Surgery 166 (2019) 69–74

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Clinical factors associated with worse quality-of-life scores in United States thyroid cancer survivors

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ARTICLE INFO

Article history:
Accepted 27 January 2019
Available online 18 March 2019

ABSTRACT

Introduction: Thyroid cancer survivors are a rapidly growing population in the United States. The factors that drive health-related quality of life (HRQOL) in this population have not been well characterized. We hypothesized that more aggressive treatments and greater treatment-related adverse effects would be associated with worse HRQOL scores in thyroid cancer survivors.

Methods: Thyroid cancer survivors (18–89 years of age) completed an online survey regarding their clinical history in addition to the Patient-Reported Outcomes Measurement Information System (PROMIS) 29 instrument. Univariable and multivariable modeling were performed to evaluate factors associated with worse HRQOL scores. We generated β-values and 95% confidence intervals to quantify the effect of each independent variable in the model.

Results: Thyroid cancer survivors ($n = 1{,}743$) reported a high incidence of complications related to surgery and radioactive iodine ablation. Postoperative dysphonia (ß 1.83–3.07) and dysphagia (ß 2.05–3.65) predicted worse HRQOL scores across multiple PROMIS domains. Younger patient age (age <45 years) and short- or long-term complications of radioactive iodine, including gastrointestinal symptoms (51.9%), appetite changes (71.2%), sialadenitis (58.1%), xerostomia (73.3%), and xerophthalmia (45.1%) were associated with worse HRQOL scores ($P < .01$).

Conclusion: The factors associated with significantly worse HRQOL scores across multiple PROMIS domains for thyroid cancer survivors included patient age <45 years, postoperative hypocalcemia, dysphonia, dysphagia, scar appearance, and complications from radioactive iodine. Methods of evaluation, management, and prevention of these factors might positively impact HRQOL.

Introduction

The National Cancer Institute (NCI) estimates that there are more than 760,000 thyroid cancer survivors living in the United States.[1] Because of the three-fold increase in the incidence of thyroid cancer in recent decades and excellent survival associated with most cases, the population of thyroid cancer survivors in the Unite States is rapidly growing.[2] Although thyroid cancer is associated with lower mortality than most other cancers, recent studies have shown that the self-reported health-related quality of life (HRQOL) of patients with thyroid cancer is similar to, or worse than, that of patients diagnosed with cancers with poorer prognoses.[3–5] The factors driving poor HRQOL scores in this population are not well characterized.

Cancer survivors may experience changes in their physical, emotional, or psychosocial state related to the diagnosis and treatment of disease. These effects may persist for years after treatment and be associated with significant impairments in HRQOL.[6] It is well documented, for example, that thyroid cancer treatments, such as surgery and radioactive iodine (RAI) ablation, have numerous potential complications. Surgery imposes the risks of scar, hypocalcemia, pain, infection, dysphonia, and dysphagia.[7] RAI ablation may be associated with short-term or long-term

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https://doi.org/10.1016/j.surg.2019.01.034
0039-6060/

adverse effects, including salivary or lacrimal gland dysfunction, bone marrow suppression, pulmonary fibrosis, and secondary malignancy.[8,9] Furthermore, a diagnosis of thyroid cancer usually is associated with longitudinal health changes, such as a need for lifelong thyroid hormone replacement, long-term surveillance, and the risk of recurrence or metastasis.

Further research on thyroid cancer survivorship is necessary, in particular evaluation of the factors that impair quality of life.[2] The most recent American Thyroid Association (ATA) guidelines for management of well-differentiated thyroid cancer have highlighted the need for developing validated patient-reported outcome measurement tools and assessing the risks and benefits of active surveillance versus treatment.[10] Patient-reported outcome data are essential for understanding illness from the patients' perspective and developing effective interventions aimed at improving HRQOL. Herein we evaluate quality of life in thyroid cancer survivors using the Patient-Reported Outcomes Measurement Information System (PROMIS) 29-item profile. We hypothesized that more aggressive treatments and greater treatment-related adverse events would be associated with poorer HRQOL scores in thyroid cancer survivors.

