

ORIGINAL ARTICLE

## Determinants of long-term quality of life in patients with differentiated thyroid carcinoma – a population-based cohort study in Sweden

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### ABSTRACT

**Background:** Although differentiated thyroid cancer (DTC) has an excellent prognosis and a low incidence of recurrence, lifelong follow-up and medication might be needed. The aim of this study was to clarify how living with a cancer diagnosis for many years affects health-related quality of life (HRQoL) in DTC patients in Sweden.

**Material and methods:** From the national all-encompassing population-based Swedish Cancer Registry, 353 patients diagnosed with DTC between 1995 and 1998 were identified and invited to answer the HRQoL questionnaire SF-36 and a study-specific questionnaire, 14–17 years after their diagnosis. Data were compared with a reference population as well between subgroups of patients.

**Results:** Of the patients with DTC, 279 (79%) answered the questionnaires. In all, only 19 (7%) reported a recurrence, however, as many as 134 (48%) stated that they still had concerns about having a recurrence. The HRQoL in those with a recurrence was significantly lower than those without concerns of a recurrence in five of eight domains ( $p < 0.001$ – $0.049$ ). Similarly, patients with concerns of a recurrence reported poorer HRQoL than those without concerns, with significantly lower values in five domains ( $p < 0.001$ – $0.008$ ). Those few who stated that their disease had given them a negative view on life reported poor HRQoL in all eight domains ( $p < 0.001$ – $0.030$ ).

**Conclusions:** Even if DTC comes with an excellent prognosis, almost half of the patients, fully 15 years after diagnosis, worried about a recurrence which negatively impacted their HRQoL. Awareness among healthcare practitioners might improve information, supportive care and, in the end, the patient's HRQoL.

### HISTORY

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Thyroid cancer is the most commonly diagnosed endocrine malignancy and its incidence is increasing. In Sweden, over 500 patients are diagnosed with thyroid cancer every year [1]. Differentiated thyroid carcinoma (DTC) accounts for 80–90% of all thyroid cancers, and has a preponderance of women (3:1). DTC can occur in all age groups but the incidence for women rises to a peak at 55–65 years of age, while this pattern is less pronounced in men. The primary treatment for DTC is thyroidectomy with or without additional dissection of cervical lymph nodes. Postoperatively, in order to reduce recurrence and to facilitate follow-up, the majority of patients will receive radioactive iodine. After a thyroidectomy, patients are dependent on lifelong thyroid hormone supplementation. Additionally, during the first years, thyroxin is given in doses to suppress the thyroid stimulating hormone (TSH). The thyroxin treatment might give lifelong side effects, such as osteoporosis or atrial fibrillation [2] and, therefore, comprehensive guidelines for treatment are provided, e.g. by the European Society for Medical Oncology (ESMO) [3] and the American Thyroid Association (ATA) [4]. The prognosis for DTC

is excellent, with a 10-year overall survival exceeding 90%, although 15–35% of patients develop recurrences later in life [5,6].

From a patient's perspective, living with a cancer diagnosis might raise existential issues and affect health-related quality of life (HRQoL) [7]. In general, long-term HRQoL after DTC has been shown to be both similar to and decreased in comparison with the general population [8–11] but determinants of HRQoL have been sparsely described.

Therefore, we conducted a nationwide population-based all-encompassing cohort study assessing HRQoL and determinants in patients diagnosed with DTC a considerable time ago, i.e. 14–17 years ago, in Sweden.

### Material and methods

#### Study design and population

A population-based, nationwide, cross-sectional cohort study was performed in June 2012 in Sweden. From the

all-encompassing Swedish Cancer Registry [1], all patients diagnosed with DTC between 1995 and 1998 were identified. An age criteria of 35–64 years at inclusion in 2012, corresponding to 18–50 years at diagnosis, was applied since younger patients would have been children at the time of diagnosis and older patients might have had heterogeneous confounding factors [12]. Patients fulfilling these inclusion criteria were invited to participate by mail. By completing and returning the questionnaire, participants consented to their data being used for research purposes. Up to two reminder letters were sent to non-responders.

