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The sonographic features of preoperative ultrasonography of metastatic tumors of thyroid cancer confirmed by surgical pathology.

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Keywords: surgical pathology; thyroid cancer; metastatic lesions; ultrasonography; sonographic features.

Abstract. This study aimed to analyze the sonographic features of metastatic tumors in patients with thyroid cancer that underwent preoperative ultrasonography. One hundred and three thyroid cancer patients whose metastases were confirmed by surgical pathology in The First People's Hospital of Wenling from January 2020 to December 2021 were enrolled. All patients received preoperative ultrasound examinations, and the sonographic features were analyzed. Ultrasound examination showed 83.50% of cervical lymph node metastasis (CLNM), 24.27% of soft tissue invasion (STI), 3.88% of distant organ metastasis (DOM), 8.74% of CLNM + STI, 0.97% of CLNM + DOM, and 0.97% of CLNM + STI+DOM. Unilateral CLNM accounted for 72.09%, while bilateral CLNM accounted for 27.91%. The mean long diameter of metastatic lymph nodes was (1.83±0.63) cm, and the mean short diameter was (1.03±0.42) cm. Metastases to zone II, III, IV, V, VI, and VII accounted for 8.14%, 48.84%, 23.26%, 4.65%, 11.63%, and 3.49%, respectively. The L/T ratio of lymph nodes in 65 cases was lower than 2; 45 of 70 solid metastases exhibited solid hyperechoic, 15 multifocal hyperechoic, seven unifocal hyperechoic, and three diffusely distributed solid hyperechoic images. There were 25 patients with STI that experienced invasion of the thyroid capsule, ten patients experienced the invasion of the cervical fatty muscles, two patients had invasion of the trachea, and one patient had invasion of the thyroid cartilage. Of the four patients with DOM, one had parotid metastasis, one had submandibular metastasis, one had axillary metastasis, and one had uterine metastasis. The most common metastatic sites of thyroid cancer are cervical lymph nodes. However, there were also metastases in the soft tissues and distant organs. The ultrasonography exhibited typical sonographic features. An adequate familiarity with these sonographic features can aid in detecting suspicious metastases in time, which is crucial to the clinical diagnosis, treatment, and prognostic assessment.

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Características ecográficas de la ultrasonografía preoperatoria de tumores metastásicos de cáncer de tiroides confirmados por patología quirúrgica.

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Palabras clave: patología quirúrgica; cáncer de tiroides; lesiones metastásicas; ultrasonografía; Características ecográficas.

Resumen. Este estudio tuvo como objetivo analizar las características ecográficas de tumores metastásicos en pacientes con cáncer de tiroides que se sometieron a una ultrasonografía preoperatoria. Se inscribieron 103 pacientes con cáncer de tiroides cuyas metástasis fueron confirmadas por patología quirúrgica en el primer Hospital Popular de Wenling desde enero de 2020 hasta diciembre de 2021. Todos los pacientes recibieron un examen de ultrasonido preoperatorio y se analizaron sus características ecográficas. El examen de ultrasonido mostró 83,50% de metástasis de ganglios linfáticos cervicales (CLNM), 24,27% de invasión de tejidos blandos (ITS), 3,88% de metástasis de órganos distantes (DOM), 8,74% de CLNM + ITS, 0,97% de CLNM + DOM y 0,97% de CLNM + STI + DOM. La CLNM unilateral representó un 72,09%, mientras que la CLNM bilateral representó el 27,91%. El diámetro largo medio de los ganglios linfáticos metastásicos fue 1,83 ± 0,63 cm, y el diámetro corto medio fue 1,03 ± 0,42 cm. La metástasis a las Zonas II, III, IV, V, VI y VII representan 8,14%, 48,84%, 23,26%, 4,65%, 11,63% y 3,49%, respectivamente. La relación L/T del ganglio linfático en 65 casos fue inferior a 2. Cuarenta y cinco de 70 metástasis sólidas exhibieron hiperecoico sólido, 15 hiperecoico multifocal, 7 hiperecoico unifocal y 3 hiperecoico sólido distribuido difusamente. Hubo 25 pacientes con ITS experimentados por invasión de la cápsula tiroidea, 10 pacientes experimentaron invasión de los músculos grasos cervicales, 2 pacientes con invasión de la tráquea y 1 paciente con invasión del cartílago tiroideo. De los 4 pacientes con DOM, 1 tenía metástasis parótidas, 1 tenía metástasis submandibulares, 1 tenía metástasis axilares y 1 tenía metástasis uterina. Los sitios metastásicos más comunes de cáncer de tiroides son los ganglios linfáticos cervicales. También hay metástasis en los tejidos blandos y los órganos distantes. La ultrasonografía exhibió características ecográficas típicas. La familiaridad adecuada con las características ecográficas puede ayudar a detectar metástasis sospechosas a tiempo, lo cual es clave para el diagnóstico clínico, el tratamiento y la evaluación pronóstica.

