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Relationship between age and outcome in thyroid surgery: a prospective observational study

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Abstract

Background: The occurrence of thyroid nodules and goiter increases with age. In general, surgery age is a predictor of perioperative morbidity. In thyroid surgery, there are different data on the role of age on morbidity. We investigated the influence of age on the outcome in thyroid surgery in a prospective single cohort study with a follow-up after 1 year.
Methods: Total thyroidectomy or hemithyroidectomy was performed in euthyroid benign thyroid goiters (n = 152). The primary endpoint was surgery duration. The secondary endpoints were weight of resected tissue, body mass index (BMI), amount and type of perioperative and long-term complications, and quality of life (QoL) preoperatively and 1 year postoperatively.
Results: A significant three-way interactive relationship between age, surgery duration, and amount of resected tissue was found. An increase in any of these variables results in an increase in both other variables. The amount of perioperative complications was associated with resected tissue size. The QoL increases significantly after surgery by up to 10% and decreases significantly with age (mean QoL after surgery = 84.9 of 100 for the youngest group and 75.7 of 100 for the oldest group). No long-term complications were recorded.
Conclusion: The number of thyroid operations, especially of benign thyroid goiters, decreases annually in Germany. This can be explained by the fact that, on the one hand, the surgical indications are made more restrictive as conspicuous nodes are better clarified by improved technical aids. On the other hand, conservative measures (i.e. L-thyroxine and iodide administration) are used to achieve a size regimen of the goiter. Our results show that perioperative complications increase with patients' age and surgery duration. However, the more restrictive surgical decision also entails the risk that patients will have to be operated at an older age and possibly with a bigger goiter, which is associated with higher operative morbidity. Therefore, in addition to the possibility of conservative therapy of the symptomatic goiter, the affected patients should also be thoroughly informed about the option to perform elective early thyroid surgery with regard to improved postoperative QoL and to keep the overall stress at a minimum for elderly patients.

Keywords: age; benign thyroid nodules; goiter; quality of life; thyroid surgery.

Introduction

The World Health Organization (WHO) has defined "elderly" persons in developed countries as persons older than 65 years [1]. According to the German Federal Statistical Office, 28% of the population in 2030 and 33% in 2060 will be older than 65 years [2]. Therefore, more elective surgery is performed on aged patients than in the past decades [3]. Thyroid surgery is one of the most frequent elective interventions in endocrine surgery. Even in younger patients, controversies regarding benefits and drawbacks are still present.

The occurrence of thyroid nodules increases with age [4]. In an ultrasound survey of 635 adults, thyroid nodules were detected in 80% of the women and 74% of the men older than 60 years in Germany [5]. Thyroid nodules can represent cysts, adenoma (toxic/nontoxic nodular goiter), inflammation, or cancer. Nontoxic multinodular goiter can be detected in 50% of all patients older than 55 years [6]. Thus, it is believed that the number of thyroid diseases that require surgery will increase in the aging population. This is important, especially in light of the discussion

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that, in Germany, the number of thyroid surgeries is much higher than, for instance, in the US, England, or the Netherlands [7].

In general surgery, age seems to be one of the main predictive factors for perioperative morbidity [8]. With regard to the age-related morbidity in thyroid surgery, there are different data in the literature. Age itself seems to have a minor influence on the outcome in thyroid surgery [9]. However, higher rates of complications were observed in elderly patients undergoing thyroid surgery [10]. It remains unclear if seniority is associated with a higher rate of complications in the treatment of thyroid surgery and in which direction the quality of life (QoL) is influenced in elderly patients.

Therefore, we investigated in a prospective observational study if age is a risk factor in hemithyroidectomy and total thyroidectomy for benign multinodular goiter and if an age-relevant postoperative change of the QoL 1 year after surgery could be detected.

Methods

The study was approved by the Ethics Commission of the University of Oldenburg (No. 004/2016). No trial registration was needed.

