Effect of the COVID-19 pandemic on surgery for indeterminate thyroid nodules (THYCOVID): a retrospective, international, multicentre, cross-sectional study

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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Effect of the COVID-19 pandemic on surgery for indeterminate thyroid nodules (THYCOVID): a retrospective, international, multicentre, cross-sectional study

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See Online for appendix

Summary

Background Since its outbreak in early 2020, the COVID-19 pandemic has diverted resources from non-urgent and elective procedures, leading to diagnosis and treatment delays, with an increased number of neoplasms at advanced stages worldwide. The aims of this study were to quantify the reduction in surgical activity for indeterminate thyroid nodules during the COVID-19 pandemic; and to evaluate whether delays in surgery led to an increased occurrence of aggressive tumours.

Methods In this retrospective, international, cross-sectional study, centres were invited to participate in June 22, 2022; each centre joining the study was asked to provide data from medical records on all surgical thyroidectomies consecutively performed from Jan 1, 2019, to Dec 31, 2021. Patients with indeterminate thyroid nodules were divided into three groups according to when they underwent surgery: from Jan 1, 2019, to Feb 29, 2020 (global prepandemic phase), from March 1, 2020, to May 31, 2021 (pandemic escalation phase), and from June 1 to Dec 31, 2021 (pandemic decrease phase). The main outcomes were, for each phase, the number of surgeries for indeterminate thyroid nodules, and in patients with a postoperative diagnosis of thyroid cancers, the occurrence of tumours larger than 10 mm, extrathyroidal extension, lymph node metastases, vascular invasion, distant metastases, and tumours at high risk of structural disease recurrence. Univariate analysis was used to compare the probability of aggressive thyroid features between the first and third study phases. The study was registered on ClinicalTrials.gov, NCT05178186.

Findings Data from 157 centres (n=49 countries) on 87 467 patients who underwent surgery for benign and malignant thyroid disease were collected, of whom 22 974 patients (18 052 [78·6%] female patients and 4922 [21·4%] male patients) received surgery for indeterminate thyroid nodules. We observed a significant reduction in surgery for indeterminate thyroid nodules during the pandemic escalation phase (median monthly surgeries per centre, 1·4 [IQR 0·6–3·4]) compared with the prepandemic phase (2·0 [0·9–3·7]; p<0·0001) and pandemic decrease phase (2·3 [1·0–5·0]; p<0·0001). Compared with the prepandemic phase, in the pandemic decrease phase we observed an increased

occurrence of thyroid tumours larger than 10 mm (2554 [69·0%] of 3704 *vs* 1515 [71·5%] of 2119; OR 1·1 [95% CI 1·0–1·3]; p=0·042), lymph node metastases (343 [9·3%] *vs* 264 [12·5%]; OR 1·4 [1·2–1·7]; p=0·0001), and tumours at high risk of structural disease recurrence (203 [5·7%] of 3584 *vs* 155 [7·7%] of 2006; OR 1·4 [1·1–1·7]; p=0·0039).

Interpretation **Our study suggests that the reduction in surgical activity for indeterminate thyroid nodules during the COVID-19 pandemic period could have led to an increased occurrence of aggressive thyroid tumours. However, other compelling hypotheses, including increased selection of patients with aggressive malignancies during this period, should be considered. We suggest that surgery for indeterminate thyroid nodules should no longer be postponed even in future instances of pandemic escalation.**

Funding **None.**

Introduction

Since the first report of SARS-CoV-2 in China in December, 2019, the COVID-19 pandemic has threatened the sustainability of health-care systems worldwide, diverting substantial resources from non-urgent and elective procedures to the diagnosis and treatment of COVID-19. The management of oncology patients has been challenging, with surgical procedures for diagnosed cancers postponed, and screening programmes and follow-up visits slowed down or even stopped for long periods.[1–5] Several studies have reported that the COVID-19-induced delays in diagnosis and treatment led to an increased number of patients with malignancies at advanced stages worldwide, particularly for rapid-growth tumours, including oral, head and neck, breast, gastric, pancreatic, and colorectal cancers.[3,5–11] However, the effect of the delay on indolent tumours, such as differentiated thyroid cancers and most prostate cancers, remains unclear.

In a national trial in Italy, one of the countries most affected by the pandemic, patients with thyroid cancer who underwent surgery during the pandemic had more aggressive neoplasm features when compared with patients who had undergone thyroidectomy the year before the start of the pandemic.[12] However, we hypothesised that this result was due to a bias in the selection of patients, given that surgery was not postponed for aggressive cancers.

In this study, we focused our attention on patients with a cytological diagnosis of indeterminate thyroid nodules. This condition is a paradigm of a potentially malignant disease that, considering its low risk of malignancy and the indolent behaviour of most thyroid tumours, does not require prompt intervention and thus intervention could

Research in context

Evidence before this study

We searched PubMed on March 5, 2022, using the terms "surgery COVID-19 pandemic", "delayed surgery COVID-19 pandemic", "cancer management COVID-19 pandemic", "thyroid cancer COVID-19 pandemic", and "indeterminate thyroid nodules COVID-19 pandemic", with no date or study duration restrictions. Articles not published in English were not considered. As widely described in the literature, the COVID-19 pandemic has threatened the sustainability of health-care systems worldwide, diverting substantial resources from non-urgent and elective procedures to the diagnosis and treatment of COVID-19. For this reason, the management of oncology patients has been challenging, with several types of surgical procedures postponed. Several previous studies reported that the COVID-19 induced delays in diagnosis and treatment led to an increased number of patients with malignancies at advanced stages, including for oral, head, and neck, breast, gastric, pancreatic, and colorectal cancers. However, the effect of the delay on differentiated thyroid cancer is unclear due to the scarcity of data. In this study, we focused on patients with a cytological diagnosis of indeterminate thyroid nodules. In this regard, in October, 2020, a survey involving an expert panel of surgeons and endocrinologists suggested that patients with Bethesda class III nodules should have been followed up with surveillance principles until the end of the pandemic and that surgery for patients with Bethesda class IV nodules should have been postponed for 3–6 months.

