Health status of Greek thyroid cancer patients after radioiodine administration compared to a demographically matched general population sample

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Keywords: Health-related quality of life
– Papillary thyroid cancer
– Radioiodine administration

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Received:
1 March 2012
Accepted revised:
15 May 2012

Abstract

The impact of radioiodine-131 (^{131}I) treatment on thyroid cancer patients' quality of life is controversial. *We conducted a cross-sectional study* of 60 patients aged 18-73 years old who had recently underwent near total thyroidectomy due to papillary thyroid cancer and were scheduled for ^{131}I treatment. On admission to our department, prior to ^{131}I administration patients underwent clinical and laboratory investigation including routine clinical biochemistry, thyroid stimulating hormone (TSH) and thyroglobulin (Tg) measurements. Health-related quality of life (HRQoL) was estimated by the SF- 36 Health Survey a generic instrument which consisted from eight scales (four for physical and four for mental health). After ^{131}I administration patients were discharged and approximately 6 months later they were re-evaluated. *Our results* showed that HRQoL in thyroid cancer patients receiving ^{131}I treatment is independent of age/ gender and thyroid cancer-related variables. All SF-36 scales significantly improved six months after administration ($P<0.05$). Compared to Greek general population, before ^{131}I administration all scales were significantly lower ($P<0.05$). Six months post ^{131}I administration, scales were significantly lower for physical functioning ($P=0.02$), physical role ($P=0.01$), social functioning ($P=0.03$) and emotional role limitations ($P=0.04$), whereas the remaining SF-36 scales were comparable to the general population. *In conclusion,* hypothyroidism and anxiety for the outcome of their disease before ^{131}I treatment exert a negative impact on thyroid cancer patients. Quality of life improvement post ^{131}I is mainly attributed to the resumption of euthyroidism and familiarization with treatment and follow-up procedures rather than ^{131}I treatment itself. There was no significant difference between patients receiving lower (2220-3700MBq) and higher (3700-7400MBq) dosage.

Hell J Nucl Med 2012; 15(2): 98-102 *Epub ahead of print: 27 June 2012* *Published on line: 27 June 2012*

Introduction

Thyroid cancer is the most common endocrine malignancy with an incidence of 1% of all malignancies and 0.2% of all cancer deaths. The majority of cases involve well-differentiated papillary and follicular carcinomas with a 10 years survival rate exceeding 90%, while medullary and anaplastic carcinomas have poor prognosis [1]. Thyroid cancer incidence rates rose more rapidly for women than for men during 1976-2005: 9.2 versus 3.6 per 100,000 person-years respectively [2]. The advocated treatment of differentiated thyroid cancer is total thyroidectomy and if necessary cervical lymph node dissection and/or radioiodine (^{131}I) remnant ablation. Monitoring includes serum Tg level measurements along with anti-Tg antibodies and diagnostic ^{131}I whole body scanning [3].

Quality of life is defined as an individual's perceptions of his or her position in life, in the context of the respective culture and value systems in these lives and in relation to his/her goals, expectations, standards and concerns [4]. The term health- related quality of life (HRQoL) refers to a multidimensional concept which encompasses perception of both negative and positive aspects of at least the four dimensions of physical, emotional, social and cognitive function [5]. Nowadays, there is growing interest about health- related quality of life in the treatment of several malignancies. However there are approximately only ten studies assessing HRQoL in treated-off thyroid cancer patients, while studies focusing on HRQoL and ^{131}I treatment are even fewer. Thus, the influence of ^{131}I on HRQoL has not been fully elucidated. We aimed to study HRQoL in thyroid cancer Greek patients prior and post ^{131}I treatment.

Patients and methods

Patients

Sixty patients with the following inclusion criteria were enrolled to the study: a) papillary thyroid cancer on histological examination b) total or near total thyroidectomy at least 2-

6 months before c) absence of concomitant malignancy d) no prior ^{131}I administration e) absence of severe comorbidities affecting general health status such as heart failure, end stage renal failure, respiratory failure etc.

