTINUED)

<i>Instruments</i>	<i>Domains (items)</i>	<i>Domain description</i>	<i>Ferrell's QoL domains</i>				<i>Scoring and administration</i>
			<i>Physical</i>	<i>Psychological</i>	<i>Social</i>	<i>Spiritual</i>	
University of Washington QoL scale (UW-QOL)	9 (40)	Pain, disfigurement, activity, recreation/entertainment, employment, chewing/swallowing, speech, shoulder disability	x	x	x		Higher scores reflect better health Self-administered, one-time survey
TC-specific instruments—psychometric							
City of Hope QoL Scale—Thyroid Version (COH-QoL)	4 (41)	Physical, psychological, social, and spiritual well-being	x	x	x	x	Higher scores reflect better health Self-administered, one-time survey
Thyroid Cancer Quality-of-Life Survey (THYCA-QoL)	(24)	Symptoms: neuromuscular, voice, concentration, sympathetic, throat/mouth, psychological, sensory problems Single-item: problems with scar, felt chilly, tingling hands/feet, gained weight, headaches, libido	x	x			Higher scores reflect more symptoms Self-administered, one-time survey
Thyroid cancer Quality-of-Life Computerized Adaptive Test (ThyCAT)	4 (≤58)	Physical, psychological, social, and spiritual well-being	x	x	x	x	Higher scores reflect better health Self-administered via digital interface, one-time survey
European Organization for Research and Treatment of Cancer-Thyroid (EORTC QLQ-THY)	(34)	N/A	x	x			Higher scores reflect more symptoms Self-administered, one-time survey

Blank boxes indicate domain not assessed.

HRQoL, health-related quality of life; N/A, not applicable; QoL, quality of life; TC, thyroid cancer.

TABLE 2. QUALITY-OF-LIFE STUDIES IN THYROID CANCER SURVIVORS

References no.	Study	Study focus	n	Patient population	Instruments	Administered as designed?	Ferrell's QoL domains				Study results
							Phys	Psych	Soc	Spir	
(42)	Studies using general HRQoL instruments—preference-based Pelttari <i>et al.</i> (2009)	Evaluation of the impact of cured low-risk DTC on HRQoL at long-term follow-up (5–20 years)	341	DTC patients, stage I or II, after curative treatment	15D	Yes	x	x			HRQoL is comparable with that of the general population at long-term follow-up.
(22)	Gallop <i>et al.</i> (2015)	Assessment of the impact of DTC on HRQoL; review of health utilities for economic evaluation of RAI-refractory DTC treatments	52	Patients with self-reported DTC, attending the 2012 Thyroid Cancer Survivor's Association conference	SF-6D EQ-5D-5L	No ^a No ^a	x	x	x		Qualitative findings suggest greater HRQoL impact of more advanced DTC. SF-6D may be more sensitive instrument for eliciting HRQoL data suitable for economic evaluations of treatments. All scores declined at two weeks postoperatively and returned to pretreatment levels at six months. Of the instruments assessed, the SF-6D is the most responsive to treatment effects.
(28)	Lubitz <i>et al.</i> (2017)	Assessment of ability of four validated surveys to detect changes in health and clinical intervention in PTC patients	117	PTC patients undergoing first year of treatment	SF-6D EQ-5D-5L HUI2, HUI3	Yes Yes No ^b	x	x	x		Average QoL in DTC patients is lower than that of the U.K. population, and lower than that of patients with breast, colorectal, and prostate cancer; many suffer with fatigue, and depression requiring antidepressants and/or counselling.
(34)	McIntyre <i>et al.</i> (2018)	Investigation of QoL in a cohort of U.K. TC patients	82	DTC patients at U.K. patient/doctor TC forum	EQ-5D-3L	Yes	x	x			Anxiety and depression were more common in TC survivors than survivors of cervix, breast, stomach, colon, or other sites of cancer. Subjective health perception and socioeconomic factors affected HRQoL across cancer sites.
(38)	Ryu <i>et al.</i> (2019)	Assessment of differences in HRQoL based on cancer site	664 (total) 125 (TC)	Patients with history of cancer diagnosis	EQ-5D-5L	Unk ^c	x	x	x		

(continued)

TABLE 2. (CONTINUED)

References no.	Study	Study focus	n	Patient population	Instruments	Administered as designed?	Ferrell's QoL domains				Study results
							Phys	Psych	Soc	Spir	
Studies using general HRQoL instruments—psychometric											
(20)	Crevenna <i>et al.</i> (2003)	Evaluation of HRQoL and needs of TC patients on T4 replacement therapy	150	DTC patients treated with total thyroidectomy and RAI, without metastatic disease, on T4 replacement therapy	SF-36— <i>German</i>	Yes	x	x	x	x	One year after diagnosis, vitality and physical, mental, emotional, and social well-being are significantly impaired. QoL improves with time since diagnosis, but vitality and emotional well-being remain impaired.
39	Tan <i>et al.</i> (2007)	Assessment of the impact of DTC on QoL in an urban multi-ethnic Asian population	152	DTC patients	SF-36— <i>Chinese</i>	Yes	x	x	x	x	DTC significantly decreases QoL, especially in the elderly and poorer educated. Employment, education level, younger age, and Malay/Indian ethnicity all protect against decreased HRQoL.
(40)	Hoftijzer <i>et al.</i> (2008)	Evaluation of the impact of cured DTC on QoL	153	Cured DTC patients	SF-36 MFI-20 HADS SDQ	Yes	x	x	x	x	QoL is lower in DTC survivors than in age- and gender-matched controls, independent of TSH level, and improves with time since cure.
(44)	Malterling <i>et al.</i> (2010)	Comparison of long-term clinical outcome and QoL in DTC patients after “aggressive” or “conservative” treatment	52	DTC patients treated with total thyroidectomy+RAI, or subtotal thyroidectomy+occasional RAI	SF-36— <i>Swedish</i>	Yes	x	x	x	x	There are no significant differences between patients treated with total or subtotal thyroidectomy, or between the TC group and the healthy population.
(24)	Hedman <i>et al.</i> (2016)	Assessment of the effect of living with a cancer diagnosis for many years on HRQoL in DTC patients	279	Long-term DTC survivors	SF-36— <i>Swedish</i>	Yes	x	x	x	x	Over a decade after diagnosis, worry about disease recurrence continues to negatively impact HRQoL in long-term DTC survivors, with influence on HRQoL comparable with actual recurrence.

