Endocrine Practice 32 (2026) 1078–1085

Endocrine Practice™
www.endocrinepractice.org

Original Article

Determinants of Health-Related Quality of Life in Differentiated and Poorly Differentiated Thyroid Cancer Patients With Structural Incomplete Response: A Multicenter Cross-Sectional Study

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ARTICLE INFO

Article history:
Received 21 November 2025
Received in revised form
18 February 2026
Accepted 25 March 2026
Available online 2 April 2026

Key words:
thyroid cancer
tyrosine kinase inhibitor
lenvatinib
EORTC
quality of life
patient-reported outcome

ABSTRACT

Objectives: Differentiated and poorly differentiated thyroid cancer (DTC/PDTC) generally carries a favorable prognosis in the absence of persistent or recurrent disease. However, evidence indicates that long-term health-related quality of life (HRQOL) may remain impaired even in patients with good oncological outcomes. Real-world data on HRQOL among DTC/PDTC patients with a structural incomplete response (SIR), including those receiving tyrosine kinase inhibitors, are still limited. This study aimed to investigate the determinants of HRQOL in DTC/PDTC patients with SIR.

Methods: This prospective, multicenter, cross-sectional study enrolled a total of 148 adult participants with a cytologically or histologically confirmed diagnosis of DTC/PDTC and evidence of SIR. All participants completed the self-administered European Organization for Research and Treatment of Cancer questionnaires (EORTC QLQ-C30 and thyroid cancer-specific module QLQ-THY34), as well as the Hospital Anxiety and Depression Scale.

Results: Patients with SIR reported significantly reduced HRQOL compared with disease-free survivors, particularly in domains related to fatigue, sleep disturbance, concern for others, exhaustion, and joint pain. Neither disease management strategy (active surveillance vs tyrosine kinase inhibitor or other treatments) nor disease status (stable vs progressive) significantly predicted overall HRQOL. Lower physical functioning, female gender, and higher emotional distress were independently associated with poorer HRQOL, with gender-related differences emerging only among patients with preserved physical functioning.

Conclusions: Despite the absence of a longitudinal design and internal control group, this study emphasizes the importance of systematically assessing HRQOL in DTC/PDTC patients with SIR and highlights the interplay between psychosocial factors and functional status in shaping patient-reported outcomes.

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Abbreviations: DTC, differentiated thyroid cancer; HRQOL, health-related quality of life; PDTC, poorly differentiated thyroid cancer; RAI, radioactive iodine therapy; SIR, structural incomplete response; TC, thyroid cancer; TKI, tyrosine kinase inhibitor.

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https://doi.org/10.1016/j.eprac.2026.03.090
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Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy worldwide and its incidence has increased over the past decades.[1] Nevertheless, survival has remained stable, with an estimated 20-year survival of 90%.[2] The standard of treatment includes surgery, sometimes followed by adjuvant radioactive iodine therapy (RAI) and l-thyroxine therapy, when indicated, based on risk stratification.[3] Although most DTC patients have an excellent prognosis, periodic long-term monitoring is recommended, as 5-10% of cases progress to advanced disease and up to 70% of them become RAI-refractory, with a significant decrease in 10-year survival rate.[4] When structural evidence of the disease persists or recurs (ie, structural incomplete response, SIR), treatment options become limited and the prognosis worsens.[3] Therefore, patients with SIR represent a clinically distinct subgroup characterized by higher tumor burden, reduced responsiveness to adjuvant treatments, and the need for long-term surveillance or systemic therapy. In this context, clinicians should take multiple aspects into account when selecting the most appropriate treatment approach, including not only biochemical, morpho-functional and clinical data, but also patient's preferences and psychosocial factors.[5] A watchful waiting strategy can be safely adopted in selected cases, RAI or loco-regional treatments can be performed when feasible, or systemic therapies with tyrosine kinase inhibitors (TKIs) may be considered.[6] The impact of these options on patient's health-related quality of life (HRQOL) should be carefully weighed, in order to plan a personalized approach.[5]

Systematic and narrative reviews of clinical research have documented the adverse effects of DTC and its associated treatments on patients' HRQOL.[7] Previous studies reported that DTC patients are exposed to negative emotions (eg, sadness, frustration), depressive symptoms, anxiety, fear of recurrence, sleep disturbances, financial concerns, and physical impairment (ie, fatigue, paraesthesia, pain, cold intolerance, vocal symptoms).[8-10] Moreover, further studies have shown that long-term DTC survivors face persistent restrictions in regaining normal daily routine (eg, work, social roles, leisure activities), and the associated emotional disturbances can endure for several years after treatment.[11,12]

