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ORIGINAL RESEARCH

More Aggressive Cancer Behaviour in Thyroid Cancer Patients in the Post-COVID-19 Pandemic Era: A Retrospective Study

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Purpose: Many thyroid cancer patients have suffered from treatment delays caused by the coronavirus disease 2019 pandemic. Although there have been many reviews, recommendations, or clinical experiences, clinical evidence that evaluates patient disease status is lacking. The aim of our research was to evaluate thyroid cancer behaviour in the post-COVID-19 era.

Patients and Methods: A retrospective study was conducted and thyroid cancer patient data from February 1, 2017 to September 15, 2020 were pooled for analysis. The demographic, ultrasound and pathological data of the pre- and post-COVID-19 groups were compared. Lymph node metastases, tumour size, extrathyroidal extension, and multifocality were compared year-by-year to evaluate annual changes in patient characteristics. Regression analyses were adopted to reveal cancer behaviour along with the admission date interval and to reveal risk factors for lymph node metastasis. Patient ultrasound data were compared before and after the lockdown to assess tumour progression. The outcomes of delays in treatment ≤180 days were then studied.

Results: The post-lockdown patients were more likely to have multiple lesions (31.2% vs 36.5%, $p = 0.040$), extrathyroidal extension (65.5% vs 72.2%, $p = 0.011$) and lymph node metastases (37.7% vs 45.0%, $p = 0.007$), while tumour size remained stable (1.01cm vs.1.02cm, p = 0.758). The lymph node metastasis rate increased by year ($p < 0.001$). The tumour size correlated negatively with the post-lockdown admission date ($p = 0.002$). No significant difference in tumour size, multifocality or lymph node metastasis on ultrasound was revealed between the pre- and post-lockdown group. No significant difference in tumour size, multifocality, extrathyroidal extension or lymph node metastasis was revealed among patients with a delayed treatment time ≤180 days.

Conclusion: Patients with a COVID-19-induced treatment delay had more aggressive cancer behaviour. Rebound medical visits and annually increasing aggressiveness may be potential reasons for this observation, as individual patient tumour did not progress during the delay.

Keywords: treatment delay, lockdown, rebound medical visit, tumor behavior

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Introduction

Since the first patient was discovered in Wuhan, China, in December 2019, the coronavirus disease 2019 (COVID-19) pandemic has spread around the world and has led to over 220 million infections and approximately 4.6 million deaths in 220 countries worldwide.[1] To minimize the risk of interpersonal transmission, many medical institutions have adopted protection strategies, such as teleconsultation, mandatory tests for COVID-19 antibodies and nucleic acids, the wearing of masks or other personal

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protection equipment, and admission restrictions.[2–5] These methods have shown protective effects in the fight against COVID-19. Despite the beneficial effects, these protective approaches may have a negative impact on the clinical management of patients.

Some cancer patients have been advised to reduce their visits to medical institutions to avoid nosocomial infections. As a consequence, a large percentage (38.7% to 59.0%) of cancer patients were reported to have experienced a COVID-19-induced treatment delay.[6–8] Severe anxiety and depression were observed among those patients.[9] Although a three-month delay in cancer treatment was deemed tolerable in some studies and recommendations,[10,11] such advice must be adopted with great caution. Obviously, cancers originating from different tissues need to be handled according to their severity and aggressiveness. Patients with aggressive cancers, such as non-small-cell lung cancer, acute myeloid leukaemia, or melanoma, will have a much poorer prognosis if their active interventions are postponed.[12–14] In contrast, those with indolent tumours, including most prostate cancers or differentiated thyroid carcinomas, may tolerate a rather long-term delay without cancer disease progression.[15,16] The above current clinical studies have focused on the poor prognoses of high-risk cancers, while clinical evidence is lacking in low-risk cancers.