Methods

We developed a survey to assess patient demographics, diagnostic workup, clinical characteristics, treatment history, and treatment-related adverse effects in collaboration with Thyroid Cancer Survivors' Association, Inc ([ThyCa] Olney, MD). We asked about both short-term complications (defined as those that occurred "days to weeks after treatment") and long-term complications (defined as those that continued "months to years" after treatment). The survey was modeled off of an HRQOL study we conducted in multiple endocrine neoplasia patients, which is described in detail elsewhere.[11] The survey was initially administered to ten individuals with a history of thyroid cancer and four clinicians, who each provided feedback to tailor survey content.

The PROMIS 29-item profile measure was administered to assess HRQOL. This instrument evaluates mental, physical, and social health across 7 domains: depression, anxiety, pain interference, physical function, fatigue, ability to participate in social roles (ie, social function), and sleep disturbance. PROMIS has been used in a variety of clinical settings and has been validated in the US general population and in several cancer populations.[12–14] Higher scores in the domains of anxiety, depression, fatigue, pain interference, and sleep disturbance indicate worse HRQOL, whereas lower scores in the physical and social functioning domains indicate worse HRQOL.

The survey was distributed in collaboration with ThyCa from January to June 2017 via several online modalities (ThyCa Web site, online newsletter, and social media sites, such as Facebook and Twitter). Individuals who reported a diagnosis of thyroid cancer, resided in the United States, and were 18 to 89 years of age were eligible to take part in the study. Upon completing an electronic consent, individuals were administered the 2-part survey online via Research Electronic Data Capture (REDCap),[15] a secure platform for gathering survey data to be used for research purposes. Participants were assigned a unique identifier code in the REDCap database to record responses anonymously. We excluded individuals who reported they had not received a thyroid cancer diagnosis by a physician or did not complete both components of the survey. This cohort has been designated the ThyCa cohort and is more fully described elsewhere.[5]

The PROMIS metric is the T-score. These scores for each of the 7 domains were generated using the HealthMeasures Scoring Service (www.healthmeasures.net). Multivariable linear regression models were generated to evaluate the impact of clinical and demographic factors on PROMIS T-scores. Variables were included in the multivariable model based on their significance in univariable linear regression models. We generated β-values to quantify the effect of each independent variable in the model. These β-values, along with 95% confidence intervals and *P* values corresponding to each variable, were reported from these regression models. A *P* value of < .01 was used to identify statistically significant variables. Based on earlier PROMIS validation studies in cancer, a difference of 3 points or more was considered to indicate a clinically meaningful difference.[16] SAS v 9.4 (SAS Institute, Cary, NC) was used for data analysis.

Results

Characteristics of the ThyCa cohort

The survey was accessed by 3,174 individuals, and 1,922 completed both portions of the survey (participation rate of 61%). A total of 1,743 individuals reported living in the United States and were eligible to be included in the ThyCa cohort. Characteristics of the ThyCa cohort are described in Table I. The majority of respondents were female (88%) and Caucasian (95%). The mean age at time of survey was 51 years ,with a mean age at diagnosis of 44 years. All types of thyroid cancer patients were included in our sample, with the majority being papillary (85%). Most participants reported stage 1 disease (30%), with 17% reporting stage 2, 14% reporting stage 3, 11% stage 4, and 28% unknown stage or not staged. A variety of treatment modalities were reported, with 98% of participants reporting surgery, 78% RAI, 2.4% chemotherapy, 3.8% external beam radiation, and 3.2% alternative therapies.

Adverse effects of surgery

The most commonly reported adverse effects of surgery were short-term dysphagia (63%) and dysphonia (71%), reported to last days or weeks after surgery. Of patients responding, 23% reported

Table I
ThyCa cohort sample demographics and clinical characteristics

Value	Number (% or ±SD)
Sex	
Female	1,541 (88.6%)
Race	
Caucasian	1,654 (94.9%)
Mean age, years	51 (± 13)
Mean age at diagnosis, years	44 (± 13)
Thyroid cancer type	
Papillary	1,313 (85.0%)
Follicular	97 (6.3%)
Medullary	74 (4.8%)
Hürthle cell	42 (2.7%)
NIFTP	12 (0.8%)
Anaplastic	7 (0.5%)
Disease stage	
Stage 1	522 (29.9%)
Stage 2	298 (17.1%)
Stage 3	243 (13.9%)
Stage 4	199 (11.4%)
Unknown stage/not staged	481 (27.6%)
Treatment history	
Surgery	1,710 (98.1%)
Radioactive iodine	1,366 (78.4%)
Chemotherapy	42 (2.4%)
External beam radiation	66 (3.8%)
Alternative	55 (3.2%)