To sum up, clinical research has revealed that the HRQOL impairment of DTC patients is greater than expected and similar or worse to that of other cancers with poorer prognosis.[13]

According to recent American Thyroid Association guidelines, clinicians are encouraged to support patients in managing the psychosocial consequences of thyroid cancer (TC) diagnosis and treatment and to provide detailed information on available local resources to help address cancer-related distress.[3] Nevertheless, many patients continue to report unmet psychosocial support needs. Moreover, although a substantial body of evidence indicates that the favorable prognosis of disease-free DTC survivors does not necessarily translate into good HRQOL, research specifically addressing HRQOL impairment in patients with SIR remains limited.

Findings from a large population-based study showed that the subgroup of patients with persistent disease met criteria for meaningful impact in both physical and mental health, when compared with the general population norms.[14] The role played by treatment with TKIs in shaping patients' HRQOL remains inadequately documented in the literature.[15,16] The efficacy of treatment with TKIs in RAI-refractory DTC is widely supported by clinical trials and real-life studies.[17,18] Nevertheless, frequent onset of adverse events (AEs), such as asthenia, diarrhea, nausea, weigh-loss and stomatitis may undermine patients' adherence and lead to treatment discontinuation.[19] To date, documented effects of treatment with Lenvatinib on DTC patients' HRQOL include a reduction of disease-related symptoms, a general improvement of the global health status and a slight worsening of physical and social functioning.[20] During lenvatinib treatment, a marked reduction in HRQOL has been observed within the first 3 months, with a subsequent return to baseline values after 1 year of continued therapy.[15,20] Lastly, a recent large double-blinded randomized controlled study found no significant differences in HRQOL between Lenvatinib 18 and 24 mg/d starting dose.[21] However, identifying the optimal timing for initiation of TKIs remains a clinical challenge. As some patients prefer an aggressive approach to cancer treatment whereas others prioritize the preservation of physical HRQOL, shared decision-making is essential to integrate individual preferences and concerns into the clinical management strategy.[3] Set against this background this multicenter real-life study aims to 1) evaluate HRQOL in patients with DTC, including poorly differentiated thyroid cancer (PDTC), with SIR, including those treated with TKIs; (2) identify key determinants of HRQOL; (3) contribute to the limited evidence base on HRQOL in advanced DTC/PDTC.

Highlights

- Differentiated thyroid cancer patients with structural incomplete response reported significantly poorer health-related quality of life compared to survivors, with overall scores aligning with those observed in the general oncology population
- Participants treated with lenvatinib reported lower scores in multiple dimensions of health-related quality of life than patients under active surveillance or treated with therapeutic options other than tyrosine kinase inhibitors
- Physical functioning and gender were most robust independent determinants of health-related quality of life, exceeding the predictive contribution of disease status and therapeutic approach
- Gender-related differences in health-related quality of life emerged only among patients with preserved physical functioning

Clinical Relevance

This study provides clinical evidence that health-related quality of life in differentiated thyroid cancer patients with structural incomplete response is predominantly determined by physical functioning, gender, and emotional distress. Integrating systematic assessment of health-related quality of life into routine clinical practice may support patient-centered management that extends beyond conventional disease metrics.

Methods

Study Design, Participants, and Procedures

This is a cross-sectional multicenter study involving 6 Italian referral centers for DTC. Adult subjects with histologically confirmed DTC, including a limited subgroup of PDTC, were included. PDTC patients were retained in the study because they are frequently managed within the same clinical pathways as