Patients

Over a period of 1 year, 190 patients with nodular, nontoxic goiter were included in our prospective observational study. We only included patients suffering from benign multinodular goiter to keep the group as homogenous as possible with regard to pathology. All patients gave their written, informed consent before inclusion in the study. Total thyroidectomy or hemithyroidectomy was performed because of symptomatic goiter and/or suspect nodules. All patients gave their written, informed consent for participation in this study. Of the 190 patients, 8 were excluded due to postoperative malignant pathology. Follow-ups were conducted 1 year postoperatively via a two-step design. Patients received a questionnaire via mail. If there was no response after 4 weeks, patients were contacted by telephone. Thirty patients were lost to 1-year follow-up, resulting in a total of 152 patients, who were included in this analysis. For 89 patients (67 females, 22 males), total thyroidectomy was performed; for 63 patients (45 females, 18 males), hemithyroidectomy was performed (see also Table 1).

Study design

All surgeries were performed by one of four surgeons, each with more than 50 thyroid surgeries per year. The influence of hormonal status on the comparison of age-related factors on thyroid surgery was avoided by only comparing symptomatic, nontoxic benign nodular goiter (WHO-grade 2/3). Routinely, preoperative and postoperative laryngoscopy for vocal cord examination was performed by an independent ENT specialist. Intraoperatively, recurrent laryngeal nerve (RLN) was monitored during surgery via intermittent neuromonitoring and macroscopic visualization. Parathyroid gland vascularization was determined [11]. Patients were monitored for 24 h after surgery at the intermediate care unit and were discharged between 1 and 10 days after surgery. Serum calcium level was determined on the second postoperative day. In case of low calcium serum levels and/or hypocalcemia-related symptoms, calcium was substituted.

Table 1: General patient demographics.

Sex	Age group 1 (n=20)	Age group 2 (n=101)	Age group 3 (n=31)
Female/male	15/5	75/26	22/9
Type of surgery			
Total thyroidectomy/ hemithyroidectomy	9/11	56/45	24/7
% Total thyroidectomy	45	55	77
Mean surgery duration, min			
Total thyroidectomy	69±17	71±23	71±32
Hemithyroidectomy	45±17	50±14	54±20
Mean hospital stay, days			
Total thyroidectomy	4.7±2.2	3.6±1.0	4.0±1.4
Hemithyroidectomy	2.9±0.3	3.1±0.5	3.0±0.0
Complications			
Overall n (%)	4 (20)	36 (35.6)	12 (38.7)
Total thyroidectomy	4	25	12
Hemithyroidectomy	0	11	0
Transient vocal cord paralysis			
Total thyroidectomy	0	4	3
Hemithyroidectomy	0	6	0
Secondary hemorrhage			
Total thyroidectomy	0	0	0
Hemithyroidectomy	0	2	0
Infection and scarring			
Total thyroidectomy	0	4	0
Hemithyroidectomy	0	3	0
Low Ca level (only TT)	4	17	9
Perioperative values (mean and SD)			
Thyroid weight, g			
Total thyroidectomy	60.3±32.2	73.4±59.3	74.2±51.1
Hemithyroidectomy	29.1±18.5	35.1±29.0	36.5±28.7
Thyroid volume, mL			
Total thyroidectomy	55.7±41.1	58.3±40.3	78.8±54.9
Hemithyroidectomy	49.7±39.2	39.4±23.9	43.2±40.0
BMI,kg/m^2			
Total thyroidectomy	27.8±6.3	28.4±6.2	27.5±4.7
Hemithyroidectomy	26.7±7.9	27.6±5.1	29.0±3.9
Postoperative values (mean and SD)			
C, mmol/L			
Total thyroidectomy	2.0±0.3	2.1±0.2	2.1±0.2
Hemithyroidectomy	2.2±0.1	2.2±0.1	2.2±0.1
BMI, kg/m^2			
Total thyroidectomy	27.5±6.6	28.5±6.1	28.3±4.5
Hemithyroidectomy	26.9±8.0	27.7±5.3	28.4±3.4

After total thyroidectomy, all patients routinely received L-thyroxine (1.5 µg/kg body weight). Hormonal status was controlled approximately 6 weeks after surgery by the general practitioner. The resected material was weighed by the pathologist.