Table II
Short-term (days to weeks) adverse effects of RAI

Adverse effects	Number (%)
GI symptoms (nausea/vomiting)	
None	657 (48.1)
Mild	358 (26.2)
Moderate	238 (17.4)
Severe	113 (8.3)
Sialadenitis	
None	573 (41.9)
Mild	362 (26.5)
Moderate	270 (19.8)
Severe	161 (11.8)
Xerostomia	
None	365 (26.7)
Mild	464 (34.0)
Moderate	345 (25.3)
Severe	192 (14.1)
Xerophthalmia	
None	750 (54.9)
Mild	321 (23.5)
Moderate	208 (15.2)
Severe	87 (6.4)
Excessive tearing	
None	1,044 (76.4)
Mild	177 (13.0)
Moderate	76 (5.6)
Severe	69 (5.1)
Taste/appetite changes	
None	393 (28.8)
Mild	402 (29.4)
Moderate	334 (24.5)
Severe	237 (17.3)

Table III
Long-term (months to years) adverse effects of RAI

Adverse effects	Number (%)
Bone marrow suppression	
None	1,187 (86.9)
Mild	120 (8.8)
Moderate	45 (3.3)
Severe	14 (1.0)
Pulmonary fibrosis	
None	1,273 (93.2)
Mild	68 (5.0)
Moderate	20 (1.5)
Severe	5 (0.4)
Chronic xeropthalmia	
None	771 (56.4)
Mild	325 (23.8)
Moderate	170 (12.4)
Severe	100 (7.3)
Xerostomia (chronic)	
None	688 (50.4)
Mild	331 (24.2)
Moderate	211 (15.4)
Severe	136 (10.0)
Infertility	
None	1,265 (92.6)
Mild	45 (3.3)
Moderate	25 (1.8)
Severe	31 (2.3)
Dental caries or other dental issues	
None	725 (53.1)
Mild	282 (20.6)
Moderate	201 (14.7)
Severe	158 (11.6)
Difficulty swallowing dry food	
None	791 (57.9)
Mild	312 (22.8)
Moderate	167 (12.2)
Severe	96 (7.0)

no concern about scar appearance; 47% reported hypocalcemia after surgery (including both transient and permanent), and 4% reported surgical site infection after surgery.

Adverse effects of radioiodine

The short-term and long-term adverse effects of RAI reported by respondents are described in Tables II–IV. The most common short-term side effects experienced by respondents were mild xerostomia (34%) followed by mild taste or appetite changes (29%) in the days and weeks after RAI. The most common long-term side effects of RAI experienced by survivors were chronic dry eye (xerophthalmia 24%) and chronic xerostomia (24%), persisting months to years after RAI.

Association with poor HRQOL scores

Several of these adverse effects of RAI and surgical complications along with other demographic and clinical variables were associated with worse HRQOL scores in thyroid cancer survivors. The disease and treatment factors associated with statistically significantly worse HRQOL in thyroid cancer survivors are summarized in Table V. The factors associated with significantly worse HRQOL scores across multiple PROMIS domains for thyroid cancer survivors included the following: patient age <45 years; postoperative hypocalcemia; dysphonia; dysphagia; scar appearance; and complications attributed to RAI, including short-term gastrointestinal symptoms, short-term taste or appetite changes, chronic xerophthalmia, and chronic dental caries.