Table 1
Participant Characteristics

Variable	N = 148
	n (%)
Age group (y)	
≤30	7 (4.7)
31-40	16 (10.8)
41-50	15 (10.1)
51-60	20 (13.5)
61-70	30 (20.3)
>71	60 (40.5)
Sex	
Male	70 (47.3)
Female	78 (52.7)
Education	
Primary/secondary school	66 (44.6)
High school	48 (32.4)
University degree	34 (23.0)
Marital status	
Married/defacto	113 (76.4)
Single/divorced/widowed	35 (23.6)
Employment	
Paid work/retired	128 (86.5)
Not working	20 (13.5)
Cigarette smoking	
No	130 (87.8)
<10/die	12 (8.1)
≥10/die	6 (5.1)
Alcohol consumption	
No	115 (77.7)
Occasionally	28 (18.2)
Habitually	5 (4.1)
Years from diagnosis of thyroid cancer	
<1	8 (5.4)
1-5	42 (28.4)
5.1-10	51 (34.5)
>10	47 (31.8)
ECOG PS	
0	105 (70.9)
1	32 (21.6)
2	7 (4.7)
3	4 (2.7)
Histology	
Follicular	75 (50.7)
Papillary	38 (25.7)
Poorly differentiated	24 (16.2)
Hürthle	11 (7.4)
Locoregional disease	99 (66.9)
Metastases	
Lung	85 (57.4)
Liver	12 (8.1)
Bones	49 (33.1)
Mediastinum	42 (28.4)
Brain	12 (8.1)
Disease status	
Stability	103 (69.6)
Progression	45 (30.4)
Previous treatment*	
Surgery	79 (53.7)
Radiotherapy	36 (24.3)
Radioiodine therapy	135 (91.2)
Targeted therapy	12 (8.1)
Interventional radiology techniques	6 (4.1)
Disease management	
Active surveillance	30 (20.3)
TKI therapy (lenvatinib)	63 (42.6)
Active therapy (other than TKI)	55 (37.2)
TKI (lenvatinib) daily dose (mg)	
10	25 (16.9)
14	20 (13.5)
20	11 (7.4)
24	7 (4.7)
Months since the start of TKI therapy	
≤12	10 (16.1)
13-24	13 (21.0)
25-36	12 (19.4)
>37	27 (43.5)

(*continued on next column*)

Table 1 (*continued*)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; TKI, tyrosine kinase inhibitor.
* completed at least 6 mo before the study period (except initial surgery and l-thyroxine treatment).

advanced DTC and may experience similar treatment-related and survivorship burdens.[3] The proportion of PDTC patients in the cohort is reported in Table 1. Eligible patients were consecutively identified by clinicians from outpatient follow-up clinics and institutional databases of thyroid cancer units at the 6 participating centers. Screening for eligibility was based on medical record review and multidisciplinary case discussion, ensuring that all participants met ATA criteria for structural incomplete response. According to clinicians' judgement, participants had been placed under active surveillance, in active treatment with TKI or other therapeutic approaches, such as RAI or loco-regional procedures (eg, surgery, radiotherapy, interventional radiology treatments). Subjects were analyzed according to the disease status, assessed by using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).[22] Subjects who were not speaking the Italian language fluently or those with significant cognitive impairment and/or a major psychiatric disorder were excluded from the study. After having given their written informed consent, participants were asked to complete validated questionnaires anonymously before the consultation with the clinician in the waiting room and to give him/her them back in a closed envelope. To ensure confidentiality and minimize social desirability bias, questionnaires were completed in the waiting room without supervision, placed in a sealed envelope, and returned directly to the attending clinician. The envelopes were collected unopened by the research team. All participants were clearly informed, both verbally and in writing, that their responses would remain strictly anonymous and would not be accessible to their treating physicians. This procedure guaranteed full confidentiality of responses and prevented any link between clinical data and individual answers. This study was in accordance with the principles of the Declaration of Helsinki and its later amendments and was approved by the ethics board committees of all participating centers (protocol number of the Principal Investigator's Institution: 0099352).

Measures

Sociodemographic data were self-reported by the participants. Clinical features were collected from digital clinical records. HRQOL domains, physical symptoms, and concerns related to DTC/PDTC were assessed through the self-rated European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and its module for thyroid cancer (QLQ-THY34).[23,24] QLQ-C30 considers a general index of health status, 5 domains of functioning (physical, role, emotional, cognitive, and social), and a list of cancer-related symptoms (ie, symptoms scales). QLQ-THY34 considers a list of symptoms, adverse effects related to thyroid cancer and its treatment grouped into 17 subscales. Higher scores

Table 2
Participants' Quality of Life Measured Through EORTC Quality of Life Questionnaires C30 and THY34 Scores: Comparison With Previous Studies

