






# Health-Related Quality of Life in Asian Differentiated Thyroid Cancer Survivors

Wing-Lok Chan, MBBS, MSc<sup>1</sup> , Horace Cheuk-Wai Choi, PhD<sup>1</sup>,  
 Brian Lang, MBBS, MS<sup>2</sup>, Kai-Pun Wong, MBBS, MS<sup>2</sup>,  
 Kwok-Keung Yuen, MBChB, MSc<sup>3</sup> , Ka-On Lam, MBBS<sup>1</sup>,  
 Victor Ho-Fun Lee, MBBS, MD<sup>1</sup> , and Dora Kwong, MBBS, MD<sup>1</sup>

## Abstract

**Background:** Health-related quality of life (HRQoL) is important for differentiated thyroid cancer survivors, but data for Asian survivors is lacking. This study aimed to have an overview of, and identify any disease-or treatment-related factors associated with, HRQoL in Asian differentiated thyroid cancer survivors.

**Patients and Methods:** Thyroid cancer survivors were recruited from the thyroid clinics at Queen Mary Hospital, Hong Kong from February 2016 to December 2016. All adult differentiated thyroid cancer patients with stable disease more than or equal to 1 year received a survey on HRQoL using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and Thyroid cancer specific quality of life (THYCA-QoL) questionnaire. Clinical information was collected retrospectively from the computerized clinical management system. To identify factors associated with poor HRQoL, univariable and stepwise multivariable regression analysis were performed.

**Results:** A total of 613 survivors completed the questionnaires (response rate: 82.1%; female: 80.1%; median survivorship: 7.4 years (range: 1.0-48.2 years)). The QLQ-C30 summary score mean was 84.4 (standard deviation (SD): 12.7) while the THYCA-QoL summary score mean was 39.9 (SD: 9.7). The 2 highest symptom subscales were fatigue (mean: 26.4, SD: 20.6) and insomnia (mean: 26.2, SD: 27.6). Factors associated with worse HRQoL included serum thyrotropin (TSH) greater than 1.0 mIU/L, unemployment, and concomitant psychiatric disorders. Concomitant psychiatric illness (n = 40/613, 6.5%) also showed significant association with most of the symptom and functional subscales.

**Conclusions:** Fatigue and insomnia were the 2 most common symptoms experienced by our differentiated thyroid cancer survivors. Long-term survivorship care with monitoring serum TSH level, supporting return-to-work and screening for concomitant psychiatric disorders should be offered.

## Keywords

thyroid cancer, quality of life, survivorship, follow up, health care

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## Introduction

In recent years, the incidence of thyroid cancer has increased considerably.<sup>1,2</sup> According to the Global cancer statistics 2018, thyroid cancer ranks ninth place for incidence, and is responsible for 567,000 cases worldwide.<sup>3</sup> Its incidence in women is 3 times higher than in men. By 2040, it is projected that its incidence will increase by 36.0%. In Hong Kong, thyroid

<sup>1</sup> Department of Clinical Oncology, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong

<sup>2</sup> Department of Surgery, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong

<sup>3</sup> Department of Clinical Oncology, Queen Mary Hospital, Hong Kong

### Corresponding Author:

Wing-Lok Chan, Department of Clinical Oncology, I/F Professorial Block, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong.  
 Email: [winglok@hku.hk](mailto:winglok@hku.hk)



cancer is the ninth most common cancer.<sup>4</sup> In 2018, there were 1037 new cases diagnosed. Compared to the previous decade, age-standardized incidence rates have increased by 2.6% in males and 3.8% in females. Patients are usually diagnosed at a younger age compared to other adult cancers. The prognosis for differentiated thyroid cancer is very good with 5-year survival exceeding 95%.<sup>5</sup> A rising incidence combined with long survival and a young age at diagnosis has resulted in a high prevalence and increasing number of thyroid cancer survivors.

The primary treatment for differentiated thyroid cancer generally involves surgery—either total thyroidectomy or hemithyroidectomy. For patients with total thyroidectomy, according to risk stratification, radioactive iodine is given to ablate the remaining thyroid tissue and facilitate subsequent disease monitoring using serum thyroglobulin.<sup>6,7</sup> Patients who have undergone total thyroidectomy need lifelong levothyroxine (T4) with thyrotropin (TSH) suppression based on their dynamic risk stratification. Depending on the pathology including completeness of surgical clearance, histological features and lymph node involvement, a proportion of patients may require external beam radiotherapy (ERT) to the head and neck region. These treatments are accompanied by long-term discomfort or complications, such as scar discomfort and changes in voice after surgery, changes in taste and xerostomia after a high cumulative dose of RAI, and neck stiffness after ERT.