(continued)

TABLE 2. (CONTINUED)

References no.	Study	Study focus	n	Patient population	Instruments	Administered as designed?	Ferrell's QoL domains			Study results
							Phys	Psych	Soc	
(29)	Hedman <i>et al.</i> (2017)	Assessment of the effect of thyroid- related symptoms on HRQoL in long-term DTC patients	279	Long-term DTC survivors	SF-36— <i>Swedish</i>	Yes	x	x	x	DTC patients reporting symptoms scored lower in HRQoL compared with those with no symptoms >14 years after diagnosis even with adjustment for numerous factors.
(18)	Hedman <i>et al.</i> (2018)	Assessment of changes in HRQoL in DTC patients from diagnosis to one year of follow-up	235	Patients diagnosed with DTC	SF-36— <i>Swedish</i>	Yes	x	x	x	Patients reporting negative view of life and FoR at time of diagnosis had significantly lower HRQoL in five of eight domains. HRQoL at diagnosis was the most important predictive factor for HRQoL at one-year follow-up. TSH- suppression did not negatively impact HRQoL.
(30)	Gou <i>et al.</i> (2017)	Comparison of HRQoL in PTC patients with that of the general population	186	PTC patients >18 years old after thyroidectomy	SF-36— <i>Chinese</i>	Yes	x	x	x	PTC patients had significantly lower HRQoL scores across domains at one month after surgery, with recovery at six months, but even two years after surgery, few domain scores had recovered to levels found in the general population.
(36)	Goswami <i>et al.</i> (2018)	Comparison of HRQoL in TC survivors with other cancer type survivors and the normative population	1743	Patients with a history of TC	PROMIS-29	Yes	x	x	x	TC patients reported statistically significantly worse QoL across domains, and clinically significantly worse HRQoL in the anxiety, fatigue, and sleep disturbance domains compared with U.S. normative data. Compared with other cancers, they reported worse anxiety, depression, fatigue, sleep disturbance, and social functioning, but better physical functioning and less pain.

(continued)

TABLE 2. (CONTINUED)

References no.	Study	Study focus	n	Patient population	Instruments	Administered as designed?	Ferrell's QoL domains				Study results
							Phys	Psych	Soc	Spir	
Studies using cancer-specific QoL instruments—psychometric											
(31)	Lloyd <i>et al.</i> (2003)	Examination of QoL in head and neck cancer patients up to one year after treatment	40 total, 4 TC	Patients with head and neck cancer, including TC (<i>n</i> =4), with ≥1-year life expectancy	UW-QoL	Yes	x	x	x		QoL scores decrease at 3 and 6 months but return to preoperative levels at 12 months, with effects on specific domains varying by tumor subsite. Anxiety improves at 12 months, but appearance, activity, speech, shoulder, and saliva QoL scores remain low.
(43)	Lee <i>et al.</i> (2010)	Comparison of HRQoL in cured DTC survivors versus general population	316	DTC patients after surgery, on T4 replacement therapy for ≥6 months	EORTC QLQ-C30— <i>Korean</i> BFI HADS	No ^d	x	x	x		Disease-free survivors of DTC experience a significantly decreased HRQoL, with major determinants being anxiety, depression, and fatigue.
(25)	Drabe <i>et al.</i> (2016)	Examination of diagnosis and treatment burden, anxiety, and depression, and fatigue in TC patients and their partners	71 patients, 40 partners	Patients diagnosed with and treated for TC, and their partners	EORTC QLQ-C30— <i>German</i> WHO QoL BAI, BDI, BFI	Yes	x	x	x		Both patients and partners suffer from the diagnosis and treatment of DTC. Only patients are at risk of developing anxiety symptoms or fatigue.
(27)	Singer <i>et al.</i> (2016)	Assessment of QoL issues that are relevant to TC patients cross-culturally	110	Patients diagnosed with TC	EORTC QLQ-C30	Yes	x	x	x		TC patients cross-culturally rate fatigue-related issues as highly impactful on QoL, as well as psychological issues, especially fear of progression and of additional treatments.
(37)	Wang <i>et al.</i> (2018)	Evaluation of HRQoL of TC survivors in Hangzhou, China, and important correlates defining HRQoL	970	Patients diagnosed with TC	SF-36— <i>Chinese</i> EORTC QLQ-C30— <i>Chinese</i>	Yes Yes	x	x	x		Survivors experience more problems than the community reference population. Sex, education, marital status, employment status, weight status, per capita disposable income, physical activity per week, and levothyroxine intake per day are important correlates of HRQoL of TC survivors.

