Clinical Predictors of Quality of Life in Patients With Initial Differentiated Thyroid Cancers

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Background: Patients with differentiated thyroid cancer (DTC) usually have a good prognosis. Traditionally, treatment success in patients with cancer has been evaluated by survival time. Recently, it has been observed that the diagnosis and treatment of cancer also have a strong effect on the quality of life (QOL) of these patients.

Objective: To assess the QOL of patients with DTC and its potential clinical predictors.

Design: Cross-sectional analysis.

Setting: A tertiary cancer institution.

Patients: One hundred fifty-four patients submitted to thyroidectomy (1997-2006) were evaluated using the University of Washington Quality of Life questionnaire.

Main Outcome Measures: Descriptive analysis of the results was done, as bivariate and multivariate analyses to compare each independent variable with each of 13 QOL domains.

Results: Patients 45 years or younger had better recreation scores than did patients older than 45 years (P = .04). Thirty-eight patients were submitted to neck dissection. Patients submitted to modified radical neck dissection reported worse chewing and shoulder scores than did patients submitted to selective paratracheal lymph node dissection only and those without neck dissection (P = .003 and P = .004, respectively). Patients who received more than 150 mCi of radioactive iodine therapy (RIT) reported significantly worse pain, swallowing, chewing, speech, taste, anxiety, and composite scores. Co-morbidities showed significant effect on recreation, activity, speech, saliva, and composite scores (P = .02, P = .046, P = .02, P = .01, and P = .008, respectively). In multivariate analysis, RIT is the only variable associated with a worse composite score (P = .003).

Conclusion: Although QOL after treatment of thyroid cancer can be considered good for most patients, those submitted to RIT at doses higher than 150 mCi are at risk for poor QOL and, therefore, may need more intensive follow-up and treatment.


Patients with differentiated thyroid cancer (DTC), in general, have a very good prognosis, and overall long-term survival is higher than 90%, with variations in subsets of patients. In DTC, surgery is the therapy of choice. Surgical options include lobectomy with isthmectomy or total thyroidectomy with or without neck lymph node dissection. The choice of procedure is affected by well-defined prognostic factors. Ablative surgery of the thyroid and possible neck disease and postoperative radioactive iodine therapy (RIT) result in prolonged survival but may lead to voice alterations, dysphagia, sialadenitis, taste disturbance, and xerostomia.

Traditionally, the main outcome measure in oncology patients has been survival, based on tumor control, but recently it has been increasingly recognized that the diagnosis and management of cancer can have a major effect on every aspect of the quality of life (QOL) of a patient. The aims of cancer treatment became not only to increase survival but also to preserve QOL, and measuring these changes has been considered to be of paramount importance.

The QOL is defined as the perceptions of an individual regarding his or her position in life in the context of the culture and value systems in which he or she lives and in relation to his or her goals, expectations, standards, and concerns (WHO-QOL, 1993). Health-related QOL (HR-QOL) refers to a multidimensional concept that encompasses perception of negative and positive aspects of physical, emotional, social, and cognitive functions, which could be affected by the disease or its treatment. Several instruments have been developed to assess QOL in patients with cancer.
with head and neck cancer. Among them, the University of Washington Quality of Life (UW-QOL) questionnaire is a validated, accurate, and internationally accepted survey instrument. The use of such a questionnaire allows the evaluation of HR-QOL and leads to a better understanding of the patient's expectations.\textsuperscript{8,11}

In the past 20 years, an increasing number of studies have measured QOL as an end point in the evaluation of the effect of the disease and its treatment on the daily life of the patient.\textsuperscript{6,8} However, there have been relatively few HR-QOL studies looking specifically at patients with thyroid cancer.\textsuperscript{1,10,11} The aims of this study are to assess QOL in patients with DTC and to evaluate whether different modalities of treatment can interfere in the QOL of these patients.

### METHODS

#### DESIGN

A cross-sectional analysis was performed of adults with initial DTC treated with total thyroidectomy, some of whom had undergone adjuvant RIT, between January 1, 1997, and December 31, 2006, at a single tertiary cancer institution. Patients who had received previous head and neck radiation therapy or had sicca syndrome symptoms were excluded. The study was approved by the ethics committee of Hospital A. C. Camargo, and all participants signed an informed consent form. The patients were invited to participate in this study at their follow-up medical consultation. All of them had normal thyroid hormone levels, and patients who had ended treatment 4 months to 10 years before (median, 2 years) were included. The independent variables were age, sex, time since treatment, RIT dose, neck dissection, and comorbidities. The dependent variables were 13 QOL scales from the UW-QOL questionnaire.

