

# Long term quality of life in differentiated thyroid cancer patients after thyroidectomy and high doses of $^{131}\text{I}$ with or without suppressive treatment

**Evanthia Giannoula<sup>1</sup> MD, MSc,  
Ioannis Iakovou<sup>1</sup> MD, MSc, PhD,  
Frederik A. Verburg<sup>2</sup> MD, PhD**

*1. Third Department of Nuclear Medicine, Medical School, Aristotle University of Thessaloniki, Papageorgiou General Hospital, Thessaloniki, Macedonia, Greece  
2. Nuclear Medicine Clinic, University Hospital Gießen-Marburg, Standort Marburg, Germany*

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## Corresponding author:

Ioannis Iakovou MD, MSc, PhD,  
3<sup>rd</sup> Nuclear Medicine dpt of  
Aristotle University, Papageorgiou hsp, 56403 Thessaloniki,  
Macedonia, Greece  
iiakovou@icloud.com,  
iiakovou@auth.gr  
+302313323506/+30231991491/+  
306976677431,  
fax +302310991491,

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## Abstract

According to international guidelines, the most frequently applied diagnostic procedures and therapeutic interventions for differentiated thyroid cancer (DTC) patients are those of nuclear medicine. Differentiated thyroid cancer is the most common endocrine malignancy and over the past decades has shown the fastest increasing incidence of all malignancies. This cancer has a detrimental impact on a patients' quality of life (QoL), not very well considered in general practice. In this paper we aimed to review the QoL of DTC patients who received high doses of  $^{131}\text{I}$  and had (or not) a supplementary treatment. Our review includes physical, mental and social well-being and emotional and physical discomfort. Quality of life is related to the diagnostic and therapeutic procedures which DTC patients still have to undergo. Nuclear medicine physicians can maintain or restore the highest achievable QoL of these patients based on guidelines as well as individualized patient centered practice.

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## Introduction

Patients with DTC, who receive nuclear medicine services at all stages from diagnosis to therapy and during their follow up, are affected by the quality and safety of treatment which influences their QoL [1]. The physician often only sees the favorable prognosis of their disease and tends to neglect their QoL issues which nonetheless may arise in DTC patients [2].

Thyroid malignancies are characterized by a wide range of symptoms which may induce both emotional and physical discomfort and may affect all aspects of patients' life. At diagnosis patients are not aware with the kind of symptoms they will face, nor with the diagnostic and therapeutic procedures to which they are to be submitted and the impact of these on their physical and mental health. As a result, the DTC patients often remain trapped in their fears and anxieties caused by the disease, most often choosing not to express them to the attending physician. On the other hand, clinicians frequently go no further than to emphasize the favorable prognosis of DTC [3]. In this review, we briefly describe the diagnostic procedure, the clinical image and usual treatment of DTC patients related to the QoL of these patients.

## Thyroid cancer

### Incidence, Prognosis and Treatment

Thyroid cancer (TC) is the most common endocrine malignancy and over the past decades has shown the fastest increasing incidence of all malignancies [4]. Differentiated thyroid cancer is the most frequent subtype of thyroid cancer. It is a type of cancer that predominantly affects young and middle aged patients as 2 out of 3 new cases are younger than 55 years old, while approximately 2% include children and adolescents [5]. According to international guidelines and evidence based protocols concerning patients with thyroid neoplasms, the most frequently applied diagnostic procedures and thera-

peutic interventions. for patients with progressive or symptomatic disease are those of nuclear medicine [1]. External beam radiation is also considered in progressive disease. Exciting new drugs and approaches to therapy are also on the horizon for future DTC treatment [6-8]. When early appropriate treatment is given, prognosis of the disease is excellent. Differentiated thyroid cancer epidemiological trends and favorable prognosis for stages I to III, depending on the histological type as well as the stage of the disease is usually 5 years up to 98,1%. This survival has an unimpaired life expectancy and so it is important that during this long survival period the physician should also take care of his patients QoL [9]. The 5 years survival rate of DTC patients with stage IV is about 50% [12].

Surgery is the most effective treatment for DTC followed by radioactive iodine ablation (RAI). Thyroid stimulating hormone (TSH) suppression has traditionally been used after surgery. In recent decades targeted treatments with multikinase inhibitors offer a prolonged progression-free survival. However, they are not curative and therefore are reserved for patients with progressive or symptomatic disease. External beam radiation is also considered in progressive disease. Exciting new drugs and approaches to therapy are also on the horizon for future DTC treatment [10, 11].

