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Comparison of Clinical and Pathological Characteristics of Thyroid Cancer Surgery in the Pandemic Era

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Abstract

Background: The COVID-19 pandemic brought significant challenges for oncology centers and cancer patients, necessitating the implementation of various preventive and restrictive protocols and postponing elective surgeries. We aimed to assess and compare tumor characteristics, including the size, metastasis, and duration of hospitalizations between the periods before and during COVID-19 in patients with thyroid cancer.

Methods: The present cross-sectional study was performed at The Institute of Cancer, Tehran University of Medical Sciences, with 143 patients observed 2 years before the pandemic and 92 during March 2020 and March 2022. Clinical and pathological tumor characteristics were compared between the 2 groups, including surgical details, hospitalization and intensive care unit (ICU) admission durations, time intervals between diagnoses and surgeries, and various metastatic factors. All data were analyzed using SPSS software 21. The chi-square test was used for the statistical analysis of qualitative data, and the t test was used for the statistical analysis of continuous data. $P < 0.05$ was considered statistically significant.

Results: The most frequent tumor type was papillary thyroid cancer (134 [93.7%] and 82 [89.13%]; $P = 0.209$). The right lobe was the most prevalent tumor site both before and during COVID-19, respectively (55 [38.5%] and 29 [31.5%]; $P = 0.278$). Central (64 [50.8%] and 62 [49.2%]; $P < 0.001$), and lateral (45 [34.5%] and 45 [48.9 %]; $P = 0.045$) lymph node metastasis in the first surgery and recurrence ($P = 0.006$ and $P = 0.022$, respectively) were significantly higher in patients admitted during the COVID-19 pandemic, respectively. The mean interval between the first surgery and subsequent surgery due to recurrence ($P < 0.001$), duration of ICU admission ($P = 0.010$), and hospitalization after the second operation were significantly lower during the pandemic ($P = 0.006$).

Conclusion: During the COVID-19 pandemic, patients exhibited larger tumors, increased lymph node metastasis, and shorter intervals between surgeries. This underscores the need for healthcare decision-makers to implement effective thyroid cancer management strategies in future outbreaks.

Our study stands out by analyzing hospitalization and ICU admissions and duration for each patient, unlike any other study. Moreover, we extended our observation period beyond the typical duration found in most of the literature.

Keywords: Thyroid Cancer, COVID-19, Pathology, Metastasis, Thyroidectomy

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Introduction

The COVID-19 pandemic has disrupted cancer treatment, presenting challenges for oncology centers and pa-

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↑What is "already known" in this topic:
The COVID-19 pandemic caused significant disruptions in cancer treatment, including thyroid cancer, due to delays in surgeries and medical consultations. These delays may worsen clinical outcomes, although some cancers can tolerate postponed treatment without disease progression.

→What this article adds:
This study compares tumor characteristics and hospitalization durations in thyroid cancer patients before and during COVID-19. It provides crucial evidence on how pandemic-related delays impacted disease progression and surgical outcomes, informing future decision-making for cancer treatment during health crises.

tients (1-3).

Preventive protocols, such as restricting admissions and postponing surgeries, led to hesitations among patients to seek medical care, potentially worsening their conditions (4-7).

In addition, due to fears of COVID-19 infection, numerous patients hesitated to attend medical centers for follow-ups, screenings, and treatments. This hesitation may have resulted in delayed treatment and a deterioration in the clinical condition of patients with critical health issues, such as life-threatening cancers.

However, for some cancers, delayed treatment may not result in disease progression (8, 9). Thyroid cancer, the most common endocrine malignancy, has rapidly increased in incidence due to advanced diagnostics (10-12). Prognosis factors include cancer stage, pathology, and lymph node metastasis (13-18).

Although thyroid cancer has an indolent nature, postponing necessary surgeries due to the pandemic may cause more aggressive cancer behavior, leading to a poor prognosis of cancer. The impact of this situation remains unknown and controversial.