Thyroid carcinoma is the most frequently diagnosed cancer of the endocrine system, and its incidence has increased threefold over the past 2 decades.[17] Although most studies have attributed the increasing incidence to overdiagnosis,[18,19] some other scholars have debated whether there is a concurrent true increase in disease occurrence. Evidence supporting this hypothesis includes an increasing mortality rate (by an average of 2.9% per year) and increasing numbers of large tumours, extrathyroidal extension and cervical metastases.[20,21] A hypothesis may thus be deduced that there has been a true increase in severity over the years. In addition, patient worry is another factor to be considered. A previous study supported that thyroid cancer patients with more aggressive cancer behaviour tended to be more worried.[22] Those worried patients may have been more active in seeking for medical care,[23,24] which may have led to a pseudo-increase in the perceived severity of the disease after the lockdown. Moreover, although thyroid cancers are indolent in most cases, there is a possibility that some patients have suffered tumour progression during the pandemic-induced lockdown. According to guideline, cervical ultrasound is the first choice in monitoring tumour progression,[25] and some patients underwent cervical ultrasound examinations both before and after the pandemic-induced lockdown.

During the COVID-19 pandemic, Wuhan implemented a lockdown policy from January 23rd to April 8th, 2020. Some oncology departments were partly closed for 3 to 6 months (varying by hospital) when almost all thyroid cancer patients were advised to stay at home to reduce social contact.[26] This study took the rare and valuable opportunity presented by the lockdown to evaluate the natural development of thyroid cancer and to investigate the change in cancer behaviour in the pre- and post-lockdown era and its potential reasons.

Materials and Methods

Study Design and Participants

This single-centre, retrospective, cohort study was conducted at Renmin Hospital of Wuhan University. Data were collected from February 1st, 2017 to September 15th, 2020. All patients ≥18 years old, and admitted to Renmin Hospital of Wuhan University with any histological types of thyroid cancer as evidenced by postsurgical pathological sections were included in this study. Included patients had to have complete pathological data. This was a four-step study. First, the demographic and postsurgical pathological characteristics were compared between the pre- and post-lockdown groups to assess whether cancer behaviour after the lockdown was more aggressive. If the hypothesis was confirmed, the remaining three steps were designed to evaluate the potential reasons. Divided according to the year of their admission, patients' characteristics were then compared to evaluate the annual change in the thyroid cancer patient spectrum. Afterwards, patients admitted after the lockdown were analyzed as a subgroup and their characteristics, along with their admission dates, were evaluated to study the hypothesis of an increase in cases being due to rebound medical visits. Finally, those patients, who were scheduled for surgery but failed to be admitted before the lockdown and then received surgery after the reopening, were considered separately to study the change in individual tumour behaviour among this subset. All patients included in our study were scheduled for surgery based on ultrasound or/and fine-needle aspiration biopsy findings. Medical equipment and criteria remained unchanged over the four years. This study was approved by the Independent Ethics Committee (IEC) of Renmin Hospital

of Wuhan University (number: WDRY2020-K231) and was conducted in compliance with the Declaration of Helsinki. Patients were anonymized and their data confidentiality was protected. Since this was a retrospective observational study with no intervention, the requirement for informed consent was waived according to the IEC guidelines.

Data Collection and Definition

Six independent investigators collected the data in standardized case report forms and cross-checked them with each other. The patients' demographic characteristics, clinical presentations, pathological data, sonographic data, laboratory values, treatments, and postsurgical conditions were obtained from the Hospital Information System. Comorbidities included hypertension, diabetes mellitus, cerebrovascular diseases and other chronic diseases. Other concomitant thyroid diseases were excluded from comorbidities. The pre-COVID-19 ultrasound data were collected based on the last ultrasound before the pandemic. Lesions were evaluated in accordance with the Thyroid Imaging, Reporting and Data System (TI-RADS) of the American College of Radiology.[27] The delay time was defined as the interval between the date of the last pre-pandemic ultrasound and the date of the pre-surgical ultrasound. The admission date interval (ADI) was defined as the interval between the patient admission date and April 8th, 2020, which was the last day of lockdown. The data were then input into a database for further analysis.

