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ORIGINAL ARTICLE

Thyroid surgery during coronavirus-19 pandemic phases I, II and III: lessons learned in China, South Korea, Iran and Italy

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Abstract

Objective We compared demographic and clinic-pathological variables related to the number of surgeries for thyroid conditions or for cancer, morbidity, and fine needle aspiration (FNA) practices among Covid19 pandemic phases I, II, III and the same seasonal periods in 2019.

Methods The prospective database of the Division of Thyroid Surgery, China-Japan Union Hospital of Jilin University, Changchun, China was used for this study. Covid19 emergency levels were stratified according to the World Health Organization: phase I (January 25–February 25, 2020), phase II (February 26–March 19), phase III (March 20–April 20).

Results There were fewer outpatient FNAs and surgeries in 2020 than in 2019. There were no thyroid surgeries during phase I. There were also fewer surgeries for cancer with a significant reduction of advanced stage cancer treatments, mainly stage T1b N1a in phase II and T3bN1b in phase III. Operative times and postoperative stays were significantly shorter during the pandemic compared to our institutional baseline. In phase III, vocal cord paralysis (VCP) increased to 4.3% of our baseline numbers ($P=0.001$). There were no cases of Covid19-related complications during the perioperative period. No patients required re-admission to the hospital.

Conclusion The Covid19 outbreak reduced thyroid surgery patient volumes. The decrease of Covid19 emergency plans contributed to unexpected outcomes (reduction of early stage cancer treatment, decreased operative times and hospital stays, increased VCP rate).

Keywords Thyroid · Surgery · Covid19 · SARS-CoV-2 · Thyroidectomy · Cancer · Morbidity · Surgical practice · Recurrent laryngeal nerve palsy · Italy · China · Iran · South Korea

Introduction

The historical moment that we are experiencing because of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic has forced a reformulation of the rules for the delivery of health services in surgical departments [1–3].

As the number of cases continued to rise, a rapidly increasing number of hospitals were designated by Governments for the exclusive admission of patients with SARS-CoV-2 (Covid19) to contain cross-infection [4–13]. Politicians recommended the limitation of certain scheduled clinical activities [14–21] (Supplementary File 1).

The expected effect of the constraint on surgical planning due to the need to limit hospital access was to preserve only essential surgical procedures, freezing waiting times for surgeries for conditions without developmental risk and freeing professionals and patient care facilities for SARS-CoV-2 patients [5, 7, 10].

In these unprecedented circumstances, Chinese surgeons first, promptly, published strategic proposals for the treatment of neoplasms during the Covid19 epidemic [6, 7, 9, 10, 13]. Surgical societies developed practical recommendations for elective surgery calibrated on the basis of the scientific literature (Supplementary Files 2, 3) (Supplemenatry Table 1) [2, 3, 15, 22–29].

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The impact of the SARS-CoV-2 endemic on thyroid surgery, is yet to be investigated [16]. The objectives of the current report were:

A. Compare thyroid surgery patient volumes, operations for cancer, morbidity, and trends for fine needle aspiration (FNA) practices, between the Covid19 outbreak and the same seasonal period during 2019.
B. Evaluate changes during the different phases of the Covid19 epidemic emergency levels [30–33].
C. Qualitatively compare opinions from thyroid surgery experts in those countries that were most severely affected in the first stage of the spread of the infection—China, the Republic of Korea, the Islamic Republic of Iran and Italy [30]—(Supplementary Fig. 1).

Materials and methods

Study design and data sources

Retrospective analysis linked to the Institutional prospective web-based registry platform.

Study approval and ethics statement

No ethical license is required according to the Science Ethics Committee. Written informed consent was waived. The study complied with the Declaration of Helsinki.

Study patients

Case patients were recruited from the population of patients who were consecutively treated at the Division of Thyroid Surgery of the China-Japan Union Hospital of Jilin University (Changchun, China).