This study aims to assess and compare tumor characteristics, such as size and metastasis, and hospitalization durations before and during COVID-19 in patients with thyroid cancer. These findings are crucial for making evidence-based decisions in future outbreaks.

Methods

Study Population

Patients over 18 years who underwent surgery for thyroid cancer or its recurrence 2 years before the COVID-19 period (between November 2018 and November 2020) and those who underwent surgery during the first 2 years of the pandemic (between March 2020 and March 2022) at The Institute of Cancer, Tehran University of Medical Sciences, with preoperative pathology report indicative of malignancy, were included in the study. Exclusion criteria were death during the admission time due to intra- or postoperative complications or any other cause, missing data on the pathology report of the primary tumor, patients with postoperative malignant pathology but preoperative benign pathology, and incomplete demographic information. All patients with missing data were excluded. The inclusion and exclusion criteria were applied, leaving us with 263 patients (143 patients before COVID-19 and 92 patients during the pandemic). All patients underwent thyroid cancer surgery during the mentioned period by a group of 4 head and neck surgeons with the same training, level of experience, and types of techniques employed.

Sample Size Determination and Power Analysis

The sample size was determined based on an anticipated effect size of 0.5 for differences in tumor characteristics (such as size and metastasis) and hospitalization durations between the pre-COVID-19 and during COVID-19 periods. Using a 2-tailed test with a significance level (alpha) of 0.05 and a power (1-beta) of 0.80, a minimum of 88 patients per group was required to detect a significant difference. Our study includes 143 patients before COVID-19 and 92 patients during the pandemic, which exceeds the minimum required sample size and ensures adequate power to detect meaningful differences between the groups.

Data Collection and Variables Definition

The following information was collected for all the included patients based on the records before and during COVID-19: age, sex, comorbidity, lymph node central and lateral metastasis in ultrasound, histological characteristics (papillary, medullary, follicular, Hürthle), and pathological characteristics of the mass (mass size, multicenter, metastasis out of thyroid, lymph node metastasis, perineural metastasis, lymph vascular metastasis, place of mass in thyroid, lymph node ratios), type of initial and recurrence surgery, the durations of hospitalization and intensive care unit (ICU) admission after first and recurrence surgery, the time interval between the first or recurrence diagnosis and subsequent surgical procedure, and the time interval between the first and recurrence surgeries. The present study used the latest version of the National Comprehensive Cancer Network (NCCN) guidelines for primary considerations and the American Joint Committee on Cancer (AJCC) staging system to determine thyroid tumors. According to the AJCC, the staging of different pathologies of thyroid cancer—such as papillary cancer, follicular, medullary, and Hürthle—has slight differences that were addressed accordingly in this study. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part are appropriately investigated and resolved. The study was conducted by the Declaration of Helsinki of 1975, as revised in 2013. This study was approved by the Institutional Review Board of Tehran University of Medical Sciences, with the ethics code "IR.TUMS.IKHC.REC.1401.052". All participants provided written informed consent before their inclusion in the study.

Statistical Analysis

All data were analyzed using SPSS software 21 (SPSS Inc), and continuous data were reported as mean ± standard deviation. The chi-square test was used for the statistical analysis of qualitative data, and the t test was used for the statistical analysis of continuous data. $P < 0.05$ was considered statistically significant.

Results

The present study was conducted on 236 patients with thyroid cancer, including 143 (61%) patients admitted before COVID-19 and 92 (39%) during COVID-19. Among these patients, 170 (72%) were women, and 66 (28%) men. The demographic characteristics of study participants are presented in Table 1.

The mean age of the study participants was 41.58 ± 13.2 years, with the minimum age of 18 and the maximum age of 80 years. Most studied participants (N = 182 [77.1 %]) had no remarkable past medical history. Furthermore, hypertension was the most common comorbidity in the studied participants. In addition, the mean age of patients

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with thyroid cancer admitted during COVID-19 was higher than that of before COVID-19. However, this difference was not statistically significant.