In spite of the high efficacy of primary treatment, and excellent long-term survival rates, 15%-35% of patients experience locoregional recurrence or develop distant metastases, even decades later.<sup>8,9</sup> Thus, long years of cancer surveillance is needed. In cases of recurrence, additional investigations and treatments would possibly cause patients physical and psychological stress and impair their quality of life (QoL).

Given the longevity of thyroid cancer patients, determining of health-related quality of life (HRQoL) during surveillance is essential. Though thyroid cancer is often described as a “good cancer,” previous studies showed that HRQoL among differentiated thyroid cancer survivors was worse compared to the normal population or survivors of other cancers with worse prognosis.<sup>10-13</sup> Majority of these studies were carried out in the Western countries and there are few Asian patients’ data.<sup>14-17</sup> Furthermore, these studies were limited by small population size, inconsistency of tools used, or use of tools not specific to thyroid cancer.

The aim of this cross-sectional study was to provide an overview of, and identify any disease-or treatment-related factors associated with, HRQoL in Asian thyroid cancer survivors.

## Materials and Methods

### Sample and Setting

All participants were recruited from the thyroid cancer clinics in the Department of Clinical Oncology and the Department of Surgery at Queen Mary Hospital, Hong Kong from February 2016 to December 2016. All individuals aged 18 years or older with histologically confirmed differentiated thyroid cancer,

and who had completed treatment for more than 1 year with no distant metastases, were eligible to participate. We excluded patients who (1) had history of radiation or operations due to other head and neck diseases or malignancies, (2) were mentally incapacitated and therefore unable to give consent or complete the study questionnaire themselves, (3) had other comorbidities that impaired activities of daily living (ADLs), e.g. loss of limb function, total blindness, etc.; (4) had received TSH stimulation therapy or thyroxine-withdrawal treatment in the last 4 months, (5) had medullary or anaplastic thyroid cancers and (6) had other malignancy with active disease or on active treatment.

### Procedures

The Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) approved the study protocol. All eligible participants were invited to take part in the study during clinic visits and written consent was obtained. This included consent for collection of both disease-and treatment-related clinical data. After giving informed consent, participants completed self-administered hard copy questionnaires that included basic demographics: sex, marital status, religion, educational level, employment status, presence of other illnesses, as well as 2 tools on HRQoL. The 2 tools used were the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30,<sup>18</sup> version 3.0, and the Thyroid cancer specific quality of life (THYCA-QoL) questionnaire.<sup>19</sup>

**EORTC QLQ-C30, version 3.0.** EORTC QLQ-C30, version 3.0 is a 30-item HRQoL questionnaire consisting of 5 functional (physical, role, cognitive, emotional and social), 3 symptom (fatigue, pain, nausea and vomiting), 6 single-item common symptom (dyspnoea, loss of appetite, constipation, diarrhea, sleep disturbance, and financial difficulty) and global health status (GHS) subscales. The time frame of the questions is the preceding week. All items have 4 response categories (not at all, a little, quite a bit and very much), except GHS which contains 2 questions scored on a 7-point Likert scale from very poor (1) to excellent (7). After linear transformation, all subscales range from 0 to 100. A higher score in the functional subscales and GHS means better functioning and HRQoL, whereas a higher score in the symptom subscales indicates more discomfort and complaints. Additionally, the QLQ-C30 summary score is used to measure the overall HRQoL and is calculated with the means of all subscales except the GHS and financial difficulty subscales.<sup>20</sup> It ranges from 0 to 100, with the lower the score meaning the worse the HRQoL. Compared to the individual QLQ-C30 scales and GHS, the QLQ-C30 summary score exhibits equal or superior known-groups validity and responsiveness to change over time.

**THYCA-QoL.** THYCA-QoL is a thyroid cancer-specific QoL questionnaire with 24 total items. It consists of 7 symptom (neuromuscular, voice, concentration, sympathetic, throat/

mouth, psychological, and sensory problems) and 6 single item (problems with scar, chills, tingling hands/feet, weight gain, headache, and interest in sex) subscales. Each item is scored based on a response with 4 categories (not at all, a little, quite a bit, and very much). It measures symptoms from the previous week, except for sexual interest, which is 4-week. Subscale scores are then summed, with the higher the score meaning the more the symptoms.