Hospital category and setting

The Division of Thyroid Surgery is a high-volume University-affiliated teaching hospital that provides health care to the entire Changchun. Changchun has a total population of 7,674,439 [31].

Time frame for analysis

To reflect the effect of the Covid19 outbreak, patients who visited the hospital from January 25 to April 20, 2020 were included. Data from the same temporal period of the previous year (January 25–April 20, 2019) were collected for comparison.

Definitions

Covid19 This is a positive-sense single-stranded RNA virus, infecting humans [4, 30].

National and institutional policies Supplementary File 2 describes Chinese policies for thyroid surgery practice.

Classification of pandemic Covid19 phases In China, the public health emergency was stratified into three pandemic phases:

- *Phase I* From January 25 to February 25, 2020 (time at which the Covid19 alert level was raised to the highest level).
- *Phase II* February 26 to March 19, 2020.
- *Phase III* March 20—April 20, 2020 [30–33] (Supplementary Fig. 2).

Outpatient clinic, ultrasound examination and FNA

Detail are offered in Supplementary File 2. FNA was offered according to the guidelines [34].

Pre-operative screen test Covid19

High resolution computerized tomography (CT) scan initially was proposed. The patient was required to be ambulatory 24–48 h before hospitalization. Subsequently, a swab test for detection of Covid19 was substituted for the CT scan [4, 5]. Surgery was postponed if the patient tested positive (Supplementary File 2).

Laryngeal examination

Pre-operative video laryngeal examination was scheduled after the SARS-CoV-2 screening test [35].

Team model and procedures

All procedures across phases were performed by a team comprised of the same surgeons. Intraoperative neural monitoring (IONM), antibiotic prophylaxis and early parathyroid hormone (PTH) determinations (reference value is 15–65 pg/ml) were offered preoperatively, and postoperatively across subsequent phases.

Multidisciplinary oncological meetings

Telemedicine had a fundamental role in screening, follow-up and consultation during the SARS-CoV-2 periods of forced social distancing (Supplementary File 2).

Study outcomes

Data extracted from patients' notes included demographic, clinical, and pathologic variables. Surgical procedures were considered representative markers to evaluate patient volumes. The number of outpatient visits was collected as was the number of FNAs performed. Postoperative complications were recorded [21].

Statistical analysis

Continuous variables were expressed as mean (standard deviation), and categorical variables were expressed as percentage (frequency). Continuous variables were analyzed by t tests or analysis of variance, and categorical variables were analyzed by χ^2 tests or F exact tests. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 22.0 SPSS, Chicago, USA, windows version).

Results

Baseline characteristics of patients

Table 1 compares baseline demographic and clinical-pathological characteristics of patients treated during Covid19 phases I, II, and III with our institutional baseline data from 2019. All patients had an ASA score I or II.

Comparison of pandemic phase I vs. 2019

There were 549 outpatients, a decrease of 93.3% compared to the same period in 2019. FNAs decreased by 99.7% ($P = 0.000$) (Fig. 1 and Supplementary Table 2). There were no newly diagnosed thyroid malignancies and no surgeries.

Phase II vs. 2019

There was a 59% reduction in the number of outpatients ($n = 3505$, Fig. 1), and a reduction of 62.9% in FNAs performed ($n = 195$, $P = 0.271$). One hundred patients (51.3%) were diagnosed as malignant, a 3% decrease ($P = 0.502$). There were 117 inpatients (56.3% reduction). The mean surgical time was reduced to 58.3 ± 11.26 min ($P = 0.000$). The postoperative hospital stay declined to 2.8 ± 0.9 ($P = 0.000$) (Table 1). Mean tumor diameter was 3.92 cm, a 14% decrease ($P = 0.000$). There were 107 malignant thyroidectomies (91.5% of the inpatients), a 2.5% decrease (mainly stage T1bN1a) (Table 2) ($P = 0.015$). There were 17 combined thyroiditis patients (15.9% of inpatients), a 1.2% decrease ($P = 0.878$). There was one endoscopic thyroidectomy (0.9% of inpatients, a 2.8% decrease, ($P = 0.184$); 51 total thyroidectomies (47.7% of inpatients, a 0.5% increase, $P = 0.939$); 106 central lymph node dissections (99.1% of inpatients, a 1.1% increase, $P = 0.674$); and 13 lateral lymph node dissections (12.1% of inpatients, a 0.6% decrease, $P = 0.886$). Postoperative vocal cord paralysis decreased by 1.8% ($P = 0.568$). In patients undergoing bilateral thyroidectomy ($n = 51$), postoperative PTH decreased by 41.2% compared to 49.9% in 2019 ($P = 0.409$). There was a 7% decrease in postoperative hypoparathyroidism ($n = 8$, $P = 0.408$). There were no cases of Covid19 pneumonia or related complications in the perioperative period. No patients required intensive care treatment. No patients were re-admitted to the hospital.