#### SAMPLE

Four hundred patients who met the inclusion criteria were invited to participate in this study. Of those, 184 patients agreed to participate and 154 completed the questionnaire and had clinical stage I or II tumors. A total of 137 patients (89.0%) were women, and 17 (11.0%) were men; the mean patient age was 46.9 years (median age, 46 years; age range, 21-87 years). All the patients underwent a total thyroidectomy, and 38 patients were also submitted to a neck dissection of levels II through IV (2 patients), II through VI (9 patients), and VI (27 patients). One hundred fifty-one patients had papillary carcinoma and 3 had follicular carcinoma. Regarding clinical stage, 85.1% of tumors were in stage I and 14.9% were in stage II. Ninety-three patients (60.4%) underwent RIT, and the median dose was 130 mCi (range, 30-700 mCi). Seventy-three patients received doses up to 150 mCi, and 20 patients received doses higher than 150 mCi. Comorbidities were evaluated using the American Society of Anesthesiologists (ASA) classification in 137 patients. Thirty-eight patients were classified as ASA I, 97 as ASA II, and 2 as ASA III. These data are summarized in Table 1.

#### MEASURES

Demographic measures included age (≤45 or >45 years) and sex. Age 45 years was used as a reference owing to its important prognostic value in patients with DTC. The classification of neck dissection was paratracheal (level VI), radical (levels II-IV), and extended radical (levels II-VI). At the analysis, these patients were grouped as none (no neck dissection), paratracheal (neck dissection of level VI), and radical (neck dissection of levels II-IV and II-VI).

Many studies\textsuperscript{5,12-14} have discussed that radioactive iodine effects are dose dependent, and a recent study by us showed that doses higher than 150 mCi are associated with more adverse effects on the salivary glands. In this way, we categorized the variable RIT as patients who were not submitted to RIT, patients who received up to 150 mCi, and those who received more than 150 mCi. Time since treatment was measured in months and was categorized into 12 months or less and more than 12 months.

The physical status classification of the ASA\textsuperscript{13} (I, healthy patients, no medical problems; II, mild systemic disease; III, severe systemic disease but not incapacitating; IV, severe systemic disease that is a constant threat to life; and V, moribund, not expected to survive without the operation) was used to grade the comorbidities of the patients and to associate them with the QOL of these patients. See Table 1 for details.

#### QOL ASSESSMENT

A Brazilian-Portuguese version of the UW-QOL questionnaire validated by Vartanian et al\textsuperscript{18} was used. The UW-QOL questionnaire was designed as a self-reported scale and, for this reason, the patients completed it by themselves. Patients who did not feel able to complete the UW-QOL questionnaire independently were helped by their companion. The UW-QOL questionnaire was applied during 2006 in days reserved for only this study.

The questionnaire consists of 12 questions that evaluate the following domains: pain, appearance, activity, recreation, chewing, swallowing, speech, shoulder, taste, saliva, humor, and anxiety. Scores can range from 0 to 100, with 100 indicating the best level of overall function. The composite score is the mean of the scores of all 12 domains. There is general agreement that a composite score of 75 to 100 has little effect on QOL, a score of 50 to 74 has a relative effect on QOL, and a score less than 50 has an important effect on QOL. Three general questions

<table>
<thead>
<tr>
<th>Table 1. Demographic and Treatment Variables</th>
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<tbody>
<tr>
<td>Variable</td>
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<td>≤45</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>RIT</td>
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<tr>
<td>None</td>
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<tr>
<td>≤150 mCi</td>
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<td>&gt;150 mCi</td>
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<td>Neck dissection</td>
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<tr>
<td>None</td>
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<tr>
<td>Paratracheal</td>
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<td>Radical</td>
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<td>Clinical stage</td>
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<td>ASA classification\textsuperscript{a}</td>
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<td>II</td>
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<td>III</td>
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Abbreviations: ASA, American Society of Anesthesiologists; RIT, radioactive iodine therapy.

\textsuperscript{a}Only 137 patients provided this information.
evaluate overall QOL and HR-QOL. We scored the individual domains according to the UW-QOL questionnaire guidelines.

**STATISTICAL ANALYSES**

Statistical analysis was performed using a software program (SPSS for Windows version 15.0; SPSS Inc, Chicago, Illinois). A descriptive analysis of the results was performed. Bivariate analyses were conducted by comparing each of the independent variables of age, sex, neck dissection, RIT, time since treatment, and comorbidities with each of the 13 QOL scales on the UW-QOL questionnaire using nonparametric Mann-Whitney or Kruskal-Wallis tests. To determine significant predictors of QOL controlling for one another, multivariate analysis was conducted using multiple linear regression.