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INTRODUCTION

The thyroid is a vital hormone gland that critically impacts the body's metabolism. Thyroid cancer refers to malignant tumors originating from the thyroid [1]. Regarding pathological types, papillary thyroid carcinoma has the highest incidence and a higher degree of differentiation than other types. However, it is less malignant, resulting in a relatively better prognosis. Patients can survive longer, while local and distant

metastases primarily invade the lymph nodes [2]. Evidence on metastasis of papillary thyroid carcinoma found that the incidence of CLNM surpassed 80% [3]. Another study found that more than 60% of patients with medullary thyroid carcinoma already have lymph node metastases in the neck when receiving surgery. In comparison, about 80% of undifferentiated thyroid carcinomas will induce lymph node metastases [4].

Since thyroid cancer does not present specifically in its early stage, most patients see a doctor due to neck lumps and palpable nodules. Some patients even have swellings that have been present for years upon consultation [5,6]. Once local invasion or distant metastases occurs, the probability of postoperative recurrence is significantly higher, severely increasing the risk of patient death [7]. Metastasis of thyroid cancer is widely recognized as an independent factor affecting prognosis [8]. Thus, early clinical detection of metastases in patients with thyroid cancer can guide physicians to formulate a comprehensive treatment plan and determine the efficacy as well as patient prognosis by observing the metastatic lesions.

Ultrasound, as the most common imaging method, has shown good value in clinical applications with simple operation and accurate results As diagnosis and treatment technologies advance, the performance of ultrasound instruments is gradually improved, and high-frequency ultrasound can not only show the internal structure of the lesion but also visualize the blood flow of the lesion site, which can guide the clinical judgment of the nature of the lesion [9,10]. Most studies have explored ultrasound's role in examining thyroid cancer [11,12]. However, there is a lack of research on its effectiveness in the diagnosis of metastatic thyroid cancer. This study was conducted to investigate the value of the preoperative implementation of ultrasound in 103 patients with pathologically confirmed metastatic thyroid cancer.

MATERIALS AND METHODS

Baseline data

One hundred and three thyroid cancer patients whose metastases were confirmed by surgical pathology in The First People's Hospital of Wenling from January 2020 to December 2021 were enrolled, including 45 males and 58 females, with patient ages ranging from 22 to 71 years, with an average age of 51.16±10.38 years. All patients had pathologically confirmed metastasis after surgery and underwent preoperative ultrasonography. All patients were aware of the study procedures and voluntarily signed the study consent form. This study got ethical approval from our hospital.

Methods

SONOLINE, a color Doppler ultrasound diagnostic instrument (Type: MylabClassC), was used for examination with a probe frequency set from 7.0 to 12.0 MHz. During the examination, the patient lay in a supine position with the head slightly tilted back, and the shoulder and neck were elevated with soft pillows to ensure complete exposure of the examined area. The parameter settings of the color Doppler diagnostic instrument were tuned, and the patient's position was adjusted to ensure the most satisfactory ultrasound images. For patients diagnosed with metastatic thyroid cancer on ultrasonography, the type and location of the metastasis were recorded, and its characteristics, such as long and short diameters, morphology, borders, fusion, internal echogenicity, calcification, cystic changes, and blood flow signals were recorded. Metastases were typed according to the metastatic patterns, including Type I: CLNM, Type II: STI, and Type III: DOM. The subdivision of the lymph nodes was completed according to the neck dissection classification [13,14] (Fig. 1) and endorsed by the relevant organizations and committees. If there were metastatic lymph nodes in a zone that were present for more than one month, the largest of these lymph nodes was examined.