(continued)

TABLE 2. (CONTINUED)

References no.	Study	Study focus	n	Patient population	Instruments	Administered as designed?	Ferrell's QoL domains			Study results
							Phys	Psych	Soc	
Studies using TC-specific QoL instruments—psychometric										
(41)	Roberts <i>et al.</i> (2008)	Assessment of HRQoL and information/care delivery needs following TC treatment	62	Patients treated for TC	EORTC QLQ-C30 COH-QoL	Yes No ^e	x	x	x	QoL in treated patients is high; most informational needs are addressed. Information on emotional support, and ongoing information access, are desired.
(23)	Aschebrook-Kilfoy <i>et al.</i> (2015)	Evaluation of physical and psychosocial morbidity of TC via a large-scale survivorship QoL study.	1174	Patients diagnosed with TC	COH-QoL	No ^f	x	x	x	Mean overall QoL was 5.56/10 (0 = worst); QoL scores begin to improve 5 years after diagnosis. Female sex, young age at diagnosis, and lower educational attainment are highly predictive of decreased QoL.
(45)	Husson <i>et al.</i> (2013)	Development and pretesting of a TC-specific HRQoL questionnaire (THYCA-QoL) (Phase I–III testing)	306	Patients diagnosed with TC	EORTC QLQ-C30 THYCA-QoL	Yes N/A	x	x	x	The THYCA-QoL is the first TC-specific HRQoL questionnaire developed using methodologically proven guidelines, to be used in combination with the EORTC QLQ-C30.
(21)	Husson <i>et al.</i> (2013)	Assessment of HRQoL among long-term TC survivors compared with general population	306	Patients diagnosed with TC	EORTC QLQ-C30 THYCA-QoL	Yes Yes	x	x	x	Long-term TC survivors have decreased HRQoL compared with the general population. Neuromuscular, sympathetic, concentration, and psychological symptoms are more strongly associated with HRQoL than clinical and sociodemographic factors alone.

(continued)

TABLE 2. (CONTINUED)

References no.	Study	Study focus	n	Patient population	Instruments	Administered as designed?	Ferrell's QoL domains			Study results
							Phys	Psych	Soc	
(26)	Goldfarb and Casillas (2016)	Assessment of sociodemographic and clinical factors influencing TC-specific HRQoL; comparison of HRQoL in young adult and adult TC survivors	1028	Young adult (age 17–39, $n = 277$) and adult (age ≥ 40 , $n = 751$) TC survivors	THYCA-QoL SF-12 SF-6D	Yes Yes Yes	x	x	x	Female young adult survivors have lower HRQoL than the normal age-matched population. Young adults had fewer neuromuscular, voice, and throat/mouth complaints, but more grievances regarding scar, headaches, and anxiety. Neuromuscular, anxiety, and concentration complaints had the greatest impact on HRQoL across the study population.
(47)	Singer <i>et al.</i> (2017)	Pilot testing a questionnaire measuring HRQoL in TC patients, to be used with the EORTC QLQ-C30 (Phase III testing)	182	Patients treated for TC within the last two years	EORTC QLQ-C30 EORTC QLQ-THY	Yes N/A	x	x	x	Based on patient feedback, a question assessing shoulder dysfunction was added to the original questionnaire. The 34-item EORTC QLQ-THY is well accepted across cultural backgrounds and languages.
(32)	Rogers <i>et al.</i> (2017)	Employment of a screening question on FoR, and HRQoL in treated DTC patients	169	Patients with DTC	EORTC QLQ-C30 THYCA-QoL Emotion scales FoR test item	Yes Yes	x	x	x	HRQoL in this group was generally good, with most adverse effects on global health status and emotional function. One in seven patients reported preoccupation with FoR. The ThyCAT assesses QoL with strong correlation ($r = 0.96$) with the original NATCSS, using <10 questions, administered in <2 minutes.
(33)	Aschebrook-Kilfoy <i>et al.</i> (2018)	Development of a QoL computerized adaptive test (ThyCAT) for TC survivors	1078	Respondents to the NATCSS	ThyCAT	N/A	x	x	x	

(continued)

TABLE 2. (CONTINUED)

References no.	Study	Study focus	n	Patient population	Instruments	Administered as designed?	Ferrell's QoL domains			Study results
							Phys	Psych	Soc	
(35)	Mols <i>et al.</i> (2018)	Comparison of HRQoL and disease-specific symptoms among adolescents and young adults, middle-aged adults, and elderly TC survivors	293	Patients diagnosed with TC	EORTC QLQ-30 THYCA- QoL	Yes Yes	x	x	x	Adolescents and young adult survivors reported worse physical, role, social, and cognitive well-being. Middle-aged survivors more frequently reported fatigue, dyspnea, insomnia, constipation, diarrhea, nausea/vomiting, appetite loss, and financial issues. Elderly survivors reported more insomnia than the normative sample. All findings were of small to medium clinical significance.

See Table 1 for disease-specific instrument acronyms.

^aQualitative data gathered from study participants were mapped onto elements of SF-6D and EQ-5D by investigators.

^b40 question version of HUI to be administered by an interviewer.

^cSurvey scores gathered from pre-existing national database.

^dFunctional domains and global scales only, symptom domains excluded.

^eScaling and time frame modified to match coadministered EORTC QLQ-C30.

^fAdditional thyroid-specific questions added.

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BFI, Brief Fatigue Inventory; DTC, differentiated thyroid cancer; FoR, fear of recurrence; HADS, Hospital Anxiety and Depression Scale; MFI-20, 20-item Multidimensional Fatigue Inventory; NATCSS, North American Thyroid Cancer Survivorship Study; PTC, papillary thyroid cancer; RAI, radioactive iodine ablation; SDQ, Somatoform Disorders Questionnaire; T4, thyroxine; TSH, thyrotropin.

and psychological) (45,47). Four instruments were designed to evaluate TC-specific HRQoL (33,45–47).

Cancer-specific psychometric instruments and their properties

The psychometric properties of the six reported cancer-specific instruments—including TC-specific instruments—varied in the strength of their validation metrics (Table 3). All instruments reported internal consistency of Cronbach's $\alpha > 0.7$ in the majority of scales, with the exception of ThyCAT for which reliability was not reported (33,45–50). Validity measures were reported in five of six instruments. THYCA-QoL reported convergent validity for five out of seven scales, but poor correlation ($r < 0.4$) with EORTC QLQ-30. Responsiveness across treatment course was reported only for UW-QoL, which measured responsiveness in both tumor stage and treatment course (50). All instruments were also evaluated for IRT calibration of individual items. No study had included documentation of IRT calibration, although the PROMIS-29 items were calibrated with IRT methods when this generic instrument was created (51).