Added value of this study

This large international study found that surgical procedures for indeterminate thyroid nodules were overall reduced during the COVID-19 pandemic, compared with the prepandemic period. Additionally, we observed an increase in the postoperative diagnosis of aggressive thyroid tumours among surgeries for indeterminate thyroid nodules in the last 6 months of 2021 compared with the prepandemic period. We believe that these findings might be related to increased selection of patients with suspicious nodule features and to the delay in surgeries due to COVID-19 pandemic restrictions.

Implications of all the available evidence

Our findings suggest that surgical procedures for indeterminate thyroid nodules with a high suspicion of malignancy should not be postponed, even in future instances of restrictions due to new pandemic escalations or other causes.

be postponed in an extreme situation such as the COVID-19 pandemic. Indeed, in October, 2020, a survey involving 64 experienced surgeons and endocrinologists suggested that patients with Bethesda class III thyroid nodules on fine-needle aspiration cytology (FNAC) should have been followed-up with surveillance principles until the end of the pandemic, and that surgery for patients with Bethesda class IV nodules should have been postponed for 3–6 months.[13]

The main aims of the thyroid surgery during the COVID-19 pandemic (THYCOVID) study were to quantify the reduction in surgical activity for indeterminate thyroid nodules during the pandemic; and to evaluate whether the delay in surgery was associated with an increased occurrence of aggressive thyroid tumours.

Methods

Study design and patients

THYCOVID was a retrospective, international, multicentre, cross-sectional study. Invitations to join the study were sent to 1544 centres in 115 countries by email in June 22, 2022, retrieving from Scopus the corresponding authors of articles published from Jan 1, 2014, to May 31, 2022, containing the words "thyroidectomy" or "indeterminate thyroid nodule" in the title, abstract, or keywords. Each centre joining the study was asked to provide data on all thyroidectomies consecutively performed during the study timeframe. There were no other criteria for inclusion of patients and there were no age restrictions.

For the purpose of the study, patients were divided into three groups based on when they underwent thyroidectomy (figure): the first group included patients who had undergone thyroidectomy before the COVID-19 pandemic (from Jan 1, 2019, to Feb 29, 2020; phase 1); the second group included patients who had undergone surgery during the first global escalation of the COVID-19 pandemic (from March 1, 2020, to May 31, 2021; phase 2); and the third group included patients who underwent surgery during the pandemic decrease period (from June 1 to Dec 31, 2021; phase 3), when there was a reduction in SARS-CoV-2 infections and improved control of COVID-19, partly due to the distribution of vaccines. The third phase ended soon after the recrudescence of the pandemic, which we assisted with, from Dec 21, 2021, to April 30, 2022. These pandemic periods were defined according to data from the Our World in Data COVID-19 dataset. During the second phase, even at different times, almost all countries experienced the pandemic, had to reorganise their health-care systems, and had to divert resources to manage COVID-19.

For the **Our World in Data COVID-19 dataset** see https://ourworldindata.org/covid-cases

The study was registered before data collection on ClinicalTrials.gov (NCT05178186), and approval was obtained from the local ethics committee of each centre. Written informed consent was obtained from each patient involved in the study. The study protocol is available online.

For the **study protocol** see https://www.unica.it/unica/protected/412855/0/def/ref/DRC412853/

Procedures

Cytological findings were reported via different classification systems, including the Italian Society for Anatomic Pathology and Cytology–Italian Thyroid Association 2014 reporting system, the 2016 UK Royal College of Pathologists thyroid reporting system, and the 2017 Bethesda System for Reporting Thyroid Cytopathology. For the purpose of this study, cytological findings were reported according to the Bethesda system, as widely accepted in the literature.[14,15] The nodules classified as Bethesda class III or Bethesda class IV on FNAC were defined as indeterminate thyroid nodules.

For each centre between Jan 1, 2019, and Dec 31, 2021, aggregate data from medical records were collected on: the number of surgeries performed for benign and malignant disease, the number of surgeries for indeterminate thyroid nodules, patient demographics (ie, sex, which was reported according to biological sex as male or female), cytological category according to Bethesda classification, the use of molecular testing, the type of surgery performed, and pathological features of the tumour (size ≤10 mm or >10 mm, histotype, and the presence of lymph node metastasis, the presence of angioinvasion, microscopic and gross extrathyroidal extension, and distant metastasis). The risk of structural disease recurrence according to the American Thyroid Association (ATA) guidelines[16] was reported for differentiated thyroid cancers, including papillary, follicular, Hürthle cell, and poorly differentiated thyroid cancers. To compare surgical activity during the three phases of the study, considering that the length of each phase was different, data were reported on a monthly basis, with cases divided by the number of months in each phase, and were reported as median (IQR).