Phase III vs. 2019

There was an 18.3% reduction in the number of outpatients treated ($n = 8467$, Fig. 1), and a reduction in inpatients ($n = 211$). FNAs decreased by 30.1% ($n = 408$, $P = 0.013$). There were 225 newly diagnosed malignant patients (55.1% of inpatients), a 2.3% decrease (Supplementary Table 2). Mean surgical time was reduced to 55.3 ± 13.32 min ($P = 0.000$). Postoperative hospitalization was reduced to 3.3 ± 1.0 days ($P = 0.008$). The mean tumor diameter was 3.92 cm, a 16.1% decrease ($P = 0.000$). There were 186 thyroidectomies for cancer (88.2% of inpatients, a 4.8% decrease) (Table 1). There were 27 combined thyroiditis patients (14.5% of inpatients, a 2.3% decrease, $P = 0.521$); six endoscopic thyroidectomies (2.8% of inpatients, a 0.8% increase, $P = 0.564$); 83 total thyroidectomies (44.6% of inpatients, a 4.5% decrease, $P = 0.394$). 182 central lymph node dissections (97.8% of inpatients, a 1.4% decrease, $P = 0.223$); and 20 lateral lymph node dissections (10.8% of inpatients, a 0.7% decrease, $P = 0.064$). There was a significant reduction of T3bN1b PTC treated (Table 2). Thirteen inpatients (4.3%) had vocal cord paralysis, a 4.1% increase ($P = 0.000$). In patients undergoing bilateral thyroidectomy ($n = 83$), postoperative PTH decreased by 40.3% compared with 7.9% during the same period in 2019. Postoperative hypoparathyroidism was found in 11 inpatients (13.4%), a 1.9% decrease. There were no cases of Covid19-related complications in the perioperative period. No patients required intensive care treatment, and none were re-admitted to the hospital.

Table 1 Baseline demographic and clinics-pathological characteristics of patients treated during Covid19 phase I, II, III and 2019 same period time

