

# A prospective follow-up study on completion thyroidectomy for well-differentiated thyroid cancer.

## A single-center report



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## A prospective follow-up study on completion thyroidectomy for well-differentiated thyroid cancer. A single-center report

**BACKGROUND:** Completion thyroidectomy (cT) becomes a choice after any type of less than total thyroid surgery, when a "total" would have been indicated on primary intervention if malignancy diagnosis had been available. The study main aim is to define predictive factors of malignancy in the thyroid remnant and to assess the morbidity risk after cT according to the type of initial intervention.

**MATERIAL AND METHOD:** Sixty-three patients on whom cT was performed were finally included with 61 surgeries performed in our department.

**RESULTS:** Our cohort included 55 (87.3%) women and 8 men (12.7%), with a mean age of 48.3 on whom were primary performed 34 lobectomies with isthmusectomies (LwI=53.96%) and 29 subtotal thyroidectomies or hemithyroidectomies (STT=46.03%). Histopathological examination after reintervention detected malignancy in 30.15% of excised thyroid remnants (19 patients), in the majority of these cases microcarcinoma. We found statistically significant correlations between the risk of malignancy in the thyroid remnant and both the primary thyroid tumor multicentricity ( $p=0.001$ ) and its extracapsular and/or vascular invasion ( $p=0.006$ ) respectively. The time span between the two interventions ranged from 3 days to 12 months (mean 63 days). No 30-day mortality occurred in our group of patients. We noted 3 cases of RLN palsy (4.76%) of which one permanent (1.58%) and 12 cases (19.04%) of postoperative hypoparathyroidism, of which two (3.17%) permanent.

**CONCLUSIONS:** Multicentricity and capsular and/or vascular invasion of the initial tumor are factors predictive of malignancy in the remnant thyroid. The rate of postoperative hypoparathyroidism is higher after initial subtotal thyroidectomy.

**KEY WORDS:** Completion thyroidectomy, Incidental parathyroidectomy, Multifocality, Thyroid cancer

## Introduction

Modern treatment strategies for thyroid cancer are multimodal and, apart from surgery, may include radioiodine ablation, hormonal therapy, and occasionally

radiochemotherapy<sup>1</sup>. Extracapsular total thyroidectomy, with or without lymphadenectomy, was widely considered the gold standard surgical approach for almost all well-differentiated thyroid carcinoma (WDTC)<sup>2</sup>.

Completion thyroidectomy (cT) became a surgical option after any type of less than total thyroidectomy, when a total thyroidectomy (TT) would have been indicated on primary intervention had diagnosis of malignancy been<sup>3</sup>. The widespread use of thyroid fine-needle aspiration (FNA) and cytopathology reporting, according to the Bethesda System, have greatly improved the standardization of surgical treatment and significantly reduced the number of both thyroidectomies for benign diseases as well as cTs<sup>4</sup>.

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## ABBREVIATIONS

ATA	American Thyroid Association
cT	completion thyroidectomy
STT	subtotal thyroidectomy
LwI	lobectomy with isthmusectomy
WDTC	well-differentiated thyroid carcinoma
TT	total thyroidectomy
FNA	fine-needle aspiration
CCLA	central compartment lymphadenectomy
RLN	recurrent laryngeal nerve

However, as far as cytopathology is concerned, it remains a “gray zone” of thyroid FNA, which covers atypia of undetermined significance and follicular neoplastic lesions in which cytopathology diagnosis is frequently equivocal<sup>4,5</sup>. In such cases, there is a risk of malignancy of 5-15% for atypia of undetermined significance (Bethesda III category) and 15-30% for follicular neoplasms (Bethesda IV category), respectively<sup>6</sup>. In the case of follicular neoplasms, lobectomy with histopathological examination remains the only means of ascertaining malignancy in terms of capsular and/or vascular invasion and, as such, it is an indicator for cT<sup>4,7</sup>. Apart from this somewhat classical scenario, cT comes into discussion after subtotal thyroidectomies (STT) or hemithyroidectomies, procedures which are still performed by some surgeons following an initial benign diagnosis. our study analyzed the results of ct performed in a single east-european centre with the main aim of defining predictive factors of malignancy for the thyroid remnant in our patient group; furthermore, we assessed the morbidity risk after ct according to the type of initial intervention.

