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Total thyroidectomy versus lobectomy for intermediate-risk papillary thyroid carcinoma: A single-institution matched-pair analysis

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ABSTRACT

Background: Total thyroidectomy (TT) is recommended by guidelines for intermediate-risk papillary thyroid carcinoma (PTC) but its survival advantage over lobectomy has not been proven. The aim of this study was to examine the association between the extent of surgery and the clinical outcome of patients with intermediate-risk PTC.

Methods: Adult patients with PTC in the institutional database from 1996 to 2008 were retrospectively reviewed. Intermediate-risk patients were defined according to the 2015 American Thyroid Association (ATA) guidelines. Patients who underwent TT and patients who underwent lobectomy were then matched according to individual risk factors. Survival analysis was performed within the two paired groups, focusing on recurrence-free survival (RFS) and disease-specific survival (DSS) rates.

Results: Among 4230 PTC patients, 1087 intermediate-risk patients were included, in total 341 pairs were matched based on sex, age, primary size, clinical nodes (cN), extrathyroidal extension (ETE), pathological lateral neck metastasis (pN1b) and lymph node ratio (LNR). For these paired cases, with a median follow-up of 125 months (46–192), the lobectomy and TT groups were similar with respect to both 10-year RFS rate (77.4% vs 80.2%, log rank = 0.244, p = 0.622) and DSS rate (97.2% vs 98.4%, log rank = 0.351, p = 0.554). When excluding pairs of cases (62 pairs) who received radioiodine ablation (RAI), survival results were also similar in lobectomy and TT groups with respect to 10-year RFS rate (81.2% vs 83.1%, log rank = 0.63, p = 0.42) and DSS rate (97.3% vs 98.1%, log rank = 0.95, p = 0.33).

Conclusions: For intermediate-risk PTC, no advantages of TT over lobectomy were found with respect to RFS rate or DSS rate.

Introduction

The incidence of thyroid cancer has rapidly increased worldwide in recent years. PTC represents > 90% of all thyroid cancer cases [1,2], which exhibits indolent behavior and is curable under most circumstances [3–5]. The mainstay of treatment for PTC is surgical resection but no definite consensus has been reached regarding the appropriate extent of surgery for this disease.

According to ATA risk stratification system, patients with PTC are divided into three groups based on their relative rates of recurrence and mortality [3,6,7]. Excellent prognosis is obtained for patients in the low-risk group, and it appears that TT and subsequent radioiodine ablation (RAI) are not necessary for most of these patients. Patients with extrathyroidal, metastatic PTC or positive surgical margin are typically divided into intermediate- and high-risk groups; TT and RAI are generally recommended for such patients to promote the continued absence of persistent or recurrent disease [8,9]. However, for intermediate risk PTC, there is a paucity of data regarding the long-term prognosis of patients in this risk group, furthermore, the definition of intermediate-risk group has always been adjusted in the past few years. We wonder whether recurrent and survival outcomes are associated with extent of surgery for intermediate-risk group defined by current ATA guidelines.

In this study, we designed a single institutional matched-pair retrospective analysis to see whether TT show survival benefit comparing with lobectomy in cases with intermediate-risk PTC.

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Table 1
Baseline characteristics of 1087 cases involving intermediate-risk PTC and univariate analysis for RFS.

	All cases	TT (n = 420)	Lobectomy (n = 667)	P value	Univariate analysis p value
Sex					
Female	772	306 (72.8%)	466 (69.8%)	0.290	0.018
Male	315	114 (27.2%)	201 (30.2%)		
Age					
≤45 years	613	215 (51.2%)	398 (59.7%)	0.006	0.307
> 45 years	474	205 (48.8%)	269 (40.3%)		
Treatment period					
Before 2004	258	118 (28.1%)	140 (21.0%)	0.007	0.101
2004–2008	829	302 (71.9%)	527 (79.0%)		
cN					
Negative	417	143 (34.0%)	274 (41.0%)	< 0.001	< 0.001
Positive	670	305 (66.0%)	365 (59.0%)		
Central neck dissection					
Absent	56	14(3.3%)	42 (6.3%)	0.020	0.2640
Present	1031	406 (96.7%)	625 (93.7%)		
Primary size					
≤2 cm	575	202 (48.1%)	373 (55.9%)	< 0.001	< 0.001
2–4 cm	334	119 (28.3%)	215 (32.2%)		
> 4 cm	178	99 (23.6%)	79 (11.9%)		< 0.001
ETE					
Absent	745	276 (65.7%)	469 (70.3%)	0.112	< 0.001
Present	342	144 (34.3%)	198 (29.7%)		
Multifocality					
Absent	619	117 (27.9%)	502 (75.3%)	< 0.001	0.102
Present	468	303 (72.1%)	165 (24.7%)		
Pathological mediastinal metastasis					
Absent	993	352 (83.8%)	641 (96.1%)	< 0.001	< 0.001
Present	94	68 (16.2%)	26 (3.9%)		
pN1b					
Absent	380	212 (50.5%)	168 (25.2%)	< 0.001	0.004
Present	707	208 (49.5%)	499 (74.8%)		
LNR					
pN0*	290	120 (28.6%)	170(25.5%)	0.161	0.035
≤0.4	531	208 (49.5%)	323 (48.4%)		
> 0.4	276	94 (22.4%)	182 (27.3%)		< 0.001
Vascular invasion**					
No	1049	401 (95.5%)	648 (97.2%)	0.143	0.155
Yes	38	19 (4.5%)	19 (2.8%)		
RAI					
No	1007	340 (81.0%)	667 (100%)	NA	0.105
Yes	80	80 (19.0%)	0		