QoL evaluation using psychometric instruments

Several studies using psychometric instruments examined the impact of age and life stage on HRQoL in TC survivors, demonstrating decreased HRQoL in various subpopulations,

including patients older than 50 years (39) and young female patients (23,26) using both preference-based indexes and THYCA-QoL. Multiple studies using THYCA-QoL demonstrated reduced physical impairment, but worse psychological symptoms and overall HRQoL, in younger TC survivors when compared with older survivors (26,35).

Summary

As the incidence of TC increases and the population of survivors expands, understanding of the impact of TC diagnosis and treatment on QoL has become increasingly important. There are currently over 50,000 patients diagnosed with TC in the U.S. annually (52). As this cancer is largely a nonlethal disease, there is a rapidly rising population of TC survivors for whom optimizing QoL is of paramount importance.

This demand for optimizing QoL has taken on two dimensions. First, and more established, this patient demographic has generated a shift toward increasingly conservative treatment with reduced radioiodine use and thyroid hormone for thyrotropin suppression and less aggressive surgical intervention. With changes in clinical practice thus being shaped by attention to patient priorities, it is imperative that this patient population undergoes a detailed analysis of QoL as it relates to both treatment and monitoring.

The second dimension—which is relatively new and still emerging—is the emphasis not only on assessing short-term

TABLE 3. PSYCHOMETRIC PROPERTIES OF CANCER-SPECIFIC QUALITY-OF-LIFE INSTRUMENTS USED IN THYROID CANCER SURVIVORS

<i>Instrument</i>	<i>Reliability</i>	<i>Validity</i>	<i>Responsiveness</i>	<i>References</i>
Cancer-specific instruments				
European Organization for Research and Treatment of Cancer (EORTC QLQ-C30)	$\alpha > 0.52$ –0.89 for functional scales $\alpha > 0.7$ for all symptom scales	Convergent, divergent	Not reported	Niezgoda and Pater (48) ^a Aaronson <i>et al.</i> (49) ^b
University of Washington QoL (UW-QOL)	$\alpha > 0.9$	Strong correlation $r > 0.8$ with SIP and KAF	Responsive across tumor stage and treatment course	Hassan and Weymuller (50) ^c
TC-specific instruments				
City of Hope-QoL Scale—Thyroid Version (COH-QoL)	$\alpha = 0.97$	Strong correlation 0.78 with FACT-G	Not reported	Dow <i>et al.</i> (46) ^d
Thyroid Cancer quality-of-life survey (THYCA-QoL)	$\alpha = 0.45$ –0.82 $\alpha > 0.7$ for 4 of 7 scales	Weak correlation $r < 0.4$ with EORTC QLQ-C30 Convergent validity in five out of seven scales	Not reported	Husson <i>et al.</i> (45)
Thyroid cancer quality-of-life computerized adaptive test (ThyCAT)	Not reported	Strong correlation $r = 0.96$ with NATCSS QoL questionnaire	Not reported	Aschebrook-Kilfoy <i>et al.</i> (33)
EORTC QLQ-THY	$\alpha > 0.70$ for 30 of 34 items	Not reported	Not reported	Singer <i>et al.</i> (47)

α = Cronbach's alpha (internal consistency, $\alpha > 0.7$); r = correlation coefficient.

^aValidated in patients undergoing chemotherapy.

^bValidated in patients with nonresectable lung cancer.

^cValidated in head and neck cancer.

^dValidated in thyroid patients undergoing T4 withdrawal.

FACT-G, Functional Assessment of Cancer Therapy-General; KAF, Karnofsky Performance Scale; NATCSS QoL, North American Thyroid Cancer Survivorship Study Quality of Life; SIP, Sickness Impact Profile.

physical side effects of treatment but on longitudinal data regarding the emotional, psychological, and social impacts of carrying a cancer diagnosis throughout a normal life expectancy as well. The majority of instruments used to evaluate HRQoL in TC survivors focus on the physical, psychological, social, and spiritual QoL domains as outlined by Ferrell *et al.* in the evaluation of QoL in breast cancer survivors (5). In their validation of a breast cancer QoL model, Ferrell *et al.* conducted a qualitative interview and survey-based study of 21 breast cancer survivors, and derived themes of HRQoL impairment within these four domains (6,7). While results demonstrated significant physical and psychological burden in breast cancer survivors, several aspects of spiritual well-being were shown to be positively impacted by survivorship.

Of note, only two instruments reviewed in the present study address Ferrell's spiritual domain of HRQoL. Spiritual well-being, defined as the ability to maintain and derive meaning from the cancer experience (4), is a core component of the overall assessment of HRQoL for some and has been shown to have a direct correlation with health outcomes (53). As changes in one domain can impact and influence the evaluation of all four domains, exclusion of this domain in the evaluation of TC QoL might result in an incomplete understanding of QoL survivorship using a psychometric approach. Utility indexes, in contradistinction, which are by nature designed for structural independence (i.e., no double counting), may show an impact by spiritual items on other domains (e.g., anxiety). Furthermore, because spirituality may be difficult to define, it may be difficult to measure it alone and in terms of its effects.

Many of the studies reviewed here demonstrated impaired psychological and emotional well-being in TC survivors, with anxiety, depression, and fatigue commonly cited as contributors to decreased HRQoL in these patients. Several studies suggested that younger patients are especially likely to be negatively affected by these symptoms, and that fear of recurrence can be significantly detrimental to QoL up to decades after diagnosis. However, these findings were not uniformly demonstrated across studies. The impact of TC on HRQoL varied widely; while a small number of studies demonstrated no long-lasting HRQoL detriments in TC survivors compared with the general population (41,42,44), others reported comparable or worse HRQoL to other cancer types with significantly worse prognoses (34,36,38)—a finding previously demonstrated by others (54).