## Methods

### STUDY DESIGN

We retrospectively analyzed the prospectively collected data of thyroid reinterventions performed in our department (Second Surgery Department, University of Medicine and Pharmacy, Tirgu Mures) between 2008 and 2017.

### PATIENTS AND METHOD

Our initial database included 72 patients who underwent a cT after an initial less than total thyroidectomy. We excluded reinterventions performed for a relapsing nodular or multinodular goiter, confirmed by the histopathological report (n=3). Furthermore, cases in

which a type of lymphnode dissection other than central compartment lymphadenectomy (CCLA) was performed (n=4), as well as patients with recurrent nerve injury or hypocalcemia after the first intervention (n=2), were excluded.

Thereafter, 63 patients remained eligible for our study and underwent cT as a result of histopathology reports confirming WDTC after the initial less than total thyroidectomy. Of these patients, 61 (96.82%) underwent surgery in our department; the remaining two patients were referred to us after primary thyroid surgeries performed in other clinics. We prospectively followed clinical data for the patients (demographics, initial diagnosis, type of surgery, and time interval between the two surgeries) as well as histopathology reports after both the initial surgery and reintervention. Data regarding the postoperative evolution and complications were also gathered by contacting patients through mail, e-mail or phone. Our routine preoperative work-up for thyroid surgery included thyroid hormone assessment, ultrasonography and occasionally scintigraphy. Indirect laryngoscopy examination was not performed consistently before the first surgery; however, this was indicated when cT was considered. Postoperative hoarseness or voice modifications were attributed to a recurrent laryngeal nerve (RLN) injury only when vocal cord paralysis was documented through indirect laryngoscopy. Calcium levels below 8 mg/dl after both initial and secondary interventions were considered to indicate postoperative hypoparathyroidism, while the persistence of both RLN palsy symptoms and hypocalcemia beyond 6 months were considered permanent.

The re-thyroidectomy cases were performed by surgeons with different experience in endocrine surgery. Primary interventions consist of three types of less than total thyroidectomy i.e.: STT, hemithyroidectomies, near total thyroidectomy and lobectomy with isthmusectomy (LwI). From our data it was difficult to distinguish between STT and near total thyroidectomy (intended remnant more or less than 2 g), thus both techniques were considered STT. A total resection of the ipsilateral thyroid lobe and isthmus was performed in cases of LwI. Reinterventions were indicated due to the size of the tumor (>1 cm), its multifocality or significant dimensions of thyroid tissue remnants after STT, documented both clinically and via imaging. Central compartment lymph node dissection was performed in patients with node involvement demonstrated prior to reintervention. The study was approved by the Hospital Ethics Committee and all patients involved gave informed consent.

### STATISTICAL ANALYSIS

Statistical analysis was performed using the MedCalc Software, Version 12.5.0.0. Qualitative data were pre-

sented as counts and percentages. The association between qualitative variables was assessed using the Chi-square test or Fisher's exact test. Quantitative data were presented as means and standard deviations (for normally distributed data) or by medians and interquartile ranges (for non-normally distributed data). The level of statistical significance was set at  $p < 0.05$ .

## Results

Patient characteristics, including demographics, types of initial intervention, first and second histopathology and other clinical variables are presented in Table I. We did not encounter significant differences between patients as regards their race (all included patients were Caucasian) and medical history; all patients underwent surgeries in euthyroid status.

Our study involved 55 (87.3%) women and 8 men (12.7%) between the ages of 22 and 85 years, with a mean age of 48.3 years. Sixty-one patients (96.82%) underwent surgery in our center; the remaining two patients had undergone intervention in other hospitals. Indications for the first thyroid surgery were a solitary thyroid nodule in 40 cases (63.49%), including cases with Bethesda III and IV cytopathology results, a multinodular goiter in 22 patients (34.92%) and Graves' disease in 1 patient (1.58%). Only 43 patients (68.25%) from our group had an FNA prior to the first intervention and the types of initial surgeries performed were 34 LwI (53.96%) and 29 STT (46.03%). We decided to perform cT based on cancer multifocality, including multifocal microcarcinoma, in the primary histopatho-