Patients were classified according to the TMN classification and were scheduled for ^{131}I ablation treatment. The dosage of ^{131}I was determined according to the TNM stage and the postsurgery ^{131}I thyroid bed uptake after administrating 111MBq of ^{131}I [6]. According to Greek radioprotection law, patients receiving ^{131}I equal or more than 740MBq must be hospitalized for at least 48h due to the hazard of radiation exposure for the people in their environment [7]. In order to achieve elevated thyroid stimulating hormone (TSH) levels >30mIU/L that are necessary for ablation, patients were hypothyroid, off L-thyroxine treatment for at least 6 weeks. One patient was given human recombinant **(**hr**)**TSH (Thyrogen, Genzyme, Naarden, Netherlands) in two daily doses of 0.9 mg i.m. two days before ^{131}I administration due to atrial fibrillation.

The study was carried out from December 2009 until April 2011. Protocol included two phases. The first phase lasted from December 2009 until October 2010. On the first day of hospitalization and prior to ^{131}I administration, all patients underwent physical examination and routine laboratory investigation. Regarding thyroid function tests, TSH and thyroglobulin (Tg) and anti-Tg antibodies serum levels were determined by chemiluminescence assay (Siemens, USA). Afterwards, participants were asked by the doctor in charge to evaluate HRQoL by means of the SF-36 generic instrument. Missing values due to question misunderstanding represented 0.06% for general health scale, 0.03% for mental health and vitality and 0.01% for emotional role limitations.

In the second phase from June 2010 until April 2011, six months post-surgery, patients were phoned by the same doctor and asked to re-evaluate HRQoL again by SF-36 Health Survey. Missing values represented 0.05% for general health scale and 0.01% for mental health and vitality.

All participants provided written informed consent and the study was approved by the Ethical Committee of "Evangelismos Hospital".

Table 1. *Demographic, clinical and laboratory data of the patients scheduled for ^{131}I treatment*

	Patients	Controls
Gender	N(%)	N(%)
females	42 (30)	42 (30)
males	18(70)	18(70)
Age		
Mean±1SD	46.02±13.67	43.17±14.18
Range	18-73	19-73
TNM stage	N(%)	
I	48(80)	
II	5(8.3)	
III	5(8.3)	
IV	2(3.3)	
Tg (ng/mL)		
Mean±1SD	33.80±123.15	
Range	0.7-5,500	
^{131}I dose (MBq)		
Mean±1SD	3071.00±1001.59	
Range	2220-9250	

Healthy controls

Sixty age and sex-matched subjects from the Greek SF-36 Health Survey validation study [8, 9] were selected for controls. Table 1 shows the demographic, clinical and laboratory data of our study population.

Methods

Our aim was to evaluate a) differences in HRQoL assessment associated with demographic (age, gender) and disease-dependent (TNM stage, ^{131}I dosage, serum Tg levels) variables and b) differences in HRQoL assessment of thyroid cancer patients before and after ^{131}I administration.

We divided our study population into three age-related subgroups; younger (18-40 years old), middle-aged (41-60 years old) and older (>60 years old) in order to examine age-related differences regarding HRQoL assessment.

Regarding thyroid cancer-dependent variables such as TNM stage, serum Tg levels consisting of thyroid cancer marker and ^{131}I dosage, patients were classified as follows: a) According to TNM staging patients were divided into the following subgroups; 48 (80% of total sample) rated stage I. Five patients rated stage II, 5 rated stage III and 2 patients rated stage IV. b) According to serum Tg levels, patients were divided into 3 subgroups; 46 (76.6%) patients with low (0-10ng/mL) Tg levels compatible with thyroid remnant, 8 (13.3%) patients with moderately elevated (11-50ng/mL) Tg levels indicating local disease and 6 patients with high (>50ng/mL) Tg levels having distant metastases. c) Finally regarding ^{131}I dosage 3 subgroups were defined as follows: 46 (73.3%) patients who received ablation dose of 2220-3700MBq and 15 (25%) patients diagnosed with metastatic disease who received higher dose: 3700-7400MBq. Only 1 patient rated TNM stage IV with skeletal metastases at first diagnosis received a high (9250MBq) dose of ^{131}I and consequently >7400MBq. Patients' subgroups in relation to disease-dependent variables are depicted in Table 2.