Variable	Present study	Singer et al, 2023[26]	Thiagarajan et al, 2024[27]	Büttner et al, 2020[28]	Italian norm data[29]
	N = 148	N = 135	N = 220	N = 75	N = 1036
	m ± sd				
QLQ-C30					
Functional scales					
Global health (QL)	69.4 ± 19.9		73.0 ± 22.0	72.8 ± 15.9	64.9 ± 20.3
Physical functioning (PF)	79.5 ± 22.4		84.9 ± 15.1†	92.6 ± 14.1†	85.2 ± 17.0
Role functioning (RF)	81.0 ± 27.6		92.1 ± 16.0†	83.6 ± 27.7	86.1 ± 22.2
Emotional functioning (EF)	80.6 ± 18.0		78.3 ± 20.7	78.9 ± 23.5	73.5 ± 22.7
Cognitive functioning (CF)	86.8 ± 18.9		86.1 ± 19.1	86.0 ± 22.8	87.0 ± 18.6
Social functioning (SF)	84.2 ± 24.1		89.5 ± 18.9*	87.6 ± 24.8	88.1 ± 20.6
Symptom scales					
Fatigue (FA)	29.9 ± 26.6		21.6 ± 20.8†	26.1 ± 26.2	28.5 ± 23.9
Nausea and vomiting (NV)	6.1 ± 17.2		7.1 ± 14.5	1.6 ± 5.6*	6.5 ± 15.9
Pain (PA)	17.8 ± 26.0		14.0 ± 19.8	15.6 ± 25.9	20.2 ± 23.9
Dyspnea (DY)	12.3 ± 20.6		11.5 ± 19.6	15.6 ± 29.2	15.7 ± 23.0
Insomnia (SL)	24.5 ± 28.9		11.5 ± 20.8†	17.8 ± 30.7	22.9 ± 27.1
Appetite loss (AL)	15.2 ± 25.7		15.8 ± 24.7	5.3 ± 16.5†	8.5 ± 19.0
Constipation (CO)	12.8 ± 25.3		8.3 ± 18.4*	4.0 ± 13.4†	14.2 ± 23.4
Diarrhea (DI)	12.4 ± 23.1		6.1 ± 17.5†	5.3 ± 17.4*	9.3 ± 19.5
Financial difficulties (FI)	7.6 ± 19.9		32.7 ± 36.0†	6.2 ± 18.7	9.7 ± 21.6
Summary score	83.2 ± 13.3				
QLQ-THY34 (*symptom scales*)					
Exhaustion (EX)	25.1 ± 24.2	27.0 ± 25.9	19.8 ± 20.5*	21.9 ± 26.0	
Discomfort in head and neck (DI)	10.1 ± 15.7	13.3 ± 16.2	14.3 ± 16.4*	11.7 ± 17.1	
Voice (VO)	19.0 ± 24.8	14.1 ± 21.5	11.9 ± 18.3†	8.7 ± 14.3†	
Hair problems (HA)	16.2 ± 23.2	16.4 ± 26.3	17.4 ± 23.0	12.2 ± 25.6	
Swallowing (SW)	10.9 ± 18.4	9.2 ± 16.7	9.6 ± 17.3	2.7 ± 11.0†	
Treatment-/disease-related worry (TD)	21.9 ± 18.4	21.8 ± 21.4	20.5 ± 20.1	13.0 ± 15.4†	
Tingling or numbness (TI)	9.1 ± 15.3	15.2 ± 20.5†	19.0 ± 21.5†	14.9 ± 20.4†	
Worry about important others (WO)	29.7 ± 23.8	27.1 ± 29.3	29.1 ± 23.5	25.3 ± 27.4	
Social Support (SO)†	69.0 ± 26.9‡	25.4 ± 30.8	80.6 ± 26.7†	5.2 ± 11.5	
Dry mouth (DM)	23.3 ± 30.6	21.9 ± 29.5	15.4 ± 22.3†	16.0 ± 30.2	
Altered temperature tolerance (TO)	20.6 ± 25.4	26.1 ± 33.0	19.7 ± 25.0	20.1 ± 32.8	
Body image (BI)	14.0 ± 23.7	12.9 ± 23.8	12.4 ± 22.0	5.3 ± 17.4†	
Shoulder functioning (SH)	10.9 ± 23.5	9.3 ± 21.8	17.3 ± 25.5*	7.1 ± 22.1	
Joint pain (JP)	26.6 ± 29.3	33.3 ± 33.2	22.3 ± 26.4	20.0 ± 30.5	
Cramps (CR)	18.3 ± 26.9	24.1 ± 30.8	12.4 ± 22.0*	12.9 ± 28.4	
Impact on job/education (JE)	14.2 ± 27.1	10.7 ± 24.2	16.4 ± 28.2	5.8 ± 18.5*	
Rapid heartbeat (RH)	19.2 ± 18.2	18.0 ± 25.5	15.8 ± 19.3	18.2 ± 24.4	
Summary score	81.0 ± 12.2				

Abbreviation: EORTC, European Organization for Research and Treatment of Cancer.
* $P < .05$.
† $P < .01$.
‡ Scored as a Functional scale; ‡Mean comparison performed with Thiagarajan et al, 2024.[27]

in functional domains indicate better HRQOL, whereas higher scores in symptom scales indicate greater symptom burden (ie, lower HRQOL). Emotional distress was assessed using the self-rated Hospital Anxiety and Depression Scale (HADS), consisting of 14 items yielding scores based on 2 independent subscales measuring symptoms of anxiety (HADS-A) and depression (HADS-D) and a cumulative Total score.[25]