At least 24 h before operation, and 1 year after surgery, patients answered a question regarding their current overall QoL using a Visual Analogue Scale (VAS) ranging from 0 (worst) to 100 (best). The following complications were recorded: (transient) postoperative symptomatic hypocalcemia, (transient) vocal cord paralysis, secondary hemorrhage, and infection and/or scarring.

Statistics and graphs

Statistical analysis was performed with SigmaPlot 13 [12] or IBM SPSS Statistics 23 [13]. We used descriptive and exploratory statistics [correlations: Pearson in case of normal distribution and Spearman rank in case of nonnormal distribution of the data; tests for differences between groups: two-way analysis of variance (ANOVA) for normally distributed data; Mann-Whitney U for two independent samples with nonnormal distribution; Kruskal-Wallis in case of more than two independent samples; Wilcoxon signed rank for two independent samples with nonnormal distribution]. The analysis of specific risk factors was beyond the scope of this study. Graphs were prepared with Origin8 [14].

Results

Patients were divided into three age groups: younger than 40 years (n = 20), ages between 40 and 64 years (n = 101), and 65 years and older (n = 31). Table 1 presents the general patient demographics for the three age groups. Figure 1 depicts the mean surgery duration for all age groups separated by surgery type. The surgery duration is approximately 70 min for the thyroidectomies in all three groups, whereas the mean duration increases from 45 to 55 min for the age groups undergoing hemithyroidectomies.

A two-way ANOVA (age group and surgery type as factors and duration as the dependent variable; normality test and equal variance test passed) revealed a statistically significant difference for the duration between thyroidectomies and hemithyroidectomies. Differences were mostly due to significant differences between surgery types in both younger age groups (Holm-Sidak pairwise multiple comparison: younger than 40 years $t = 2.980$, $p = 0.003$ and between 40 and 64 years $t = 4.926$, $p < 0.001$). Thyroidectomies and hemithyroidectomies did not differ significantly in the older group. However, a slight trend was observed ($t = 1.75$, $p = 0.082$). No overall differences between the age groups and no interactions between age group and surgery duration were found. There was no influence of age on the surgery duration in total thyroidectomies. In hemithyroidectomized patients, surgery duration increased with age. This relation between surgery duration and age also showed a significant correlation (Pearson $r = 0.206$, $p = 0.011$). In addition, surgery duration was influenced by body mass index (BMI; Figure 2; Pearson $r = 0.284$, $p < 0.001$).

There was a significant correlation between surgery duration and weight of the resected thyroid tissue (Spearman rank $r = 0.544$, $p < 0.0001$). Additionally, the size of the resected thyroid tissue depended on the patients' age (Figure 3; Spearman rank $r = 0.209$, $p = 0.012$).

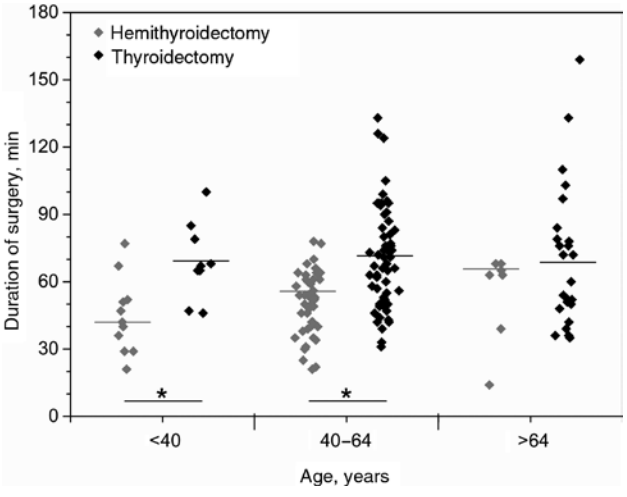

Figure 1: Dot-plot and median surgery duration for three different age groups; sorted by the surgery type performed.
Gray diamonds: hemithyroidectomies; black diamonds: thyroidectomies. Asterisks denote significant differences between respective groups.