Data from each centre were independently reviewed by four authors (FM, GLC, FC, and CD) to assess its validity and completeness. In case of discrepancies, data were sent back to the centre to amend the data. We excluded centres not providing fundamental data, including sex, cytological classification, the full pathological examination report, and ATA classification of risk of structural disease reccurence. We classified the countries according to the world continents and merged the data for the Americas.

Statistical analysis

We did not establish the number of centres a priori and did not precalculate a sample size as the study was retrospective. The main outcomes of the study were the number of surgeries for indeterminate thyroid nodules, and in patients with a postoperative diagnosis of thyroid cancers, the occurrence of tumours larger than 10 mm, extrathyroidal extension, lymph node metastases, vascular invasion, distant metastases, and tumours at high risk of structural disease recurrence. We compared patients included in different phases of the study through univariate analysis. Furthermore, we

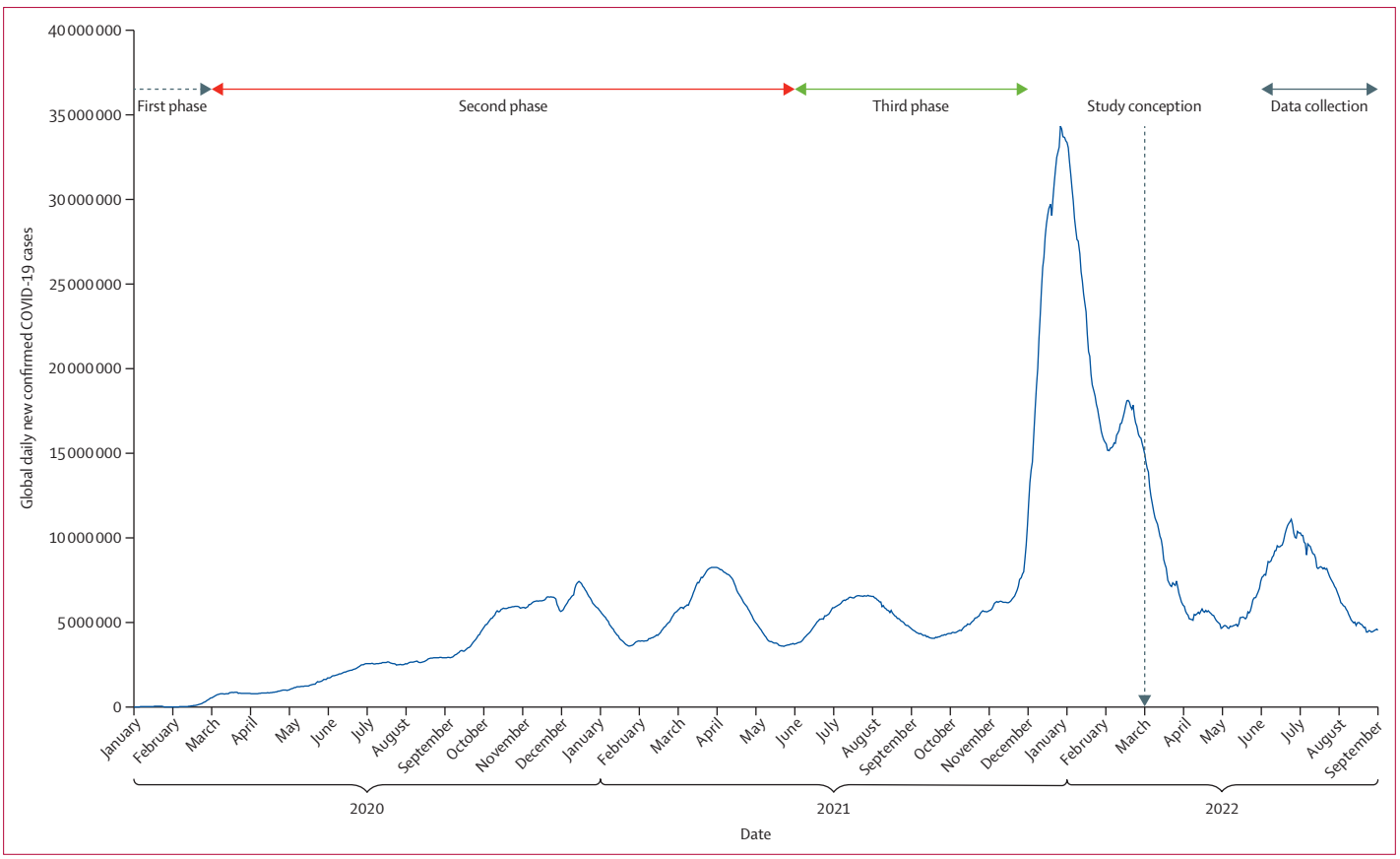

Figure: **Study timeline and COVID-19 infections**
The line represents the global daily new confirmed COVID-19 cases (7-day rolling average). The study was conceptualised in March, 2022, and data were collected from June to August, 2022. The first phase of the study (from Jan 1, 2019, to Feb 29, 2020) represents the prepandemic period. The second phase (from March 1, 2020, to May 31, 2021) corresponds to the first global escalation of the pandemic. The third phase (from June 1 to Dec 31, 2021) corresponds to the period when infections decreased and disease control improved.

conducted a post-hoc subanalysis by histotype via univariate analysis. Continuous data were preliminarily evaluated with the D'Agostino-Pearson test, resulting in non-normal distributions. For this reason, results were reported as median and IQR, and the Wilcoxon test for paired samples was used to test the differences in parameters between study phases. The χ^2 test was used to compare categorical variables. Odds ratios (ORs) for the probability of aggressive thyroid features in all patients with thyroid cancers between the first and third phases were calculated with univariate analysis, and relative 95% CIs within each group were calculated via the modified Wald method for main outcomes.