Statistical Analysis

Patient numbers and percentages were calculated for categorized data. Continuous data are presented as the means (SDs) or medians (quantiles). The comparisons of clinical characteristics between different cohorts were conducted using the Pearson chi-square test or McNemar test for categorized data, the *t*-test or analysis of variance for continuous data, and the Mann–Whitney *U*-test or Wilcoxon's signed-rank test for ordinal data. Logistic regression analysis was employed to analyse the risk factors for lymph node metastasis. Logistic and linear regression analyses were also adopted to evaluate the correlation between admission date interval and pathological characteristics. A p value <0.05 was considered statistically significant. The statistical analysis was performed with SPSS version 23.0 (SPSS Inc, Armonk, NY).

Results

Demographic and Clinical Characteristics

From February 1, 2017 to September 15, 2020, a total of 3216 thyroid cancer patients with pathological evidence of disease were included in our study (Figure 1). Patients were divided into the pre-lockdown and post-lockdown groups according to their surgery dates (Supplementary Figure 1). Female patients accounted for 75.5% of all in-hospital patients. The mean and median ages were 45.9 and 47 years, respectively, with no significant difference between the pre- and post-lockdown groups. Comorbidities were more common before the pandemic (p = 0.001). Hashimoto's thyroiditis was discovered in 10.0% of patients with no significant difference observed between the two groups (p = 0.061). Among the patients, 13.7% reported that at least one of their family members had cancer or a personal history of another malignancy (Table 1).

The Comparison of Pathology Before and After the Lockdown

The dominant histological type was papillary thyroid carcinoma, which accounted for 98.7% of the total number of patients. Follicular (0.9%) and medullary (0.5%) carcinomas accounted for the remaining proportion, while anaplastic carcinoma was discovered in only six patients. A small number of patients had more than one type of cancer. Papillary thyroid microcarcinomas (PTMC) were found in 61.5% of all patients. The average maximum size of tumour was 1.01 cm in the pre-lockdown group and 1.02 cm in the post-lockdown group (p = 0.758). Patients after the lockdown tended to have a greater number of multiple lesions

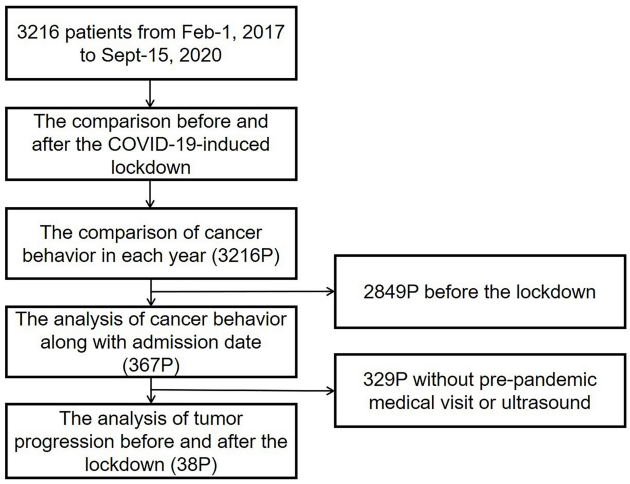

Figure 1 The flow chart of the study. P is the abbreviation of "cases".

Table 1 Cohort Clinical Characteristics of 3216 Patients with Thyroid Cancer Before and After the COVID-19-Induced Lockdown[a]