The study was approved by the Regional Ethical Review Board in Stockholm (2011/718-31/2).

## Data collection

### Socio-demographic variables and co-morbidities

Participants provided information on gender, age in years, and education. Education was categorised into three groups based on the Swedish education system: low (elementary school, i.e. 0–9 years), middle (secondary school, i.e. 10–12 years) or high (university, i.e. >12 years). Information on co-morbidities was gathered by asking the patients whether they had received a diagnosis by a physician of any of the following: previous myocardial infarction, hypertension, atrial fibrillation, previous stroke, diabetes, chronic obstructive pulmonary disease, asthma, kidney failure, rheumatoid arthritis/osteoarthritis, osteoporosis, depression under treatment or other specified psychiatric disease, cancer or any other specified disease.

Response alternatives were “Yes” or “No”. Patients were grouped based on their number of co-morbidities: none, one, or at least two.

### Cancer-related variables

Patients reported their primary treatment in the following categories; none, total thyroidectomy, hemi-thyroidectomy, with or without cervical lymph node dissection uni- or bilateral, radioiodine treatment and external radiotherapy. Regarding recurrence, patients were asked whether they had had a loco-regional recurrence or distant metastasis (Yes or No) and, if so, which treatment was given.

### Health-related quality of life

HRQoL was assessed with the Swedish version of the Short Form-36 (SF-36) version 2.0 [13,14], a well validated and standardised questionnaire that has been used in many international studies [15]. SF-36 is a multi-purpose, short form survey with 36 questions concerning physical and mental health. Responses were subsequently linearly transformed to a score between 0 and 100 according to the SF-36 scoring manual [16] on each of the eight domains: physical functioning (PF), physical role functioning (role limitations due to physical problems) (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role functioning (role limitations due to emotional problems) (RE), and mental health (MH). A higher score on the domains signifies a better HRQoL

and functioning. The SF-36 form was distributed first in the mailed questionnaire.

Additionally, a study-specific questionnaire addressed patients' views on life and their concerns of recurrence. The final format of these questions was determined after using a pilot questionnaire in consultation with five thyroid cancer patients. Patients were asked whether their disease had influenced their views on life (Yes, in a positive direction; Yes, in a negative direction; or No). Patients were also asked if they were concerned about a recurrence (No; Yes, but rarely; or Yes, often).

## Statistical analysis

Patient characteristics were described by standard descriptive statistics. Patient scores derived from the SF-36 were compared with mean scores in an age- and gender-matched control group from the Swedish population [17]. In all comparisons on all domains in the SF-36, a difference of at least five points (scale 0–100) between groups was interpreted as a clinically relevant minimal important difference (MID) [18]. Statistical significance was tested by one sample t-test, Kruskal-Wallis test or Mann-Whitney test at the 0.050 level.

Missing responses were handled according to the SF-36 scoring software [16].

The statistical software STATA<sup>®</sup> 12.1 was used for data in Table I and the statistical software package R version 3.1.2 was used for all other analyses.

## Results

### Patient characteristics

Of 353 eligible individuals, 279 (79%) answered the questionnaires, 11 patients (3%) returned unanswered questionnaires and two envelopes were returned undelivered. The vast majority of patients (78%) were women. The mean age was 51 (35–64) years and follow-up time was 14–17 years according to the inclusion criteria. Regarding education level, 85% had at least 10 years of schooling (Table I). Half of the patients reported no co-morbidity. Surgery was the primary treatment reported by all the patients; a further 105 (38%) stated that they had received radioiodine treatment and additionally five (2%) reported receiving external radiotherapy. Only a few, 19 (7%) mentioned any kind of recurrence.

Regarding GH, VT, SF and MH, patients reported poorer HRQoL than the general population ( $p < 0.001$ – $0.020$ ). Three of these four domains were also clinically significant (i.e. at least a five-point difference between the groups) (Table II). Interestingly, DTC patients reported significantly better physical role functioning compared with the general Swedish population ( $p < 0.001$ ).