Statistical Analysis

Data were analyzed with SPSS software V. 25.0 for Mac (IBM Corp). A two-sided *P*-value <.05 was considered statistically significant. Descriptive statistics were calculated to summarize the data. Summary score for QLQ-C30 was calculated following the scoring algorithm proposed by the EORTC group to generate a cumulative score representing overall HRQOL (QLQ-C30 Summary score).[23] Using the same procedure, a summary score was also calculated for the QLQ-THY34, treating the Social Support (SO) domain as a functional scale and all other domains as symptom scales (QLQ-THY34 Summary Score). Means comparison between 2 unrelated populations was performed by means of Independent-samples *t* test. Most robust predictors of QLQ-C30 and QLQ-THY34 Summary scores were investigated by means of separate Stepwise Linear Regression models with predefined criteria (entry = $P \leq .05$; removal = $P \geq .10$, ie, variables that do not significantly contribute to the model after adjustment for other predictors are automatically removed to obtain the most parsimonious model).

Multicollinearity was assessed by calculating the Variance Inflation Factor (VIF) for all predictors, with values < 2.0 indicating the absence of significant collinearity. The full set of sociodemographic and clinical characteristics of the participants reported in Table 1 was included in the models. A Two-way Analysis of Covariance was performed as a more in-depth approach to study the effect of the most robust predictors identified by regression models on HRQOL measures (i.e., QLQ-C30 and QLQ-THY34 Summary scores), while controlling for possible confounders (i.e., HADS scores).

Table 3
Summary of Stepwise Regression Models Predicting QLQ-C30 and QLQ-THY34 Summary Scores

Variable	Regression coefficients					
	B	SE	β	t	*P* value	Part
QLQ-C30 Summary score						
Constant	89.675	1.451		61.823	<.001	
ECOG PS	−7.647	1.372	−0.404	−5.573	<.001	−0.401
Gender	−6.763	1.938	−0.253	−3.490	<.001	−0.251
QLQ-THY34 Summary score						
Constant	90.487	2.539		35.077	<.001	
ECOG PS	−11.183	3.039	−0.392	−3.679	<.001	−0.377
Gender	−11.746	2.935	−0.413	−4.001	<.001	−0.410

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; B, Unstandardized regression coefficient; SE, standard error of the regression coefficient; *β*, standardized regression coefficient; *t*, *t* test statistic; *P*, *P* value; *Part*, semi-partial correlation.

Results

Participant Characteristics

The sample included 148 patients (52.7% females). The distribution of participants across the recruiting centers was as follows: 46 (31.1%) in Turin, 25 (16.9%) in Milan, 39 (26.4%) in Pisa, 15 (10.1%) in Siena, 12 (8.1%) in Rome, and 11 (7.4%) in Catania. This distribution provided a comprehensive representation of the Italian territory. Detailed data about demographics, clinical and therapeutic features are reported in Table 1. Most participants had good physical functioning (70.9% with ECOG PS = 0). A watchful waiting strategy was adopted in a limited subgroup (20.3%). Among participants on active treatment, most (63/118, 53.4%) received a TKI (Lenvatinib in all cases). Other treatment ($n = 55$) included surgery ($n = 20, \% = 36.4$), radiotherapy ($n = 10, \% = 18.2$), interventional radiology procedures ($n = 4$, $\% = 7.3$) and RAI therapy ($n = 21, \% = 38.2$). The groups did not differ significantly in age, gender distribution, or disease duration (all *P*-values > 0.05). Stable disease was ascertained in 69.6% of the sample.