Variable	Total	Pre-Lockdown	Post-Lockdown	*P* value
Sex, female (%)	2427 (75.5)	2137 (75.0)	290 (79.2)	0.079
Age				
Mean (SD)	45.9 (11.9)	46.0 (11.9)	45.3 (11.5)	0.275
Median (IQR)	47 (37, 54)	47 (37, 54)	46 (36, 53)	0.381
≤50y (%)	2009 (62.5)	1776 (62.3)	233 (63.5)	0.668
Comorbidities (%)[b]	836 (26.0)	768 (27.0)	68 (18.5)	**0.001****
Hashimoto's thyroiditis (%)	323 (10.0)	276 (9.7)	47 (12.8)	0.061
Familial or personal history of cancer (%)	442 (13.7)	400 (14.0)	42 (11.4)	0.174
Histological type and subtype (%)				
Papillary	3174 (98.7)	2811 (98.7)	363 (98.9)	0.699
PTMC	1978 (61.5)	1750 (61.4)	228 (62.1)	0.795
Follicular	30 (0.9)	27 (0.9)	3 (0.8)	0.807
Medullary	16 (0.5)	16 (0.6)	0 (0.0)	0.150
Postoperative pathological information				
Maximum size (SD)	1.01 (0.83)	1.01 (0.83)	1.02 (0.84)	0.758
Multifocal lesion (%)	1023 (31.8)	889 (31.2)	134 (36.5)	**0.040***
Extrathyroidal extension (%)	2132 (66.3)	1867 (65.5)	265 (72.2)	**0.011***
Lymph node metastasis[c]	1240 (38.6)	1075 (37.7)	165 (45.0)	**0.007****
CLNM (%)	1199 (37.3)	1038 (36.4)	161 (43.9)	**0.006****
LLNM (%)	262 (8.1)	222 (7.8)	40 (10.9)	**0.041***
CLN positive number (SD)	3.79 (3.60)	3.78 (3.60)	3.81 (3.60)	0.942
LLN positive number (SD)	6.20 (5.27)	5.97 (5.19)	7.45 (5.62)	0.102

Notes: Bold font: significant difference. *$p<0.05$, **$p<0.01$. [a]A number of 2849 patients before the lockdown and 367 after the lockdown were included in the analysis. The admission date of included patients ranged from Feb. 1, 2017 to Sept. 15, 2020. [b]Other concomitant thyroid diseases were excluded from comorbidities. [c]CLN and LLN positive number was calculated in 1200 patients with CLN metastasis and 259 with LLN metastasis, respectively.
Abbreviations: PTMC, papillary thyroid micro carcinoma; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis.

than patients before the pandemic ($p = 0.040$). In the post-lockdown patient groups, extrathyroidal extension ($p = 0.011$), and lymph node metastases ($p = 0.007$) were more common than in the pre-pandemic patient group. In addition, the central and lateral lymph node positive rates increased in the post-pandemic group (36.4% vs 43.9%, $p = 0.006$, 7.8% vs 10.9%, $p = 0.041$) (Table 1 and Supplementary Figure 2A and B).

The Comparison of Pathology in Each Year

A comparison of postoperative pathology was then conducted for each year of the study's duration. Patients were divided into four groups based on their admission year. The main postoperative pathological characteristics, including tumor size, lymph node metastasis (LNM), and extrathyroidal extension (ETE), were compared. The proportion of patients with LNM increased gradually from 32.2% in 2017 to 45.0% in 2020 ($p < 0.001$). The uprising rate of central LNM was the principal cause ($p < 0.001$) while the rate of patients with lateral LNM remained stable over the same four years ($p = 0.150$). In addition, no significant difference was observed in tumour size ($p = 0.194$), multifocality ($p = 0.168$) or ETE ($p = 0.071$) (Table 2 and Supplementary Figure 2C–F).

Regression analyses were then applied to evaluate the correlations between LNM and demographic characteristics, ultrasound data and admission year. Age ≤50 years (OR = 2.272, $p < 0.001$), female sex (OR = 0.596, $p < 0.001$), tumour size (OR = 1.391, $p < 0.001$), and the TI-RADS score (OR = 1.296, $p < 0.001$) showed to have correlations with central LNM. In addition, female sex (OR = 0.502, $p = 0.002$), tumour size (OR = 1.487, $p < 0.001$), and the TI-RADS score (OR = 1.589, $p < 0.001$) were correlated with lateral LNM. Interestingly, the rate of central LNM increased with admission year (OR = 1.214, $p < 0.001$) (Figure 2 and Supplementary Table 1).