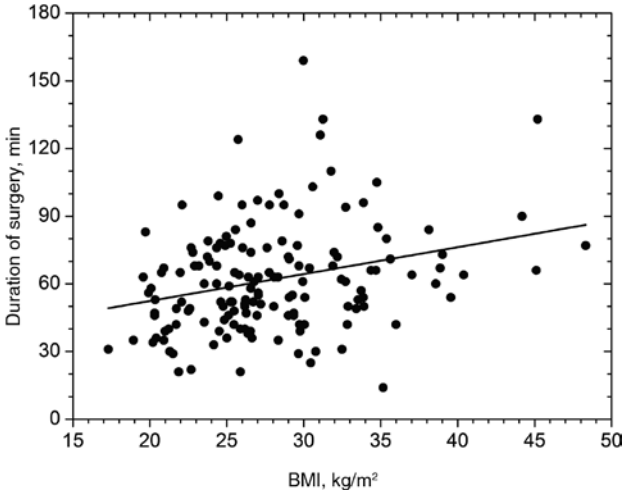

Figure 2: Surgery duration plotted against the BMI of the patients. The black line indicates the fitted linear regression.

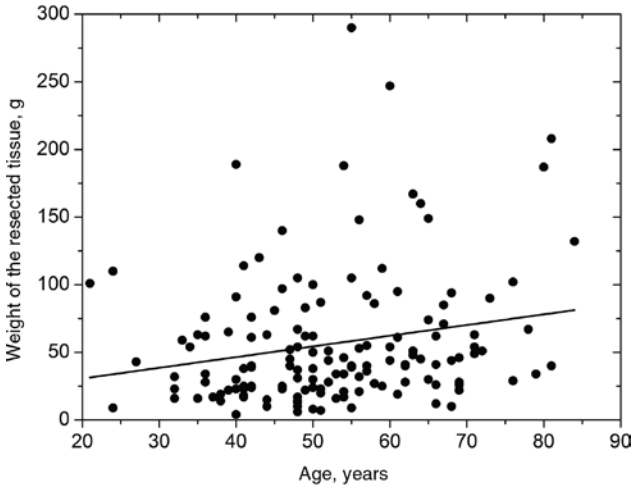

Figure 3: Weight of the resected thyroid tissue plotted against the age of the patients.
The black line indicates the fitted linear regression.

Figure 4 depicts the weight of the resected thyroid for patients with and without postoperative complications. Fifty-one patients showed one or more complications. These complications included transient postoperative symptomatic hypocalcemia [n = 30 (20%)], transient vocal cord paralysis [n = 13 (9%)], secondary hemorrhage [n = 2 (1%)], and infection and/or scarring [n = 7 (5%)]. Permanent hypocalcemia or permanent vocal cord paralysis were not observed. The resected thyroids of patients, which later showed complications, were markedly larger than the thyroids of patients without complications (median 37 vs. 51 g; see also Figure 4). This effect was significant (Mann-Whitney U = 2812.5, p = 0.042), indicating an increasing probability of potential postoperative complications with increasing amount of resected thyroid tissue.

Patients with and without postoperative complications do not differ in mean age (53.9 vs. 51.9 years) and mean BMI (28.7 vs. 27.5 kg/m^2). Twenty of the patients with no complications were 65 years and older (20%). Eleven of the patients with complications were 65 years and older (22%). If the age line was drawn at 70 years, the percentage of older patients in the group with complications remained high [n = 7 (14%)], whereas 83% of all patients with complications were 70 years or older (n = 7), indicating that the probability for complications rose markedly somewhere between ages 65 and 70 years.

Surgery duration and length of hospital stay after surgery were correlated significantly (Spearman rank $r = 0.209$, p = 0.0098). Both for patients 65 years and older (n = 31) and for younger patients (n = 121), the median stay in hospital after surgery was 3 days (Mann-Whitney U = 1620.5, p = 0.153). If the age line was drawn at 70 years, younger patients (<70 years, n = 138, median = 3 days) had significantly shorter postoperative hospital stays than older patients (≥70 years, n = 14, median = 4 days; Mann-Whitney U = 666, p = 0.024).