logical specimen in 24 cases (38.09%). Other arguments for re-thyroidectomy were initial tumor dimension above 1 cm (24 cases, 38.09%), extracapsular and/or vascular tumor invasion (9 cases, 14.28%), or significant thyroid remnants after STT (6 cases, 9.52%), documented clinically and on imaging after the primary intervention. In 15 cases (23.80%), a CCLN dissection was performed at the time of cT, with no differences between STT and LwI groups. In the study group of 63 patients, histopathological examination after reintervention detected malignancy in 30.15% of excised thyroid remnants (19 patients). In the majority of these cases we noted microcarcinoma (84.2%); however, we also encountered 3 patients (15.8%) with secondary tumors larger than 1 cm in the remnant thyroid tissue. In the excised thyroid remnants of the remaining 44 patients (69.84%), normal thyroid tissue was found in 29 cases (65.9%), benign lesion in 7 cases (15.9%) and thyroiditis in 8 cases (18.18%). We found significant correlations between the risk of malignancy in the thyroid remnant removed after the second intervention and the primary thyroid tumor multicentricity; out of 24 patients with multicentric primary tumors 13 (54.16%) presented malignancy in the excised thyroid remnant ( $p=0.001$ ) while only 6 malignant remnants (15.38%) were discovered among 39 patients without multicentric primary tumors. A clear tendency toward statistical significance was also found when the correlation between the risk of malignancy at the second intervention and the primary tumor extracapsular and/or vascular invasion was analysed ( $p=0.06$ ). We found no significant trends in terms of cancer risk according to demographics, tumor dimension or stage. The time span between the two surgical interventions ranged from 3 days to 12 months (mean 63 days). We encountered very few cases of reoperation in the first 10-15 days after primary thyroidectomy, therefore we could not analyze comparatively the impact of the timing of reintervention on complication rates. No 30-day mortalities were recorded in our patient group. We noted 3 cases of RLN palsy (4.76%) of which one was permanent (1.58%). Furthermore, we encountered 12 cases (19.04%) of postoperative hypoparathyroidism with calcium levels below 8 mg/dl in the first 48 hours following reintervention; of these, two patients (3.17%) displayed permanent hypoparathyroidism. In addition, we also performed reintervention on one patient from our cohort for an expansive cervical postoperative hematoma. Taking into consideration the type of initial intervention (STT or LwI), we found more cases of postoperative hypoparathyroidism after reinterventions on ipsilateral or bilateral remnants. Nonetheless, the rate of incidental parathyroidectomy was significantly higher after this category of reinterventions (STT) when compared with LwI group. The postoperative complications, grouped according to the type of initial intervention are presented in Table II.

TABLE I - Patient characteristics.

Mean age ( $\pm$ SD) years	48.3 $\pm$ 10.7
Gender, female	55 (87.3%)
Initial surgery	
Subtotal thyroidectomy	29 (46.03%)
Lobectomy with isthmusectomy	34 (53.96%)
First histopathology	
Papillary carcinoma	27 (42.85%)
Papillary microcarcinoma	24 (38.09%)
Follicular carcinoma	5 (7.93%)
Other	7 (11.11%)
Tumor dimensions, mean( $\pm$ SD), mm	25.4 ( $\pm$ 9.6)mm
Multicentricity*	24 (38.09%)
Invasion (extrathyroid, capsular, vascular)#	9 (14.28%)
Second histopathology	
Malignancy*#	19 (30.15%)
Benign	7 (11.11%)
Thyroiditis	8 (12.69%)
Normal	29 (46.03%)
Central compartment lymphadenectomy	15 (23.80%)

\*chi square test ( $p=0.001$ ), # chi square test ( $p=0.06$ )

Table II - Complications according to the type of initial intervention. Statistical significance assessed by chi square test.