Table 2 Cohort Clinical Characteristics of 3216 Patients with Thyroid Cancer of Every Year[a]

Variable	2017 Feb-	2018 Feb-	2019 Feb-	2020 Feb-	*P* value
Sex, female (%)	503 (74.6)	771 (77.1)	863 (73.5)	290 (79.2)	0.074
Age					
Mean (SD)	46.4 (12.1)	46.2 (12.2)	45.5 (11.6)	45.2 (11.5)	0.198
≤50y (%)	396 (58.8)	610 (60.9)	770 (65.6)*	233 (63.5)	**0.019**
Comorbidities (%)[b]	200 (29.7)	276 (27.6)	292 (24.9)	68 (18.5)*	**0.001**
Hashimoto's thyroiditis (%)	80 (11.9)	104 (10.4)	92 (7.8)*	47 (12.8)*	**0.007**
Familial or personal history of cancer (%)	99 (14.7)	120 (12.0)	181 (15.4)	42 (11.4)	0.057
Histological type and subtype (%)					
Papillary	662 (98.2)	990 (98.9)	1159 (98.7)	353 (98.9)	0.648
PTMC	398 (59.1)	639 (63.8)	713 (60.7)	228 (62.1)	0.224
Follicular	10 (1.5)	7 (0.7)	10 (0.8)	3 (0.8)	0.401
Medullary	5 (0.7)	5 (0.5)	6 (0.5)	0 (0.0)	0.448
Anaplastic	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.3)	0.460
Postoperative pathological information					
Maximum size (SD)	1.07 (0.94)	1.00 (0.83)	0.98 (0.76)	1.02 (0.84)	0.194
Multifocal lesion (%)	208 (30.9)	323 (32.3)	358 (30.5)	134 (36.5)	0.168
Extrathyroidal extension (%)	448 (66.5)	648 (64.7)	771 (54.7)	265 (72.2)	0.071
Lymph node metastasis (%)[c]	217 (32.2)	383 (38.3)	475 (40.5)*	165 (45.0)*	**<0.001**
CLNM (%)	211 (31.3)	368 (36.8)	459 (39.1)*	161 (43.9)*	**<0.001**
LLNM (%)	48 (7.1)	85 (8.5)	89 (7.6)	40 (10.9)	0.150
CLN positive number (SD)	3.63 (3.38)	3.78 (3.66)	3.86 (3.64)	3.81 (3.60)	0.885
LLN positive number (SD)	5.87 (5.28)	6.32 (4.33)	5.28 (4.43)	7.45 (5.62)	0.109

Notes: Bold font: significant difference. *Significant difference was reached in these subgroups. [a]An amount of 674 patients from 2017 Feb. to 2018 Jan, 1001 in 2018–2019, 1174 in 2019–2020 and 367 after the COVID-19-induced lockdown were included in the analysis. The patients in 2020 were limited to Sept. 15, 2020. [b]Other concomitant thyroid diseases were excluded from comorbidities. [c]CLN and LLN positive number was calculated in 1200 patients with CLN metastasis and 259 with LLN metastasis, respectively.

Abbreviations: PTMC, papillary thyroid micro carcinoma; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis.

Post-Pandemic Admission Date in Predicting Tumour Behaviour

The correlation between the tumour behaviour and the admission date interval was then evaluated using regression analysis. The data from 367 post-lockdown patients were pooled for the analysis. The admission date interval (ADI) was defined as the time interval between the patient's admission date and April 10, 2020, which was the last day of lockdown. A p value of 0.002 was reached in the correlation between tumour size and the ADI (Supplementary Figure 3). Linear regression analysis showed that the average postoperative pathological tumour diameter decreased by 4 mm every 100 days. Pathological LNM (OR = 1.000, p = 0.916), tumour number (slope = 0.000, p = 0.951) and ETE (OR = 0.998, p = 0.494), however, had no correlation with the ADI (Table 3).

Ultrasound Changes Due to a Treatment Delay

Thirty-eight patients who were scheduled for surgery but who failed to be admitted before the lockdown and received surgery after the reopening were extracted as a subset. These patients received thyroid ultrasound examinations both before and after the COVID-19-induced lockdown. The pre-COVID-19 ultrasound was defined as the last ultrasound before the pandemic. Their demographic and clinical characteristics were similar to the total patient sample. The average and median delay time for these patients were 201.3 days and 189 days, respectively (Supplementary Table 2 and Supplementary Figure 4).

