




The COVID-19 outbreak and de-escalation of thyroid cancer diagnosis and treatment

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The COVID-19 outbreak in Italy forced the healthcare system to cancel all non-urgent outpatient activities in order to avoid further spread of the disease inside hospitals and other healthcare facilities. At our institution, all thyroid nodule activities were canceled between March and May 2020, though the hospital allowed treatment and consultations for all cancer patients. For these patients, the medical team distinguished patients with immediate needs from patients whose procedures could be postponed [1]. Even after this timeframe, the capacity of the hospital to perform non-urgent thyroid surgeries was reduced [2]. All patients were reassured that these changes would not have any impact on their disease-related outcomes. Indeed, a de-escalation process of care and a risk-adapted approach to thyroid cancer management had already been underway in recent years in accordance with main international guidelines [3]. Our team had started several years ago to reduce the procedures performed, both for the diagnostic workup of thyroid nodules and for the treatment and follow-up of diagnosed thyroid cancers [4]. Namely, we had already reduced the number of unnecessary fine-needle aspiration biopsies [5], proposed more conservative surgery, suggested active surveillance for non-threatening papillary thyroid microcarcinomas [6], and used ancillary tools to avoid diagnostic surgeries for indeterminate thyroid nodules, such as sonographic risk stratification and

molecular testing [7]. Furthermore, we reduced the frequency of neck sonographies in the follow-up of differentiated thyroid cancer [8] and the use of radioiodine treatment [9]. All these decisions required thorough discussion with patients, caregivers, and other physicians, and as a result the de-escalation of treatment burden was not easily accepted, partially due to the underestimation of the risks of healthcare interventions. While the COVID-19 pandemic has forced hospitals to withhold many useful services, it has also provided an opportunity to focus on the risk-benefit balance of medical choices. The aim of this report was to investigate how the disruption of usual activities impacted the features of differentiated thyroid cancers diagnosed after the outbreak by comparing the 12 months before and after March 2020.

This analysis was conducted as a single-center subgroup analysis of a prospective observational study on the outcomes of thyroid cancer patients (NCT04031339). The study protocol was approved by the institutional review board and written informed consent was obtained from all patients whose data were analyzed. The database used contained records on all patients who received follow-up in our center after surgical pathology confirmed a diagnosis of thyroid cancer. Our early follow-up protocol included an initial assessment about 1, 3, and 12 months after initial treatment. Each assessment included serum thyroglobulin (Tg) determination performed while the patient was on levothyroxine (LT4) and a radioimmunometric assay of circulating Tg antibody levels. High-resolution gray-scale and color Doppler ultrasound studies of the thyroid bed and cervical lymph node compartments were performed for all patients. Additional procedures were performed at the clinician's discretion, in accordance with evidence-based guidelines [10].

We reviewed cases in the center's database to identify patients diagnosed with differentiated thyroid cancer between March 2019 and February 2021. Patients referred

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Table 1 Clinical and pathological features of the two groups