EORTC Quality of Life Questionnaire Scores

Participants QLQ-C30 and QLQ-THY34 scores are provided in Table 2, along with comparisons with recent studies involving TC patients without radiological evidence of the disease and without antineoplastic treatment within the last year (QLQ-THY34 available only),[26] disease-free Indian patients in follow-up,[27] German patients 1-year after surgery for TC[28] and normative data for Italian cancer populations (QLQ-C30 available only).[29] Study participants reported significant lower scores on Functional scales (i.e., Physical and Role functioning) and higher scores on most Symptom scales (i.e., Fatigue, Appetite loss, Sleep Disturbances, Constipation, Diarrhea) of the QLQ-C30, when compared to survivors.[28,30] Fatigue was the most relevant cancer-related symptom reported by study participants. QLQ-C30 scores observed in this study were fairly consistent with normative data from the Italian cancer populations.[29] Overall, participants' QLQ-THY34 scores were similar to higher to those observed in other studies involving DTC survivors, indicating a greater symptom burden, particularly in relation to head and neck symptoms (ie, voice-related concerns, swallowing, dry mouth).[26,28,30] Conversely, the discomfort related to tingling and numbness reported by study participants was consistently less pronounced than what has been found previously.[26,28,30] Concerns regarding the worry of significant others, alongside symptoms of exhaustion and joint pain emerged among the most prevalent issues. Perceived social support was lower than observed in the study by Büttner et al,[28] indicating a moderately good though not optimal level. Supplementary Table 1 presents the EORTC questionnaires scores of participants across the 3 disease management subgroups (ie, active surveillance, TKI therapy, active therapy other than TKI). Participants receiving lenvatinib reported significant lower scores on Global Health and Functional scales (i.e., Physical and Role functioning), higher scores on most Symptom scales (i.e., Fatigue, Pain, Appetite Loss, Diarrhea) and higher Social Support.

EORTC Quality of Life Questionnaires Predictors

The final stepwise regression model predicting QLQ-C30 Summary score was statistically significant ($F = 24.507$, $P = <0.001$), explaining approximately 24% of the variance ($R^2 = 0.244$) and including 2 significant predictors: ECOG PS ($\beta = -0.404$, $P < .001$) and gender ($\beta = -0.253$, $P < .001$). The "Disease status," "Disease management," "TKI daily dose," and "Months since the start of TKI therapy" independent variables were excluded from the final model due to not-significant coefficients.

Similarly, the final stepwise regression model predicting QLQ-THY34 Summary score was statistically significant ($F = 22.326$, $P = <0.001$), explaining approximately 23% of the variance ($R^2 = 0.234$) and including 2 significant predictors: ECOG PS ($\beta = -0.333$, $P < .001$) and gender ($\beta = -0.327$, $P < .001$). As in the previous model, the "Disease status," "Disease management," "TKI daily dose," and "Months since the start of TKI therapy" independent variables were excluded from the final model due to not-significant coefficients. VIF values were below 2.0 for all predictors, indicating no significant multicollinearity. These findings indicate that patients' physical functioning and gender were the most consistent independent determinants of overall HRQOL in this cohort, whereas disease-related variables and treatment characteristics did not significantly contribute to explaining variability in HRQOL scores. Model summaries are provided in Table 3.

Effects of Gender and ECOG Scores on EORTC Quality of Life Questionnaires Scores

A Two-way Analysis of Covariance (ANCOVA) was specified to study the effect of gender and physical functioning (i.e., ECOG PS) on HRQOL (i.e., QLQ-C30 and QLQ-THY34 Summary scores), while controlling for emotional distress (i.e., HADS total score). The results showed that the ECOG PS score significantly affected both QLQ-C30 ($P < .001$) and QLQ-THY34 ($P = .003$) Summary scores: the poorer the physical functioning, the lower the HRQOL. Gender had a significant effect on QLQ-THY34 Summary score ($P = .002$) only, with females reporting lower scores. HADS Total score significantly influenced both QLQ-C30 and QLQ-THY34 Summary scores ($P < .001$), with higher emotional distress associated with lower HRQOL. No significant interaction between physical

Table 4
Tests Statistics and Estimates Marginal Means of Two-Way Analysis of Covariance Models Testing the Effect of Gender and ECOG Score on QLQ-C30 and QLQ-THY34 Summary Scores Controlling for HADS Score

	QLQ-C30 Summary score		QLQ-THY34 Summary score	
	F	*P*	F	*P*
Corr. model	26.521	<.001	18.233	<.001
ECOG PS	20.386	<.001	9.324	.003
Gender	2.781	.098	7.448	.007
ECOG PS*gender	0.671	.414	1.019	.315
HADS	43.706	<.001	30.986	<.001

	Estimates				Estimates			
	m(SE)	95% CI		*P*	m(SE)	95% CI		*P*
		Lower	Upper			Lower	Upper	
ECOG PS 0								
Male	88.2 (1.4)*	85.3	91.0	.019	86.0 (1.4)†	83.2	88.8	<.001
Female	83.3 (1.4)*	80.5	86.2		78.7 (1.4)†	75.9	81.5	
ECOG PS 1-3								
Male	77.8 (2.6)*	72.7	82.8	.606	79.6 (2.6)†	74.4	84.7	.306
Female	76.1 (2.1)*	72.0	80.1		76.2 (2.0)†	72.1	80.2	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; F, F-test statistic; m(SE), mean(standard error); HADS, Hospital Anxiety and Depression Scale; *P*, *P* value; 95% CI, 95% confidence interval.
* HADS covariate evaluated at 9.6 value.
† HADS covariate evaluated at 9.5 value.