### Influence of co-morbidities on HRQoL

Regarding co-morbidities, patients with one co-morbidity reported poorer GH, VT, SF and RE than those with none (all  $p$ -values  $< 0.001$ , Table III). Furthermore, patients with at least two co-morbidities reported worse HRQoL in all eight domains compared with those with none (all  $p$ -values  $< 0.001$ , Table III).

**Table I.** Characteristics of 279 patients assessed regarding HRQoL in 2012, i.e. 14–17 years after diagnosis of DTC in Sweden.

	Number (%)
Gender	
Male	61 (22)
Female	218 (78)
Age, year	
Mean (range)	51 (35–64)
Educational level	
Low (Elementary school ≤9 years),	43 (16)
Medium (Upper secondary School 10–12 years)	110 (40)
High (University >12 years)	125 (45)
Co-morbidity	
None	141 (51)
Yes, one	77 (28)
Yes, at least two	61 (22)
Primary treatment	
Surgery	169 (61)
Surgery and radioiodine	105 (38)
Surgery and external radiotherapy	5 (2)
Patient reported recurrence	
No	260 (93)
Yes	19 (7)

HRQoL, health-related quality of life.

**Table II.** Long-term HRQoL, i.e. 14–17 years after diagnosis measured with the SF-36 in patients with DTC compared to the Swedish general population.

SF-36 domains <sup>a</sup>	Patients n = 279 Mean (SD)	Swedish general population n=4514	p-Value <sup>c</sup>
		Mean (SD) <sup>b</sup>	
Physical functioning	87 (21)	86 (0)	0.344
Physical role functioning	<b>87</b> (24)	81 (0)	<0.001
Bodily pain	74 (28)	72 (0)	0.279
General health	70 (24)	73 (0)	0.020
Vitality	<b>62</b> (24)	69 (0)	<0.001
Social functioning	<b>82</b> (25)	88 (0)	<0.001
Emotional role functioning	87 (23)	86 (0)	0.515
Mental health	<b>75</b> (20)	81 (0)	<0.001

HRQoL, health-related quality of life; SD, standard deviation, SF-36, Short Form-36 Health Survey.

<sup>a</sup>Domain values in bold correspond to at least a small clinically significant difference of ≥5 points between patients and the Swedish general population;

<sup>b</sup>SD = in general population is fixed (SD = 0);

<sup>c</sup>p-value assessed with one sample t-test between groups.

### The effect of recurrence on HRQoL

In all, only 19 (7%) patients reported a recurrence, however, as many as 134 (48%) stated that they had concerns about having a recurrence (Table IV). The HRQoL in those with a recurrence was lower than those without concerns of a recurrence in five of eight domains: PF, GH, VT, SF and MH ( $p < 0.001$ – $0.049$ ). Similarly, patients with concerns of a recurrence reported poorer HRQoL than those without concerns in five of eight domains: GH, VT, SF, RE and MH ( $p < 0.001$ – $0.008$ ).

### View on life after disease on HRQoL

The 30 (11%) patients who stated that their disease had given them a negative view on life reported remarkably poorer HRQoL in all eight domains compared with those who reported a positive or unchanged view on life (all  $p$ -values  $< 0.001$ – $0.030$ , Table V). Among the 19 patients with a recurrence, 12 (63%) stated that their disease had a positive influence on their view on life and only two reported that the disease had negatively affected their view on life.

**Table III.** Differences in long-term HRQoL, i.e. 14–17 years after diagnosis measured with the SF-36 in patients with DTC analysed on number of co-morbidities.