More irregular margins were discovered by ultrasound after a long treatment delay (p = 0.012). Although there seemed to be some more aggressive features in the post-lockdown ultrasound images, no significant difference in

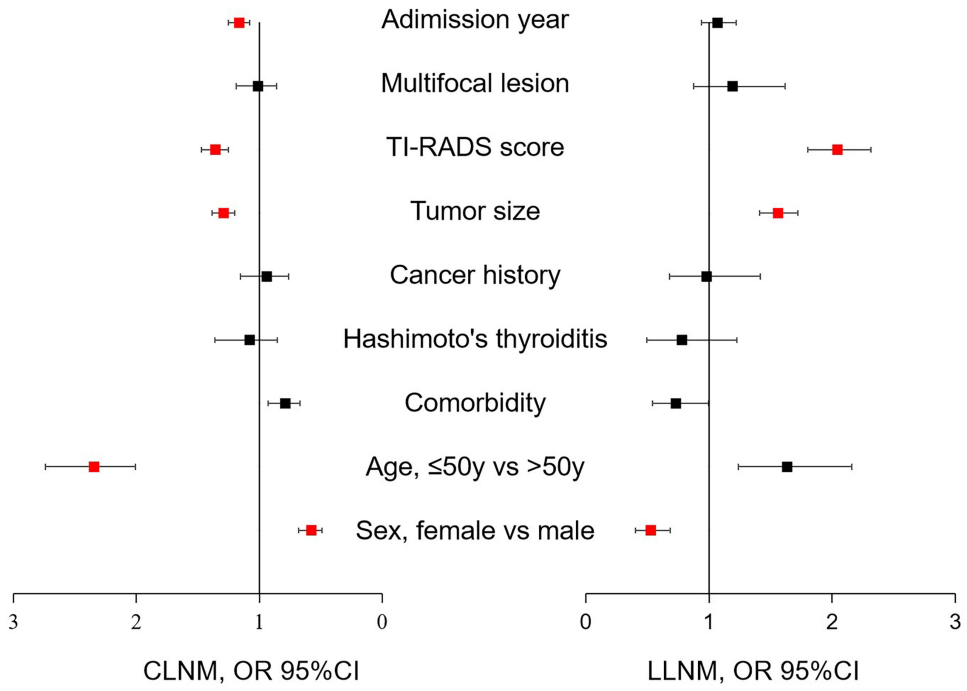

Figure 2 The univariate regression analysis of the correlations between CLNM, LLNM and demographic characteristics, pre-operative ultrasonic data and admission year. Risk factors with red marks had statistical significance in multivariate regression analysis.
Abbreviations: CLNM, lymph node metastasis; LLNM, lateral lymph node metastasis; OR, odd ratios.

the tumour size, aspect ratio, irregular margins, peripheral location, site, microcalcification, multiple lesions, or lymph node metastases was detected across these 38 patients (Table 4).

Outcomes of Treatment Delay in Tumours ≤10mm and Treatment Delay ≤180 Days in All Patients

The pre- and post-lockdown ultrasound characteristics were compared across 19 PTMC patients. There was no significant difference in tumour size, aspect ratio, microcalcification, or other ultrasound characteristics. There was no significant difference among the 16 patients whose delay time was less than 180 days (Table 5).

The total patient sample was then divided into two subgroups based on their tumour size. The subgroup with tumours ≤10mm in diameter showed minimal differences before and after the pandemic-induced lockdown. Those with tumours >10mm, however, had more tumour (1.67 vs 2.02, $p = 0.016$) and a higher risk of LNM (72.0% vs 57.4%, $p = 0.002$) after the lockdown (Supplementary Table 3).

Discussion

Since its outbreak, the COVID-19 pandemic has been a tremendous challenge to oncology institutions and cancer

Table 3 Regression Analysis of Admission Date in Predicting the Tumor Behavior

Dependent Variable	Admission Date Interval[a]		
	Effect Size	**95% CI**	***p* value**
Postoperative pathology			
Tumor size	−0.004 (Slope, B value)	−0.006, −0.001	**0.002****
Lymph node metastasis	1.000 (OR)	0.994, 1.005	0.916
Tumor number	0.000 (Slope, B value)	−0.003, 0.004	0.951
Extrathyroidal extension	0.998 (OR)	0.992, 1.004	0.494

Notes: Bold font: significant difference. **$p<0.01$. [a]The admission date interval was defined as time interval between the patient admission date and April 10, 2020, which was the last day of lockdown.