## Quality of life

### Definition

Several authors have attempted to approach, interpret, define and evaluate QoL [15, 16]. According to Crevenna R et al. (2003) QoL is defined as the concept of a person's position in life, in relation to the set objectives, his expectations, standards and concerns [17]. Most of the literature highlights its multidimensional nature, which includes physical, mental and social well-being [18]. Diener (2003) describes quality of life as a subjective view of the degree of happiness and satisfaction achievement [19]. Garavito (2010) refers to the term as the personal sense of "integration", which is correlated with biological, psychological, economic and social factors [20]. The World Health Organization (WHO) tried to "embrace" the complexity of the term "Quality of Life", describing it as "the perception of a person's own existence, his position in a wider social and cultural context, his values, objectives and expectations, his rules and concerns". In this sense, QoL is affected in complex ways by numerous factors such as physical health, psychological state, level of independence, social relationships and is associated with the environment in which the person is living [20, 21].

### Quality of life assessment of DTC patients in the light of medical services provided by nuclear medicine departments

Differentiated thyroid cancer has a detrimental impact on a person's QoL [13]. However, there is a comparative lack of health related QoL research in DTC patients [14]. This is probably both due to the good prognosis that usually charac-

terizes DTC and to difficulties on defining and objectively evaluating QoL of these patients.

Despite the generally good prognosis of DTC its symptoms may have a broad range, from emotional to physical discomfort, also depending on the thyroid hormone status, which can affect the patient severely. Moreover, the diagnostic and therapeutic procedures, such as thyroidectomy, radioiodine therapy (RAI), follow up, TSH suppressive thyroid hormone treatment for a lifetime, which DTC patients have to undergo, can significantly affect their mental and physical well being. In DTC patients who take high doses of <sup>131</sup>I because either relapse after the first <sup>131</sup>I dose or receive more than two <sup>131</sup>I treatments, their QoL is seriously impaired. The physician often neglects or forgets to discuss with these patients their QoL issues which exist even with a favorable prognosis. Recent literature shows that the QoL of DTC patients is not only lower than that of general population but may show patterns of degradation even worse than the QoL of patients with other malignancies [22].

Haymart MR et al. (2013) reported that the actual <sup>131</sup>I dose suggested for the treatment of DTC patients was individualized depending on many different factors [23]. It is clear that such a decision making, especially when such a sensitive group of patient is concerned, has the potential to dramatically affect both patients' prognosis and QoL.

Applewhite et al. (2016) based on The North American Thyroid Cancer Survivorship Study (NATCSS) [24], compared DTC patients' QoL to that of patients with other cancer types (including colon, glioma, breast, and gynecologic cancers) which are all associated with a much worse survival. By evaluating not only physical well-being, but also psychological, social, and spiritual well-being they found that DTC survivors had an overall similar QoL to the survivors of other cancers. Interestingly DTC patients reported the lowest individual QoL scores for distress after initial diagnosis, RAI ablation, surgery, withdrawal from thyroid hormone, and fear of a second cancer, highlighting the main discomfort and possible complications they have to face. This suggests that QoL in DTC patients is not dependant on prognosis alone [25]. Therefore, it is important for DTC patients to receive proper QoL care services starting from their physicians in order to ensure both their physical and psychological well-being.

In clinical practice DTC patients are often only told that they have the "good" cancer or even more emphatic expressions such as: "you have won a lottery". However, this does not reflect their patients' personal experience of the disease. In 2015 Gamper EM et al. studied the health related quality of life (HRQOL) of <sup>131</sup>I- DTC patients in comparison with the general population, investigating the course of HRQOL up to 30 months after RAI remnant ablation and sought to identify patients' characteristics associated with HRQOL [26]. They provided further evidence that DTC patients' burden from symptoms and function impairment was unrelated to the favorable clinical outcome. They demonstrated that psychosocial distress as well as persistent problems with fatigue, possibly resulting difficulties at work and during leisure time were frequently overlooked and/or often falsely attributed to hypothyroidism only. Thyroid cancer patients with HRQOL after treatment were not uncommon, concluding

that as long as DTC patients' physical, psychological and mental burden is essential, it is important to improve their care especially when it comes to psychosocial issues [26].