To address potential sources of bias, we remained strictly adherent to the initial protocol, we excluded centres with incomplete data, the statistical analysis was done independently by two authors (FM and CD), and all prespecified outcomes were completely reported. Hypothesis tests were two-sided, and results were considered significant at a p value of less than 0·05. Statistical analyses were done with MedCalc (version 20.123; MedCalc Software, Osterd, Belgium).

Results

Initially, 246 centres accepted the invitation to join the study, of which 163 (66·3%) sent data. After validation, six (3·7%) of 163 centres were excluded due to inadequate data: three (1·8%) due to an absence of ATA classification of risk of structural disease recurrence and three (1·8%) due to inconsistency of data (appendix p 2). Consequently, 157 (63·8%) of 246 centres were included in the THYCOVID study. The 157 centres were in 49 countries. 88 (56·1%) of the 157 centres were in Europe, 36 (22·9%) were in Asia, 26 (16·6%) were in the Americas, four (2·5%) were in Africa, and three (1·9%) were in Oceania. Overall, data on 87 467 surgeries for benign and malignant thyroid disease were reported, of which 22 974 (26·3%) across all 157 centres were for indeterminate thyroid nodules (table 1).

The number of thyroid surgeries for benign and malignant thyroid diseases was 37 037 (42·3% of the 87 467 total surgeries) in the prepandemic phase, 31 595 (36·1%) in the pandemic escalation phase, and 18 835 (21·5%) in the pandemic decrease phase (table 2, figure). The number of surgeries for indeterminate thyroid nodules was 9448 (25·5%; 95% CI 25·1–26·0) of

	Centres	Surgeries in phase 1 (Jan 1, 2019, to Feb 29, 2020)		Surgeries in phase 2 (March 1, 2020, to May 31, 2021)		Surgeries in phase 3 (June 1 to Dec 31, 2021)		Total surgeries in phases 1–3 (Jan 1, 2019, to Dec 31, 2021)	
		Benign and malignant disease	Indeterminate thyroid nodules*	Benign and malignant disease	Indeterminate thyroid nodules*	Benign and malignant disease	Indeterminate thyroid nodules*	Benign and malignant disease	Indeterminate thyroid nodules*
Europe	88	26 053	7186 (27·6%)	22 669	6635 (29·3%)	12 532	3748 (29·9%)	61 254	17 569 (28·7%)
Asia	36	5699	1153 (20·2%)	4665	910 (19·5%)	2953	642 (21·7%)	13 317	2705 (20·3%)
The Americas	26	4018	877 (21·8%)	3235	693 (21·4%)	2700	546 (20·2%)	9953	2116 (21·3%)
Africa	4	778	149 (19·2%)	532	118 (22·2%)	424	95 (22·4%)	1734	362 (20·9%)
Oceania	3	489	83 (17·0%)	494	98 (19·8%)	226	41 (18·1%)	1209	222 (18·4%)
Overall	157	37 037	9448 (25·5%)	31 595	8454 (26·8%)	18 835	5072 (26·9%)	87 467	22 974 (26·3%)

Data are n or n (%). Percentages are the proportion of all thyroid surgeries that were for indeterminate thyroid nodules in each category. *Class III and IV according to the Bethesda classification.[14]

Table 1: **Centres participating across continents and number of surgeries**

	Phase 1 (Jan 1, 2019, to Feb 29, 2020)	Phase 2 (March 1, 2020, to May 31, 2021)	Phase 3 (June 1 to Dec 31, 2021)	p values
Thyroid surgeries	37 037	31 595	18 835	NA
Thyroid surgeries per centre	135·0 (61·7–250·5)	96·0 (45·7–231·0)	68·0 (31·0–123·2)	NA
Monthly thyroid surgeries per centre	9·6 (4·4–17·9)	6·4 (3·0–15·4)	11·3 (5·2–20·5)	Phase 1 *vs* phase 2: <0·0001; phase 1 *vs* phase 3: <0·0001; phase 2 *vs* phase 3: <0·0001
Surgeries for indeterminate thyroid nodules	9448 (25·5%; 25·1–26·0)	8454 (26·8%; 26·3–27·3)	5072 (26·9%; 26·3–27·6)	Phase 1 *vs* phase 2: <0·0001; phase 1 *vs* phase 3: <0·0001; phase 2 *vs* phase 3: 0·68
Surgeries for indeterminate thyroid nodules per centre	28·0 (11·7–52·5)	22·0 (10·0–52·2)	14·0 (6·0–30·0)	NA
Monthly surgeries for indeterminate thyroid nodules per centre	2·0 (0·9–3·7)	1·4 (0·6–3·4)	2·3 (1·0–5·0)	Phase 1 *vs* phase 2: <0·0001; phase 1 *vs* phase 3: <0·0001; phase 2 *vs* phase 3: <0·0001

Data are n or n (%; 95% CI), where the denominator is the number of thyroid surgeries; or median (IQR). Data were reported on a monthly basis, with cases divided by the number of months in each phase. NA=not applicable (not tested).