* Including patients without central neck dissection
** Variable not available before 2008; values are presented as percentages of the known (after 2008).

Materials and methods

Patient selection

This investigation was a retrospective case-control study performed at a national cancer center. Cases were obtained from the database of the National Cancer Center (NCC), Cancer Institute and Hospital, Chinese Academy of Medical Sciences (CAMS). Patients aged 18 years or older diagnosed with PTC from January 1996 to December 2008 were first included, Patients with multiple cancer diagnoses were excluded to ensure that outcomes were not confounded by other cancer diagnoses and/or treatments; aggressive variants such as tall cell, columnar, and poorly differentiated PTC were also excluded. In addition, for clear demarcation, cases involving near-total thyroidectomy, subtotal thyroidectomy, partial thyroidectomy were also excluded.

This study was approved by the Institutional Review Board.

Intermediate-risk PTC definition

Intermediate-risk PTC was defined according to the 2015 ATA guidelines [7] using detailed selection items, including microscopic invasion of the tumor into perithyroidal soft tissues (T1-2NxM0); clinical N1 stage or > 5 pathologic N1 lymph nodes with all involved lymph nodes < 3 cm in the largest dimension (T1-2N1M0) and vascular invasion. BRAF V600E status and postoperative radioactive iodine (RAI) scans were not evaluated due to insufficient information in most cases. Patients with high-risk factors such as presence of distant metastasis orincomplete resection were excluded.

Matching and statistical analysis

Demographic and clinical pathological characteristics were reported, with frequencies and proportions used for categorical variables. Descriptive data were compared across groups using the Kruskal-Wallis test for continuous variables and the Pearson χ^2 test or Fisher's exact test for categorical variables. Lobectomy and TT cases were then 1:1 matched according to potential prognostic factors, which were selected from among widely accepted factors and Cox regression-based multivariate analysis of the cohort. The multivariate analysis wasbased on the estimated propensity scores of each patient using R software version 3.4.4, each categorical variable was exactly matched, allowed difference of propensity scores between two groups was 0.01. The paired cohort was analyzed using Kaplan-Meier curves and log-rank tests to assess the RFS and DSS rates.

Diseasemanagement and follow-up protocol

General treatment strategies at the institute during the study period

included performing TT on patients with bilateral carcinoma, contralateral node metastasis, or distant metastasis; individualized surgical resection was generally conducted by surgeons when patients exhibited small extrathyroidal extension, unilateral cervical metastasis and unilateral multifocal lesions. RAI was recommended for patients with distant metastasis, regional metastasis with a heavy burden, or T4 primary tumor. The follow-up period was from the time of surgery, and both ultrasonography and enhanced CT were performed at least once per year. Tg and ATg were measured for TT cases; local and regional recurrence was recognized using ultrasound or CT and confirmed with Fine needle aspiration (FNA) or postoperative pathology, whereas distant metastasis was identified using CT and/or ECT.

Results

Patient selection and univariate prognostic analysis via Cox regression

From the institutional database, 4230 patients with previously untreated PTC were first involved. A total of 1087 intermediate-risk cases were then selected based on the aforementioned criteria with exclusion of aggressive histology. The selected cases included 667 (61.4%) cases that involved lobectomy and 420 (38.6%) cases that involved TT; in the selected cases, the median patient age was 42 years (18–76 years), and 772 (71.0%) of the patients were female. Patient age > 45 years ($p = 0.006$), treatment from 2004 to 2008 ($p = 0.007$), cN+ ($p < 0.001$), central neck dissection ($p = 0.020$), large primary size ($p < 0.001$), multifocality ($p < 0.001$), pathological mediastinal metastasis ($p < 0.001$) and pN1b ($p < 0.001$) were significantly more frequent in the TT group than in the lobectomy group (Table 1).