Notably, several studies suffered from varying degrees of selection bias. Utilization of patient samples from survivorship groups is likely to overestimate HRQoL impact of TC, as patients may be more likely to join survivorship groups if they experience QoL issues, making the results less generalizable to the entire population (22,34). Other studies may have suffered from selection bias by surveying exclusively long-term survivors, who may have been more likely to respond if they were experiencing persistent symptoms after definitive treatment (24,29).

Nonetheless, the marked discrepancies demonstrated in the findings of these studies emphasize the challenges of accurately assessing patient perspectives, reinforcing the importance of using well-constructed instruments to measure patient-reported outcomes in the target population, including not only the physical and psychosocial impact of diagnosis and treatment but also the financial toxicity associated with

the disease. To date, the financial component of QoL has been largely underappreciated. Ramsey *et al.* evaluated the bankruptcy rate associated with various cancer types, showing a bankruptcy rate of 9.3 per 1000 person-years (55). While the etiology of this finding is not fully understood, recognition that financial toxicity likely impacts QoL in TC survivors should prompt researchers in this field to incorporate this domain into future instruments (56).

The use of instruments in disease-specific QoL assessment requires a thorough understanding of how the instrument was developed and the intended use for it. Most importantly, such tools must be reliable and responsive to the domains of life quality being assessed, thus relevant to the disease being evaluated. TC patients have disease-specific QoL changes that may differ from other cancer types. Thus, the population being evaluated must be similar to the population in which the tool was developed and should be used in the same language in which the tool was developed.

The decision to use generic instruments versus disease-specific instruments has specific advantages and disadvantages. Generic instruments are most often supported by strong validation across numerous populations, but if not validated specifically in the target population being evaluated, they may fail to detect disease-specific QoL changes that have significant effects on that population. This review identified no instruments that have undergone thorough validation of psychometric properties in the TC population, although many of the instruments used to assess HRQoL in this population have been well-validated in other populations.

Because TC survivors face unique HRQoL concerns, these generic instruments are neither comprehensive in their assessment of symptoms nor completely relevant in the HRQoL content they address, and may be poorly responsive to treatment effects. For example, many TC survivors are relatively young at the time of diagnosis; the prolonged survival period they face, although prompting their cancer diagnosis to be labeled as “the good cancer,” in fact increases their susceptibility to long-term financial vulnerability and anxiety (16,19,20,22,43). The usual list of symptoms measured in standard PROMs is inadequate in TC, as it fails to identify and measure the key health and nonhealth contributors to clinical anxiety, including prolonged fear of recurrence and financial toxicity. Recent research has demonstrated the magnitude and prevalence of psychological financial hardship in TC survivors, emphasizing the need for tools and further studies to better understand its impact (57).

In the current literature, assessment of HRQoL in TC survivors has relied heavily on general HRQoL instruments that have not been validated in the TC population. Although instruments designed to assess QoL in cancer survivors exist, only two—EORTC QLQ-C30 and the UW QoL—have been applied to studies of HRQoL in TC survivors. Few instruments are available that specifically assess QoL in TC; all are included in this review. The City of Hope—Thyroid Version instrument developed by Dow *et al.* is the oldest instrument, developed in 1997 to evaluate QoL in patients undergoing thyroxine withdrawal before scanning procedures (46). The THYCA-QoL developed by Husson *et al.* was the first rigorously validated instrument, designed for use in combination with the EORTC QLQ-C30 for holistic assessment of HRQoL in TC survivors (45). Singer *et al.* developed the

EORTC QLQ-THY from the EORTC QLQ-C30 general cancer instrument, and it is currently undergoing phase IV testing (47). Most recently, Aschebrook-Kilfoy *et al.* developed the ThyCAT, a computerized adaptive test, using questionnaire response data from a longitudinal cohort study of QoL in 1078 TC survivors in the North American Thyroid Cancer Survivorship Study (33).

Of these four thyroid-specific instruments, phase IV testing has been completed in only three instruments. Rigorous evaluation of psychometric properties has shown acceptable validity and reliability in three instruments; responsiveness has not been demonstrated in any of the four instruments. Responsiveness, defined as the measurement of longitudinal validity or the ability to capture change in health status over time (58,59), is a critical component of QoL assessment.

The identification of subtle changes in HRQoL is an important component of survivorship evaluation and may be influenced by treatment and monitoring approaches. A static evaluation of HRQoL misses the natural and variable progression of patient survivorship over time, and studies that have evaluated HRQoL and instrument responsiveness longitudinally, as performed by Lubitz *et al.*, are rare (28). The ability to detect these changes in the HRQoL of TC survivors is especially important, as the long-term persistence of mood symptoms and fear of recurrence has been demonstrated in several studies, but may not be accurately captured by nonthyroid-specific HRQoL instruments (28).

In general, psychometric, nonpreference-based instruments have traditionally been constructed with the methods of Classical Test Theory (CTT). In CTT, reliability and validity at the level of the scale as a whole are of importance with summated scoring usually used in a unidimensional instrument. However, CTT has been found to have substantial limitations, since it does not emphasize the proper structure of the items. Individual items can be fraught with problems in their construction, which cause measurement issues.

IRT, on the contrary, plots the behavior of items as a logistic function where, by the slope and breadth of the function, one can see how well an item discriminates different levels of a construct as well as showing where the item best functions to detect patients with lower versus higher degrees of a construct (i.e., pain, fatigue, anxiety). IRT then shows how well an item functions in a population and where the patient's level of morbidity or "location" is with respect to that item. Furthermore, CTT does not look at the structure of the response set of an item. For example, in an item about pain, a response set (e.g., none, somewhat, moderate, severe, extreme) may confuse patients in our efforts to differentiate their level of pain.

IRT analysis can show that the item characteristic curves generated for each level of pain are not a monotonic function with increasing severity, so that the item level curves are distorted. For example, data may show that a patient is more likely to endorse a (higher) "moderate" level of pain rather than (lower) a "somewhat" level. IRT can also evaluate situations where an item is not performing equally in different groups when it should, say in different sex or ages, because of the language used (differential item functioning). Finally, IRT can establish relative "invariant measurement" for an item for use in any TC population once it shows good performance in a reasonably sizeable TC population.