SF 36 domains <sup>a</sup>	Number of self-reported co-morbidities <sup>b</sup>			p-Value <sup>c</sup>
	None n = 141 Mean (SD)	One n = 77 Mean (SD)	At least two n = 61 Mean (SD)	
Physical functioning	93 (13)	91 (14)	<b>67</b> (29)	<0.001
Physical role functioning	93 (15)	90 (19)	<b>66</b> (35)	<0.001
Bodily pain	82 (23)	76 (25)	<b>50</b> (31)	<0.001
General health	78 (16)	<b>72</b> (21)	<b>47</b> (30)	<0.001
Vitality	69 (18)	<b>63</b> (24)	<b>43</b> (27)	<0.001
Social functioning	90 (18)	<b>85</b> (22)	<b>61</b> (61)	<0.001
Emotional role functioning	94 (14)	<b>89</b> (21)	<b>68</b> (33)	<0.001
Mental health	81 (16)	77 (21)	<b>60</b> (22)	<0.001

HRQoL, health-related quality of life; SD, standard deviation; SF-36, Short Form-36 Health Survey.

<sup>a</sup>Domain values in bold correspond to at least a small clinically significant difference i.e. ≥5 points, between those with none and either one or at least two co-morbidities;

<sup>b</sup>co-morbidities assessed as yes or no regarding the following conditions; myocardial infarction, hypertension, cardiac arrhythmia, stroke, diabetes mellitus, chronic obstructive pulmonary disease, asthma, kidney disease, rheumatoid arthritis/arthritis, osteoporosis, depression, other psychiatric disease, other cancers;

<sup>c</sup>p-value assessed with Kruskal-Wallis test.

## Discussion

This nationwide population-based cohort study focused on determining factors for long-term HRQoL in patients with DTC, i.e. a group with a good or even excellent prognosis but with a lifelong risk of recurrence. In line with previous research, our patients reported poorer HRQoL than the general population, which might be due to the lifelong thyroid hormone treatment and diffuse symptoms, such as muscle ache, fatigue, difficulties coping with heat, and palpitations influencing daily life [8].

Regarding co-morbidities, the greater the number, the poorer the HRQoL, which is shown in the general population [19] and was expected as we assessed *health-related* QoL. It is possible that the long-term thyroid hormone treatment and co-morbidities might have had additive or synergetic effects on HRQoL.

Interestingly, DTC patients reported significantly and clinically better physical role functioning compared to the general Swedish population. According to our clinical experience patients might change their way of living by taking better care of their physical health status, which might affect this domain.

The incidence of recurrence (7%) was low as expected, however, about every second patient had concerns about recurrence which negatively affected their HRQoL. Interestingly, to be *concerned* about a recurrence seems to have had an equal influence on HRQoL as *actually having* a recurrence.

To be diagnosed with a cancer can be considered a death threat and patients might not fully comprehend the meaning of a good prognosis, especially as they come for lifelong follow-ups. The majority of long-term cancer survivors worry about a recurrence [20], which in itself carries more anxiety and fear of death [21,22] and may impair HRQoL [20]. In DTC concern of a recurrence is even more interesting, when the prognosis is very good compared to other cancer diseases. Especially in young patients, who have an excellent prognosis

**Table IV.** Differences in long-term HRQoL, i.e. 14–17 years after diagnosis measured with SF-36 in patients with recurrence of DTC compared to patients with and patients with no concern of recurrence after DTC in Sweden.

SF-36 domains <sup>a</sup>	Self-reported recurrence			p-Value <sup>b</sup>
	Patients with self-reported recurrence n = 19 Mean (SD)	Patients with concern of recurrence n = 134 Mean (SD)	Patients with no concern of recurrence n = 126	
Physical functioning	<b>84</b> (18)	85 (23)	89 (19)	0.118 <sup>c</sup>
Physical role functioning	84 (22)	84 (27)	89 (20)	0.130
Bodily pain	66 (24)	71 (31)	77 (26)	0.143
General health	<b>58</b> (19)	<b>65</b> (25)	77 (22)	<0.001
Vitality	<b>56</b> (19)	<b>58</b> (26)	66 (22)	0.010
Social functioning	<b>76</b> (24)	<b>78</b> (27)	88 (22)	0.001
Emotional role functioning	83 (28)	<b>83</b> (26)	91 (19)	<0.009 <sup>d</sup>
Mental health	<b>72</b> (15)	<b>71</b> (22)	80 (19)	<0.001

HRQoL, health-related quality of life; SD, standard deviation; SF-36, Short Form-36 Health Survey.