Variables	RLN injuries (n=3)	Hypoparathyroidism (n=12)	Incidental parathyroidectomy (parathyroids in specimen)
STT no: 29 (46.03%)	2 (6.89%)	8 (27.58%)	14 (48.27%)
LwI no: 34 (53.96%)	1 (2.94%)	4 (11.76%)	5 (14.70%)
P values	0.59	0.20	0.008

## Discussion

Until recently, previously published guidelines have endorsed extracapsular total thyroidectomy as initial treatment of choice for nearly all WDTC greater than 1 cm<sup>1,2</sup>. However, not all patients with this diagnosis benefited from such an intervention per primam<sup>3,8</sup> due to various reasons: some objective, such as the degree of difficulty or uncertainty associated with the preoperative thyroid cancer diagnosis, while other subjective, such as the patient's refusal of a thyroid FNA or the surgeon's preference for less than total surgeries as they are less risky<sup>9</sup>. In all of these situations, there was a need to perform cT in histologically diagnosed malignant cases<sup>10-12</sup>; reinterventions were also recommended in rare cases of<sup>13</sup> there is a shift in the paradigm concerning intrathyroidal papillar carcinoma or low risk follicular carcinoma which both can be treated with either lobectomy or total thyroidectomy, thus the need of cT in such cases being questioned.

The decision to carry out cT after less than total primary surgery was always controversial<sup>8,14,15</sup>. The arguments for reintervention are numerous and include the presence of significant percentages of malignant lesions in thyroid remnants, a reduced risk of local recurrence and the fact that the procedure allows for appropriate postoperative radioiodine ablation or thyroglobulin level measurement during follow-up<sup>8</sup>. Nonetheless, some authors argue that reintervention should be avoided because it unjustifiably increases the risk of complications<sup>16,17</sup> while others suggest that the decision for reintervention should take into account not only the biological characteristics of the first ipsilateral cancer, but also the risk group stratification<sup>18,19</sup>.

Many authors consider multifocality of the primary tumor a strong argument for reintervention<sup>10,20,21</sup> having a higher likelihood of cancer on the other side<sup>22</sup>. More than one third of our patients exhibited multifocal primary tumors, including a few cases of multicentric microcarcinomas. We considered multifocality as a reason for reoperation, along with the size of the initial tumor, capsular and/or vascular invasion, nodal status on imaging, or whether the size of the thyroid remnants after primary surgery may impede radioiodine ablation. An important argument for reoperation is the incidence of cancer in thyroid remnant tissue. Turlani et al.<sup>23</sup> observed microcarcinomas in the contralateral lobe in

20% of patients with cT, but the incidence reported in literature can reach 77%<sup>24,25</sup>. In our group, we found 19 patients with malignancies in the remnant thyroid tissue, most of which were microcarcinomas. However, what is particular to the study group is that remnant microcarcinomas were found on the ipsilateral thyroid tissue in 16 cases, which we consider an important argument for avoiding STT or near total thyroidectomy. Similar to the findings of other studies<sup>8,18,19,23</sup> we report significant correlations between the presence of cancer foci in the remnant tissue and multicentricity; as regards the correlation between capsular or vascular invasion of the primary tumor and malignancy risk, the level of statistical significance would have been probably reached in the case of an extended lot of patients.

Not all of our patients benefited from preoperative FNA and cytological diagnosis, particularly those who underwent initial surgery in the early time period covered by this study. There are numerous reasons for this, ranging from difficulties in accessing the procedure to patient refusal or the intervention choice of certain surgeons. This became relevant in the types of primary surgeries performed in the study group. Indeed, apart from diagnostic LwI, most often performed in patients with a solitary nodule together with FNA and preoperative cytological examination, our patient group comprised a significant number of STT, generally performed in cases of multinodular goiters. In these cases, reinterventions were certainly more laborious and have a higher risk for inadvertent parathyroidectomy, as shown also by others<sup>26,27</sup>. Several papers, in particular those performed more than a decade ago<sup>28,29</sup> recommend reintervention either within the first 10 days or at 3 months after primary surgery. However, recent studies report that the timing of reintervention has no impact on the likelihood of complications<sup>8,30,31</sup>. We were unable to analyze these aspects statistically since the majority of our patients underwent reinterventions between 30 and 60 days after primary thyroidectomy, with few patients undergoing surgery in the first 10 days after primary intervention. Comparing the two types of primary interventions performed in the study group, namely STT and LwI, we found no significant differences after reinterventions in terms of RLN palsy frequency, although the only permanent paralysis occurred after a reoperation performed for significant bilateral thyroid remnants. As regards postoperative hypoparathyroidism, even if statistical significance was not reached,