A Comparison of the clinical characteristics of patients with thyroid cancer before and during COVID-19 is provided in Table 2.

The mean time intervals between the first surgery and subsequent surgery due to recurrence, duration of hospitalization, and duration of ICU admission in recurrence were significantly lower among patients admitted during the COVID-19 pandemic (mean ± SD: 1.46 ± 5.18 vs 10.38 ± 25.91, 0.57 ± 1.51 vs 1.39± 2.58, 0.21 ± 0.69 vs 0.55± 1.13; $P < 0.001$, P = 0.006, and $P = 0.010$, respectively). The mean duration of hospitalization and ICU admission for the first operation did not differ significantly during the pandemic compared to before.

The pathological characteristics of thyroid tumors in patients with thyroid cancer before and during COVID-19 are presented in Table 3.

The most frequent tumor type was papillary thyroid cancer, and the right lobe was the most prevalent size of the tumor. Central as well as lateral LN metastasis in the first operation and recurrence is more prevalent among patients admitted during the COVID-19 pandemic (frequency, 62 [67.4%] vs 64 [44.8%], $P < 0.001$, 45 [48.9%] vs 45 [34.6%], $P = 0.045$), respectively. Central lymph node metastasis in recurrence during the pandemic was lower than before the pandemic period. (5 [5.4%] vs 25 [17.5%], $P < 0.006$). The mean tumor size was considerably higher during COVID-19 (mean + SD: 33.37 ± 26.96 vs 25.13 ± 18.41, $P = 0.005$).

Moreover, the mean left lateral lymph node ratio in the first operation was significantly higher during COVID-19 (mean ± SD: 1.95 ± 5.39 vs 0.83 ± 2.19, $P = 0.027$).

Discussion

The aggressive behavior of thyroid cancer is recognized through larger tumor size, the presence of lymph node metastasis, extrathyroidal metastasis, and additional contributing factors (19, 20).

The present study revealed that patients admitted with thyroid cancer during the pandemic exhibited noticeably larger tumor sizes, which is consistent with the previous data from the literature (21-24). Medas et al observed a total of 1570 patients from 28 surgical units and noted that the mean tumor size was higher in the group that underwent surgery during the pandemic than that before COVID-19 (21). In 2023, his group performed a more extensive review among 157 centers around the world and observed a raised incidence of thyroid tumors more significant than 10 mm in 2021 compared with the data from 2019 (24).

Our research also demonstrated increased central and lateral lymph node metastasis and an elevated lymph node, left lateral ratio in patients undergoing their first operation during the COVID-19 pandemic. There was no difference in extrathyroidal, lymphovascular, and perineural metastasis. In accordance with our study, increased

Table 1. The demographic characteristics of study participants based on the time of admission. The variables are presented as frequency (column, %) or mean (SD)

Demographic Items		Before COVID-19 (N=143)	During COVID-19 (N=92)	*P*
Sex	Women	101 (70.6%)	68 (73.9%)	
	Men	42 (29.4%)	24 (26.1%)	0.584
PMH	None	116 (81.1%)	66 (71.7%)	
	HTN	9 (6.3%)	16 (17.4%)	0.093
	Cardiac Disease	0 (0.0%)	1 (1.1%)	
	Pulmonary Disease	1 (0.7%)	0 (0.0%)	
	Renal Disease	1 (0.7%)	0 (0.0%)	
	DM	7 (4.9%)	3 (3.3%)	
	Multi-comorbidities	9 (6.3%)	6 (6.5%)	
Age		40.85±12.30	42.48±14.48	0.356

Table 2. Clinical characteristics of the patients with thyroid cancer based on time of admission. Qualitative variables are presented as frequency (Row, %) and quantitative variables are presented as mean (SD)