Fig. 1. Image of levels and sublevels of the neck (Modified image from Robbins *et al*. [14]).

Outcome Measurements

The metastases of 103 patients with thyroid cancer were analyzed. The ultrasound features of metastatic lymph nodes, including location, number, size, morphology, and internal echogenicity, were analyzed. The ultrasound features of soft tissue invasion and distant organ metastases were also analyzed.

Statistical Methods

All data were analyzed using SPSS 23.0. Count data [n (%)] were tested by χ^2.

ANOVA with post hoc F test was performed for multi-point comparisons. Measurement data were indicated by mean ± standard deviations, $p<0.05$ was considered statistically significant.

RESULTS

Overall thyroid cancer metastasis

Among the 103 patients with thyroid cancer, there were 86 cases (83.50%) of CLNM, 25 cases (24.27%) of STI, and 4 cases (3.88%) of DOM revealed by preoperative ultrasonography. There were nine patients with CLMN and STI, accounting for 8.74%, and one patient presented with CLMN and DOM, accounting for 0.97%. Some of the ultrasound findings are shown in Fig. 2 and Fig. 3.

The ultrasound features of CLNM

Preoperative ultrasonography showed 86 patients with CLNM, of which 62 cases were unilateral CLNM, accounting for 72.09%, and 24 cases were bilateral CLNM, accounting for 27.91%. The long diameter of metastatic lymph nodes in these 86 patients ranged from 0.6-2.9 cm, with a mean long diameter of 1.83±0.63 cm, and short diameter ranged from 0.3-1.7 cm, with a mean short diameter of 1.03±0.42 cm.

In terms of location, there were seven cases in zone II, accounting for 8.14%; 42 cases in zone III, accounting for 48.84%; 20 cases in zone IV, accounting for 23.26%; four cases in zone V, accounting for 4.65%; 10 cases in zone VI, accounting for 11.63%, three cases in zone VII, accounting for 3.49%, and no metastasis in zone I. Morphologically, 65 of the 86 patients with CLNM had a lymph node L/T ratio <2 and showed a round-like or round shape.

Regarding internal echogenicity, 66 cases of CLNM showed no medullary manifestations. Punctate hyperechogenicity could be observed within the lymph nodes in 43 patients, and the pathological examination showed microcalcified colloid. Coarse calcification could be observed within the lymph nodes in three patients, and the metastatic lymph nodes in six patients with pathologically confirmed papillary thyroid cancer showed internal cystic necrosis with partial or complete cystic changes.

Fig. 2. Morphology of thyroid metastases. (A) shows an enlarged lymph node in the right cervical region III, partly with intense echogenicity, clear borders, full shape, indistinct corticomedullary demarcation, and absence of the lymphatic hilum; (B) shows an enlarged lymph node in the right cervical region VI; (C) shows the right axillary metastasis.

The sonograms of metastatic lymph node cystic changes showed mostly heterogeneous thickness separation, some with wall nodules or with punctate hyperechogenicity, and larger wall nodules showed the presence of blood flow signal within them. Seventy cases developed solid metastases, including 45 cases of solid hypoechogenicity, 15 cases of multifocal hyperechogenicity, seven cases of unifocal hyperechogenicity, and three cases of diffusely distributed solid hyperechogenicity (Table 1).

Ultrasound features of soft tissue invasion

Cervical soft tissue invasion occurred in 25 cases, manifesting as the invasion of the thyroid peritoneum in all patients, invasion of the fatty muscles in 10 patients, invasion of the trachea in two cases, and invasion of the thyroid cartilage in one case. Ultrasonography showed capsule disruption, no clear line of demarcation between the primary lesion and the soft tissues, heterogeneous echogenicity, and calcification (Table 2). Some of the ultrasound findings are shown in Fig. 4.