Patients were asked to rate their current overall QoL on a VAS ranging from 0 (bad) to 100 (good) preoperatively

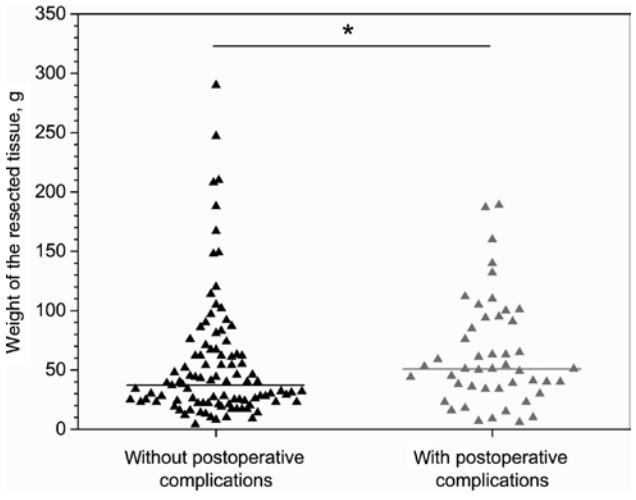

Figure 4: Dot-plot and median of the weight of resected thyroid tissue. Data are grouped by patients showing no postoperative complications (black triangles) and patients with postoperative complications (gray triangles).
Complications included transient postoperative symptomatic hypocalcemia (n = 30), transient vocal cord paralysis (n = 13), secondary hemorrhage (n = 2), and infection and/or scarring (n = 7).

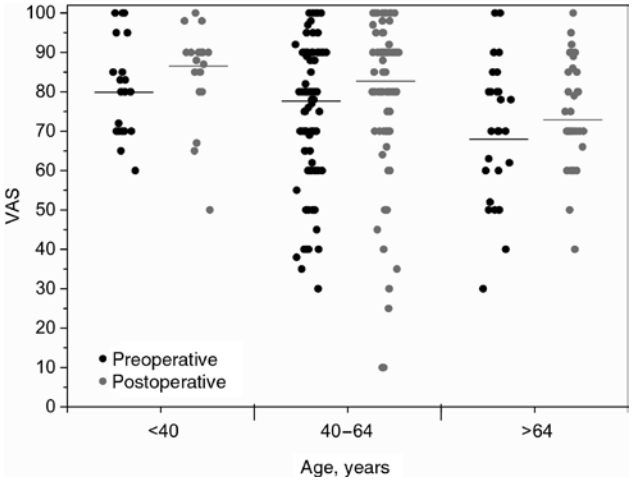

Figure 5: Dot-plot of the results of the QoL question obtained via VAS. Depicted are VAS scores taken preoperatively (black dots) and 1 year after surgery (gray dots) grouped by age (younger than 40 years, between 40 and 64 years, and 65 years and older). Differences between age groups and between preoperative and postoperative VAS are statistically significant.

and 1 year after surgery. Figure 5 depicts the respective results preoperatively (black dots) and 1 year after surgery (gray dots) grouped by age (<40 years, between 40 and 64 years, and 65 years and older). VAS got worse with age by about 10 points. There was a significant effect of age group (Kruskal-Wallis $H = 8.935$, $df = 2$, $p = 0.011$). In addition, VAS significantly increased postoperatively by about 5–10 points in each age group (Wilcoxon signed rank $W = 3560$, $Z = 4.346$, $p < 0.001$).

The median difference between postoperative and preoperative QoL score as measured by the VAS was 9.5 for patients without complications, indicating an overall rise in the QoL, whereas the median difference for patients with complications was 0. This difference between groups was statistically significant (Mann-Whitney $U = 1900$, $p = 0.006$).

Discussion

Surgery of the elderly (65 years and older) will increase up to 50% by 2020 [15]. As the prevalence of thyroid nodules increases with age, and due to the increasing quality of technical imaging devices (e.g. high-resolution ultrasonography), thyroid nodules are often found incidentally [5, 16, 17]. Therefore, endocrinologists and endocrine surgeons are increasingly becoming confronted with the question of thyroid surgery in the elderly. It is assumed that, due to the increased risk of complications in the elderly, the indication for thyroid surgery is provided restrictively and mainly in case of vital compression symptoms, therapy-refractory thyrotoxicosis, and suspected malignancy [18–20].