### Data Collection

Clinical information of the participants who completed the questionnaires were retrospectively collected from the computerized clinical management system (CMS) under Hospital Authority, Hong Kong. Clinical data including age at diagnosis, age at study, date and type of surgery, cancer characteristics (size, histology, stage, number of lymph nodes involved), use of RAI and doses, ERT records, thyroid function test results which were taken within 2 weeks of the questionnaire, use of calcium supplements, any local recurrence and treatment, and presence of psychiatric disorders, other comorbidities, and other cancers were gathered.

### Statistical Analysis

Descriptive analyses were performed to summarize patient, disease and treatment characteristics, and HRQoL scores. Differences in HRQoL by years of survivorship (<5 years; 5-10 years; or >10 years since diagnosis) were analyzed using analysis of variance (ANOVA). For continuous variables (e.g., age, years of survivorship, serum TSH level), both the initial continuous values and the binary transformations suggested from recursive partitioning analysis (RPA) were tested. Univariate linear regression analyses were carried out to investigate the associations between the clinico-pathological variables and the summary scores and subscales of the 2 HRQoL tools. Variables with a *P*-value of less than or equal to 0.1 in univariate analysis were selected into the subsequent multivariable regression models to identify factors associated with impaired HRQoL by backward elimination. Variables are considered significantly associated with HRQoL if *P* < 0.05. Assumptions of linear regression, including homoscedasticity of residuals, independence of residual and lack of multicollinearity among independent variables, were checked. All statistical analyses were carried out using SPSS Statistics (version 25) and R (version 3.6.1).

### Results

A total of 747 thyroid cancer survivors were invited to participate in the study. 134 survivors refused to participate or were excluded for incomplete questionnaires. Reasons for not completing the questionnaire included: 91 patients (67.9%) felt the questionnaire was too long; 22 patients (16.4%) had missed some pages; 21 patients (15.6%) were illiterate. The remaining 613 survivors (response rate 82.1%) who completed the entire questionnaire were included in the final analysis. 491 (80.1%)

were female and the median age was 53 years old (range: 18-91). The percentage with survivorship <5 years, 5-10 years and over 10 years were 35.4%, 24.1% and 40.5%, respectively. The median duration of survivorship was 7.4 years (range: 1.0-48.2). Of the participants, 79.8% had papillary thyroid carcinoma, 10.9% had follicular carcinoma, 9.1% had papillary thyroid carcinoma with follicular variant, and 0.3% had Hurthle cell carcinoma. The majority underwent a total thyroidectomy (91.4%) and RAI (70.8%) with accumulative dose of 1.1-7.5 GBq. A few patients received ERT (5.1%). Based on the dynamic risk stratification, participants were distributed into low risk (123, 20.1%), intermediate risk (349, 56.9%), and high risk (141, 23.0%) groups. 160 participants (26.1%) had other comorbidities and 40 (6.5%) had concomitant psychiatric disorders. Table 1 shows detailed socio-demographic and clinical characteristics.

The QLQ-C30 summary score mean was 84.4 (standard deviation (SD): 12.7) and the GHS mean was 74.4 (SD: 19.2). For the functional subscales, the 2 lowest subscales were emotional functioning (mean: 78.2, SD: 20.9) and cognitive functioning (mean: 78.5, SD: 21.0). For the symptom subscales, the 2 highest were fatigue (mean: 26.4, SD: 20.6) and insomnia (mean: 26.2, SD: 27.6), suggesting fatigue and sleeping problems affected more patients. The THYCA-QoL summary score mean was 39.9 (SD: 9.7). Psychological (mean: 6.6, SD: 2.3) and neuromuscular (mean: 5.3, SD: 1.7) were the 2 highest subscales.

When stratified by years of survivorship (<5 years; 5-10 years; or >10 years since diagnosis), no difference was seen in either summary scores or subscales of QLQ-C30 and THYCA-QoL (Table 2).

Multivariable linear regression models, which included variables with *P* ≤ 0.1 in univariate analysis (Supplementary Table 1), suggested that concomitant psychiatric disorders, unemployment, and serum TSH greater than 1.0 mIU/L were significantly associated with both QLQ-C30 and THYCA-QoL summary scores. Unemployment also included patients who were retired or housewife. The presence of psychiatric illness was also significantly associated with most of the subscales in both tools, except constipation, cold intolerance, weight gain and dyspnea (Supplementary Table 2).