Surgical Items		Before COVID-19	During COVID-19	*P*
Type of initial surgery	Total Thyroidectomy	68 (73.9%)	24 (26.1%)	<0.001
	Total Thyroidectomy + central dissection	30 (54.5%)	25 (45.5%)	
	Total Thyroidectomy + Central & lateral dissection	35 (49.3%)	36 (50.7%)	
Type of surgery in recurrence	Without recurrence [a]	97 (56.1%)	76 (43.9%)	0.012
	Central lymph node metastasis	4 (80.0%)	1 (20.0%)	
	Lateral lymph node metastasis	20 (64.5%)	11 (35.5%)	
	Central and lateral lymph node recurrence	22 (84.6%)	4 (15.4%)	
Duration between first and recurrence surgeries (month)[b]		10.38±25.91	1.46 ±5.18	<0.001
Duration of ICU admission in recurrence (day)		0.55±1.13	0.21± 0.69	0.010
Duration of hospital admission in first surgery (day)		4.31±3.72	4.09±2.97	0.633
Duration of hospital admission in recurrence (day)		1.39±2.58	0.57±1.51	0.006

[a] Undergone surgery just once.
[b] The time interval between first and subsequent surgical procedure due to recurrence.

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Table 3. The pathological characteristics of patients with thyroid cancer based on the time of admission. Qualitative variables are presented as frequency (Row, %) and quantitative variables are presented as mean (SD)

Pathologic Items		Before COVID-19	During COVID-19	*P*
Tumor Type	Papillary	134 (93.7%)	82 (89.13%)	0.209
	Follicular	1 (0.69%)	2 (2.17%)	
	Medullary	6 (4.19%)	8 (8.69%)	
	Hurthle	2 (1.39%)	0 (0.0%)	
Tumor location	Right lobe	55 (38.46%)	29 (31.52%)	0.278
	Left lobe	35 (24.47%)	23 (25%)	
	Isthmus	2 (1.39%)	2 (2.17%)	
	Right lobe and isthmus	5 (3.49%)	3 (3.26%)	
	Left lobe and isthmus	7 (4.89%)	4 (4.34%)	
	N/A (Missed)	30 (20.97%)	31(33.69%)	
Multifocal	Yes	85 (59.5%)	58 (63.0%)	0.580
	No	58 (40.5%)	34 (37.0%)	
Invasion outside of thyroid	Yes	34 (23.7%)	21 (22.8%)	0.866
	No	109 (76.3%)	71 (77.2%)	
Perineural Invasion	Yes	20 (14%)	11 (12%)	0.653
	No	123 (86%)	81 (88%)	
Lymphovascular Invasion	Yes	91 (63.7%)	65 (70.7%)	0.266
	No	52 (36.3%)	27 (29.3%)	
Lymph node central metastasis in first operation	Yes	64 (44.8%)	62 (67.4%)	<0.001
	No	79 (55.2%)	30 (27.5%)	
Lymph node lateral metastasis in first operation	Yes	45 (34.5%)	45 (48.9%)	0.045
	No	98 (65.5%)	47 (51.1%)	
Lymph node central metastasis in recurrence	Yes	25 (17.5%)	5 (5.4%)	0.006
	No	22 (15.4%)	11 (12%)	
	Without Recurrence	96 (67.1%)	76 (82.6%)	
Lymph node lateral metastasis in recurrence	Yes	42 (29.4%)	15 (16.3%)	0.022
	No	5 (3.5%)	1 (1.1%)	
	Without recurrence	96 (67.1%)	76 (82.6%)	
Tumor size (mm)		25.13 ±18.41	33.37 ±26.96	0.005

aggressive behavior is mentioned in several studies (22-27). A large study on Renmin Hospital of Wuhan University divided 3216 patients into the pre-lockdown and post-lockdown groups and reported that the occurrence of lymph node metastasis (37·7% vs 45%) and extrathyroidal extension (65·5% vs 72%) was higher in the post-lockdown group. It also showed that favorable rates of central and lateral lymph nodes elevated in the post-pandemic group (36.4% vs 43.9%, 7.8% vs 10.9%) (28). A Korean study revealed higher proportions of extrathyroidal, lymphatic, vascular, and cervical lymph node metastasis among patients with papillary thyroid carcinoma during COVID-19 despite no significant change in overall frequency (23).