	<i>n</i>	Total	Groups		<i>p</i>
			March 2019–February 2020	March 2020–February 2021	
		91	55	36	
Sex	Males	27	15 (27.3%)	12 (33.3%)	0.53
	Females	64	40 (72.7%)	24 (66.7%)	
Age at diagnosis	years (IQR)		48 (36–61)	52 (33–61)	0.93
Cytology	Not performed	7	6 (10.9%)	1 (2.8%)	0.006
	Non-diagnostic	1	1 (1.8%)	0 (0.0%)	
	Benign	7	6 (10.9%)	1 (2.8%)	
	Indeterminate	20	13 (23.6%)	7 (19.4%)	
	Suspicious	22	17 (30.9%)	5 (13.9%)	
	Malignant	34	12 (21.8%)	22 (61.1%)	
Nodule diagnosis	Not specified	6	2 (3.6%)	4 (11.1%)	0.37
	Clinical	26	15 (27.2%)	11 (30.5%)	
	Incidental	30	17 (30.9%)	13 (36.1%)	
	Screening for family history	6	5 (9.1%)	1 (2.8%)	
	Screening for other reasons	23	16 (29.1%)	7 (19.4%)	
Cancer diagnosis	Incidental	27	24 (43.6%)	3 (8.3%)	<0.001
	Pre-surgical	64	31 (56.4%)	33 (91.7%)	
Previous radiation exposure	Unknown	15	7 (12.7%)	8 (22.2%)	0.48
	No	73	46 (83.6%)	27 (75%)	
	Yes	3	2 (3.6%)	1 (2.8%)	
History of thyroiditis	Unknown	10	5 (9.1%)	5 (13.9%)	0.77
	No	55	34 (61.8%)	21 (58.3%)	
	Yes	26	16 (29.1%)	10 (27.8%)	
Family history of thyroid nodules	Unknown	9	2 (3.6%)	7 (19.4%)	0.04
	No	43	27 (49.1%)	16 (44.4%)	
	Yes	39	26 (47.3%)	13 (36.1%)	
Family history of thyroid cancers	Unknown	9	3 (5.5%)	6 (16.7%)	0.29
	No	74	47 (85.5%)	27 (75%)	
	Yes, DTC	7	4 (7.3%)	3 (8.3%)	
	Yes, MTC	1	1 (1.8%)	0 (0.0%)	
Subtypes of DTC	PTC	79	49 (84.5%)	30 (78.9%)	0.47
	aggressive PTC variants or PDTC	8	3 (5.2%)	5 (13.2%)	
	MI-FTC	3	2 (3.4%)	1 (2.6%)	
	WI-FTC	1	1 (1.7%)	0 (0.0%)	
Size	mm (IQR)		9 (6–20)	14 (10–25)	0.010
Microcarcinomas		45	33 (60%)	12 (33.3%)	0.018
Multifocal		39	20 (36.4%)	19 (52.8%)	0.13
Extrathyroidal extension	No	51	35 (63.6%)	16 (44.4%)	0.067
	Gross	5	1 (1.8%)	4 (11.1%)	
	Minimal	35	19 (34.5%)	16 (44.4%)	
Invasion of strap muscles (if minimal)	No	31	19 (100.0%)	12 (75%)	0.035
	Yes	4	0 (0.0%)	4 (25%)	
Vascular invasion	Not specified	63	42 (76.4%)	21 (58.3%)	0.06
	No	15	5 (9.1%)	10 (27.8%)	
	Yes	13	8 (14.5%)	5 (13.9%)	
Lymph node metastases	pNx (cN0)	21	14 (25.4%)	7 (19.4%)	0.15
	pN0	39	27 (49.1%)	12 (33.3%)	
	pN1a	13	7 (12.7%)	6 (16.7%)	
	pN1b	18	7 (12.7%)	11 (30.5%)	
Lymph node metastases	No	60	41 (74.5%)	19 (52.8%)	0.04
	Yes	31	14 (25.5%)	17 (47.2%)	
If lymph node metastases. extracapsular invasion	Not specified	2	1 (7.1%)	1 (5.9%)	0.69
	No	15	7 (50%)	8 (47.1%)	
	Yes	13	5 (35.7%)	8 (47.1%)	
	Unknown	1	1 (7.1%)	0 (0.0%)	

Table 1 (continued)

	<i>n</i>	Total	Groups		<i>p</i>
			March 2019–February 2020	March 2020–February 2021	
		91	55	36	
Surgical margins	Not specified	10	8 (14.5%)	2 (5.6%)	0.05
	R0	79	46 (83.6%)	29 (80.6%)	
	R1	5	0 (0%)	4 (11.1%)	
	R2	2	1 (1.8%)	1 (2.8%)	
Radioiodine treatment	No	73	46 (79.3%)	27 (71.1%)	0.42
	Yes	18	9 (15.5%)	9 (23.7%)	
Distant metastases	Mx	74	46 (83.6%)	28 (77.8%)	0.58
	M0	14	8 (14.5%)	6 (16.7%)	
	M1	3	1 (1.8%)	2 (5.6%)	
ATA risk	Low	40	29 (52.7%)	11 (30.6%)	0.036
	Intermediate-low	41	23 (41.8%)	18 (50%)	
	High	10	3 (5.5%)	7 (19.4%)	
Evidence of disease at 1-yr follow-up	Lost to follow-up	3	2 (3.6%)	1 (2.8%)	0.58
	Excellent response (no evidence of disease)	50	29 (52.7%)	21 (58.3%)	
	Indeterminate response	20	14 (25.5%)	6 (16.7%)	
	Biochemical incomplete response	5	4 (7.3%)	1 (2.8%)	
	Structural incomplete response	13	6 (10.9%)	7 (19.4%)	

ATA American Thyroid Association, DTC differentiated thyroid cancer, MI-FTC minimally invasive follicular thyroid cancer, MTC medullary thyroid cancer, PTC papillary thyroid cancer, WI-FTC widely invasive follicular thyroid cancer

to our center soon after initial treatment (surgery with or without radioactive iodine therapy) were excluded. Early follow-up data (6–12 months after initial treatment) were used to estimate the initial response to treatment. Unstimulated serum Tg levels on LT4 were used to classify patients as having an *excellent*, *indeterminate*, or *biochemical incomplete response* according to the thresholds suggested by European Society of Medical Oncology (ESMO) guidelines [10]. For the assessment of locoregional metastases, we evaluated the size, location, and features of each neck lymph node visualized during the ultrasound examinations according to the scheme proposed in 2013 by the European Thyroid Association (ETA) [11]. At each timepoint, the patient's ultrasound-defined neck lymph node status was classified as *normal* if all visible nodes were considered normal and as *indeterminate* if there were no suspicious nodes but at least one node classified as indeterminate. When at least one lymph node was classified as *suspicious* or other imaging studies documented local or distant metastases, the patient was classified as having a *structural incomplete response*.