HRQoL assessment

We assessed HRQoL using the SF-36 health survey (Medical Outcome Study 36-item Short Form Health Status Survey) validated for Greek population [8, 9]. The instrument explores eight dimensions of quality of life namely physical functioning (PF), physical role (PR) limitations due to health problems, bodily pain (BP), general health perceptions (GH), vitality (VT) tapping energy levels and

Table 2. *Patients' subgroups in relation to thyroid cancer-specific variables*

TNM stage	N valid (%)	Tg (ng/mL)	N valid (%)	^{131}I (MBq)	N valid (%)
1	48 (80%)	1-10	46 (78%)	2220-3700	44 (73.3%)
2	5(8.3%)	11-50	8 (13.6%)	3700-7400	15 (25%)
3	5 (8.3%)	>50	5 (8.5%)	>7400	1 (1.7%)
4	2 (3.3%)				
Total	60 (100%)	Total	60 (100%)	Total	60 (100%)

fatigue, social functioning (SF), role limitations due to emotional problems (RE) and mental health (MH). For each item, responses are coded, summed, and transformed into a scale ranging from 0 (worst possible health status) to 100 (best possible health status) [10]. Based on factor analytic methods, two summary measures of physical and mental health component summary scores named physical component summary (PCS) and the mental component summary (MCS) that aggregate eight scales can be constructed [11]. According to the patients' answers to the SF-36 Health Survey, scale scores involving physical and mental health pre and post ^{131}I administration were calculated.

Statistics

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, release 11.0, Chicago, 2001). Distribution normality was checked by Kolmogorov-Smirnoff test.

Gender-related differences in HRQoL were evaluated by Mann-Whitney non-parametric test and for the rest of the continuous variables by Kruskal-Wallis test. Thyroid cancer patients' SF-36 scores before and after ^{131}I administration were compared to controls' SF-36 scores using Mann-Whitney test.

Differences in HRQoL assessment of thyroid cancer patients before and after ^{131}I administration were assessed by Wilcoxon test. Tests were formulated two-tailed. The level of significance was set at 0.05.

Results

The total sample consisted of 18 men (30%) and 42 women (70%), aged 18 to 73 years as depicted in Table 1. Physical examination was unremarkable and routine laboratory evaluation was within normal ranges in all patients. SF-36 scale scores prior to ^{131}I administration matched for age/gender and thyroid cancer-specific variables are depicted in Table 3. Table 4 depicts mean ± SD values for all domains of SF-36 scales plus physical and mental component summaries prior and post ^{131}I treatment and respective mean ± SD values for Greek norm population as well.

Our data analysis demonstrated that there was no statistically significant difference in patients' assessment of HRQoL associated with age, gender, serum Tg levels or ^{131}I dosage. Although we detected a trend not reaching statistical significance (P=0.077) towards impaired emotional role in patients rated TNM stage III compared with patients rated TNM stage I or II, we consider that only TNM stage I patients are reliably evaluated as the other groups are not numerically significant. Our results about Tg levels and HRQoL assessement should also be interpreted with caution due to the limited number of patients with moderately elevated (n=8) and high Tg levels (n=5) compared with those with low Tg levels (n=46). Considering ^{131}I administration as a possible independent factor determining HRQoL, there was no significant difference between patients receiving lower (2220-3700MBq) and higher (3700-7400MBq) dosage.