This study has several limitations. Inclusion and exclusion of studies, as well as assessment of validation metrics, were

dependent on methodology reported by the authors. Only those studies explicitly documenting or providing references for tool validation or specific assessment of psychometric properties were included and reported as such in this review. Notably, the studies included for review were heterogeneous in nature: while many assessed HRQoL of TC survivors in comparison with the general population, others simply reported stages of instrument development and validation or assessed correlation of validated instrument domains with patient focus groups. With so few studies meeting the inclusion criteria, the authors allowed for this heterogeneity to more comprehensively review the HRQoL instruments available for use in the TC patient population, with the understanding that these instruments were being applied in a variety of ways across studies. There was no major disagreement between independent reviewers regarding the application of inclusion and exclusion criteria to individual studies.

Taken together, the results of this study indicate a need for development and a thorough validation of a standardized HRQoL assessment tool for TC survivors, using a complete and rigorous developmental process as described above using IRT and CTT methods as appropriate. Critical in such an instrument would be the capability to function as a preference-based index, either by a valuation process to use all of the chosen items or a proper subset of more conceptually nonredundant psychometric items.

Given the substantial financial ramifications of TC care for both patients and the health care system, a view toward cost-effectiveness is reasonable. A usual concern with disease-specific instruments is that the quality-adjusted life years (QALYs) generated will not be conceptually similar to the QALYs generated by generic indexes—thus not comparable across diseases.

Prior work by the National Health Measurement Study showed that in factor analysis, all generic indexes have three basic factors/domains: Pain, Physical, and Psychosocial (60). The psychosocial domain often emphasizes psychological aspects over social, since many feel the index-based domains should only be aspects "within the skin," noted by the HUI2/3. Such an approach usually eliminates social aspects. If a proposed index has coverage of these three areas, then the QALYs that result are likely valid and are arguably more valid than a generic tool. An optimal tool would adequately cover TC QoL, given the differences in treatment, prognosis, and HRQoL impact of DTC compared with other cancer types, but therefore scaled so that the QALYs are meaningful.

Evaluation of the effects of definitive treatment on HRQoL should reflect current shifts in clinical practice toward conservative treatment approaches. Assessment of necessary QoL domains and sensitivity to the longitudinal impact of psychological stressors (including fear of recurrence) are essential to accurately understand the burden of TC survivorship.

Conclusions

This review identifies the HRQoL instruments in the literature, which have been used in TC survivors, and summarizes their psychometric properties. We also systematically review the current literature and evaluate published

studies using HRQoL instruments in TC survivors. Care providers involved in the treatment of TC survivors should be aware of longitudinal effects on HRQoL, especially pertaining to the various components that contribute to chronic psychological debilitation, to most effectively monitor symptoms and guide care. Further development and rigorous validation of TC-specific instruments will allow for better data gathering and understanding of the barriers to achieving high long-term HRQoL in TC survivors throughout their long post-treatment survival course.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

This research was funded by NIH/NCI-R37CA231957 (CCL).