Multiple factors were identified that had a statistically significant ($P < .01$) impact on HRQOL (Table V). Younger patient age (< 45 years) was associated with statistically and clinically worse HRQOL scores in the domains of anxiety (β 5.3), depression (β 3.7), and fatigue (β 4.4). Dysphonia (β 3.1) and dysphagia (β 3.6) were also associated with statistically and clinically worse scores for fatigue. Surgical site infection (β 3.7), dysphagia (β 3.4), and short-term xerophthalmia after RAI (β 3.3) were associated with worse scores for pain. Treatment with chemotherapy (β 5.2), the manifestation of surgical site infection (β 4.4), and the occurrence of pulmonary fibrosis after RAI (β 4.3) were associated with impaired physical functioning scores. Surgical site infection (β 4.2) and long-term dental caries after RAI (β 3.4) were associated with worse scores for social functioning. No factors were clinically significant for the domain of sleep disturbance.

Time since diagnosis was statistically significant and inversely associated with anxiety, depression, fatigue, and sleep disturbance and was significantly and directly associated with physical and social functioning when univariate analyses were examined (Spearman coefficient magnitudes ranging from 0.023 to 0.158).

Discussion

This study is the first to describe—using the NIH-funded PROMIS instrument—clinical factors associated with decreased

Table IV
Adverse effects after surgery

Adverse effects	Number (%)
Dysphagia	1,076 (62.9)
Dysphonia	1,205 (70.6)
Concern about scar appearance	1,321 (77.4)
Hypocalcemia (transient and/or permanent)	800 (46.8)
Surgical site infection	66 (3.9)

Table V
Clinical factors significantly* associated with impaired HRQOL

Variables	ß (95% CI)
PROMIS: Anxiety	
Patient age < 45 years	5.22 (4.05–6.39)
Concern about scar appearance	2.96 (1.78–4.14)
Dental caries (chronic)	2.71 (1.42–4.00)
Dysphagia	2.05 (0.80–3.29)
Dysphonia	1.83 (0.64–3.02)
Hypocalcemia	1.56 (0.46–2.66)
PROMIS: Depression	
Patient age < 45 tears	3.67 (2.51–4.82)
Concern about scar appearance	2.67 (1.51–3.82)
Dental caries (chronic)	2.37 (1.07–3.66)
Dysphagia	2.36 (1.12–3.59)
Dysphonia	1.83 (0.66–3.00)
PROMIS: Fatigue	
Patient age < 45 tears	4.37 (3.13–5.61)
Dysphagia	3.65 (2.35–4.94)
Dysphonia	3.07 (1.84–4.30)
Dental caries (chronic)	2.91 (1.58–4.24)
Female sex	2.77 (1.04–4.50)
Xerophthalmia (chronic)	2.07 (0.59–3.55)
Hypocalcemia	2.01 (0.86–3.15)
GI symptoms—nausea/vomiting (acute)	2.01 (0.64–3.38)
Taste/appetite changes (acute)	1.89 (0.67–3.12)
PROMIS: Pain interference	
Infection after thyroidectomy	3.67 (1.05–6.29)
Dysphagia	3.36 (2.14–4.58)
Xerophthalmia (acute)	3.26 (1.89–4.63)
Xerostomia (chronic)	2.97 (1.58–4.36)
Dysphonia	2.67 (1.52–3.82)
Dental caries (chronic)	2.00 (0.72–3.29)
PROMIS: Physical functioning	
Chemotherapy	−5.16 (−8.83 to −1.48)
Surgical site infection	−4.40 (−6.60 to −2.19)
Pulmonary fibrosis after RAI	−4.31 (−7.61 to −1.00)
Dysphagia	−2.59 (−3.61 to −1.58)
Dysphonia	−2.53 (−3.49 to −1.56)
Diagnosed with multiple types of thyroid cancer	−2.40 (−3.77 to −1.03)
Xerophthalmia (acute)	−2.32 (−3.51 to −1.13)
Dental caries (chronic)	−2.28 (−3.37 to −1.20)
Xerostomia (chronic)	−2.02 (−3.19 to −0.84)
Taste/appetite changes (acute)	−1.61 (−2.55 to −0.66)
PROMIS: Social functioning	
Surgical site infection	−4.16 (−6.62 to −1.71)
Dental caries (chronic)	−3.41 (−4.60 to −2.22)
Dysphagia	−2.88 (−4.02 to −1.74)
Dysphonia	−2.87 (−3.96 to −1.79)
Xerostomia (acute)	−2.13 (−3.25 to −1.01)
Xerophthalmia (chronic)	−2.09 (−3.40 to −0.79)
GI symptoms—nausea/vomiting (acute)	−1.90 (−3.07 to −0.74)

GI, gastrointestinal.
* Only factors found to be clinically meaningful (PROMIS T-score mean difference ≥ 3) and statistically significant ($P < .01$) are included.