Thyroid cancer patients have to undergo a series of diagnostic, therapeutic procedures and follow-up testing, depending on the initial findings, staging and restaging following original therapy. These interventions include usually measurements of serum thyroid stimulating hormone (TSH), thyroglobulin (Tg) and Tg antibodies (TgAbs), thyroid sonography with survey of the cervical lymph nodes, fine needle aspiration (FNA) and radionuclide thyroid scans when clinically indicated, preoperative use of cross-sectional imaging studies like, computed tomography (CT), magnetic resonance imaging (MRI), as an adjunct to ultrasound for patients with clinical suspicion for advanced disease, thyroidectomy and lymph node dissection, radioiodine therapy, adjunctive external beam irradiation, chemotherapy or systemic therapy (kinase inhibitors, other selective therapies, bisphosphonates, denosumab) when indicated, TSH suppressive thyroid hormone treatment, follow-up ultrasound in conjunction with serum Tg measurement and radioisotope whole body scanning or other imaging techniques like, RAI single photon emission tomography (SPET)/CT, CT, MRI, positron emission tomography/CT (PET)/CT during follow-up [7]. These interventions, their preparation and possible complications may cause a negative impact in patients' QoL.

The most commonly reported complications of FNA are local pain and minor haematomas, while serious ones are rare [27]. Long-term risks of radiation exposure and contrast-induced nephropathy (CIN) or immediate complications from contrast-enhanced CT (CE) CT imaging are rare too as well as the side effects of the use of gadolinium-based contrast agents (GBCA), including possible allergic reactions to the contrast agent [28]. Thyroidectomy for instance may cause functional impairments, including voice and discomfort during swallowing due to injury of the recurrent laryngeal nerve often called: The post-thyroidectomy syndrome [29]. Serious acute complications and adverse reactions are extremely rare after RAI treatment because the incidence of DTC survivors is rapidly rising due to the combination of high survival rates and young age at diagnosis, long-term side effects of high-dose RAI therapy become important for the patient's QoL [30]. Potential early sequelae of RAI treatment include ageusia, abnormalities in smell, nausea, acute sialoadenitis, epistaxis, thyroiditis, cystitis, gastritis, bleeding or edema in metastatic deposits, acute pneumonitis, transient ovarian or testicular failure, transient effects such as hair loss and fatigue due to hypothyroidism. Late side effects of RAI ablation include chronic sialoadenitis and resultant xerostomia or salivary gland obstruction, chronic or recurrent conjunctivitis, lacrimal gland inflammation and resultant exophthalmia, epistaxis, nasolacrimal duct obstruction, radiation fibrosis, hematologic toxicity and bone marrow depression, as well as secondary malignancies [31-34].

### Suggestions for a better QoL

Proper patients' education is important as it ensures that patients understand the potential side effects of  $^{131}\text{I}$  in order to give informed consent for their treatment. A patient who is

informed and aware of all side effects of his treatment, is likely to be more tolerant of treatment than an uninformed patient [35]. It is also important for the patients to understand the seriousness of the potential side effects in order to comply with the physician's recommendations to help prevent and/or minimize radiation-induced sequelae. In order to enhance understanding of the experiences and educational needs of patients receiving  $^{131}\text{I}$  treatment of DTC, healthcare providers should have a better understanding of DTC disease, its treatment and side effects of  $^{131}\text{I}$ . Furthermore, educational programs are required to adequately prepare healthcare professionals and patients for future care of their patients according to the kind of cancer diagnosed [36]. If nurses are to provide comprehensive cancer care, both psychosocial and physical needs of patients would be addressed. Fulfilling these needs requires a collaborative approach among patients, nurses, and other healthcare professionals is necessary [36].

However, therapy complications are not the only obstacles TC patients have to overcome in order to reach normal QoL. The effectiveness of RAI treatment as well as the sensitivity of diagnostic and follow-up tests depend on TSH levels in patient's serum. Levels  $>30\text{mU/L}$  are able to increase the expression of the sodium-iodide symporter (NIS), thereby to promote the uptake of RAI. To achieve the proper TSH levels, two different protocols are applied. The first includes LT3 and LT4 withdrawal, and the second includes the administration of recombinant human TSH (rh-TSH). Deprivation of thyroid hormones results in a prolonged period in which the patient is in a state of deep hypothyroidism, which has been shown to severely affect QoL. It is associated with among others increased levels of fatigue, decreased appetite, problems with constipation and motor skills, and fluid retention. Furthermore, during withdrawal, patients show associated psychological symptoms and social changes, such as family distress or decreased motivation to work [37]. Several studies have examined the use of rhTSH compared to conventional thyroid hormone withdrawal. It was shown that the use of rhTSH not only ensures an ablation success rate and effective imaging comparable to that seen after thyroid hormone withdrawal but also that it preserves patients' QoL [38]. On their meta-analysis of randomized controlled trials to compare the effects of recombinant human thyrotropin (rhTSH) and thyroid hormone withdrawal (THW) on thyrotropin (TSH) stimulation prior to remnant ablation of DTC, Tu et al. (2014) found that the use of rhTSH can lead to a higher QoL during the early period of RAI treatment compared to LT4 withdrawal alone [39].