References

- Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) SEER Cancer Statistics Review (CSR) 1975–2016. National Cancer Institute, Bethesda, MD.
- SEER Preliminary Cancer Incidence Rate Estimates for 2017, and diagnosis years 2000 to 2017. SEER 18, National Cancer Institute, Bethesda, MD.
- Ferrell BR, Dow KH, Leigh S, Ly J, Gulasekaram P 1995 Quality of life in long-term cancer survivors. *Oncol Nurs Forum* **22**:915–922.
- Ferrell BR 1996 The quality of lives: 1,525 voices of cancer. *Oncol Nurs Forum* **23**:909–916.
- Ferrell BR, Grant M, Funk B, Garcia N, Otis-Green S, Schaffner ML 1996 Quality of life in breast cancer. *Cancer Pract* **4**:331–340.
- Ferrell BR, Grant M, Funk B, Otis-Green S, Garcia N 1997 Quality of life in breast cancer. Part I: physical and social well-being. *Cancer Nurs* **20**:398–408.
- Ferrell BR, Grant M, Funk B, Otis-Green S, Garcia N 1998 Quality of life in breast cancer. Part II: psychological and spiritual well-being. *Cancer Nurs* **21**:1–9.
- Meropol NJ, Weinfurt KP, Burnett CB, Balshem A, Benson AB, Castel L, Corbett S, Diefenbach M, Gaskin D, Li Y, Manne S, Marshall J, Rowland JH, Slater E, Sulmasy DP, Van Echo D, Washington S, Schulman KA 2003 Perceptions of patients and physicians regarding phase I cancer clinical trials: implications for physician-patient communication. *J Clin Oncol* **21**:2589–2596.
- Meropol NJ, Egleston BL, Buzaglo JS, Benson AB, Cegala DJ, Diefenbach MA, Fleisher L, Miller SM, Sulmasy DP, Weinfurt KP, Group CSR 2008 Cancer patient preferences for quality and length of life. *Cancer* **113**:3459–3466.
- Shrestha A, Martin C, Burton M, Walters S, Collins K, Wyld L 2019 Quality of life versus length of life considerations in cancer patients: a systematic literature review. *Psychooncology* **28**:1367–1380.
- Deng Y, Tu H, Pierzynski JA, Miller ED, Gu X, Huang M, Chang DW, Ye Y, Hildebrandt MAT, Klein AP, Zhao R, Lippman SM, Wu X 2018 Determinants and prognostic value of quality of life in patients with pancreatic ductal adenocarcinoma. *Eur J Cancer* **92**:20–32.
- Roncolato FT, Gibbs E, Lee CK, Asher R, Davies LC, Gebiski VJ, Friedlander M, Hilpert F, Wenzel L, Stockler MR, King M, Pujade-Lauraine E 2017 Quality of life predicts overall survival in women with platinum-resistant ovarian cancer: an AURELIA substudy. *Ann Oncol* **28**:1849–1855.
- Wong E, Rowbottom L, Tsao M, Zhang L, McDonald R, Danjoux C, Barnes E, Chan S, Chow E 2017 Prognostic value of pre- and post-treatment health-related quality of life in predicting survival of patients with brain metastases. *CNS Oncol* **6**:119–129.
- Cella D, Stone AA 2015 Health-related quality of life measurement in oncology: advances and opportunities. *Am Psychol* **70**:175–185.
- Velikova G, Stark D, Selby P 1999 Quality of life instruments in oncology. *Eur J Cancer* **35**:1571–1580.
- McHorney CA, Ware JE, Raczek AE 1993 The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* **31**:247–263.
- Group E 1990 EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* **16**:199–208.
- Hedman C, Djärv T, Strang P, Lundgren CI 2018 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* **28**:1609–1617.
- Lubitz CC, Sosa JA 2016 The changing landscape of papillary thyroid cancer: epidemiology, management, and the implications for patients. *Cancer* **122**:3754–3759.
- Crevenna R, Zettinig G, Keilani M, Posch M, Schmidinger M, Pirich C, Nuhr M, Wolzt M, Quittan M, Fialka-Moser V, Dudeczak R 2003 Quality of life in patients with non-metastatic differentiated thyroid cancer under thyroxine supplementation therapy. *Support Care Cancer* **11**:597–603.
- Husson O, Haak HR, Buffart LM, Nieuwlaet W-A, Oranje WA, Mols F, Kuijpers JL, Coebergh JW, van de Poll-Franse L V 2013 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* **52**:249–258.
- Gallop K, Kerr C, Simmons S, McIver B, Cohen EEW 2015 A qualitative evaluation of the validity of published health utilities and generic health utility measures for capturing health-related quality of life (HRQL) impact of differentiated thyroid cancer (DTC) at different treatment phases. *Qual Life Res* **24**:325–338.
- Aschebrook-Kilfoy B, James B, Nagar S, Kaplan S, Seng V, Ahsan H, Angelos P, Kaplan EL, Guerrero MA, Kuo JH, Lee JA, Mitmaker EJ, Moalem J, Ruan DT, Shen WT, Grogan RH 2015 Risk factors for decreased quality of life in thyroid cancer survivors: initial findings from the North American Thyroid Cancer Survivorship Study. *Thyroid* **25**:1313–1321.
- Hedman C, Djärv T, Strang P, Lundgren CI 2016 Determinants of long-term quality of life in patients with differentiated thyroid carcinoma—a population-based cohort study in Sweden. *Acta Oncol* **55**:365–369.
- Drabe N, Steinert H, Moergeli H, Weidt S, Strobel K, Jenewein J 2016 Perception of treatment burden, psychological distress, and fatigue in thyroid cancer patients and their partners—effects of gender, role, and time since di-