To analyze the reasons for this behavior, there are several rationales. During the COVID-19 pandemic, the appointments of patients with cancer and chronic diseases were postponed as a result of multiple lockdowns. Moreover, concerns about the high transmission rate of the virus and the potential for increased morbidities and mortalities in these patients held them back from adhering to regular follow-up protocols. Consequently, physicians might have overlooked tumor progression and missed further evaluations, such as fine needle aspiration (FNA) and ultrasound, to detect changes. In a study by Rana et al (29), in line with Spartalis et al (30) and Stefanou et al (31), the FNA of thyroid tissue decreased significantly during the pandemic, as did outpatient visits. Although thyroid cancers generally have an excellent prognosis and slow-growing characteristics in most of them, we should not neglect the hypothesis that a delay in treatment may lead to a more aggressive behavior pattern in cancer.

The COVID-19 pandemic also influenced the pattern of patient selection for thyroid surgery among surgeons, leading to higher stages of tumor upon admission. Our study supports this hypothesis. During the pandemic, in our institution, thyroidectomy with central and lateral neck dissection became the most commonly performed surgery, whereas before COVID-19, thyroidectomy held the position. In line with these findings, Medas et al reported an increased rate of central compartment lymph node dissections between June 1 and Dec 31, 2021 (24).

Another hypothesis is that we included both patients with newly diagnosed cancer and with recurrence. This inclusion may lead to the involvement of higher-stage tumors and more aggressive ones (32). According to a study in 2022, patients with early-stage cancer experienced about a 7% risk of recurrence, while in advanced-stage disease, the rate was 28% (33).

A possible hypothesis is that the SARS-CoV-2 virus, responsible for COVID-19, can induce proliferation in tumor cells. A study showed SARS-CoV-2 and thyroid sarcoma coexistence may lead to synergistic interaction, potentially favoring both viral persistence and tumor proliferation (34). Another study (23) concluded that the virus can infiltrate cells by binding to the angiotensin-converting enzyme-2 (ACE2) receptor, a receptor present in thyroid cells (35). Alongside ACE2, another essential protein, TMPRSS2, is highly expressed in thyroid cells and is crucial for viral entry (36). These proteins can make thyroid cells susceptible to SARS-CoV-2 infection. As a result of severe damage to thyroid cells in COVID-19-infected patients, follicle disruptions can be observed. Also, the inflammation caused by the virus in associated

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with the development of thyroid cancer. However, further research is necessary to investigate the potential association.

There is an ongoing debate about a possible reason for these results. With the increased use of advanced and highly sensitive diagnostic techniques, more incidental diagnoses of cancers occurred in the last few years, resulting in an "epidemic of overdiagnosis"—the detection of cancers and nodules, which would not have caused harm, if left untreated (12, 37-39). While the COVID-19 pandemic restricted the prior protocols of diagnosis and treatments, it might provide an opportunity to reassess and revise the guidelines.

Therefore, during the pandemic, these techniques were applied to patients requiring intervention. A study examined ultrasound characteristics before and after lockdown, finding no significant difference among patients with tumors ≤10 mm and treatment delay of <180 days (28). Another study reported that despite an increased rate of high-risk patients and a decreased rate of low-risk patients during the lockdown—defined according to the American Thyroid Association risk stratification for differentiated thyroid cancer—the short-term outcomes were not negatively affected by this stratification (27). If this is also validated in long-term outcomes, active surveillance can be carried out with more confidence.

Active surveillance is an approach for managing low-risk patients that allows clinicians to customize the treatment plan according to the tumor characteristics of each patient—achieved through close interactions and scheduled visits between surgeons and patients. This approach can minimize unnecessary treatments in healthcare institutions and conserve valuable resources, both financial and human (40-42). Thus, we suggest close observation for low-risk cancers, noting that careful selection must be done according to the tumor pathologies.