Ultrasound features of distant organ metastases

Distant organ metastases occurred in four cases, including one case, with uterine metastasis, in which the ultrasonography showed a solid mass with septa. One case presented with parotid metastasis and showed as a solitary and solid hypoechoic nodule in the parotid gland with clear borders, sharp margins, and posterior acoustic enhancement, very close to mixed tumors of the salivary gland. One case presented with axillary metastasis, and ultrasonography showed axillary lymph nodes with a L/T ratio of <2 and no medullary type. Finally, one case presented metastasis in the submandibular gland, and ultrasonography showed a solid, hypoechoic nodule with coarse margins (Table 3). Some of the ultrasound findings are shown in Fig. 5.

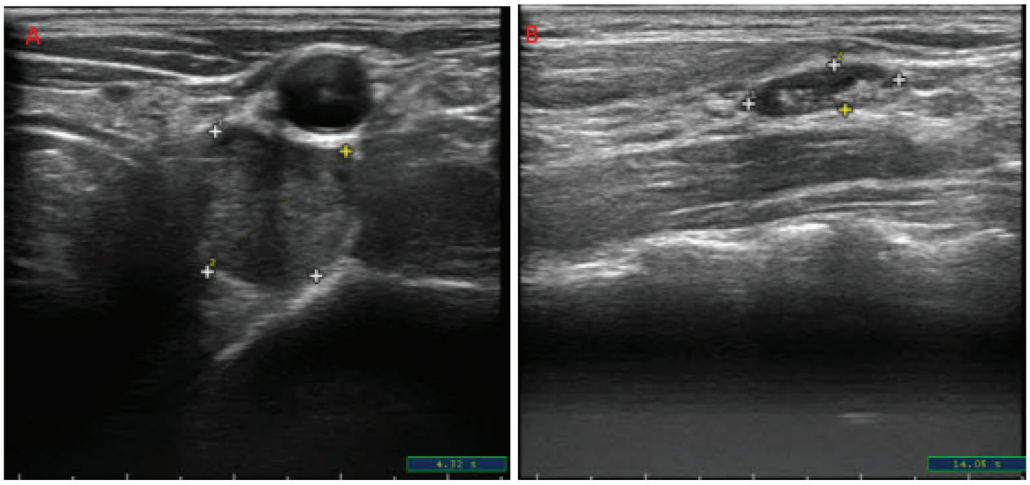

Fig. 3. Internal echo image of the thyroid gland. (A) shows an enlarged lymph node in the right cervical region IV; (B) shows a left cervical enlarged lymph node with clear borders, indistinct corticomedullary demarcation, and multiple intense echogenic foci.

Table 1
The ultrasound features of cervical lymph node metastasis from thyroid cancer

Ultrasound features and manifestations		Number of cases/results	%	p
L/T ratio <2		65	75.58	/
Loss of cortical medulla		66	76.74	/
Cystic changes		6	6.98	/
Mean length diameter of metastatic lymph nodes		1.83±0.63	/	/
Mean short diameter of metastatic lymph nodes		1.03±0.42	/	/
The side	Unilateral metastases	62	72.09	<0.01
	Bilateral metastases	24	29.91	
Calcification	Microcalcification	43	50.00	<0.01
	Coarse calcification	3	3.49	
Solid metastases	Diffuse hyperechoic	3	3.49	<0.05
	Unifocal hyperechoic	7	8.14	
	Multifocal hyperechoic	15	17.44	
	Solid hypoechoic	45	52.33	
Location of lymph node	Zone I	0	0.00	<0.05
metastases	Zone II	7	8.14	
	Zone III	42	48.84	
	Zone IV	20	23.26	
	Zone V	4	4.65	
	Zone VI	10	11.63	
	Zone VII	3	3.49	

Note: The parametric test was used, including the t-test and the analysis of variance (ANOVA, namely the F test).

Table 2
The ultrasound features of soft tissue invasion

Ultrasound sonographic features	Number of cases	%
Invasion of the thyroid capsule	25	100.00
Invasion of the fatty muscles	10	40.00
Invasion of trachea	2	8.00
Invasion of the thyroid cartilage	1	4.00

Note: $\chi 2$ test was used.