HRQOL scores in thyroid cancer survivors. This instrument has been used to assess HRQOL in the general US population, a variety of cancer populations, and chronic disease conditions, but has not been used in thyroid cancer survivors before the ThyCa cohort.[5] Studies using other modalities of patient-reported outcome assessment have shown that thyroid cancer patients experience impaired HRQOL compared with the general population, and outcomes can be on par with survivors of other more aggressive cancers.[3] However, the factors associated with decreased HRQOL scores in this population have not been well characterized.[17] Other studies have characterized HRQOL based on demographic data, but little data exist on associated clinical factors. Risk factors for lower HRQOL, as identified by the North American Thyroid Cancer Survivorship Study, include female sex, younger age at diagnosis and treatment, and lower levels of education.[4] To develop interventions aimed at improving patient outcomes, a more complete understanding of contributing disease and treatment factors is needed.

We have shown elsewhere that patients with thyroid cancer reported worse HRQOL in all 7 PROMIS-29 domains when compared with the reference US population.[5] These results suggest that there is a significant psychosocial burden associated with thyroid cancer survivorship. We found that only 1 variable, dysphonia, was associated with worse HRQOL scores in every domain. Postoperative dysphagia and dental caries were associated with worse outcomes in 6 of 7 PROMIS domains. All other significant factors impacted 3 or fewer domains.

Dysphonia and dysphagia are commonly reported after thyroid surgery, even in patients with no obvious laryngeal nerve damage.[18] The chance of permanent dysphonia is reported to be 1% to 2%, and the chance of temporary dysphonia that resolves during the first year is 5% to 20%.[19] In contrast to these data, only 29% of our sample population reported retaining their normal voice after surgery. The average time since surgery was 7 years in this study. We found that there was a weak but statistically significant association between time since diagnosis and HRQOL in multiple PROMIS domains. The North American Thyroid Cancer Survivorship Study also found that the prevalence of self-reported dysphonia was much higher than suggested by the literature.[4] Our study demonstrates the broad impact of dysphonia on patient-reported quality of life. Dysphagia was also broadly associated with quality-of-life impairments in multiple domains. This is consistent with other studies in the literature assessing the relationship between dysphagia and HRQOL. An extensive literature review by Jones et al[20] documents the inverse relationship between dysphagia severity and HRQOL. Improvement in HRQOL was found after interventions targeted at reducing dysphagia severity. Given the significant effect of both dysphonia and dysphagia on HRQOL in thyroid cancer patients, methods of prevention, evaluation, and management of these symptoms merit further study.[21,22]

Concern about the appearance of a postsurgical scar was associated with worse outcomes in 3 domains: anxiety ($P < .0001$), depression ($P < .0001$), and social function ($P < .01$). Because the average age at time of response was 51 years and the average age at diagnosis was 44 years, on average respondents were approximately 7 years from initial diagnosis and operation. This may indicate that the importance of scarring, and the scar itself, fades with time. Further research on the correlation between time since surgery and concerns about scarring should be conducted to define the magnitude and duration of these effects.

Complications from RAI ablation can be seen temporarily after treatment or can persist many years beyond treatment. We asked participants about their short-term (days to weeks after treatment) and long-term (months to years after treatment) complications from RAI. The most common short-term complications reported by respondents in our study were mild xerostomia (34%), mild gastrointestinal (GI) symptoms such as nausea and vomiting (26%), and taste or appetite changes (29%). The most common long-term complications of RAI reported by survivors were chronic xerophthalmia (24%) and chronic xerostomia (24%). These findings are consistent with the frequency of complications associated with RAI reported in the literature. A 2014 literature review found that the most common early effects of RAI were GI symptoms (nausea and vomiting) in about 30% of adults and sialadenitis or xerostomia also in about 30% of adults.[8] Chronic xerostomia has been reported at a rate of 4.4% to 20%.[8] Thus, the self-reported frequency of complications in our study is similar to rates reported in the literature.