patients with reinterventions after less than total primary operations developed more frequently this complication. Nonetheless, we encountered significantly more cases with inadvertent parathyroidectomy in patients with initial subtotal surgery and, as expected, in cases where a CCLN dissection was performed at the time of cT. A compromise in these risky situations of reintervention for bilateral thyroid remnants would be ablation by radioactive iodine. On the other hand, it should be noted that radioactive ablation of a large remnant tissue requires large and repeated doses and such treatments have well-established risks including leukemia, medullary aplasia and pulmonary fibrosis<sup>32</sup>. Our rate of complications after thyroid reinterventions is close to the upper limit reported in the literature<sup>1,8,11,24</sup>. This is likely as a result of both the number of cT procedures performed after subtotal surgeries, commonly practiced in our service in the first period of the study, and the time interval between the initial surgery and cT.

Our study has certain limitations which restrain us to draw firm conclusions: it is a small prospective followed-up study biased in terms of the heterogeneous type of primary surgery and different experience of operating surgeons. As others we noted that multicentricity and capsular and/or vascular invasion of the initial tumor are factors predictive of malignancy in the remnant thyroid. The rate of major complications, primarily of hypoparathyroidism, is higher in cases of reinterventions after subtotal surgery, particularly bilateral surgeries. However, the study emphasizes few health system deficiencies in our country; in this respect we call for the standardization of therapeutic protocols under the view of recently published guidelines, the centralization of these difficult oncologic cases in surgical excellence centers and their referral to high-volume endocrine surgeons.

## Conclusions

Multicentricity and capsular and/or vascular invasion of the initial tumor are factors predictive of malignancy in the remnant thyroid. The rate of postoperative hypoparathyroidism is higher after initial subtotal thyroidectomy.

## Riassunto

**BACKGROUND:** La tiroidectomia di completamento (cT) è diventata un'opzione chirurgica dopo qualsiasi tipo di tiroidectomia non totale, quando una tiroidectomia totale (TT) sarebbe stata consigliata se la diagnosi di tumore maligno fosse stata disponibile prima dell'intervento. Lo scopo del nostro studio è quello di definire i fattori predittivi di tumori maligni nel tessuto tiroideo residuo e di valutare i rischi di morbidità dopo una tiroidectomia di completamento in base al tipo di intervento iniziale.

**MATERIALI E METODI:** Sessantatre pazienti, su cui è stata eseguita una tiroidectomia di completamento, sono stati infine inclusi nel nostro studio, con 61 interventi eseguiti nel nostro dipartimento.

**RISULTATI:** Il nostro studio di coorte include 55 donne (87.3%) ed 8 uomini (12.7%), con un'età media di 48.3 anni, su cui sono state eseguite 34 lobectomie con istmectomie (53.96%) e 29 tiroidectomie subtotali o emi-tiroidectomie (46.03%). L'esame istopatologico dopo il reintervento ha rivelato presenza di tumori maligni del tessuto tiroideo rimanente 30.15% dei casi (19 pazienti), rivelandosi essere microcarcinoma nella maggior parte dei casi. Abbiamo riscontrato correlazioni statisticamente significative tra il rischio di tumori maligni nel tessuto tiroideo residuo e la multicentricità del tumore tiroideo primario ( $p=0.001$ ) e l'invasione extracapsulare e/o vascolare ( $p=0.006$ ). Il lasso di tempo trascorso tra i due interventi si estende dai 3 giorni ai 12 mesi (in media 63 giorni). Nel nostro gruppo di pazienti non c'è stata mortalità a 30 giorni. Abbiamo notato 3 casi di paralisi del NRL (4.76%) di cui uno permanente (1.58%), e 12 casi (19.04%) di ipoparatiroidismo postoperatorio, di cui due permanenti (3.17%).

**CONCLUSIONI:** La multicentricità e l'invasione capsulare e/o vascolare del tumore iniziale sono entrambi fattori predittivi di tumori maligni nel tessuto tiroideo residuo. Il tasso di ipoparatiroidismo postoperatorio è più alto dopo un'iniziale tiroidectomia subtotale.