In our study, the surgery duration for total thyroidectomy was constant across age groups. For hemithyroidectomies, the surgery duration increased over the three age groups. Significant differences for surgery duration were only found for both younger age groups. These results indicate that, at least for patients with indication for hemithyroidectomy, early intervention might be beneficial.

A significant three-way interactive relationship between age, surgery duration, and amount of resected tissue was observed. An increase in any of these variables resulted in an increase in both other variables as well. The fact that the prevalence of goiter increases considerably with age [21] was confirmed by our results, as we saw a significant increase of resected tissue in the elderly, which led to longer operations. Ríos et al. [22] compared thyroid surgery in multinodular goiter in patients ages 30–65 years to patients older than 65 years. The older group had a higher incidence of transient hypoparathyroidism (25% vs. 9%; $p = 0.003$). In both groups, transient RLN injury was detected in 12%. A comparison of 55 patients ages 75 years and older to 683 younger patients was done by Passler et al. [19]. They found a rate of 25.5% of early postoperative complications in the older group compared to 21.8% in the younger group. Transient paralysis of the laryngeal nerve occurred in 6.3% in the older group versus 3.9% in the younger group and hypoparathyroidism in 13.6% versus 14.1% of the patients, respectively. The trend for higher complications in the elderly group was explained by higher rates of recurrent thyroid surgery and retrosternal goiters. In our study, there was no significant difference in age between the groups with and without postoperative complications. However, the findings of both studies regarding the complication rates in older and younger patient groups fit well with our data, somewhat depending on where we draw the age line. Potential differences might be due to our smaller sample size.

Most of the patients in our study were discharged from the hospital 3–4 days after surgery, with age leading to larger amounts of resected tissue, leading to longer hospital stay. Mekel et al. [21] showed a significant longer stay for patients older than 80 years. In their study, 78% of the octogenarians and 94% of the younger control group were discharged within 1 day after thyroid surgery. However, 1.1% of the octogenarian group was readmitted to hospital within the first 30 postoperative days due to symptomatic hypocalcemia. Although the length of stay was longer in our study certainly because of the different national healthcare systems, the same trend for longer treatment of aged patients could be noted. If the age line was drawn at 70 years, older patients had significantly longer hospital stays than the younger patients. This might be due to the presence of comorbidities more often associated with aged patients, for example, pneumological or cardiac risk factors with rates between 50% and 95% [19, 23]. Recent studies have revealed that, when thyroid surgery in the elderly is performed in a well-prepared perioperative setting by experienced surgeons, the mortality rate is negligible [19, 22, 24]. Thus, an individualized preoperative preparation and risk analysis is mandatory to reduce avoidable complications [25].

One of the aims of surgery in general is at least maintaining or ideally improving the QoL, especially in elderly people [23]. Thus, it is important to note that, regardless of age, the overall postoperative QoL as measured with the VAS is significantly better than the preoperative status. A weak point of the present study is the use of a generic VAS for measurement of QoL as opposed to disease-specific QoL. However, VAS can be used as a simple instrument to identify tendencies in the change of the QoL. Across

all three age groups, a decrease in both preoperative and postoperative QoL scores with increasing age is shown. However, as this effect is not significant preoperatively, preoperative QoL might be obscured by other factors not observed in this study, for example, general anxiety because of the impending surgery. Postoperatively, in all age groups, a higher QoL score is given. As socioeconomic factors did not change significantly over all patients, it can be assumed that at least part of this increase in the QoL is due to the successful surgery. These results are in line with the literature where a positive impact of thyroidectomy on the QoL is seen [26, 27]. However, we purport that, for a more in-depth evaluation of postoperative changes of health-related QoL after thyroid surgery, more prospective studies with thyroid-specific questionnaires are required.