	1.25–2.25			2.26–3.20			3.21–4.20		
	2020	2019	P1	2020	2019	P2	2020	2019	P3
Number	0	163	–	117	268	–	211	300	–
Age (years)	–	42.5 ± 10.8	–	42.6 ± 10.9	43.0 ± 9.6	0.719	43.2 ± 12.5	42.0 ± 10.7	0.245
Gender (M/F)	–	36/127	–	24/93	50/218	0.675	33/178	62/238	0.167
ASA grade									
I	–	135 (82.8)	–	106 (90.6)	227 (84.7)	0.079	183 (86.7)	246 (82.0)	0.094
II	–	28 (17.2)		11 (9.4)	41 (15.3)		28 (13.3)	54 (18.0)	
Mean operating time (min)	–	53.8 ± 10.23	–	58.3 ± 11.26	63.2 ± 13.21	0.000**	55.3 ± 13.32	60.9 ± 15.11	0.000**
Postoperative hospital stay time (D)	–	3.5 ± 1.1	–	2.8 ± 0.9	3.2 ± 1.0	0.000**	3.3 ± 1.0	3.7 ± 2.0	0.008**
Endoscopic/robot thyroidectomy (*n*, %)	–	9 (5.5)	–	1 (0.9)	10 (3.7)	0.184	6 (2.8)	6 (2.0)	0.564
Open thyroidectomy (*n*, %)	–	154 (94.5)		116 (99.1)	258 (96.3)		205 (97.2)	294 (98.0)	
Benign (*n*, %)	–	9 (5.5)	–	10 (8.5)	16 (6.0)	0.380	25 (11.8)	21 (7.0)	0.083
Unilateral	–	7	–	7 (70.0)	12 (75.0)	0.780	18 (72.0)	17 (81.0)	0.514
Bilateral	–	2	–	3 (30.0)	4 (25.0)		7 (28.0)	4 (19.0)	
Maximum nodule diameter (cm)	–	4.73 ± 1.81	–	3.92 ± 1.39	4.60 ± 1.50	0.000**	3.92 ± 1.42	4.67 ± 1.94	0.000**
Malignant (*n*, %)	–	154 (94.5)	–	107 (91.5)	252 (94.0)	0.380	186 (88.2)	279 (93.0)	0.083
Unilateral	–	72	–	56 (52.3)	133 (52.8)	0.939	103 (55.4)	142 (50.9)	0.394
Bilateral	–	82	–	51 (47.7)	119 (47.2)		83 (44.6)	137 (49.1)	
PTH (preoperative) (pg/ml)	–	51.99 ± 23.5	–	44.44 ± 19.47	48.75 ± 17.13	0.030*	51.47 ± 16.4	52.71 ± 21.3	0.478
PTH (30 min after operation) (pg/ml)	–	23.98 ± 18.33	–	26.11 ± 22.38	24.42 ± 21.77	0.488	30.75 ± 25.53	27.33 ± 22.11	0.107
Reduce the ratio (%)	–	53.9		41.2	49.9	0.409	40.2	48.1	0.559
Hypoparathyroidism (*n*, %)	–	19 (23.2)	–	8 (15.7)	27 (22.7)	0.408	11 (13.4)	21 (15.3)	0.844
Transient/persistent	–	15/4	–	–	25/2	–	–	18/3	–
Combined thyroiditis (*n*, %)	–	38 (24.7)	–	17 (15.9)	43 (17.1)	0.878	27 (14.5)	47 (16.8)	0.521
Central lymph node dissection (*n*, %)	–	154 (100)	–	106 (99.1)	247 (98.0)	0.674	182 (97.8)	277 (99.2)	0.223
Lateral lymph node dissection (*n*, %)	–	23 (14.9)	–	13 (12.1)	32 (12.7)	0.886	20 (10.8)	32 (11.5)	0.064
Postoperative vocal cord paralysis (*n*, %)	–	12 (4.9)	–	3 (1.8%)	11 (2.8)	0.568	13 (4.3)	1 (0.2)	0.000**
Transient/persistent	–	12/0	–	–	11/0	–	–	1/0	–

*$P < 0.05$, **$P < 0.01$

Discussion

This is the first report to review the impact of Covid19 on thyroid surgery specialists' practice stratified into the three pandemic phases. In the case of subsequent waves of SARS-CoV-2 pandemic, we may use our results as a clinical guide.

In phase I, we recorded a 93.3% decrease in outpatients, a 99.7% reduction in FNAs, no newly diagnosed thyroid malignancies and no surgeries. Recent research applying a statistical model to a series of real data collected worldwide estimated that in March 2020 more than 28 million surgeries may have been canceled due to the Covid19 pandemic [29]. The research was based on a series of interviews with surgical experts in 190 countries who were asked what interventions would be postponed during the peak of the pandemic [29]. It appeared that on average, 72% of non-essential interventions would be canceled, corresponding to a total of 28,404,603 operations globally. Of the total, 90% of the canceled operations would be linked to a benign pathology, 8.2% would be represented by surgery for a tumor and 1.6% by obstetric operations such as an elective cesarean section. The major limitation of the study is that it is presumptive, i.e. based on estimates by respondents in countries where the pandemic had just arrived or had not yet reached its peak [29].