Table 2: **Surgical activity for thyroid disease and indeterminate thyroid nodules before and during the COVID pandemic**

37 037 in the first phase, 8454 (26·8%; 26·3–27·3) of 31 595 in the second phase, and 5072 (26·9%; 26·3–27·6) of 18 835 in the third phase. The median monthly thyroid surgeries per centre was 9·6 (IQR 4·4–17·9; range 0·1–391·8) in the first phase, 6·4 (3·0–15·4; 0·3–349·1) during the second phase, and 11·3 (5·2–20·5; 1·3–468·8) in the third phase (table 2, appendix p 4). Similarly, the median monthly surgeries per centre for indeterminate thyroid nodules was 2·0 (IQR 0·9–3·7; range 0·0–193·1) in the first phase, 1·4 (0·6–3·4; 0·0–171·5) in the second phase, and 2·3 (1·0–5·0; 0·0–244·2) in the third phase. The differences were significant (p<0·0001) for median monthly surgeries per centre in pairwise comparisons of the three study phases, both for the median number of overall surgeries per centre and the median number of indeterminate thyroid nodules surgeries per centre. Surgical activity across different world regions is reported in the appendix (pp 3, 6).

For the patients who underwent surgery for indeterminate thyroid nodules (n=22 974), comparisons of baseline and clinical characteristics are reported in table 3. Across all phases of the study, 18 052 (78·6%) female patients and 4922 (21·4%) male patients had surgery for indeterminate thyroid nodules, although no significant differences were evident in the proportions of female and male patients between study phases. We could not calculate medians, means, or ranges for age because we had aggregate data. The preoperative diagnosis was Bethesda class III in 3094 (32·7%) of 9448 patients in the prepandemic phase, 2770 (32·8%) of 8454 in the pandemic escalation phase, and 1672 (33·0%) of 5072 in the pandemic decrease phase. Correspondingly, Bethesda class IV was diagnosed in 6354 (67·3%) patients in the first phase, 5684 (67·2%) in the second phase, and 3400 (67·0%) in the third phase. The proportions of patients with class III or IV thyroid nodules did not differ significantly between the study phases. The use of preoperative molecular testing increased over time, with testing in 733 (7·8%) patients in the first phase, 717 (8·5%) in the second phase, and 493 (9·7%) in the third phase. The difference in the numbers of patients tested was significant between

	Phase 1 (Jan 1, 2019, to Feb 29, 2020)	Phase 2 (March 1, 2020, to May 31, 2021)	Phase 3 (June 1 to Dec 31, 2021)	p values
Patients with indeterminate thyroid nodules	9448	8454	5072	NA
Sex				
Male	2035 (21·5%)	1834 (21·7%)	1053 (20·8%)	..
Female	7413 (78·5%)	6620 (78·3%)	4019 (79·2%)	Phase 1 *vs* phase 2: 0·81*; phase 1 *vs* phase 3: 0·28*; phase 2 *vs* phase 3: 0·21*
Preoperative fine needle aspiration cytology				
Bethesda III	3094 (32·7%)	2770 (32·8%)	1672 (33·0%)	..
Bethesda IV	6354 (67·3%)	5684 (67·2%)	3400 (67·0%)	Phase 1 *vs* phase 2: >0·99†; phase 1 *vs* phase 3: 0·80†; phase 2 *vs* phase 3: 0·82†
Molecular testing performed	733 (7·8%)	717 (8·5%)	493 (9·7%)	Phase 1 *vs* phase 2: 0·081; phase 1 *vs* phase 3: <0·0001; phase 2 *vs* phase 3: 0·016
Thyroid malignancies	3704 (39·2%)	3313 (39·2%)	2119 (41·8%)	Phase 1 *vs* phase 2: >0·99; phase 1 *vs* phase 3: 0·0027; phase 2 *vs* phase 3: 0·0031
Type of surgery				
Total thyroidectomy	4443 (47·0%)	3855 (45·6%)	2269 (44·7%)	..
Thyroid lobectomy	5005 (53·0%)	4599 (54·4%)	2803 (55·3%)	Phase 1 *vs* phase 2: 0·058‡; phase 1 *vs* phase 3: 0·0088‡; phase 2 *vs* phase 3: 0·33‡
Central lymph node dissection	735 (7·8%)	742 (8·8%)	489 (9·6%)	Phase 1 *vs* phase 2: 0·017; phase 1 *vs* phase 3: <0·0001; phase 2 *vs* phase 3: 0·097

Data are n, or n (%), or p values. NA=not applicable. p values are for comparisons of the distribution of: *male patients and female patients; †Bethesda class III and IV; and ‡total thyroidectomy and lobectomy surgeries.

Table 3: **Baseline and clinical characteristics of patients with indeterminate thyroid nodules**

the first and third phases (p<0·0001) and between the second and third phases (p=0·016). Thyroid lobectomy rather than total thyroidectomy was done in 5005 (53·0%) patients in the first phase, 4599 (54·4%) patients in the second phase, and 2803 (55·3%) patients in the third phase, with a significant difference in the proportions of patients who received lobectomy or total thyroidectomy between the first and third phases (p=0·0088). Central lymph node dissection was associated with thyroidectomy in 735 (7·8%) patients in the first phase, 742 (8·8%) patients in the second phase, and 489 (9·6%) patients in the third phase, with a significant difference in these proportions between the first and second phases (p=0·017) and between the first and third phases (p<0·0001). Pathological examination identified a thyroid malignancy in 3704 (39·2%) patients in the first phase, 3313 (39·2%) patients in the second phase, and 2119 (41·8%) patients in the third phase, with a significant difference in these proportions between the first and third phases (p=0·0027) and between the second and third phases (p=0·0031).