- agnosis: treatment burden and psychiatric morbidity in thyroid cancer. *Psychooncology* **25**:203–209.
26. Goldfarb M, Casillas J 2016 Thyroid cancer–specific quality of life and health-related quality of life in young adult thyroid cancer survivors. *Thyroid* **26**:923–932.
 27. Singer S, Husson O, Tomaszewska IM, Locati LD, Kiyota N, Scheidemann-Wesp U, Hofmeister D, Winterbotham M, Brannan C, Araújo C, Gamper EM, Kulis D, Rimmele H, Andry G, Licitra L, Group on behalf of the EQ of L, Group the EH and NC, Force the EET 2016 Quality-of-life priorities in patients with thyroid cancer: a multinational european organisation for research and treatment of cancer phase i study. *Thyroid* **26**:1605–1613.
 28. Lubitz CC, De Gregorio L, Fingeret AL, Economopoulos KP, Termezawi D, Hassan M, Parangi S, Stephen AE, Halpern EF, Donelan K, Swan JS 2017 Measurement and variation in estimation of quality of life effects of patients undergoing treatment for papillary thyroid carcinoma. *Thyroid* **27**:197–206.
 29. Hedman C, Djärv T, Strang P, Lundgren CI 2017 Effect of thyroid-related symptoms on long-term quality of life in patients with differentiated thyroid carcinoma: a population-based study in sweden. *Thyroid* **27**:1034–1042.
 30. Gou J, Cheng W, Lei J, Pan Q, You W, Cai M, Tang H, Lei Y, Li Z, Gong R, Zhu J 2017 Health-related quality-of-life assessment in surgical patients with papillary thyroid carcinoma: a single-center analysis from Mainland China. *Medicine (Baltimore)* **96**:e8070.
 31. Lloyd S, Devesa-Martinez P, Howard DJ, Lund VJ 2003 Quality of life of patients undergoing surgical treatment of head and neck malignancy. *Clin Otolaryngol* **28**:524–532.
 32. Rogers SN, Mepani V, Jackson S, Lowe D 2017 Health-related quality of life, fear of recurrence, and emotional distress in patients treated for thyroid cancer. *Br J Oral Maxillofac Surg* **55**:666–673.
 33. Aschebrook-Kilfoy B, Ferguson BA, Angelos P, Kaplan EL, Grogan RH, Gibbons RD 2018 Development of the ThyCAT: a clinically useful computerized adaptive test to assess quality of life in thyroid cancer survivors. *Surgery* **163**:137–142.
 34. McIntyre C, Jacques T, Palazzo F, Farnell K, Tolley N 2018 Quality of life in differentiated thyroid cancer. *Int J Surg* **50**:133–136.
 35. Mols F, Schoormans D, Smit JWA, Netea-Maier RT, Links TP, van der Graaf WTA, Husson O 2018 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* **40**:2235–2245.
 36. Goswami S, Mongelli M, Peipert BJ, Helenowski I, Yount SE, Sturgeon C 2018 Benchmarking health-related quality of life in thyroid cancer versus other cancers and United States normative data. *Surgery* **164**:986–992.
 37. Wang T, Jiang M, Ren Y, Liu Q, Zhao G, Cao C, Wang H 2018 Health-related quality of life of community thyroid cancer survivors in Hangzhou, China. *Thyroid* **28**:1013–1023.
 38. Ryu M, Hwang J-I 2019 Cancer site differences in the health-related quality of life of Korean cancer survivors: results from a Population-based Survey. *Public Health Nurs* **36**:144–154.
 39. Tan LGL, Nan L, Thumboo J, Sundram F, Tan LKS 2007 Health-related quality of life in thyroid cancer survivors. *Laryngoscope* **117**:507–510.
 40. Hoftijzer HC, Heemstra KA, Corssmit EPM, van der Klaauw AA, Romijn JA, Smit JWA 2008 Quality of Life in Cured Patients with Differentiated Thyroid Carcinoma. *J Clin Endocrinol Metab* **93**:200–203.
 41. Roberts K, Lepore S, Urken M 2008 Quality of life after thyroid cancer: an assessment of patient needs and preferences for information and support. *J Cancer Educ* **23**:186–191.
 42. Pelttari H, Sintonen H, Schalin-Jäntti C, Välimäki MJ 2009 Health-related quality of life in long-term follow-up of patients with cured TNM stage I or II differentiated thyroid carcinoma. *Clin Endocrinol (Oxf)* **70**:493–497.
 43. Lee J, Kim S, Tan AH, Kim H, Jang H, Hur K, Kim J, Kim K-W, Chung J, Kim S 2010 Decreased health-related quality of life in disease-free survivors of differentiated thyroid cancer in Korea. *Health Qual Life Outcomes* **8**:101.
 44. Malterling RR, Andersson RE, Falkmer S, Falkmer U, Niléhn E, Järhult J 2010 Differentiated thyroid cancer in a Swedish county—long-term results and quality of life. *Acta Oncol (Madr)* **49**:454–459.
 45. Husson O, Haak HR, Mols F, Nieuwenhuijzen GA, Nieuwlaat W-A, Reemst PH, Huysmans DA, Toorians AW, van de Poll-Franse L v. 2013 Development of a disease-specific health-related quality of life questionnaire (THYCA-QoL) for thyroid cancer survivors. *Acta Oncol* **52**:447–454.
 46. Dow KH, Ferrell BR, Anello C 1997 Quality-of-life changes in patients with thyroid cancer after withdrawal of thyroid hormone therapy. *Thyroid* **7**:613–619.
 47. Singer S, Jordan S, Locati LD, Pinto M, Tomaszewska IM, Araújo C, Hammerlid E, Vidhubala E, Husson O, Kiyota N, Brannan C, Salem D, Gamper EM, Arraras JI, Ioannidis G, Andry G, Inhestern J, Grégoire V, Licitra L, on behalf of the EORTC Quality of Life Group and the EORTC Endocrine Task Force the EH and NCG 2017 The EORTC module for quality of life in patients with thyroid cancer: phase III. *Endocr Relat Cancer* **24**:197–207.
 48. Niezgoda HE, Pater JL 1993 A validation study of the domains of the core EORTC quality of life questionnaire. *Qual Life Res* **2**:319–325.
 49. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC 1993 The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* **85**:365–376.
 50. Hassan SJ, Weymuller EA 1993 Assessment of quality of life in head and neck cancer patients. *Head Neck* **15**:485–496.
 51. Rose M, Bjorner JB, Gandek B, Bruce B, Fries JF, Ware JE 2014 The PROMIS physical function item bank was calibrated to a standardized metric and shown to improve measurement efficiency. *J Clin Epidemiol* **67**:516–526.
 52. Society AC 2019 Cancer Facts & Figures 2019. American Cancer Society, Atlanta, GA.
 53. Puchalski CM, King SDW, Ferrell BR 2018 Spiritual considerations. *Hematol Oncol Clin North Am* **32**:505–517.
 54. Applewhite MK, James BC, Kaplan SP, Angelos P, Kaplan EL, Grogan RH, Aschebrook-Kilfoy B 2016 Quality of life in thyroid cancer is similar to that of other cancers with worse survival. *World J Surg* **40**:551–561.
 55. Ramsey S, Blough D, Kirchhoff A, Kreizenbeck K, Fedorenko C, Snell K, Newcomb P, Hollingworth W,

- Overstreet K 2013 Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. *Health Aff (Millwood)* **32**: 1143–1152.
56. Perry LM, Hoerger M, Seibert K, Gerhart JJ, O'Mahony S, Duberstein PR 2019 Financial strain and physical and emotional quality of life in breast cancer. *J Pain Symptom Manage* **58**:454–459.
57. Barrows CE, Belle JM, Fleishman A, Lubitz CC, James BC 2020 Financial burden of thyroid cancer in the United States: an estimate of economic and psychological hardship among thyroid cancer survivors. *Surgery* **167**:378–384.
58. Terwee CB, Dekker FW, Wiersinga WM, Prummel MF, Bossuyt PMM 2003 On assessing responsiveness of health-related quality of life instruments: guidelines for instrument evaluation. *Qual Life Res* **12**:349–362.
59. Eurich DT, Johnson JA, Reid KJ, Spertus JA 2006 Assessing responsiveness of generic and specific health related quality of life measures in heart failure. *Health Qual Life Outcomes* **4**:89.
60. Cherepanov D, Palta M, Fryback DG 2010 Underlying dimensions of the five health-related quality-of-life measures used in utility assessment: evidence from the National Health Measurement Study. *Med Care* **48**:718–725.

Address correspondence to:
Benjamin C. James, MD, MS, FACS
Section of Endocrine Surgery
Division of Surgical Oncology
Department of Surgery
Beth Israel Deaconess Medical Center
185 Pilgrim Road, Palmer 605
Boston, MA 02215
USA

E-mail: bjames1@bidmc.harvard.edu