Table 4 Comparison of Ultrasound Characteristics in 38 Thyroid Cancer Patients Receiving Ultrasound Examination Before and After the COVID-19-Induced Lockdown

Variable	Pre-Lockdown	Post-Lockdown	*P* value
Tumor size (cm, SD)	1.00 (0.92)	1.10 (1.18)	0.127
Aspect ratio>1 (%)	10 (26.3)	15 (39.5)	0.227
Irregular margin (%)	20 (52.6)	29 (76.3)	**0.012***
Peripheral location (%)	7 (18.4)	8 (21.1)	1.000
Site (%)			0.687
Unilateral	16 (42.1)	14 (36.8)	
Bilateral	22 (57.9)	24 (63.2)	
Microcalcification (%)	8 (21.1)	14 (36.8)	0.070
Multiple lesion (%)	24 (63.2)	28 (73.7)	0.219
Lymph node metastasis (%)	3 (7.9)	4 (10.5)	1.000

Notes: Bold font: significant difference. *$p < 0.05$.

patients. Many medical institutions have had to adopt various measures to reduce nosocomial infections, including limiting patient admission or even lockdowns.[28–30] These measurements, although effective in minimizing nosocomial infections, have inevitably led to diagnosis and treatment delays among cancer patients. Wuhan, which was the first centre of the pandemic, underwent a regional lockdown for 76 days.[31] Many oncologists in Wuhan believe that thyroid cancers, although indolent in general, have shown more aggressive behaviour after the lockdown. There were some reviews or clinical experiences reported on thyroid cancer in the pandemic period,[32,33] but clinical evidence is lacking.

Our study supports this hypothesis. Although demographic characteristics remained stable in general, thyroid cancer patients after the pandemic had a greater number of multifocal lesions, extrathyroidal extensions, and lymph node metastases on postoperative pathological examinations. Lymph node metastases have been widely recognized as risk factors for aggressiveness and metastasis.[34] In addition, multifocality and extrathyroidal extension are powerful predictors for thyroid cancer.[35,36] We may think with evidence that patients enduring a treatment delay will have a poorer prognosis in the future.

There is, obviously, more than one interpretation for the clinical findings. One may easily think that thyroid cancers have become more aggressive year by year. Our study showed that although tumour size and ETE remained almost unchanged, the incidence of LNM, especially central LNM, has increased by more than 12% in the past four years. These clinical findings may be explained by the increase in cervical lymph node ultrasounds and fine-needle aspiration biopsies being performed in clinical practice. Morris et al also found that the rate of cervical metastases has doubled over the past 40 years.[21] Although evidence supports that increasing numbers of diagnostic tests leads to an increase in thyroid cancer incidence,[37] we cannot abandon the hypothesis that the incidence has truly increased.

Rebound medical visits were another competing hypothesis. Rebound medical visits are defined as the increasing number of medical visits by worried patients after lockdown. Many thyroid cancer patients undergo surveillance before medical interventions. Those with more high-risk tumours may be more worried about their illness, and thus have been passionate to take on medical visits, which might have subsequently led to the observation of a pseudo-deterioration after the lockdown.

Table 5 Comparison of Ultrasound Characteristics in 19 PTMC Patients and 16 Patients with Treatment Delay ≤180 Days