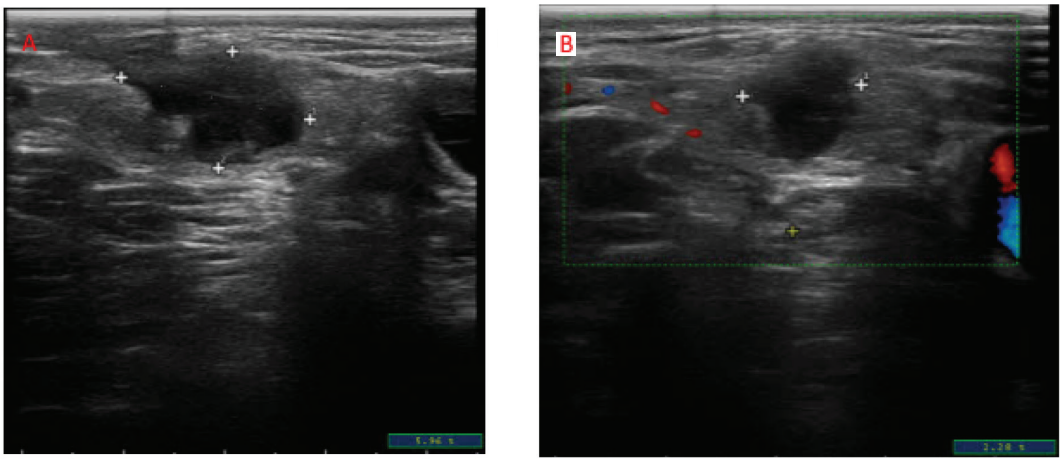

Fig. 4. Cervical soft tissue invasion. The hypoechoic mass in the subcutaneous soft tissue of the left neck has a clear border, irregular shape, and uneven edge; CDFI: no evident blood flow signal was observed.

Table 3
The ultrasound features of distant organ metastases

Ultrasound sonographic features	Number of cases	%
Uterine metastasis	1	25.00
Parotid metastases	1	25.00
Axillary metastasis	1	25.00
Submandibular metastases	1	25.00

Note: χ^2 test was used.

DISCUSSION

The types of metastasis in patients with thyroid cancer include cervical lymph node metastasis, soft tissue invasion, and distant organ metastasis, and the incidence of cervical lymph node metastasis is the highest [15]. Clinical data showed that half of the patients with thyroid cancer had developed regional lymph node metastasis upon consultation, with the highest incidence of ipsilateral and middle CLNM, which contains bilateral CLNM and supraclavicular lymph node metastasis [16]. A small fraction of patients developed lymph node metastasis when the primary tumor was tiny, which

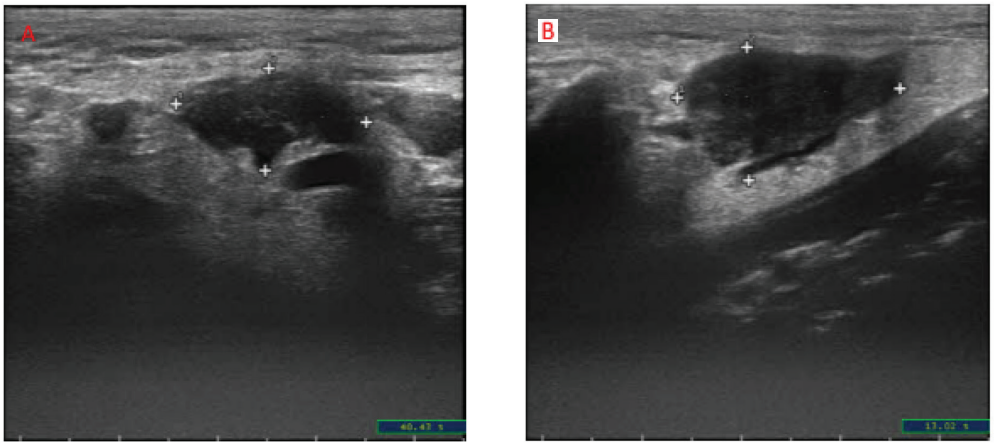

Fig. 5. Distant metastases. Figure A: left side; Figure B: right side. Hypoechoic masses were observed in both parotid glands, with clear borders, uneven edges, partially angular and irregular shapes, and no evident internal blood flow signal.

was the first symptom of metastatic lymph node enlargement in some patients [17].