We could show that, in the elderly, thyroid surgery can be safely performed without any mortality and very low early postoperative morbidity (e.g. transient hypocalcemia and paralysis of the laryngeal nerve). However, surgery duration for nontoxic multinodular goiter and thyroid resection size are age-dependent factors at least in hemithyroidectomy. As comorbidities increase with age and goiters grow with time, which leads to longer operation time with the possibility of increasing perioperative morbidities, a surgical therapy for multinodular goiters in early lifetime might be discussed, as it has been shown that, in younger patients, perioperative mortality and morbidity is very low [19]. According to our results, this especially holds for patients being 70 years or older. In addition, the probability for the need to perform a total thyroidectomy seems to increase with age, as in both younger groups the ratio between thyroidectomies and hemithyroidectomies is about 50%, whereas in the older groups nearly 80% of all cases are total thyroidectomies. As the probability of complications seems to increases with the amount of resected tissue, and the probability for suffering from permanent hypoparathyroidism is larger after total thyroidectomy, early resection might be beneficial.

Furthermore, an improvement of the QoL can be achieved by surgery, which might additionally support the decision for early surgery. We could only observe a significant increase in the QoL score 1 year after surgery for patients without early postoperative complications. As the amount of complications strongly relates to the amount of resected tissue, and the amount of resected tissue increases with increasing wait for surgery, this could be viewed as additional evidence for the importance of performing thyroid surgery as soon as the indications are met to increase the probability for an increasing QoL after surgery.

Conclusion

Our findings relate well to the known literature regarding age and its effect on surgical outcomes. New findings of this study include the interdependency of age, surgery duration, and amount of resected tissue. In addition, our results suggest that surgical intervention before age 70 years might reduce the risk for complications while simultaneously increasing the QoL irrespective of patient age. These findings might heat up the debate about the high number of thyroid surgeries in Germany compared to the US or to England, as our results support systematic and early surgical intervention at least in patients potentially undergoing hemithyroidectomy. Nevertheless, to further support our findings, more and larger prospective studies in regard to overall outcomes, to the postoperative change of QoL, to long-term complications, and to survival in case of thyroid cancer are needed.

Author Statement

Research funding: Authors state no funding involved. Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals. Ethical approval: The research related to human use complied with all the relevant national regulations and institutional policies and was performed in accordance with the tenets of the Helsinki Declaration and has been approved by the Ethics Commission of the University of Oldenburg (No. 004/2016). No trial registration was needed.

Author Contributions

Navid Tabriz: Data curation; Investigation; Methodology; Project administration; Writing – original draft; Writing – review and editing. Verena Nicole Uslar: Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft; Writing – review and editing. Inga Tabriz: Conceptualization; Data curation; Investigation; Project administration; Writing – review and editing. Dirk Weyhe: Conceptualization; Methodology; Resources; Supervision; Writing – original draft; Writing – review and editing.

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Supplemental Material: The article (DOI: 10.1515/iss-2017-0023) offers reviewer assessments as supplementary material.

Reviewer Assessment **Open Access**

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Reviewers' Comments to Original Submission

Reviewer 1: anonymous

Jun 05, 2017

Reviewer Recommendation Term:	Accept
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Custom Review Questions	**Response**
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	3
Are units and terminology used correctly?	4
Is the number of cases adequate?	4
Are the experimental methods/clinical studies adequate?	4
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	4
Please rate the practical significance.	4
Please rate the accuracy of methods.	3
Please rate the statistical evaluation and quality control.	4
Please rate the appropriateness of the figures and tables.	4
Please rate the appropriateness of the references.	3
Please evaluate the writing style and use of language.	3
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

The question that remains open is why indication to operation was seen in the elderly patient series. Was it local complaints, was it just the size, was it unclear dignity of thyroid?

Reviewer 2: anonymous

Jun 07, 2017

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	76

Custom Review Questions	**Response**
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	5 - High/Yes
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	4
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	3
Are the experimental methods/clinical studies adequate?	4
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	4
Please rate the practical significance.	4
Please rate the accuracy of methods.	5 - High/Yes
Please rate the statistical evaluation and quality control.	5 - High/Yes
Please rate the appropriateness of the figures and tables.	5 - High/Yes
Please rate the appropriateness of the references.	5 - High/Yes
Please evaluate the writing style and use of language.	5 - High/Yes
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:
Good Paper, accepted without changes or corrections, a revision is not necessary.