Among the patients with thyroid malignancies, tumour size of up to 10 mm was diagnosed in 1150 (31·0%; 95% CI 29·6–32·6) of 3704 patients in the first phase, 972 (29·3%; 27·8–30·9) of 3313 in the second phase, and 604 (28·5%; 26·6–30·5) of 2119 in the third phase, with a significant difference in these proportions between the first and third phases (p=0·045; table 4). Analysis of histotype revealed significant differences in the overall distribution of histotypes among the three phases; thus, a subanalysis considering each histotype alone was done (appendix pp 4, 7). We observed similar distributions among the three phases for papillary thyroid cancer, follicular thyroid cancer, and poorly differentiated thyroid cancer. Conversely, Hürthle cell cancer was significantly more frequent in the second phase than in the first phase (176 [5·3%] patients *vs* 153 [4·1%] patients; p=0·0225), and the occurrence of anaplastic thyroid cancer was significantly higher in the third phase than in the pandemic phase (18 [0·8%] *vs* 11 [0·3%]; p=0·018; table 4).

We also assessed features of the thyroid malignancies (table 4, appendix p 8). The occurrence of extrathyroidal extension was similar among the three phases, ranging from 324 patients (8·7%; 95% CI 7·9–9·7) in the first phase to 316 patients (9·5%; 8·6–10·6) in the second phase and 172 patients (8·1%; 7·0–9·4) in the third phase. Conversely, the occurrence of lymph node metastasis was significantly higher in the second phase (389 patients; 11·7%; 10·7–12·9; p=0·0008) and in the third phase (264 patients; 12·5%; 11·1–13·9; p<0·0001) than in the first phase (343 patients; 9·3%; 8·4–10·2). Vascular invasion was found in 419 patients (11·3%;

	Phase 1 (Jan 1, 2019, to Feb 29, 2020	Phase 2 (March 1, 2020, to May 31, 2021)	Phase 3 (June 1 to Dec 31, 2021)	p value
Malignancies	3704	3313	2119	NA
Tumour size				
≤10 mm	1150 (31·0%; 29·6–32·6)	972 (29·3; 27·8–30·9)	604 (28·5%; 26·6–30·5)	..
>10 mm	2554 (69·0%; 67·5–70·4)	2341 (70·7%; 69·1–72·2)	1515 (71·5%; 69·5–73·4)	Phase 1 *vs* phase 2: 0·13*; phase 1 *vs* phase 3: 0·045*; phase 2 *vs* phase 3: 0·52*
Histotype				
Papillary thyroid cancer	2922 (78·8%; 77·6–80·2)	2552 (77·0%; 75·6–78·5)	1629 (76·9%; 75·1–78·7)	..
Follicular thyroid cancer	460 (12·4%; 11·4–13·5)	434 (13·1%; 12·0–14·3)	249 (11·8%; 10·5–13·2)	..
Hürthle cell cancer	153 (4·1%; 3·6–4·8)	176 (5·3%; 4·6–6·1)	94 (4·4%; 3·6–5·4)	..
Poorly differentiated thyroid cancer	49 (1·3%; 1·0–1·8)	35 (1·1%; 0·8–1·5)	32 (1·5%; 1·0–2·1)	..
Anaplastic cancer	19 (0·5%; 0·3–0·8)	11 (0·3%; 0·2–0·6)	18 (0·8%; 0·5–1·3)	..
Others	101 (2·7%; 2·3–3·5)	105 (3·2%; 2·6–3·8)	97 (4·6%; 3·8–5·6)	Phase 1 *vs* phase 2: 0·071†; phase 1 *vs* phase 3: 0·0032†; phase 2 *vs* phase 3: 0·0016†
Extra thyroidal extension	324 (8·7%; 7·9–9·7)	316 (9·5%; 8·6–10·6)	172 (8·1%; 7·0–9·4)	Phase 1 *vs* phase 2: 0·26; phase 1 *vs* phase 3: 0·43; phase 2 *vs* phase 3: 0·082
Lymph node metastasis	343 (9·3%; 8·4–10·2)	389 (11·7%; 10·7–12·9)	264 (12·5%; 11·1–13·9)	Phase 1 *vs* phase 2: <0·0008; phase 1 *vs* phase 3: <0·0001; phase 2 *vs* phase 3: 0·45
Vascular invasion	419 (11·3%; 10·3–12·3)	515 (15·5%; 14·4–16·8)	258 (12·2%; 10·9–13·6)	Phase 1 *vs* phase 2: <0·0001; phase 1 *vs* phase 3: 0·34; phase 2 *vs* phase 3: <0·0006
Distant metastasis	38 (1·0%; 0·7–1·4)	34 (1·0%; 0·7–1·4)	29 (1·4%; 1·0–2·0)	Phase 1 *vs* phase 2: 0·91; phase 1 *vs* phase 3: 0·29; phase 2 *vs* phase 3: 0·31

Data are n or n (%; 95% CI). NA=not applicable. p values are for comparisons of the distribution of: *tumour size ≤10 mm and >10 mm; and †all histotypes.

Table 4: **Pathological examination of thyroid malignancies**

	Phase 1 (Jan 1, 2019, to Feb 29, 2020	Phase 2 (March 1, 2020, to May 31, 2021)	Phase 3 (June 1 to Dec 31, 2021)	p value
Differentiated thyroid cancers	3584	3198	2006	NA
Low risk	2683 (74·9%; 73·4–76·3)	2326 (72·7%; 71·2–74·3)	1450 (72·3%; 70·3–74·2)	..
Intermediate risk	698 (19·7%; 18·2–20·8)	674 (21·1%; 19·7–22·5)	401 (20·0%; 18·3–21·8)	..
High risk	203 (5·7%; 5·0–6·5)	198 (6·2%; 5·4–7·1)	155 (7·7%; 6·6–9·0)	Phase 1 *vs* phase 2: 0·071; phase 1 *vs* phase 3: <0·0001; phase 2 *vs* phase 3: 0·081

Data are n or n (%; 95% CI). NA=not applicable. p values are for comparisons of the distribution of all three risk classifications.