However, in a study that enlisted thyroid cancer surgeons and endocrinologists from around the world with experience managing this cancer during COVID-19 and explored their perspectives, the primary treatment clinicians reported as postponed was thyroidectomy (57.3%), followed by surveillance imaging (50.3%). When asked if they were concerned about the delayed treatment, 24.1% reported being very much or quite a bit worried, while 63.8% reported being somewhat or a little bit worried. The most commonly cited reason for clinician worry was patient anxiety (43). Therefore, encouraging patients to accept and trust active surveillance is a challenging task that can be achieved through a close relationship between the physician and the patient.

Our study revealed other intriguing findings. We reviewed the time intervals between surgeries and the durations of hospital and ICU admissions for new-onset patients and those with recurrence before and during the COVID-19 era.

The time intervals between the first and subsequent surgery due to recurrence were significantly longer before COVID-19. Additionally, the durations of hospital and ICU admission in cases of recurrence were considerably lower during the COVID-19 pandemic. On the contrary, no significant differences were observed in the durations for the first-time surgery patients. The literature also reported a reduced duration of hospitalization both before and after the operation during the pandemic (22, 26). This difference may have occurred due to safety restrictions aimed at reducing COVID-19 transmission.

On the other hand, these restrictions compelled physicians to minimize unnecessary postoperative treatments and interventions to discharge the patient as soon as possible and mitigate the risk of morbidities and mortalities associated with COVID-19. Should these approaches yield positive outcomes in both the short and long term, they can be further studied and potentially incorporated to enhance guidelines, optimizing the usage of facilities for patients in more critical conditions.

This study had some strengths and limitations. Previous studies on this topic were primarily conducted in developed countries, and very few were conducted in the Middle Eastern and North Africa (MENA) regions, which have limited healthcare resources. This study gives a clearer perspective on the changes in the characteristics of thyroid cancer in developing countries during COVID-19, which may be different from the developed countries due to other races, environmental risk factors, lifestyles, and diagnostic approaches specific to this region. Further studies in the MENA region are recommended. We are aware that our study had several limitations. This was a single-center study in a tertiary hospital; thus, the generalizability of the findings is questionable. A multicenter study with a larger sample size is suggested. Also, this study did not provide a separate analysis for each type of thyroid cancer. Considering the different characteristics of each tumor type, this could have distorted the results, but the limitation was inevitable due to our limited access to patients' datasets. Last, the clinic visits and surgeries were performed by different surgeons, which may have caused inconsistency in management approaches and surgical patterns.

Conclusion

The long-term consequences of the COVID-19 pandemic are not yet fully known. The pandemic affected the pathological characteristics of thyroid tumors. During the COVID-19 pandemic, patients had considerably higher tumor size, central and lateral lymph node metastasis, and significantly lower mean duration between the first surgery and subsequent surgery due to recurrence, the duration of ICU admission, average ICU admission, and hospitalization after the second operation. These findings could be related to various hypotheses, with the most significant and debatable one being the progression of the tumor due to a delay in treatment. We suggest that surgical interventions for tumors, identified through reliable methods, should not be delayed, and establishing a close relationship between the physician and the patient is crucial to alleviate the patient's anxiety.

Authors' Contributions

The study was conceived and designed by A.S., M.S.,

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M.Y.K., and F.M., A.J. and I.H. provided administrative support. M.M.L. contributed to the provision of study materials for patients. A.S. collected and assembled the data. Data analysis and interpretation were performed by F.M., M.Y.K., and F.A. All the authors contributed to the writing and final approval of the manuscript.

Ethical Considerations

The authors are accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Tehran University of Medical Sciences approved the study, with the ethics code IR.TUMS.IKHC.REC.1401.052.

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Conflict of Interests

The authors declare that they have no competing interests.

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