**RESULTS**

In answering the UW-QOL questionnaire on overall health, 94.4% of patients reported that their health was the same or better than it was before treatment, 83.9% of patients reported good HR-QOL, and 83.3% of patients reported good general QOL. There were no significant differences in these questions regarding age, sex, RIT, neck dissection, or comorbidities. The median composite score was 93.05 (range, 53.5-100), which is associated with good QOL.

**BIVARIATE ANALYSES**

In the evaluation of demographic variables, age had an effect on the recreation domain, with patients older than 45 years showing worse scores than younger patients ($P =.04$). In regard to the other domains, age did not have a significant association. In the same way, sex did not have an effect on any domain (Table 2).

The RIT had an effect on many domains, and doses higher than 150 mCi had a strong association with worse scores in several domains, such as pain ($P =.045$), swallowing ($P =.001$), speech ($P =.004$), shoulder ($P =.04$), taste ($P =.006$), anxiety ($P =.004$), and composite score ($P =.01$). Patients submitted to neck dissection from level II through VI had significantly worse chewing scores ($P =.003$) and shoulder scores ($P =.004$).

Time since treatment was not associated with worse scores in any domain. Patients classified as ASA II and III had worse scores in the activity ($P =.05$), recreation ($P =.02$), speech ($P =.02$), and saliva ($P =.01$) domains and in the composite score ($P =.008$). All these data are summarized in Table 2.

**MULTIVARIATE ANALYSES**

To conserve power and because sex and time since treatment were not significant in the bivariate analyses, these variables were omitted from the multivariate analyses. Variables with $P \leq .25$ were considered in multiple linear regression to determine the greatest predictor of QOL in patients with thyroid cancer controlling for one another.

The RIT was the strongest predictor factor, affecting domains such as chewing, speech, taste, saliva, and anxiety. It was the only variable that affected the composite score.
score. The presence of comorbidities, as measured by ASA classification, was the second predictor of worse QOL; it affected domains such as recreation, speech, and saliva. Neck dissection affected chewing and shoulder scores, and age affected recreation scores. The data are summarized in Table 3 with the value of unstandardized coefficient B and each P value.

### Table 3. Multiple Linear Regression With the Significant Variables From the Bivariate Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pain</th>
<th>Appearance</th>
<th>Activity</th>
<th>Recreation</th>
<th>Swallowing</th>
<th>Chewing</th>
<th>Speech</th>
<th>Shoulder</th>
<th>Taste</th>
<th>Saliva</th>
<th>Humor</th>
<th>Anxiety</th>
<th>Composite Score</th>
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<td>Age, y</td>
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<tr>
<td>None/≤150 mCi</td>
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<td>(−4.705)</td>
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<td>(−10.960)</td>
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<td>&gt;150 mCi</td>
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<td>None/paratracheal</td>
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<tr>
<td>Radical</td>
<td>(−7.200)</td>
<td>(−22.205)</td>
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<td>III</td>
<td>(−27.560)</td>
<td>(−15.584)</td>
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Abbreviations: ASA, American Society of Anesthesiologists; RIT, radioactive iodine therapy.

*The values are the P value (B value) to the 95% confidence interval.

**COMMENT**

In this study, in univariate and multivariate analyses, the greatest predictor of QOL in patients with thyroid cancer was RIT dose, with higher doses showing decreased QOL through the composite score. The composite score shows the effect of all the domains evaluated, and worse scores in specific domains will reflect on the final score. Functions such as taste, speech, chewing, and swallowing are strongly associated with RIT salivary gland effects, as is seen through the association between RIT and these domains in the UW-QOL questionnaire. Until now, in the literature review, none of the published studies showed the effect of RIT or doses of radioactive iodine on QOL in the patient with thyroid cancer. This is an important finding because the indication of RIT should also consider the late effects of the treatment.

The adverse effects of RIT are well recognized and, in general, are mild and self-limiting; severe complications are rare enough that the benefit of therapy typically outweighs its risk. The common acute adverse effects reported are nausea, vomiting, epigastralgia, taste disturbance, and saliadenitis, and the late adverse effects normally restrict themselves to the salivary glands as sialadenitis and xerostomia. Recent findings from our group reinforce the hypothesis of Maier and Bihl that patients submitted to RIT have an impairment in the ability to drain the saliva, and it reflects as clinical dysphagia.