Other factors associated with THYCA-QoL summary score included female gender, local or neck recurrence, previous ERT, and age at study greater than or equal to 45 years old. However, these factors did not show any significant association with the QLQ-C30 summary score. No factor was found to be significant in QLQ-C30 but not in THYCA-QoL. Table 3 summarizes factors that were significantly associated with QLQ-C30 and THYCA-QoL summary score in multivariable analysis, where no violation to the assumptions of linear regression was observed.

### Discussion

The number of thyroid cancer survivors is growing rapidly due to a combination of increasing incidence, high survival rates, and young age at diagnosis. The 5-year survival rate of

**Table 1.** Demographics of the Participants.

| Total, N = 613                                      | n/Median   | %/Range |
|---|------------|---------|
| Female  | 491        | 80.1%   |
| Age at diagnosis (years)                            | Median: 42 | 7-85    |
| Age at study  | Median: 53 | 18-91   |
| Years of survivorship                               |            |         |
| <5 years  | 217        | 35.4%   |
| 5 to 10 years                                       | 148        | 24.1%   |
| >10 years   | 248        | 40.5%   |
| Types of surgery                                    |            |         |
| Total thyroidectomy                                 | 560        | 91.4%   |
| Partial thyroidectomy                               | 53         | 8.60%   |
| Neck dissection                                     |            |         |
| No neck dissection                                  | 314        | 51.2%   |
| Central neck dissection                             | 185        | 30.2%   |
| Lateral neck dissection                             | 23         | 3.80%   |
| Central and Lateral neck dissection                 | 91         | 14.8%   |
| Stage of disease                                    |            |         |
| T1  | 296        | 48.3%   |
| T2  | 124        | 20.2%   |
| T3  | 166        | 27.1%   |
| T4  | 27         | 4.40%   |
| pN0   | 404        | 65.9%   |
| pN1a  | 106        | 17.3%   |
| pN1b  | 103        | 16.8%   |
| Histology   |            |         |
| Papillary thyroid carcinoma                         | 488        | 79.8%   |
| Follicular thyroid carcinoma                        | 67         | 10.9%   |
| Papillary thyroid carcinoma with follicular variant | 56         | 9.1%    |
| Hurthle cell carcinoma                              | 2          | 0.3%    |
| Dynamic Risk Stratification                         |            |         |
| Low risk  | 123        | 20.1%   |
| Intermediate risk                                   | 349        | 56.9%   |
| High risk   | 141        | 23.0%   |
| No. of RAI  |            |         |
| 0   | 179        | 29.2%   |
| 1   | 374        | 61.0%   |
| 2   | 44         | 7.2%    |
| 3   | 16         | 2.6%    |
| Accumulative dose of RAI                            |            |         |
| ≤1.5GBq   | 5          | 0.8%    |
| >1.5-≤3.7GBq  | 346        | 56.4%   |
| >3.7-≤6.0GBq  | 42         | 6.9%    |
| >6.0GBq   | 41         | 6.7%    |
| External beam radiotherapy (ERT)                    |            |         |
| No ERT  | 582        | 94.9%   |
| ERT to tumor bed + central neck                     | 9          | 1.5%    |
| ERT to tumor bed + lateral neck                     | 22         | 3.6%    |
| IMRT  | 23         | 74.2%   |
| Not IMRT (2D/ 3D)                                   | 8          | 25.8%   |
| TSH level: mIU/L                                    |            |         |
| <0.5  | 434        | 70.8%   |
| >0.5 to ≤1  | 49         | 7.8%    |
| >1 to ≤2  | 65         | 10.6%   |
| >2  | 65         | 10.6%   |
| Use of calcium supplements                          | 88         | 14.4%   |
| Presence of co-morbidities                          | 160        | 26.1%   |
| Presence of psychiatric disorder                    | 40         | 6.5%    |

(continued)

**Table 1.** (continued)

| Total, N = 613                   | n/Median | %/Range |
|----------------------------------|----------|---------|
| Depression                       | 27       | 4.4%    |
| Generalized anxiety disorder     | 5        | 0.8%    |
| Psychosis/ Schizophrenia         | 8        | 1.3%    |
| Had other cancers                | 57       | 9.3%    |
| Marital status:                  |          |         |
| Single                           | 120      | 19.6%   |
| Married                          | 421      | 68.7%   |
| Divorced                         | 39       | 6.3%    |
| Widow/ widower                   | 33       | 5.4%    |
| Education level                  |          |         |
| Primary                          | 85       | 13.9%   |
| Secondary                        | 293      | 47.8%   |
| Post-secondary/ associate degree | 74       | 12.1%   |
| University of above              | 161      | 26.3%   |
| Employment status                |          |         |
| Employed/ self-employed          | 340      | 55.5%   |
| Retired                          | 102      | 16.6%   |
| Housewife                        | 140      | 22.8%   |
| Unemployed                       | 31       | 5.1%    |
| Religious                        |          |         |
| Christian or Catholic            | 176      | 28.7%   |
| Buddhism or Chinese Folk         | 121      | 19.8%   |
| Others                           | 18       | 3.0%    |
| No religion                      | 298      | 48.6%   |