Table 5: **American Thyroid Association classification of risk of disease recurrence of differentiated thyroid cancers**

10·3–12·3) in the first phase, 515 patients (15·5%; 14·4–16·8) in the second phase, and 258 patients (12·2%; 10·9–13·6) in the third phase, with significant differences in these proportions between the first and second phases (p<0·0001) and between the second and third phases (p=0·0006). The occurrence of distant metastasis was low and similar across the three phases.

Differentiated thyroid cancer were classified according to the ATA classification for risk of disease recurrence (table 5; appendix p 9). In this analysis, 3584 patients with differentiated thyroid cancer (95·5% of 3704 with malignancies) were included in the first phase, 3198 (96·5% of 3313) in the second phase, and 2006 (94·7% of 2119) in the third phase. All patients with DTCs were included in this analysis. The occurrence of tumours at high risk of disease recurrence increased with time, ranging from 203 patients (5·7%; 95% CI 5·0–6·5) in the first phase, 198 patients (6·2%; 5·4–7·1) in the second phase, and 155 patients (7·7%; 6·6–9·0) in the third phase. Concurrently, the frequency of low-risk tumours decreased with time. The

distribution of low-risk, intermediate-risk, and high-risk tumours significantly differed between the first and third phases (p<·0001; table 5).

When comparing patients with thyroid tumors who underwent surgery in the third phase and those who underwent surgery in the first phase, those in the third phase were more likely to have tumours larger than 10 mm (OR 1·1; 95% CI 1·0–1·3; p=0·042), lymph node metastases (OR 1·4; 1·2–1·7; p=0·0001), and to be categorised as having high risk of structural disease recurrence according to the ATA guidelines (OR 1·4; 1·1–1·7; p=0·0039; appendix p 10).

Discussion

Our study indicates that surgical activity for thyroid diseases, particularly for indeterminate thyroid nodules, was overall reduced during the COVID-19 pandemic. This finding is in accordance with previous data reported by different groups.[17–19] Ikeda and colleagues analysed data from the Japanese National Clinical Database, and identified a reduction of 1956 thyroidectomies in 2020, corresponding to a decrease of 12·7%, compared with 2019.[19] Between 2019 and 2020 in Italy, a reduction of nearly 40% in surgeries for thyroid disease was reported.[18]

Our study further showed that tumours in the decreasing phase of the pandemic were more aggressive than those in the prepandemic phase. We found a significant increase in the occurrence of lymph node metastasis (which increased from 9·3% to 12·5%), tumours at high risk of structural recurrence (from 5·7% to 7·7%), and tumours larger than 10 mm (from 69·0% to 71·5%). Our results are in accordance with the work of Grani and colleagues, who found that the delayed treatment of thyroid cancers led to an increased incidence of lymph node metastasis (14/55 [26%] *vs* 17/36 [47%]) and to an increase in the rate of tumours at high risk of recurrence (3/55 [6%] *vs* 7/36 [19%]) compared between March, 2019, to February, 2020, and March, 2020, to February, 2021.[17] Liu and colleagues conducted a retrospective study of 3216 patients with thyroid cancer at Wuhan University (Wuhan, China) from February, 2017, to September, 2020.[20] They found that post-lockdown patients had an increased risk of lymph node metastases (1075/2137 [37·7%] *vs* 165/290 [45%]) and extrathyroidal extension (1867/2137 [65·5%] *vs* 265/290 [72%]) compared with prepandemic patients. It would be interesting to investigate the reasons for these differences. First, we should consider that, during the pandemic, historical trends in thyroid tumours are likely to have continued, becoming more frequent and more aggressive year by year. Furthermore, we should consider that the increased accuracy of preoperative studies has led to an increased number of lymphadenectomies and, consequently, to increased pathological diagnoses of lymph node metastases. This relationship is well described by Morris and Myssiorek, who found that the incidence of cervical lymph node metastases has doubled in the four decades since 2010.[21] Another competing hypothesis is that, as happened during the most restrictive phases of the pandemic,[12,18] surgeons might have prioritised patients with more suspicious thyroid nodule features in the pandemic decrease phase. This hypothesis is supported by the increase in the rate of central compartment lymph node dissections in the third phase in our study. Furthermore, patients with indeterminate thyroid nodules and preoperative features of aggressive nodules were likely to be the most worried about their illness after lockdowns, and probably were the patients who mostly solicited the intervention. Thus, it is possible that once restrictions of the first pandemic phase were eased, the first patients with indeterminate thyroid nodules submitted to surgery were precisely those with aggressive preoperative features. This hypothesis is in accordance with the fact that the rate of indeterminate thyroid nodules remained similar among the three phases, while the occurrence of aggressive tumours increased with time, indicating a more accurate individualised preoperative risk assessment of malignancy.