Patients' scores significantly improved in all HRQoL domains six months post ^{131}I administration. Compared to a demographically matched Greek general population sample, patients' scores before ^{131}I administration were significantly lower in all domains. Six months post ^{131}I administration patients' scores for BP, GH, VT and mental health were comparable to the Greek norm population but remained significantly lower in the remaining 4 out of 8 domains, namely in physical functioning (P=0.002), physical role (P=0.001), social functioning (P=0.003) and emotional role limitations (P=0.004) (Table 4).

Table 3. *Mean SF-36 scale scores prior to radioiodine treatment in relation to demographic and thyroid cancer-specific variables*

	PF	PR	BP	GH	ER	SF	VT	MH
Age								
18-40	80.00	46.05	62.84	61.47	45.61	67.76	62.05	62.83
41-60	75.45	45.54	72.53	61.62	58.33	66.01	54.27	56.38
>60	58.83	38.88	56.88	66.85	58.33	66.66	50.70	58.29
Gender								
Men	75.61	43.05	65.83	56.80	60.78	63.88	56.71	58.15
Women	73.88	45.41	67.66	64.42	51.85	67.85	55.62	58.90
TNM stage								
1	75.93	47.39	68.39	62.29	55.55	68,75	57.44	60.93
2	93.33	18.75	68.40	64.60	73.33	62,50	53.00	47.20
3	68.00	40.00	58.40	59.00	13.33	47,50	39.00	41.60
4	65.00	62.50		27.00		56,25	25.00	-
Tg (ng/mL)								
0-10	75.78	43.09	70.28	62.88	51.44	67.39	55.27	58.08
11-50	65.87	43.75	53.37	64.66	58.33	62.50	60.00	63.83
>50	75.16	58.33	61.16	54.20	73.33	66.66	56.93	58.10
^{131}I (MBq)								
2220-3700	76.89	44.31	70.18	62,45	52.27	66.47	56.42	59.23
3700-7400	70.96	48.83	61.93	61,61	59.99	68.33	54.46	57.14
>7400	16.00		10			50.00	56.60	56.64

PF: physical functioning, PR: physical role, BP: bodily pain, GH: general health, ER: emotional role, SF: social functioning, VT: vitality, MH: mental health

Table 4. *SF-36 scale scores (mean ±SD) prior and 6 months post ^{131}I treatment (first two columns). The third column depicts SF-36 scores (mean±SD) of age and gender-matched Greek norm population that was used as control group (c). The three last columns show the differences of SF-36 scores prior and post ^{131}I, prior ^{131}I and controls, post ^{131}I and controls, respectively.*

	Mean±SD prior	Mean±SD post	Mean±SD (c)	Prior-vs. post ^{131}I	Prior-vs. controls	Post- vs. controls
1. Physical functioning	74.40±23.83	79.62±18.68	86.50±22.36	.000	.000	.002
2. Physical role limitations	44.70±44.36	73.75±28.15	85.00±33.25	.000	.000	.001
3. Bodily pain	67.11±29.94	85.01±15.63	85.10±24.17	.000	.000	.208
4. General health	62.26±16.92	65.09±15.84	69.23±20.66	.015	.017	.098
5. Vitality	55.94±20.72	60.35±16.23	66.55±18.16	.016	.007	.092
6. Social functioning	66.66±26.00	77.08±19.95	86.25±20.80	.001	.000	.003
7. Emotional role limitations	54.23±42.38	85.55±22.43	92.77±23.84	.000	.000	.004
8. Mental health	58.68±22.06	69.86±13.09	67.40±14.55	.000	.040	.289
A. Physical health component summary	45.83±9.52	49.27±6.33	51.99±11.19	.000	.000	.001
B. Mental health component summary	41.69±12.15	48.89±6.11	49.73±6.69	.000	.001	.968

Discussion

Our study showed that HRQoL in thyroid cancer patients is independent of age and gender. Regarding thyroid cancer-related variables, there was a tendency towards impaired emotional role in advanced TNM stage. We found no significant difference between serum Tg levels and HRQoL and between patients receiving low and high ^{131}I doses although others report that patients receiving higher doses (more than 5550mBq ^{131}I) have worse HRQoL compared with patients receiving lower doses [12].