differentiated thyroid cancer is higher than 95%. Patients require long-term cancer surveillance as a high rate of relapse can occur decades later. Patients with total thyroidectomy also need life-long thyroxine replacement and to check serum TSH and thyroglobulin levels regularly. All these seemingly easy and simple monitorings are indeed anxiety inducing. Addressing survivors' post-treatment needs is crucial to providing quality health care.

Husson et al's systematic review, which identified 27 articles published between 1997 and 2010, reported HRQoL among survivors of differentiated thyroid carcinoma had similar or worse HRQoL than the normal populations.<sup>21</sup> More recently published comparative studies by Goswami et al from the United States, McIntyre et al from the United Kingdom, Haraj et al from Morocco and Singer et al from German all reported that thyroid cancer survivors experienced worse HRQoL compared to the normal populations.<sup>10-13</sup>

For Asian thyroid cancer survivors, there are few available data on HRQoL. A Chinese study showed that thyroid cancer survivors, with median years of survivorship of 2.6 +/- 3.6 years, experienced more problems than the reference community population.<sup>16</sup> A study in Singapore which included 152 well-differentiated thyroid cancer survivors showed a significant decrease in QoL compared with the general population, especially in the elderly and poorer educated.<sup>17</sup>

Thyroid cancer survivors also experienced specific medical problems after cancer treatment and follow-up tests, which can negatively affect HRQoL long years after diagnosis and treatment.<sup>22</sup> Fatigue and sleep issues are the most commonly reported complaints cross-culturally.<sup>10,13,23,24</sup> Our study