Finally, we should consider the hypothesis that delayed interventions during the pandemic have led to an increased number of aggressive thyroid cancers due to tumour progression. Similar hypotheses have been proposed for breast, skin, colorectal, gastric, and lung cancers.[22–28]

The main argument against this thesis, that a delay in the treatment of indeterminate thyroid nodules has led to an increased occurrence of aggressive thyroid neoplasms, is that thyroid tumours are characterised by slow growth in most cases. Thus, the delay in surgery caused by the pandemic, even if reaching 6–12 months in the worst-case scenario, would have had a limited effect on tumour progression and most tumours would have remained indolent throughout the pandemic. However, we speculate that a minority of thyroid tumours, characterised by faster growth and aggressive features, could have progressed during the pandemic, resulting in the increased occurrence of tumours at high risk of recurrence and lymph node metastases that we observed in our study. Furthermore, we should consider that even if thyroid cancer is usually a slow growing cancer, an early aggressive cancer that is not resected might subsequently be detected as an advanced tumour.

We should also consider that SARS-CoV-2 infection could have had a role in tumour progression. SARS-CoV-2 infection appears to alter thyroid function through an intense inflammatory response (a cytokine storm), that might damage the thyroid gland, inducing subacute or acute thyroiditis and thyrotoxicosis.[29–31] Considering the global spread of SARS-CoV-2 infection, this mechanism could have had a role in patients with a thyroid malignancy, promoting tumour growth and progression.

A large Japanese cohort study of 25 361 patients receiving levothyroxine as substitutive or suppressive therapy found an association between delayed follow-up visits and the control of thyroid function, particularly serum thyroid-stimulating hormone (TSH) levels.[32] In this study, an increased risk of elevated TSH was found during the

pandemic among patients with delayed follow-up visits, particularly those with delayed visits of 30 days or more, resulting in reduced control of thyroid hormone levels, including elevated TSH and decreased free thyroxine. Considering that TSH has been hypothesised to be one of the factors implicated in thyroid cancer initiation and progression,[33–35] this finding could help to explain the increased occurrence of aggressive tumours in the third phase of our study.

There were some interesting additional findings in our study. First, according to a recent meta-analysis,[36] the occurrence of thyroid cancer in patients with indeterminate thyroid nodules appears to be substantially higher than the 5–30% originally described by Cibas and Ali in the Bethesda system for reporting thyroid cytopathology.[14] In our study, nearly 40% of patients with indeterminate thyroid nodules had thyroid cancer. Second, the use of molecular techniques has been markedly increasing with time, even if it is still only used in a minority of cases (in our study, in less than 10% of patients). According to the capacities of each country and centre, when possible, molecular testing should be included in diagnostic routines for individual stratification of cancer risk in patients with indeterminate thyroid nodules. Finally, in our study, the size of the malignant thyroid nodules submitted to surgery was 10 mm or smaller in approximately a third of patients. This finding raises doubts over the application of current guidelines that discourage FNAC in nodules smaller than 10 mm as the high proportion of tumors less than 10 mm means that there was scarce adherence to ATA guidelines that discourage FNAC for small nodules and suggest active surveillance for nodules at low risk of malignancy.

A major strength of our study was its large sample size, involving 49 countries, and the analysis of data at different timepoints before and during the COVID-19 pandemic. However, due to the absence of information, we could not define the role of confounding factors, such as concomitant malignancies, chronic diseases, and comorbidities, which could potentially explain some of the differences found in our study.

Our study has several limitations. First, although statistically significant, the differences that we found among the groups were in some cases small, potentially representing a type 1 error, and their clinical implications could be of limited value. Second, in this type of large study, the populations included are potentially heterogeneous; it is likely that both the pandemic peak and restrictions did not occur at the same time among different countries, that there were different health-care policies among the countries, that there were different approaches among the centres, and that even the classification of the nodules, particularly as Bethesda class III, was partly dependent on the experience of the pathologist, generating possible bias and limiting our interpretation. Furthermore, we could not assess whether the study centres were fully representative of their country. The heterogeneity of our series of patients was also indicated by the non-normal distribution of the continuous variables, which precluded the possibility of ANOVA testing, which would have allowed us to better study the differences among centres and phases of the study. Finally, the different durations of the three phases might have led to selection bias affecting the internal validity of analysis through inaccurate estimation of relationships among the variables.

In conclusion, in our study we observed an increase in the postoperative diagnosis of aggressive thyroid tumours among surgeries for indeterminate thyroid nodules in the last 7 months of 2021, compared with the prepandemic period. This finding could be related to different hypotheses, among which the most compelling and valuable are increased selection of patients with suspicious nodule features and delays in surgery due to COVID-19 pandemic restrictions. We suggest that surgical activity for indeterminate thyroid nodules with a high suspicion of malignancy should not be postponed, even in future instances of restrictions due to new pandemic escalations or other causes.

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Contributors

FM, CD, PGC, GLC, and FC made substantial contributions to conception and design of the study and to analysis and interpretation of data, drafted the manuscript, and gave final approval of the version to be sent for evaluation. All other authors contributed to the acquisition, analysis, and interpretation of data, critical revision of the manuscript for intellectual content, and gave approval of the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. FM, PGC, GLC, FC, and CD accessed and verified the data.

Declaration of interests

We declare no competing interests.

Data sharing

All individual participant data collected during the trial, after deidentification and including a data dictionary, will be provided to investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. The study protocol is available at https://www.unica.it/unica/protected/412855/0/def/ref/DRC412853/. Data will be available immediately after publication for 5 years. Proposals should be directed to fabiomedas@unica.it; to gain access, data requestors will need to sign a data access agreement that will be provided from the principal investigator of the study (FM).

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