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## Commento e Commentary

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*Total or almost total thyroidectomy is the treatment of choice in well-differentiated thyroid cancer, which has been shown to reduce recurrence and mortality, promoting the efficacy of RAI therapy and monitoring measurements of thyroglobulin for recurrence. The intervention should be performed with a low complication rate, and the prognosis is excellent for most patients with differentiated thyroid carcinoma.*

*The American thyroid association has recently reviewed the guidelines for the management of patients with thyroid nodules and differentiated thyroid carcinoma, published in 2009 and 2012 and recommended only two surgical procedures: Total or almost total thyroidectomy and thyroid lobectomy (1).*

*The lobectomy plus histomectomy (Hemithyroidectomy) in the context of thyroid carcinoma can be diagnostic or therapeutic<sup>2</sup>): definitive diagnosis in case of single lesion with FNAB for follicular neoplasia; therapeutic in low-risk papillary or follicular carcinoma.*

*Subtotal thyroidectomy should not be used in thyroid carcinoma because of the high risk of residues and / or recurrence of the thyroid residue and the high rate of complications in cases of needed reoperation. (3)*

*A.A. evaluated the risk of complications after completion of thyroidectomy in patients with differentiated thyroid carcinoma who underwent initial surgery with less extensive procedures compared to total thyroidectomy. The study involved 63 patients, 29 operated with subtotal thyroidectomy and 34 with lobectomy plus histomectomy.*

*At the final histopathological diagnosis 19 of these (30%) had residual or recurrent carcinoma, with an overall complication rate of 23.8%, but in 29 patients undergoing subtotal thyroidectomy as a first intervention, the overall complication rate was 34% and in 14 of 29 patients, incidental parathyroidectomies occurred.*

*The study of AA, although limited by the low volume of patients enrolled, has the value of witnessing a well-documented and structured experience in Eastern countries that confirms what has become the standard of care in most endocrine centers and endorses the recommendations proposed by multidisciplinary guidelines in the management of thyroid cancer.*

\* \* \*

*La tiroidectomia totale o quasi totale è il trattamento di scelta nel cancro tiroideo ben differenziato, che si è dimostrato in grado di ridurre recidive e mortalità, favorendo l'efficacia della terapia RAI e le misurazioni di sorveglianza della tireoglobulina per monitorare la recidiva. L'intervento deve essere eseguita con un basso tasso di complicanze, e la prognosi è eccellente per la maggior parte dei pazienti con carcinoma tiroideo differenziato.*

*L'associazione americana per la tiroide ha recentemente rivisto le linee guida per la gestione dei pazienti con noduli tiroidei e carcinoma tiroideo differenziato, pubblicate nel 2009 e 2012 e ha raccomandato solo due procedure chirurgiche: Tiroidectomia totale o quasi totale e Lobectomia tiroidea (1).*

*La lobectomia più istinectomia (Hemithyroidectomy) nel contesto del carcinoma tiroideo può essere diagnostica o terapeutica (2): diagnostica definitiva in caso di lesione unica con FNAB per neoplasia follicolare; terapeutica nel carcinoma papillare o follicolare a basso rischio.*

*Non deve essere utilizzata la tiroidectomia subtotale nel carcinoma tiroideo per l'alto rischio di residui e / o di recidiva nel residuo tiroideo e l'alto tasso di complicanze in casi di necessità di reintervento. (3)*

*Gli A.A. hanno valutato il rischio di complicanze dopo la tiroidectomia di completamento in pazienti con carcinoma differenziato della tiroide sottoposti a intervento chirurgico iniziale con procedure meno estese rispetto alla tiroidectomia totale. Lo studio ha riguardato 63 pazienti, 29 operati con tiroidectomia subtotale e 34 con lobectomia più istinectomia.*

*Alla diagnosi istopatologica finale 19 di questi (30%) presentavano carcinoma residuo o recidivo, con tasso globale di complicanze dei 23,8%, ma nei 29 pazienti sottoposti a tiroidectomia subtotale come primo intervento, il tasso di complicanze complessive era del 34% e in 14 pazienti su 29 si sono verificate paratiroidectomie incidentali.*

*Lo studio degli AA, anche se limitato dal basso volume di pazienti arruolati, ha il valore di testimonianza di un'esperienza ben documentata e strutturata in un paese orientale che conferma quello che è diventato lo standard di cura nella maggior parte dei centri endocrini e approva le raccomandazioni proposte da linee guida multidisciplinari nella gestione del cancro alla tiroide.*

## References

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