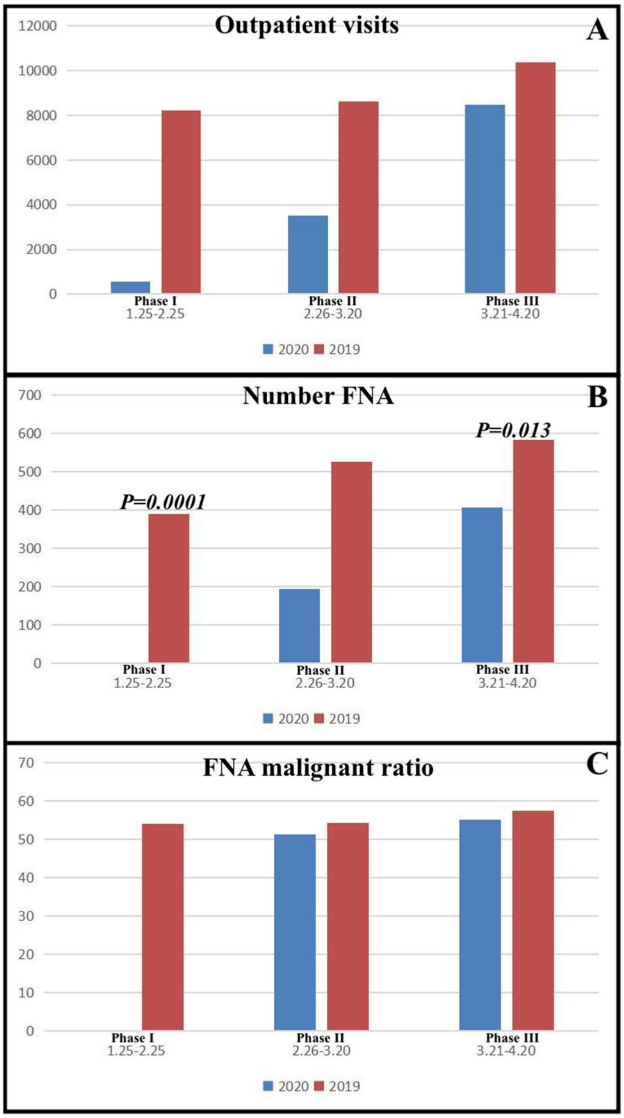

Fig. 1 Graphs showing comparison of **a** the number of outpatients visits, **b** number of FNA and **c** FNA proportion of malignancy, at the Division of Thyroid Surgery of the China–Japan Union Hospital of Jilin University (Changchun, People's Republic of China), during Covid19 emergency phases I, II, III and year 2019

Operative volume

Our results are in accordance with national policies and endocrine surgical society guidelines recommending postponement of non-emergent surgery (Supplementary Table 1, Supplementary File 2). As surgical specialists, thyroid surgeons perform routinely a high volume of scheduled surgeries. Comparing the overall trend of thyroid surgical procedures (scheduled, hospitalization, inpatient), there was a decline between 2019 and 2020 (Fig. 1). This change was reassessed following the completion of pandemic phase III. There also was a significant decrease in operative and postoperative time.

Thyroid cancer

The prevalence of interventions performed for cancer was similar to that for all surgical activity: the reduction includes the number of thyroidectomies for cancer, outpatient clinic visit, and the number and proportion of FNAs for malignancy. Interestingly, compared to 2019, there was a significant reduction of stage T1b N1a in phase II and T3bN1b in phase III (Table 2).The effect of the Covid19 lockdown on outcomes for untreated or under-diagnosed thyroid cancer patients is still unknown. De facto, most thyroid cancers have excellent prognosis [34].

ASA score and surgical complexity

The proportion of ASA score I patients in 2020 was significantly higher compared with the same period in 2019, probably due to Anesthesiologist selection bias. There were no significant differences in complexity of surgery with similar patient volumes for endoscopies, lobectomies, and lymph node dissections.