Lymph node metastasis was predominantly unilateral. Unilateral metastasis accounted for 72.09% of this study's 86 patients with thyroid cancer. Statistics showed that lymph node metastases were mostly in the middle and lower of the neck, being approximately 68% of all neck lymph nodes [18]. Studies have shown that lymph node enlargement could be detected in only 30% of patients with papillary thyroid cancer undergoing physical examination. Pathological examination revealed that over 80% of patients have lymph node metastasis, indicating some underdiagnosis of lymph node metastasis by ultrasound [19]. It was found that thyroid cancer patients with CLNM experience higher recurrence rates, mortality, and worse prognosis than patients without CLNM [20]. Early examination is required for the detection of lymph node metastasis in patients with thyroid cancer. Comprehensive observation of lymph node in terms of morphology, borders, internal echogenicity and other features was performed. The following reliable features of lymph node metastasis were summarized in this study with reference to ultrasound findings. Solid hyperechoic or hypoechoic nodules, cystic changes, and gravel-like calcifications were found, with zones III, IV, and VI being the metastatic areas with the highest incidence rate. Studies have shown that ultrasound showed an accuracy of >75% in the diagnosis of CLNM in patients with thyroid cancer [21]. Studies have proposed that thyroid cancer first metastasized to zone VI lymph nodes, showing the highest rate of metastasis [22]. A study analyzed patients with papillary thyroid cancer treated with systemic lymph node dissection. It showed that over 80% of patients had multi-divisional metastases, with the highest rates in Zone III, Zone IV, Zone II, and Zone V. However, there were no cases of metastasis to Zone I [23], which is consistent with the results of this study, demonstrating that the rate of metastasis from the highest to the lowest occurred in Zone III, Zone IV, Zone VI, Zone II, Zone V, and Zone VII. There were no patients with metastasis to Zone I. However, in clinical practice, the missed rate of lymph node metastases was highest in zone VI, and the diagnostic rate by ultrasound for metastatic lymph nodes in this region was low. However, typical features could be obtained since other primary head and neck tumors basically do not metastasize to this region [24]. It can be concluded from the above analysis that

clinical physicians should pay attention to zones III, IV and VI of the neck to reduce missed diagnoses and ensure the diagnostic accuracy.

Invasion of the surrounding soft tissues and organs is also one metastatic route of thyroid cancer, primarily affecting the thyroid capsule, the fatty muscles, the tracheal ring, the thyroid cartilage, and the larynx [25]. In this study, 25 patients developed soft tissue invasion involving the thyroid capsule, ten patients developed invasion of the fatty muscles. Two patients had invasion of the trachea, and one patient had invasion of the thyroid cartilage. If the primary lesion is in close proximity to the thyroid capsule, there is a higher risk of CLNM and also the invasion of adjacent soft tissues, in which aggressive surgical treatment and complete clearance of regional lymph nodes on the lateral side of the neck are required [26]. Although papillary thyroid carcinoma showed a slight malignant transformation, it can develop distant metastases, with bone, brain, and lung more likely involved. The limitations of ultrasonography result in a low detection rate in these sites by ultrasonography [27]. Previous evidence showed that distant metastases from papillary thyroid cancer occurred in the breast, axilla, orbit, and pancreas, and ultrasonography was performed based on patient history [28]. In this study, distant organ metastases occurred in four cases of thyroid cancer (parotid gland, submandibular gland, axilla) and one case in the uterus.

In conclusion, the most common metastatic site of thyroid cancer is the cervical lymph nodes. The soft tissues and distant organs were also involved. There are typical sonographic features in ultrasonography, and adequate familiarity with the sonographic features can help to diagnose suspicious metastases in a timely manner, which is crucial for clinical diagnosis, treatment, and prognostic assessment. However, there are shortcomings in the present study, as shown by the small sample size and the lack of sufficient representativeness of the obtained results, as well as the lack of differentiation of thyroid cancer types for the analysis of metastases, which need to be improved in future studies.

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Conflict of Interests

The authors declared no conflict of interest.

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Participation in development and writing of the paper

Concept and design: QQ and LR. Acquisition of data, literature review, and refinement of manuscript: All authors. Analysis and interpretation of data: LR and QZ. Manuscript writing: LR. Review of final manuscript: QQ.

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