Complications of RAI that significantly impacted HRQOL scores across multiple domains in our sample included GI symptoms,

changes in appetite, sialadenitis, xerostomia (acute and chronic), xerophthalmia (acute and chronic), and development of dental caries. Although these symptoms are often considered to be mild and transient, our findings suggest that they may actually have a significant durable impact on HRQOL in thyroid cancer survivors. Our findings suggest that there is an urgent need for prospective longitudinal research to evaluate whether the benefits of RAI outweigh the risks of RAI-associated complications, especially in patients with low-risk (stage I and II) well-differentiated thyroid cancer.

Another statistically significant association noted in our study was the relationship between younger age and worse HRQOL scores. Younger patients (current age <45 years) reported worse HRQOL scores for depression, anxiety, and fatigue, a finding that is consistent with the report by Aschebrook-Kilfoy et al[4] in 2015. Because the prognosis for most thyroid cancers is very good, especially in those <45 years old, it is counterintuitive that this group would report worse HRQOL. This finding indicates that further research is needed to specifically study those individuals who are diagnosed with thyroid cancer at a younger age to determine which treatment-related variables independently predict poor HRQOL.

One strength of this study is the large sample size ($n = 1,743$). To our knowledge, this is the largest study to assess clinical factors associated with HRQOL in thyroid cancer survivors in the literature to date.[3,17] This survey was made available to a large number of individuals by partnering with ThyCa Inc (New York, NY) and utilizing their public Web site and social media. However, our recruitment method introduces the possibility of selection bias in our study. Support group members likely differ from other clinical samples. Individuals joining a support group may have had worse disease or greater treatment-related complications. They may also have different methods of coping and perceptions of their disease than those who do not elect to participate in a support group. It has been shown that cancer support-group members more often use active coping mechanisms and have more of a sense of control over their health; however, they report more anxiety and distress about their disease.[23] Support-group members also may not reflect the true diversity of a disease population regarding race, sex, and socioeconomic characteristics. Because of the inherent selection bias in our study owing to our methodology, individuals in our sample may be more severely affected by their illness and thus may report worse HRQOL scores than those who elected to forgo taking this survey. In addition, because the survey was distributed online via ThyCa, patients without access to the internet or who were not connected with ThyCa may not have been aware of the survey and therefore were unable to participate. Also, because the survey was administered online and all information was self-reported, the data are subject to recall bias. Despite the fact that our sample was recruited through a support group for thyroid-cancer survivors, the demographic and clinical characteristics of our sample are similar to the general population of thyroid cancer survivors in the United States. The sample approximates the female majority of the thyroid cancer population and matches thyroid cancer diagnostic trends in terms of age and stage of diagnosis. Because of the large sample size of our study and the consistency between our findings and those reported in the literature, we believe these results to be valid and generalizable to other thyroid cancer survivors living in the United States.

By identifying the disease and treatment factors that contribute to worse HRQOL in thyroid cancer survivors, we are better able to make targeted recommendations on ways to improve disease management and therefore HRQOL. Our findings suggest that further study is needed to determine best management practices for dysphonia and dysphagia because these factors contribute broadly to worse HRQOL.

With recent American Thyroid Association guidelines encouraging a less aggressive approach, there will be more patients who undergo active surveillance, and these patients will face a new set of challenges.[2] It is important to evaluate HRQOL in patients undergoing both active surveillance and treatment to identify the optimal treatment approach and to inform the selection of appropriate patients for surgery and RAI ablation. At this time, we are initiating a prospective longitudinal study to evaluate the HRQOL of thyroid cancer survivors and validate these findings in a clinic-based setting.

Acknowledgments

The authors thank the Board of Directors and members of ThyCa (Thyroid Cancer Survivors' Association, Inc) for their partnership in this research project. We are expressly thankful for the efforts of Gary Bloom and Bridget Corcoran for their review of the project from the patients' perspective and for their assistance in launching this survey. No funding was received for this study.

Conflicts of interest

All authors declare that they have no financial conflicts of interest and they have no disclosures that apply to this research project or this manuscript. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. No funding was received for the research reported.

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