The cohort was split into two groups: the first group included cases diagnosed before the COVID-19 lockdown (March 2019–February 2020; $n = 55$), while the second included cases diagnosed during and after the lockdown (March 2020–February 2021; $n = 36$). During the lockdown period, less surgeries were performed (–34%).

Age, gender, and clinical risk features (e.g., circumstances of thyroid nodule diagnosis, family history of thyroid cancer or nodules) did not differ between the two groups (Table 1). However, the number of surgeries for presumed benign thyroid disease decreased, substantially reducing the number of incidentally-detected microcarcinomas (8.3% vs. 43.6%, $p < 0.001$). This was also reflected in the distribution of pre-surgical cytological diagnoses, with malignancy diagnoses being more common (61.1% vs. 21.8%; $p = 0.006$) and benign and indeterminate reports being relatively less common. There was no significant change in the distribution of detected histotypes. The application of better risk stratification substantially increased the median tumor size of operated patients (14 mm [interquartile range, IQR 10–25] vs. 9 mm [IQR 6–20]; $p = 0.01$) and decreased the rate of microcarcinomas (33.3% vs. 60%; $p = 0.018$). The delayed treatment did not significantly increase the rate of extra-thyroidal extension, incomplete surgical resection, extra-capsular extension, or distant metastases, considered as single features, but significantly increased the rate of lymph node metastasis (25.4% vs. 47.2%; $p = 0.04$) and high-risk patients (19.4% vs. 5.5%) while reducing low-risk patients (30.6% vs. 52.7%; $p = 0.036$) defined according to the American Thyroid Association (ATA) risk stratification for differentiated thyroid cancer. However, the short-term outcomes (i.e., disease status at the

1-year follow-up visit) were not negatively affected by this better stratification and change in baseline risk.

These considerations did not apply to medullary thyroid cancer (MTC). During the study period, five patients underwent primary surgery for MTC, three in the pre-lockdown period (5.2% of the whole cohort; median tumor size 22 mm; median age 60 years) and two during or after lockdown (5.3%; median tumor size 14.5 mm; median age 60 years), with no significant differences in clinical presentation or histological features. According to our institutional approach, suspected MTC was considered an indication for immediate surgical treatment [2].

A reduction in outpatient clinical activities and oncological surgeries has been recorded worldwide over the last two years. The delay in some elective oncology surgeries was reported to have a negative impact on survival (e.g., breast cancer, ductal carcinoma in situ, T1 pancreatic cancer, ovarian cancer, pediatric osteosarcoma, hepatocellular cancer, colon cancer, and melanoma) [12]. This was not the case for thyroid cancer (which usually does not impair short-term survival). In Italy, thyroid surgeries were rescheduled beginning in March 2020, after taking into account risk stratification and patient needs [2] as suggested by a rapid consensus statement published by scientific societies [13]. As a result, a reduction in surgical interventions was recorded by multicenter evaluations across Italy [14], including a reduction in cytological assessments [15, 16], and diagnostic surgeries for benign or indeterminate nodules. There was a larger resort to active surveillance, though without withholding needed oncological activities. Although this changing practice was due to changes in healthcare organization operational plans as a result of the pandemic, these changes were consistent with clinical practice guideline recommendations. It has previously been reported that this changing paradigm did not affect the rate of postoperative complications [14]. Our study documented a slight increase in baseline risk stratification for patients who underwent thyroid surgery after the COVID-19 lockdown, consistent with reports from China, another country hit early by the pandemic [17], though this effect was less marked in our cohort. However, short-term outcomes, evaluated as the early response to initial treatment, were not negatively impacted by the delay.

As others have observed [18], the current pandemic situation has provided necessary insight as well as the opportunity to more convincingly explain to patients that acceptance of uncertainties and active surveillance is feasible approaches in cases of indeterminate nodules or low-risk cancers. Although the situation may still create anxiety in patients [1], it may help to finally shift real-life treatment practices for low-risk thyroid cancer and provide more opportunities to discuss available options with patients. The COVID-19 pandemic may provide us, as clinicians, with a

better ability to reduce low-value care and potentially unnecessary treatments, as well as with improved clarity and communication skills, leading to a better and more shared decision-making process.

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Compliance with ethical standards

Conflict of interest The authors have no relevant financial or non-financial interests to disclose. Sebastiano Filetti is Editor-in-Chief of Endocrine. Dr. Filetti was blinded to the peer review process of this article.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics committee of Sapienza University of Rome (No. 3366).

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

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