Considering that many patients with DTC are submitted to RIT, the effect of those specific adverse effects and those resulting from the surgical procedure on the QOL of such patients were not previously extensively described. There have been relatively few and recent HR-QOL studies looking specifically into patients with thyroid cancer. The paucity of specific instruments to assess the QOL of patients with thyroid cancer associated with low mortality and morbidity rates of the treatment can explain why there are so few studies in this field.

Most published studies use the 36-Item Short Form Health Survey, that is, a generic QOL instrument, and do not have specific domains to evaluate the effect of possible adverse effects of treatment. The UW-QOL questionnaire, although not commonly used in patients with thyroid cancer, has value in predicting QOL in these patients because it makes it possible to evaluate points that can be related to adverse effects of surgery and RIT.

The main postoperative complications of thyroidectomy are vocal cord palsy owing to dysfunction of the recurrent laryngeal nerve and hypocalcemia. Neck dissection and paratracheal lymph node dissection, when associated with total thyroidectomy, were significantly associated with transitory and permanent hypocalcemia. Besides those results, swallowing changes and occasional dysphagia are sequelae reported after thyroid resection, even long after the surgical procedure.

Neck dissection was associated with chewing function instead of swallowing function, as is commonly reported in the literature, owing to injury of the recurrent nerve. As expected, neck dissection affected the shoulder domain of the QOL instrument. Preexistent comorbidities are associated with a decreased recreation score, as was expected, and with the domains of speech and saliva. Worse scores on these last domains associated with the presence of comorbidities probably can be explained by the intake of medications that can interfere with salivary flow.

To our knowledge, only 1 study has evaluated the results of the adverse effects of surgery and RIT on such patients. This study used a UW-QOL questionnaire that was adapted but not validated. The authors evaluated 20 patients with thyroid cancer and reported that those older than 45 years had worse general health, appearance, and chewing scores but did not show an association of RIT or neck dissection with any domain.

Different from the data of Dagan et al, the present patients reported a good general QOL, with a slight effect of treatment on their HR-QOL. However, our patients who were older than 45 years had worse recreation scores, and preexistent comorbidities had an effect on the activity,
recreation, speech, and saliva domains. The greatest effect on QOL with specific domains was the dose of RIT. Patients submitted to doses higher than 150 mCi had many domains affected, such as pain, swallowing, chewing, speech, taste, anxiety, and composite score. Morbidities of the surgery are detected in chewing and shoulder functions. Time since treatment and sex were not associated with alterations in QOL.

These results reveal that despite patients with thyroid cancer having a good general QOL, there is a subset of patients who live with some comorbidities of the cancer treatment. The dose of RIT can affect specific activities in the daily lives of these patients. The effects of RIT on specific functions had not been assessed and reported in the literature until now, and more studies are needed to confirm these findings. Certainly, this study has some limitations because it is a cross-sectional study, and there is neither a baseline QOL score before treatment nor follow-up across time. Evaluation of QOL at different points in time after treatment could be another limitation, but at the time of the analysis it seems not to have affected the results. Prospective studies using videofluoroscopy to evaluate the different phases of swallowing and salivary gland function in patients receiving more than 150 mCi of RIT can contribute to the clarification of these findings.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Almeida, Vartanian, and Kowalski. Acquisition of data: Almeida and Vartanian. Drafting of the manuscript: Almeida. Critical revision of the manuscript for important intellectual content: Vartanian and Kowalski. Statistical analysis: Vartanian. Obtained funding: Almeida and Kowalski. Administrative, technical, and material support: Kowalski. Study supervision: Vartanian and Kowalski.

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REFERENCES

concept and design: Duval and Daniel. Acquisition of data: Duval. Analysis and interpretation of data: Duval and Daniel. Drafting of the manuscript: Duval and Daniel. Critical revision of the manuscript for important intellectual content: Duval and Daniel. Statistical analysis: Duval and Daniel. Obtained funding: Daniel. Administrative, technical, and material support: Daniel. Study supervision: Daniel. Additional Contributions: Anthony Abela, MD, from Ste-Justine’s Hospital, allowed us access to some of the patients’ data presented in this article.

REFERENCES


Correction

Error in Author Name. In the Original Article titled “Clinical Predictors of Quality of Life in Patients With Initial Differentiated Thyroid Cancers” by Almeida et al, published in the April issue of the ARCHIVES (2009;135[4]:342-346), an error occurred in the name of one of the coauthors on page 342. The name “Juliana Almeida, DDS, MSc” should have read “Juliana Pereira Almeida, DDS, MSc.”