functioning and gender was found ($P > .40$). Estimated marginal means adjusted for HADS Total score values indicated that gender significantly impacted both QLQ-C30 and QLQ-THY34 Summary scores ($P = .019$ and $P = .003$, respectively) only among patients in good physical functioning (i.e., ECOG PS = 0). These results indicate that gender differences in HRQOL are most evident when physical functioning is preserved, whereas when physical impairment is present, the impact of gender becomes less pronounced and overall HRQOL is primarily driven by functional limitations and emotional distress. Model summaries are provided in Table 4.

Discussion

This study demonstrates that DTC/PDTC patients with SIR experience significantly poorer HRQOL compared to TC survivors, with overall scores aligning with those reported in the general oncology population, reinforcing earlier findings.[14] In line with prior research conducted across various cultural settings, fatigue and sleep disturbances emerged as the most burdensome cancer-related symptoms reported in this study.[31,32] Similarly, key TC-specific issues such as concerns about the worries of significant others, exhaustion, joint pain, as observed in this study, have also been identified in previous research as among the most distressing symptoms observed in this patient population.[28,30] Overall, study results corroborate those reported in previous research showing the widespread detrimental impact of TC on patients' physical and mental health across the illness trajectory.[7,11-13] SIR patients, in particular, are generally characterized by a greater tumor burden and a higher likelihood of receiving intensive therapeutic interventions, often resulting in elevated morbidity and treatment-related complications, ultimately leading to heightened need for supportive care.[33] Consistently with findings from previous studies, participants in this study also reported moderate-to-high levels of social support.[28,30]

In direct comparisons with those under active surveillance or treated with therapeutic options other than TKIs, participants treated with lenvatinib reported significantly lower scores on QLQ-C30 Global Health, Physical, and Role functioning scales, as well as higher scores on Symptom scales (i.e., Fatigue, Pain, Appetite Loss, Diarrhea). Encouragingly, these participants reported higher perceived Social Support, which may help to preserve adherence to a complex lifelong treatment. However, multivariate analysis revealed that differences in therapeutic approaches were not significant predictors of the overall HRQOL. In accordance with the clinical hypothesis that antitumoral efficacy may have a beneficial impact on HRQOL, in a previous study a trend toward a longer time to deterioration of HRQOL scores was observed among Lenvatinib-treated TC patients with an objective radiologic response, compared to those with progressive disease.[21] However, given the cross-sectional nature of this study, we were unable to detect any potential changes in HRQOL over time based on tumor response. Furthermore, due to the heterogeneous management of study patients and the small sample size, drawing definitive conclusions regarding the complex interaction between each therapeutic approach (ie, active surveillance, RAI or loco-regional treatments, TKIs) and disease progression in influencing HRQOL remains difficult.

Regarding treatment with lenvatinib, no significant differences in HRQOL were observed between different starting doses (18 and 24 mg/d) in a previous randomized study.[21] Similarly, in this study, drug dosage did not emerge as a determinant of HRQOL. However, it is important to note that only 42.5% of the participants in this study were treated with lenvatinib, and, of those, only 11.1% received the full daily dose (24 mg). Therefore, a robust real-life analysis to confirm or challenge these previous findings was not feasible. It can be hypothesized that HRQOL is more adversely affected by prolonged continuous treatment with TKIs, as compared to a recently initiated therapy, due to the accumulation of AEs over time. On the other hand, the growing awareness of both clinicians and patients regarding strategies to mitigate TKI-associated toxicity could have a beneficial effect on HRQOL. In support of this hypothesis, a real-life study involving lenvatinib-treated TC patients demonstrated an initial decline in HRQOL during the first months of therapy, followed by a restoration of HRQOL after 1 year of treatment.[15] In this study, the duration of lenvatinib treatment did not significantly influence HRQOL scores. HRQOL in cancer patients is shaped by a complex and multifaceted set of determinants. Although closely linked to disease progression and treatment-related AEs, which shape the degree of physical functioning and symptom burden, HRQOL also emerged from a dynamic interaction with the patient's physical and psychological responses, wherein psychosocial factors serve as critical mediators. In this study, HRQOL levels were found to be primarily influenced by physical functioning, gender and emotional distress, with lower physical functioning, being female, higher emotional distress, all associated with poorer HRQOL. More in-depth analysis showed that, when controlling for emotional distress, the effect of gender on HRQOL was observed only among individuals with good physical functioning (i.e., ECOG PS = 0), whereas gender appeared to be irrelevant when physical functioning was impaired (i.e., ECOG PS $\geq$ 1). In DTC/PDTC patients treated with lenvatinib, baseline ECOG PS score has been shown to predict key clinical outcomes, including progression-free survival, overall survival, and the severity of treatment-related AEs,[34,35] factors that are almost invariably associated with significant impairments in HRQOL.[36] Although direct evidence in TC remains limited, our findings support the use of ECOG PS as a reliable clinician-rated determinant of HRQOL. While VIF analysis excluded multicollinearity, some conceptual overlap between ECOG PS and HRQOL measures cannot be ruled out. Nonetheless, they represent distinct yet complementary constructs: ECOG PS reflects clinician-