**Table 2.** Summary Scores and Subscales Scores of QLQ-C30 and THYCA-QoL.

|                        | Overall population |       | Survivors < 5 years |       | Survivors 5-10 years |       | Survivors >10 years |       | Sig. <sup>a</sup> |
|------------------------|--------------------|-------|---------------------|-------|----------------------|-------|---------------------|-------|-------------------|
|                        | Mean               | SD    | Mean                | SD    | Mean                 | SD    | Mean                | SD    |                   |
| <b>QLQ-C30</b>         |                    |       |                     |       |                      |       |                     |       |                   |
| Summary Score          | 84.36              | 12.70 | 84.71               | 12.52 | 83.23                | 13.09 | 84.72               | 12.62 | .464              |
| Global health status   | 72.42              | 19.16 | 71.43               | 20.15 | 71.96                | 18.95 | 73.56               | 18.40 | .464              |
| Physical functioning   | 87.16              | 13.79 | 87.16               | 14.05 | 87.70                | 12.06 | 86.83               | 14.56 | .830              |
| Role functioning       | 90.81              | 16.69 | 89.86               | 17.70 | 91.22                | 15.85 | 91.40               | 16.29 | .579              |
| Emotional functioning  | 78.17              | 20.92 | 77.42               | 20.98 | 77.08                | 21.36 | 79.47               | 20.63 | .442              |
| Cognitive functioning  | 78.47              | 20.95 | 79.65               | 20.01 | 78.90                | 22.27 | 78.97               | 20.89 | .218              |
| Social functioning     | 90.76              | 17.92 | 90.40               | 17.68 | 89.41                | 18.04 | 91.87               | 18.06 | .393              |
| Fatigue                | 26.39              | 20.58 | 27.04               | 21.29 | 28.83                | 20.65 | 24.37               | 19.78 | .096              |
| Nausea/ vomiting       | 5.85               | 13.19 | 5.53                | 12.63 | 7.32                 | 15.46 | 5.24                | 12.16 | .288              |
| Pain                   | 15.36              | 21.11 | 14.59               | 20.90 | 13.96                | 19.83 | 16.87               | 22.02 | .334              |
| Dyspnea                | 19.20              | 21.04 | 12.20               | 19.80 | 21.17                | 23.05 | 19.76               | 20.77 | .180              |
| Sleeping disturbance   | 26.21              | 27.58 | 25.19               | 26.26 | 29.05                | 30.44 | 25.40               | 26.91 | .354              |
| Loss of appetite       | 7.78               | 15.92 | 7.83                | 16.51 | 8.33                 | 16.44 | 7.39                | 12.12 | .849              |
| Constipation           | 15.06              | 22.46 | 13.82               | 22.30 | 18.24                | 24.38 | 14.25               | 21.28 | .138              |
| Diarrhea               | 12.83              | 20.22 | 11.98               | 18.42 | 12.39                | 20.68 | 13.84               | 21.44 | .584              |
| Financial difficulties | 7.94               | 18.83 | 9.68                | 19.60 | 6.30                 | 17.97 | 7.39                | 18.59 | .205              |
| <b>THYCA-QOL</b>       |                    |       |                     |       |                      |       |                     |       |                   |
| THYCA-Total            | 39.87              | 9.70  | 40.30               | 9.23  | 40.48                | 10.63 | 39.12               | 9.34  | .287              |
| Neuromuscular          | 5.28               | 1.71  | 5.3                 | 1.73  | 5.42                 | 1.73  | 5.19                | 1.66  | .413              |
| Voice                  | 2.84               | 1.15  | 2.96                | 1.24  | 2.85                 | 1.14  | 2.73                | 1.06  | .109              |
| Concentration          | 3.08               | 1.30  | 3.06                | 1.26  | 3.20                 | 1.47  | 3.02                | 1.23  | .406              |
| Sympathetic            | 3.20               | 1.44  | 3.17                | 1.44  | 3.25                 | 1.43  | 3.19                | 1.46  | .860              |
| Throat/ mouth          | 4.26               | 1.32  | 4.39                | 1.43  | 4.27                 | 1.22  | 4.14                | 1.26  | .122              |
| Psychological          | 6.60               | 2.29  | 6.71                | 2.23  | 6.78                 | 2.46  | 6.40                | 2.23  | .198              |
| Sensory problem        | 3.50               | 1.27  | 3.56                | 1.38  | 3.58                 | 1.32  | 3.41                | 1.12  | .295              |
| Problem with scar      | 1.32               | 0.66  | 1.35                | 0.70  | 1.36                 | 0.72  | 1.27                | 0.57  | .249              |
| Cold intolerance       | 1.33               | 0.60  | 1.33                | 0.61  | 1.36                 | 0.68  | 1.32                | 0.55  | .819              |
| Tingling hands/ feet   | 1.76               | 0.77  | 1.78                | 0.78  | 1.73                 | 0.72  | 1.77                | 0.81  | .825              |
| Weight gain            | 1.71               | 0.79  | 1.76                | 0.79  | 1.72                 | 0.83  | 1.67                | 0.75  | .390              |
| Headache               | 1.70               | 0.73  | 1.73                | 0.70  | 1.70                 | 0.74  | 1.69                | 0.76  | .776              |
| Interest in sex        | 3.26               | 0.66  | 3.19                | 0.69  | 3.26                 | 0.64  | 3.33                | 0.63  | .091              |

<sup>a</sup>Compare the mean across the 3 categories of survivorship.

**Table 3.** Variables Associated With QLQ-C30 Summary Score and THYCA-QoL Summary Score by Multivariable Analysis.

| Factors                              | QLQ-C30 summary score <sup>a</sup> |                           |         | THYCA-QOL summary score <sup>a</sup> |               |         |
|--------------------------------------|------------------------------------|---------------------------|---------|--------------------------------------|---------------|---------|
|                                      | Coefficient                        | 95% CI                    | P-value | Coefficient                          | 95% CI        | P-value |
| Presence of psychiatric illness      | -10.6                              | (-14.50, -6.71)           | <0.001  | 7.87                                 | (4.92, 10.83) | <0.001  |
| Unemployed                           | -4.30                              | (-6.25, -2.35)            | <0.001  | 1.57                                 | (0.01, 3.13)  | 0.048   |
| TSH> 1mIU/L                          | -4.34                              | (-6.69, -2.00)            | <0.001  | 2.25                                 | (0.47, 4.03)  | 0.013   |
| Gender (Female vs Male)              |                                    | Not selected <sup>b</sup> |         | 3.97                                 | (2.13, 5.81)  | <0.001  |
| Local or neck recurrence             |                                    | Not selected <sup>b</sup> |         | 2.44                                 | (0.14, 4.74)  | 0.038   |
| External beam radiotherapy performed |                                    | Not selected <sup>b</sup> |         | 4.10                                 | (0.78, 7.41)  | 0.015   |
| Age at study ≥45 yrs                 |                                    | Not selected <sup>b</sup> |         | 2.25                                 | (0.54, 3.96)  | 0.010   |

Abbreviations: CI, confidence interval; HRQoL, health-related quality-of-life; TSH, serum thyrotropin.