<sup>a</sup>Domain values in bold correspond to at least a small clinically significant difference [16], i.e.  $\geq 5$  points;

<sup>b</sup>p-value assessed with Kruskal-Wallis t-test;

<sup>c</sup>clinically and statistically significant difference only between patients with self-reported recurrence and patients with no concern of recurrence  $p=0.049$ , assessed with Mann-Whitney test [data not shown in the summary table above];

<sup>d</sup>clinically and statistically significant difference only between patients with concern of recurrence and patients with no concern of recurrence  $p=0.002$ , assessed with Mann-Whitney test [data not shown in the summary table above].

[5], the quite aggressive treatment and follow-up might affect HRQoL. This could be an important issue when discussing future treatment strategies in DTC.

Another interesting finding was a strong correlation between a single, clinically relevant question (“*Has the disease affected your view on life?*”) and HRQoL. This may be related both to personality traits and the disease in itself. Cancer patients who are more optimistic tend to have fewer symptoms of depression and anxiety [23] whereas a low level of optimism is the strongest predictor of fear of a recurrence [21]. Other studies show that optimism, social support, and fighting spirit may have a significant influence on positive affect in a group of cancer survivors [24].

Regardless of this aspect, though, the single question used in our study captures some of these aspects and is associated with perceived HRQoL. Thus, the question might be a simple and straight-forward tool to use within clinical practice to identify patients with poor HRQoL who could benefit from support interventions. Further studies might focus on understanding in more detail the reasons behind why so many patients still worry about the disease.

### Methodological aspects

General HRQoL questionnaires such as the SF-36 might not be sensitive enough to capture the full perspective of DTC patients. However, this instrument was selected as the patients were expected to be fully recovered and facing similar issues in daily life as the general population. We also included a study-specific questionnaire with relevant questions based on the literature [2]. Recently, a validated thyroid cancer-specific questionnaire, not available at the time of our data collection, was published [8,25] which could also have been of interest.

**Table V.** Differences in long-term HRQoL, i.e. 14–17 years after diagnosis measured with the SF-36 in patients stating that having DTC has affected their view on life in a negative way compared to patients stating that DTC did not or affected their view on life in a positive way.

SF-36 domains <sup>a</sup>	Negative view of life n = 30 Mean (SD)	Positive and no change in view of life n = 249 Mean (SD)	p-Value <sup>b</sup>
	Physical functioning	72 (32)	
Physical role functioning	70 (36)	<b>88</b> (21)	0.011
Bodily pain	58 (38)	<b>75</b> (27)	0.012
General health	45 (31)	<b>73</b> (22)	<0.001
Vitality	47 (29)	<b>63</b> (23)	0.002
Social functioning	57 (30)	<b>85</b> (22)	<0.001
Emotional role functioning	63 (33)	<b>90</b> (20)	<0.001
Mental health	54 (24)	<b>78</b> (18)	<0.001

HRQoL, health-related quality of life; SD, standard deviation; SF-36, Short Form-36 Health Survey.

<sup>a</sup>Domain values in bold correspond to at least a small clinically significant difference i.e.  $\geq 5$  points, between those with negative view on life and those with either positive or no change in view of life;

<sup>b</sup>p-value assessed with Kruskal-Wallis test.

However, this questionnaire is, to our knowledge, only validated in Dutch.

Strengths of the study include identification of every single patient diagnosed with DTC in Sweden between 1995 and 1998, as well as the high participation rate even more than a decade after diagnosis. Furthermore, HRQoL was measured with the well validated questionnaire SF-36 which has previously been used in thyroid cancer survivors [11] and the use of the Swedish general population as a reference group.

### Conclusions

Even if DTC carries an excellent prognosis, many of the HRQoL domains were negatively affected and half of the patients, fully 15 years after diagnosis, still worried about a recurrence, which negatively impacted their HRQoL. For healthcare practitioners to be aware of this might improve patient information and supportive care and, in the end, HRQoL.

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### Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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