Variable	PTMC			Delayed Time ≤180ds		
	Pre-Lockdown	Post-Lockdown	*P* value	Pre-Lockdown	Post-Lockdown	*P* value
Tumor size (cm, SD)	0.74 (0.36)	0.70 (0.25)	0.357	1.00 (1.08)	1.20 (1.44)	0.092
Aspect ratio>1 (%)	5 (26.3)	5 (26.3)	1.000	5 (31.3)	6 (37.5)	1.000
Irregular margin (%)	9 (47.4)	12 (63.2)	0.375	10 (62.5)	11 (68.8)	1.000
Peripheral location (%)	2 (10.5)	3 (15.8)	1.000	3 (18.8)	4 (25.0)	1.000
Site (%)			1.000			1.000
Unilateral	8 (42.1)	8 (42.1)		8 (50.0)	7 (43.8)	
Bilateral	11 (57.9)	11 (57.9)		8 (50.0)	9 (56.2)	
Microcalcification (%)	4 (21.1)	4 (21.1)	1.000	4 (25.0)	5 (31.3)	1.000
Multiple lesion (%)	12 (63.2)	13 (68.4)	1.000	10 (62.5)	12 (75.0)	0.625
Lymph node metastasis (%)	0 (0.0)	1 (5.3)	N/C	1 (6.3)	2 (12.5)	1.000

Abbreviation: N/C, not calculable.

Our analysis supported this theory. Pathological tumour size correlated negatively with the admission date. The average tumour size decreased at a speed of approximately 4mm every 100 days from the first day of reopening. The research by Falcone et al supported that thyroid cancer patients were more anxious and distressed in the face of the pandemic.[38] A shortcoming of this theory is that the rate of LNM remained stable after the reopening, which could not explain the difference between the two cohorts of patients.

The third hypothesis was that some thyroid carcinomas, especially those with higher risks, had progressed during the pandemic, similar to the progression of breast or lung cancer.[39] Researchers thus pooled the patients with ultrasound records both before and after the lockdown for the analysis. Although the TI-RADS scores were somewhat higher in the post-lockdown ultrasound group, other variables remained stable, indicating that most tumour remained indolent through the lockdown era. In the regression analysis, tumour size on pre-pandemic ultrasound was the only predictor for tumour enlargement and LNM over the lockdown period. The results were consistent with some investigations on active surveillance.[40] These findings do not support the idea that those tumours progressed during the pandemic-induced lockdown.

In addition, the clinical management of thyroid cancer has faced challenges during the COVID-19 pandemic. Scholars noticed that the delay time has had almost no effect on patient outcomes. Subsequent analyses clarified that thyroid cancer patients can endure a period of treatment delay up to 180 days. Moreover, our study shows that the tumour size and rate of LNM remained stable after lockdown in patients with tumours no more than 10 mm. The comparison among the total patient sample before and after COVID-19 also supports this theory. Some guidelines have recommended cervical ultrasound, thyroid scintigraphy, and fine-needle biopsy as the main methods in decision-making.[25,41] Due to the pandemic and the subsequent lockdown, patients are now advised to take teleconsultations or to postpone their surgery. Low-to-intermediate-risk patients can tolerate a 180-day delay without tumour progression, a conclusion that is supported by clinical experience.[42]

There were some limitations to our study. First, the patient number in the pre- and post-pandemic ultrasound comparison was too short to draw more solid conclusions. In addition, although the 3253 patients included had either pathology or ultrasound records (most patients had both), a minority of patients had missing items, which may have led to information bias. This was a single-centre retrospective study, and the generalization of our theory is thus limited. Moreover, some pathological characteristics, including subcapsular or isthmic nodule location, were missing in our pathological records. Campennì et al revealed that isthmus topography is an important predictive factor for persistent disease and metastasis.[43,44] Further prospective studies with larger sample sizes from multiple centres are needed to evaluate our results.

Conclusion

In conclusion, our study revealed more aggressive thyroid cancer behaviour in patients after a long period of COVID-19 induced treatment delay. However, as most tumours were indolent, they did not progress during the lockdown period. The more high-risk signs in postoperative pathology can thus be interpreted as due to rebound medical visits from patients' anxiety, as well as to an annual increase in tumour aggressiveness. In addition, our study revealed that thyroid cancer patients with tumours less than 10 mm in diameter could tolerate a long treatment delay without any notable progression, and a delay of no more than 180 days is tolerable for most patients. These findings will help clinicians better evaluate thyroid cancer patients in the era of pandemics.

Data Sharing Statement

All data generated or analyzed during this study are available from the corresponding author on reasonable requests.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, agreed to the submitted journal, and agree to be accountable for all aspects of the work.

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Disclosure

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