<sup>a</sup>Lower QLQ-C30 summary score or higher THYCA-QOL summary score represents worse HRQoL.

<sup>b</sup>Factors in the multivariable regression models were selected via backward elimination.

complements with previous studies that these 2 symptoms are also the most frequent and most severe symptoms seen in our thyroid cancer survivors.

One of the strengths of our study was the inclusion of long-term survivors, with 40.5% of the participants having over 10

years of survivorship. In our study, the scores of HRQoL were not significantly different with years of survivorship. Previous studies reported that thyroid cancer survivors experienced worse HRQoL compared to survivors of other cancer types, e.g. colorectal and breast cancer, which have worse prognoses

and need more intensive treatments.<sup>10,25</sup> Survivors of other cancer usually have improved HRQoL after years of recovery from the disease. However, thyroid cancer survivors have impairment of HRQoL even several years after completion of treatment. The need for lifelong T4 replacement together with potential risk of recurrence years after diagnosis are believed to contribute to the anxiety and fear of recurrence, even many years after the completion of treatment.

In our study, serum TSH greater than 1.0 mIU/L was associated with worse HRQoL in thyroid survivors after controlling for other factors in multivariable analysis, including the serum fT4 and thyroglobulin levels. The TSH result was taken within 2 weeks of the questionnaire. So the serum TSH level reflected the most recent thyroid replacement status and compliance on thyroxine. We reviewed that all patients with TSH greater than 1.0 mIU/L had normal fT4 levels. Although a majority of our participants had a rather low TSH level, they tolerated it very well without any symptoms or signs of hyperthyroidism. We also observed in our patients that their serum TSH levels fluctuated markedly, even with a subtle change in dosage of the thyroxine replacement.<sup>26</sup> Frequent adjustment of their thyroxine replacement, requiring frequent blood checking, may place an additional psychological burden on them.<sup>27</sup>

Unemployment was significantly associated with a worse HRQoL. Thyroid cancer patients are often young and at working age at diagnosis. In our study, median age of diagnosis was 42 years old. 5.1% of the participants were unemployed, which is higher than the 3.09% general unemployment rate in Hong Kong. Similarly, the North American Thyroid Cancer Survivorship Study (NATCCS) found that 8% of its participants had filed for bankruptcy, which is significantly higher than the 0.4% bankruptcy rate per year of the general population.<sup>15</sup> Tan et al's study showed that being employed had a positive influence on physical and emotional aspect in HRQoL.<sup>28</sup> Another recently published report also showed that 43% of thyroid cancer survivors had financial difficulties which was associated with poorer HRQoL.<sup>29</sup> Although it is not clear why thyroid cancer survivors experienced a higher risk of financial hardship, thyroid cancer survivors face financial hardship and challenges in returning to work, similar to other cancer survivors.

We included both housewife and retired survivors into the unemployment group. This might make the group heterogeneous. However, we did not individually ask the reason behind for being a housewife or being retired. Quite a number of cancer survivors found difficulty in returning to work after cancer diagnosis. Moreover, being unemployed, retired or housewife all did not have regular income. It is therefore reasonable to group them into one group for easy comparison. We have searched on other studies on cancer survivorship and similar grouping was also made.<sup>16,26</sup>

Concomitant psychiatric illness is significantly associated with overall HRQoL and most of the functional and symptoms subscales. In our study, the percentage of concomitant psychiatric disorder was 6.5%, which was much lower than findings in other studies or in other cancers, with an incidence around 20%-40%, and even lower than the local prevalence of

13.3% in the Hong Kong general population suffering from depression and anxiety disorders.<sup>30</sup> This markedly low percentage of psychiatric disorders points to the issue of under-diagnosis or overlooking of psychological problems in our thyroid cancer survivors.