Ensuring safe surgery

Surgeries were performed maintaining the safety of healthcare personnel and patients. There were no cases of Covid19-related complications in the perioperative period, and no patients required intensive care treatment or re-admission to the hospital. Intraoperative neural monitoring (IONM) was offered. In phase II, postoperative VCP decreased by 1.8%. In phase III, VCP increased significantly to 4.3% of baseline ($P=0.001$). The data are in some ways unexpected. They may reflect the selection criteria for cancer surgery (Table 2). Furthermore, during the SARS-CoV-2 outbreak, the treated patients were more likely to experience a decrease in serum PTH. In phase II patients undergoing bilateral thyroidectomy, postoperative PTH decreased by 41.2%, vs. 8.7% in 2019. In phase III patients undergoing bilateral thyroidectomy, postoperative PTH decreased by 40.3% compared with 7.9% in 2019.

An international multicenter study conducted in 235 hospitals in 24 countries included all patients undergoing surgery with confirmed SARS-CoV-2 infections within seven days before or 30 days after surgery [27]. In total there were 1128 patients who underwent surgery between 1 January and 31 March 2020, of which 835 (74.0%) underwent an emergency intervention and 280 (24.8%) had an elective surgery. SARS-CoV-2 infection was confirmed before surgery in 294 patients (26.1%). The 30-day mortality rate was 23.8% (268 out of 1128).

Table 2 Postoperative pathology of patients during Covid19 phase I, II, III and 2019 same period time

	1.25–2.25			2.26–3.20			3.21–4.20		
	2020	2019 *n* (%)	P1	2020 *n* (%)	2019 *n* (%)	P2	2020 *n* (%)	2019 *n* (%)	P3
Number	0	163	–	117	268	–	211	300	–
Benign	–	9 (5.5)	–	10 (8.5)	16 (6.0)	0.380	25 (11.8)	21 (7.0)	0.083
Malignant	–	154 (94.5)		107 (91.5)	252 (94.0)		186 (88.2)	279 (93.0)	
T1a	–	80 (49.1)	–	72 (61.5)	145 (54.1)	0.182	114 (54.0)	150 (50.0)	0.429
N0	–	50 (30.7)	–	43 (36.8)	91 (34.0)	0.642	82 (38.9)	91 (30.3)	0.047
N1a	–	28 (17.2)	–	28 (23.9)	47 (17.5)	0.162	26 (12.3)	50 (16.7)	0.207
N1b	–	2(1.2)	–	1 (0.9)	7 (2.6)	0.444	6 (2.8)	9 (3.0)	0.395
T1b	–	25 (15.3)	–	5 (4.3)	34 (12.7)	0.010*	30 (14.2)	45 (15.0)	0.899
N0	–	5 (3.1)	–	1 (0.9)	11 (4.1)	0.116	10 (4.7)	17 (5.7)	0.918
N1a	–	11 (6.7)	–	1 (0.9)	17 (6.3)	0.017*	11 (5.2)	20 (6.7)	0.575
N1b	–	9 (5.5)	–	3 (2.6)	6 (2.2)	0.846	9 (4.3)	8 (2.7)	0.329
T2	–	2 (1.2)	–	3 (2.6)	8 (3.0)	0.820	10 (4.7)	8 (2.7)	0.230
N0	–	0 (0)	–	0 (0)	2 (0.7)	–	4 (1.9)	4 (1.3)	0.723
N1a	–	2 (1.2)	–	2 (1.7)	5 (1.9)	0.916	3 (1.4)	1 (0.3)	0.311
N1b	–	0 (0)	–	1 (0.9)	1 (0.4)	0.516	3 (1.4)	3 (1.0)	0.695
T3a	–	1 (0.6)	–	2 (1.7)	0 (0)	–	0 (0)	3 (1.0)	–
N0	–	1 (0.6)	–	1(0.9)	0	–	0	1(0.3)	–
N1a	–	0 (0)	–	0(0)	0	–	0	2(0.7)	–
N1b	–	0(0)	–	1(0.9)	0	–	0	0	–
T3b	–	45 (27.6)	–	24 (20.5)	63 (23.5)	0.597	32 (15.2)	68 (22.7)	0.041*
N0	–	19 (11.7)	–	14 (12.0)	23 (8.6)	0.347	20 (9.5)	42 (14.0)	0.132
N1a	–	16 (9.8)	–	7 (6.0)	25 (9.3)	0.321	11 (5.2)	18 (6.0)	0.847
N1b	–	10 (6.1)	–	3 (2.6)	15 (5.6)	0.294	1 (0.5)	8 (2.7)	0.088
T4a	–	1 (0.6)	–	1 (0.9)	3 (1.1)	0.814	0 (0)	4 (1.3)	–
N0	–	0 (0)	–	0 (0)	0 (0)	–	0	1 (0.3)	–
N1a	–	1 (0.6)	–	0 (0)	1 (0.4)	–	0	2 (0.7)	–
N1b	–	0 (0)	–	1 (0.9)	2 (0.7)	0.911	0	1 (0.3)	–