Diagnosis and treatment burden are not the only causes of discomfort and psychological distress for DTC patients and their careers. Thyroidectomy is accompanied by a life-long dependence on substitution therapy with LT4. In many patients the first years after diagnosis and treatment include dosing regimens aimed at suppressing TSH production, causing subclinical hyperthyroidism which is described as a reversible cause of fatigue. After this initial period, the doses of replacement therapy are usually lowered in all but in those with persistent or recurrent disease in order to restore the physiological state of euthyroidism. Drabe et al. (2016)

acknowledged and examined fatigue in TC patients and their partners, focusing on the effects of time since diagnosis. They found that although both patients and relatives suffer from the diagnosis and treatment burden, only patients are at risk of developing anxiety symptoms or fatigue [40]. Fatigue is a common problem among different groups of cancer survivors and it is associated with decreased HRQoL and high levels of psychological distress. Fatigue among short- and long-term TC survivors has been the object of research by Husson et al. in 2013. They demonstrated that short-term survivors reported the highest levels of mean fatigue scores, whereas the normative population reported the lowest scores. Moreover TC survivors reported more frequently being bothered by fatigue, getting tired quickly, not being able to do much, feeling exhausted physically and mentally, had indecisiveness, obscure thinking and apraxia. Surprisingly, no significant differences were found initially, between short- and long-term survivors. However, when stratified by time starting at the time of diagnosis and divided patients into three fatigue groups, significant differences were noticed between all the survivors and the normative population, which was unexpected as with decreasing doses of replacement therapy to restore euthyroidism, fatigue levels are decreased [41].

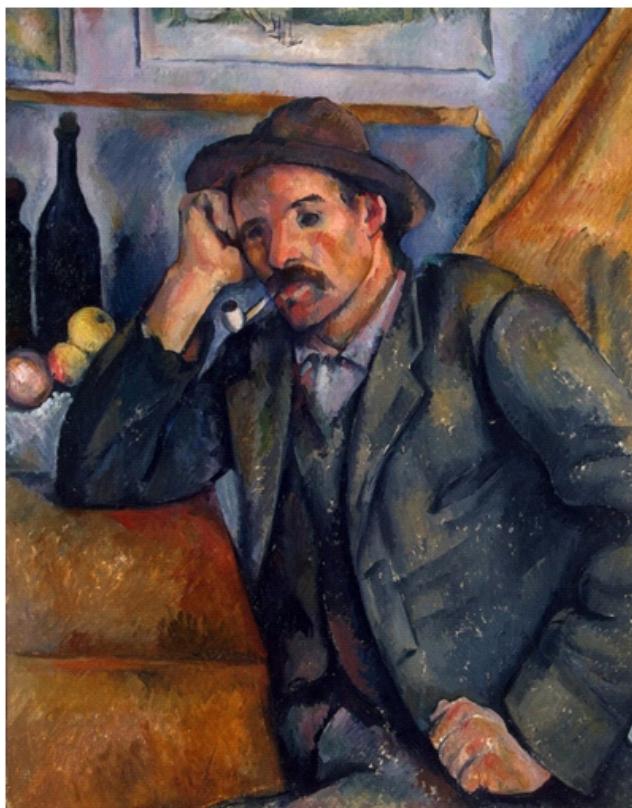
In conclusion, our short review suggests that it is important to enable long term communication between patients and healthcare providers throughout the entire disease trajectory. Changes in QoL after thyroid cancer treatment are significant.

Quality as the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge and safety as the type of process or structure, which reduces the likelihood of adverse events, that may occur when the patient receives health care services, are a sine qua non for managing thyroid cancer [42, 43]. Appropriate, high quality and safe diagnostic and therapeutic procedures that DTC patients undergo in nuclear medicine departments, should always be the cornerstone of their clinical practice to ensure satisfied patients and improvement of their QoL.

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