Our study only showed these 3 factors were significantly associated with a worse HRQoL. Most physicians would intuitively consider unemployment and concomitant psychiatric illness as significant factors affecting HRQoL, irrespective of disease type, even in the normal population. However, this finding raises physicians' awareness of thyroid cancer survivors' unmet needs. In addition to survivors' physical symptoms, physicians need to provide psychological and social support to them in a long-term and sustainable way. Measures that can be implemented in clinical practice include: monitoring of serum TSH levels; helping survivors return to work; using validated screening tools for screening anxiety and depression, e.g. the Hospital Anxiety and Depression Scale; or simply asking about their psychological or social needs during consultations.

In our study, factors that associated with significantly worse HRQoL scores in other studies, including use of calcium supplement, use of RAI, presence of other co-morbidities, presence of other cancer, age at diagnosis, were not significant in our multivariate analysis.<sup>15-17,31-33</sup> Postoperative hypocalcemia is a well-known complication after thyroid surgery. The incidence of permanent hypocalcemia is around 1%-4% with risk depending on the extent of surgery.<sup>34</sup> 14.4% of our participants were on calcium supplements. We did not investigate the reason for taking calcium supplement. Not all patients took calcium supplement because of permanent postoperative hypocalcemia. They might take calcium supplement for other diseases like osteoporosis. 9.3% of our participants had other cancer which was already cured at the time of study. The presence of another malignancy was not associated with HRQoL in thyroid cancer survivors. Hypothesis for not significant may be because the patients have already adapted well to the side effects of treatment of other malignancies or they are psychologically better prepared after 2 malignancies. Presence of other comorbidities might lead to restriction in daily function and subsequently impair HRQoL. However, this factor was not associated with HRQoL in our thyroid survivors in multivariable analysis. One of the reasons of lack of an association could be because the selected co-morbid conditions were not severe enough to impact the survivor's functional status. Moreover, we did not stratify on the number or severity of the co-morbid conditions and did not investigate the temporal relationship of these comorbidities with thyroid cancer.

The strengths of our study are the inclusion of long-term survivors, a good balance in years of survival, and its access to treatment details and pathological and biochemical profiles. Our study also used tools specific to thyroid cancer survivors: the QLQ-C30 and THYCA-QoL. There were limitations to this study. First, no normal population was recruited for comparison. Second, all participants were recruited from a single institution, which could have potentially introduced bias.

Nevertheless, the recruited sample size was large enough to allow for stratification into different demographics, and tumor and treatment characteristics. Third, the response rate was only 82.1%. We did not review the clinico-pathological data or the HRQoL data of those who refused to participate or did not complete the questionnaire. Their information would give a more comprehensive picture of HRQoL in Asian thyroid cancer survivors. However, when looking at the reasons for the drop-outs, majority considered the questionnaire in the study too long. A simpler tool to screen for impaired HRQoL in thyroid cancer survivors may be useful. Fourth, there is no cut-off in QLQ-C30 or THYCA-QoL to define poor HRQoL. The study can only give a relative comparison of HRQoL among participants. Recent studies published on the threshold of clinical importance for QLQ-C30 but the concept is new and has not yet been tested in Chinese cancer survivors.<sup>35,36</sup>

Fifth, only 20.1% of our participants were in the low-risk group. This imbalance in risk categories of our survivors likely affected the HRQoL results. Sixth, this was a cross-sectional and observational study. We could only identify factors associated with lower HRQoL but could not confirm any temporal or causal relationship. Serum TSH was only taken in a single time point within 2 weeks of the questionnaire. Longitudinal studies on change in serum TSH level and HRQoL may be interesting to confirm their temporal relationships.

## Conclusions

HRQoL is an important factor in lifelong surveillance of thyroid cancer survivors. This study provides important information about HRQoL in Asian thyroid cancer survivors, especially those with long years of survival. Factors associated with HRQoL in Asian thyroid cancer survivors included concomitant psychiatric illness, unemployment and serum TSH greater than 1.0 mIU/L. Future studies with collaborations with institutions in other Asian countries would definitely lead to a better understanding of the physical, psychosocial, and spiritual needs of our Asian thyroid cancer survivors.

## Authors' Note

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB). All eligible participants were invited to join the study during clinic visits and a written consent was obtained. This included consent for clinical data collection for both disease-and treatment-related information.

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## ORCID iDs

Wing-Lok Chan, MBBS, MSc  <https://orcid.org/0000-0001-9793-9273>

Kwok-Keung Yuen, MBChB, MSc  <https://orcid.org/0000-0001-6914-6890>

Victor Ho-Fun Lee, MBBS, MD  <https://orcid.org/0000-0002-6283-978X>

## Supplemental Material

Supplemental material for this article is available online.

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