Lung complications occurred in 51.2% of patients. The authors conclude that postoperative pulmonary complications occur in half of patients with a perioperative SARS-CoV-2 infection and are associated with high mortality [27].

Republic of Korea, Islamic Republic of Iran and Italy

Associated information from geographical regions that have been severely affected by the SARS-CoV-2 pandemic is available in Supplementary File 5. This Supplementary reports international experience with thyroid surgery during various points of the pandemic. While the time points (phases) are benchmarked using WHO dates and emergency level, there is inevitable variation in Covid19 impact depending on local surge factors. Care patterns, allowances for or restrictions on elective surgery are all based on local (hospital-level/surgeon-level) decision making.

Limitations of the study

As thyroid surgery specialists, we are often not confronted with patients diagnosed with Covid19.

Currently, there is no clear evidence that the SARS-CoV-2 has direct impact on any form of thyroid disease [16].

The present work is based on the currently available evidence concerning surgical and oncological management in the course of the SARS-CoV-2 epidemic. Recommendations may be subject to subsequent updates in case of new and relevant scientific findings(Supplementary Files 1, 2, 3, 4) (Supplemenatry Table 1).

We have presented data from academic hospitals dedicated to thyroid surgery. Data from hospitals with low volumes of thyroid surgery are missing from this report.

The data need to be further investigated. However, it does not seem that the reduced number of thyroid surgeries depends only on a decreased accessibility to hospitals because at the same time there has been an increased number of patients refusing hospitalization for the surgery.

At present, we cannot provide definitive numbers about endocrinology clinics or radioiodine treatment volumes. Furthermore, in view of the limited resources, alternative treatments should be considered. The present report didn't determine whether the number of alterative treatments (for example, alcohol or radio-frequency thyroid nodule ablations) were reduced.

The type of delivery setting for thyroid surgery was not analyzed. The hypothesis is that the reduction of thyroid surgery volume is less marked for day surgery and for outpatient surgery compared to ordinary hospitalization.

Some patients included in this report (phase III) had a short follow-up interval and hence late presentation of complications may not be accurately reported.

The impact on the thyroid surgery trainee was not specifically evaluated in the present report.

Finally, details about hospital budgets have not been calculated.

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Author contributions HS, DZ, GD: conceptualization, writing, final review and final approval; HS, DZ, GD: data analysis, drafting the article and final approval; all authors: conceptualization, data collection, critical revision for important intellectual content and final approval. This publication has been approved by all co-authors.

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Data availability All data and material are available on reasonable request. The work described has not been published before; it is not under consideration for publication anywhere else.

Compliance with ethical standards

Conflict of interest All Authors report having no relationships that could be construed as a conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and in accordance with the Declaration of Helsinki of 1964 and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants involved in the study.

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