On initial HRQoL evaluation patients, being hypothyroid, scored significantly worse compared with the healthy age-matched population. According to a systematic review by others, HRQoL was most affected after thyroid hormone withdrawal for ^{131}I remnant ablation or for follow-up procedures [13, 14]. Hypothyroidism is accompanied by a high prevalence of physical complaints like cold intolerance, dry skin, constipation, easy fatigue and sleep disorders that affect physical well-being and result in impaired HRQoL. Patients may also exhibit psychomotor slowing, depression or anxiety [15]. Regarding hypothyroidism, decline of HRQoL could be abrogated by the use of rhTSH [16, 17].

HRQoL amelioration six months post ^{131}I administration is mainly attributed to the resumption of L-thyroxine treatment and to a lesser extend to the impact of ^{131}I treatment on HRQoL [14] whereas compared to the Greek healthy population there was significant reduction in 4 of the 8 HRQoL scales of the SF-36 namely: physical functioning, physical role, social functioning and emotional role, after adjustment for age and sex.

Three studies, two randomized control trials [18, 19] and a cross-sectional Brazilian study [12], focused on the effects of ^{131}I ablation on HRQoL. In general, ^{131}I treatment affects some issues, mainly physical domains of HRQoL like: chewing, taste, speech and the amount of saliva in a dose-dependent manner as already mentioned.

In the present study, euthyroid function recovery overlaps the impact of ^{131}I on HRQoL. However, another key-point that should not be neglected is patients' perception that ^{131}I administration is beneficial for remission and consequently we could speculate that most mental aspects of HRQoL were improved in the present study on the ground that patients were considered "cured" of their disease. Another possible explanation for HRQoL improvement is that on re-evaluation six months post treatment, patients have overcome fear and uncertainty, that are usual initial reactions to the awareness of the diagnosis of cancer that exert negative influence on patients' HRQoL [20]. Indeed, patients with differentiated thyroid carcinoma perceive their illness on a subjective emotional basis unrelated to its actual severity [21] and thus QoL is not directly related to the stage of the disease [22] or to its favorable clinical follow-up [23]. According to others [24] duration of cure is an important independent factor for quality of life (QoL) and thus QoL after prolonged follow-up in treated-off patients may be profoundly improved.

Our study cannot be considered appropriate for long-term HRQoL assessment and the results of studies about HRQoL in treated-off thyroid cancer patients are rather conflicting. According to others [25] within the first year from diagnosis, many scales of HRQoL such as mental health, physical and emotional role, social functioning and vitality are adversely affected. Progressively HRQoL improves except for emotional role and vitality. A Japanese cross-sectional study demonstrated age as a prognostic factor of impaired social functioning and physical role [26]. These studies are in accordance with another study [27] suggesting that after long-term follow-up HRQoL in differentiated thyroid cancer patients is comparable to the general population except for an age-related decline similar to the general population.

The main limitations that should be briefly underlined are the current lack of thyroid cancer-specific developed questionnaire, the lack of testing HRQoL before ^{131}I treatment while patients being euthyroid and the limited number of patients at advanced TNM stage with high serum Tg levels and thus receiving high ^{131}I (>7400MBq) dose. *In conclusion,* hypothyroidism and anxiety for the outcome of their disease before ^{131}I treatment exert a negative impact on thyroid cancer patients. Quality of life improvement post ^{131}I is mainly attributed to the resumption of euthyroidism and familiarization with treatment and follow-up procedures rather than ^{131}I treatment itself. There was no significant difference between patients receiving lower (2220- 3700MBq) and higher (3700-7400MBq) dosage.

The authors declare that they have no conflicts of interest.

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