assessed physical functioning and disease-related disability, whereas the EORTC QLQ-C30 and QLQ-THY34 capture patient-reported outcomes across multiple domains, including emotional, cognitive, and social well-being. The multidimensional structure of the EORTC instruments allows them to address psychological and interpersonal aspects not encompassed by clinician evaluations. Therefore, the joint inclusion of ECOG PS and EORTC HRQOL measures provides a more integrated framework for modeling quality-of-life determinants, in line with the biopsychosocial paradigm currently guiding patient-centered medicine.

Substantial evidence across various cancer types indicates that female patients frequently report poorer HRQOL compared to their male counterparts, and this disparity has been shown to be driven by a combination of physical symptom burden and psychosocial factors.[37] In a large age-matched cohort of DTC survivors, female patients reported poorer HRQOL and were more likely to experience symptoms such as fatigue and sleep disturbances.[27] While this study found gender-related differences in HRQOL among patients with higher physical functioning, no existing studies to date have systematically examined how gender interacts with ECOG PS score in predicting HRQOL outcomes among TC patients. The preliminary pattern observed in this study raises important questions about the differential psychological and symptom burden experienced by women when physical functioning remains preserved. Given the lack of TC–specific literature addressing this interaction, future studies should explore the moderating effect of gender across different ECOG PS scores.

Limitations

This study has several limitations that should be considered when interpreting its findings. The cross-sectional design precludes causal inferences regarding the relationships between disease-related factors, treatments, and HRQOL outcomes. The absence of a within-study control group also limits the possibility of direct comparisons with patients achieving a complete or excellent response to standard therapy. Furthermore, self-reported questionnaires administered before medical consultations may have been influenced by situational anxiety or treatment expectations and remain susceptible to potential biases such as social desirability or recall effects. Nonetheless, all participants were fully informed about the study's aims, procedures, and voluntary nature, and confidentiality was ensured to minimize response bias. Detailed reporting of participant characteristics, subgroup composition, and HRQOL interpretation was also provided to enhance transparency and reproducibility.

In addition, although the predictive models reached statistical significance, the proportion of variance explained was modest, suggesting that other unmeasured factors, such as personality traits, coping styles, or the quality of social support, may also influence HRQOL outcomes.

Strengths of the study include its multicenter design (albeit limited to Italy) and the combined use of a recently validated TC-specific HRQOL instrument (QLQ-THY34) with the well-established QLQ-C30, enabling a comprehensive assessment of disease- and treatment-related quality-of-life impairments in a heterogeneous cohort of DTC/PDTC patients with structural incomplete response.

Conclusion

This study demonstrates that DTC/PDTC patients with SIR report markedly reduced HRQOL compared with TC survivors. Their quality-of-life levels approximate those observed in broader oncology populations, corroborating previous evidence. Fatigue, sleep disturbances, concerns about significant others, exhaustion, and joint pain were identified as the most burdensome symptoms, consistent with earlier findings across different cultural settings. Contrary to common clinical expectations, neither therapeutic approach (active surveillance versus TKI or other treatments) nor disease status (stable versus progressive) significantly predicted overall HRQOL. Instead, physical functioning, gender, and emotional distress emerged as key determinants, with poorer physical functioning, female gender, and higher emotional distress all associated with lower HRQOL. Notably, gender differences in HRQOL were evident only among patients with preserved physical functioning, suggesting a complex interaction between physical capacity and psychosocial dimensions of well-being.

Collectively, these findings emphasize the clinical importance of systematically incorporating HRQOL measures into the management of DTC/PDTC patients with SIR and call for further research to clarify how psychosocial and functional factors interact to shape patient-reported outcomes. Future longitudinal and controlled studies are warranted to validate these associations and to support the development of integrated, patient-centered models of care tailored to this population.

Disclosure

The authors have no conflicts of interest to disclose.

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