Multivariate analysis via Cox regression

Based on univariate analysis (Table 2) of RFS, sex ($p = 0.018$), cN ($p < 0.001$) , primary size (2–4 cm $p < 0.001$, > 4cm $p < 0.001$), ETE ($p < 0.001$), pathological mediastinal metastasis ($p < 0.001$), pN1b ($p = 0.004$) and LNR (≤0.4$p = 0.035$, > 0.4$p = 0.001$) were included in multivariate analysis, and primary size, ETE, LNR and cN were identified as independent risk factors for RFS ($p < 0.1$).

Case-control matching

Based on multivariate examination of the cohort, TT and lobectomy cases were then matched according to sex, age, primary size, cN, ETE, pN1b and LNR; in addition to the 4 independent prognostic factors, sex and age were added since they are accepted prognostic factors. In particular, 1:1 matching was performed, all 6 variables were exactly matched, and 341 pairs of cases were selected (Table 3).

Survival analysis of matched cases (n = 682)

The median follow-up time was 125 months (46–192 months), in total, 35 and 37 patients experienced recurrence in the TT and lobectomy groups, respectively and 6 and 8 disease-specific deaths were observed in the TT and lobectomy groups, respectively. The local recurrence rate was significantly higher in the lobectomy group than in

Table 2
Multivariate analysis with Cox regression.

	HR	95% confidence interval	P value
Primary size 2–4 cm	1.5881	1.0252–2.4602	0.0383
Primary size > 4 cm	3.1411	1.9943–4.9473	0.0000
ETE	1.6453	1.1486–2.3567	0.0066
LNR ≤ 0.4	1.0288	0.5920–1.7878	0.9199
LNR > 0.4	1.8254	1.0877–3.0635	0.0227
cN+	1.4902	0.9819–2.2614	0.0609

Table 3
Characteristics of 341 pairs of cases of intermediate-risk PTC.

	All cases	Total thyroidectomy	Lobectomy	Chi-square test p value
Number of patients	682	341	341	
Sex				
Male	278	139 (50%)	139 (50%)	1
Female	404	202 (50%)	202 (50%)	
Age				
≤45	366	183 (50%)	183 (50%)	1
> 45	316	158 (50%)	158 (50%)	
Treatment period				
Before 2004	144	77 (53.5%)	67 (46.5%)	0.3985
2004–2008	538	264 (49.1%)	274 (50.9%)	
cN				
Negative	278	139 (50%)	139 (50%)	1
Positive	404	202 (50%)	202 (50%)	
Central neck dissection				
Absent	18	8 (44.4%)	10 (55.6%)	0.406
Present	664	333 (50.2%)	331 (49.8%)	
Primary size				
≤2 cm	374	187 (50%)	187 (50%)	1
2–4 cm	204	102 (50%)	102 (50%)	
> 4	104	52 (50%)	52 (50%)	
ETE				
No	482	241 (50%)	241 (50%)	1
Yes	200	100 (50%)	100 (50%)	
Multifocality				
No	334	92 (27.5%)	242 (72.5%)	< 0.001
Yes	348	249 (71.6%)	99 (28.5%)	
pN1b				
Absent	266	133 (50%)	133 (50%)	1
Present	416	208 (50%)	208 (50%)	
LNR				
pN0*	186	93 (50%)	93 (50%)	1
≤0.4	354	177(50%)	177 (50%)	
> 0.4	142	71 (50%)	71 (50%)	
Vascular invasion**				
No	653	325 (49.8%)	328 (50.2%)	0.7050
Yes	29	16 (55.2%)	13 (44.8%)	
RAI				
No	620	279 (45%)	341 (55%)	< 0.001
Yes	62	62 (100%)	0	

* Including patients without central neck dissection.
** Variable not available before 2008; values are presented as percentages of the known (after 2008).

Table 4
Case follow-up results.

	Total thyroidectomy	Lobectomy	P value Kaplan-Meier curve log-rank test
Disease-specific death	6	8	0.554
Recurrence	35	37	0.622
Local	3	18	0.001
Residual thyroid	0	17	
Thyroid bed	3	1	
Regional	28	34	0.285
Central	14	13	
Lateral	17	27	
Mediastinal	3	4	
Distant	13	11	0.771
Lung	12	11	
Other	1	0	
Local only*	0	5	
Median follow-up period (months)	104	108	

* Local recurrence without evidence of regional or distant disease.

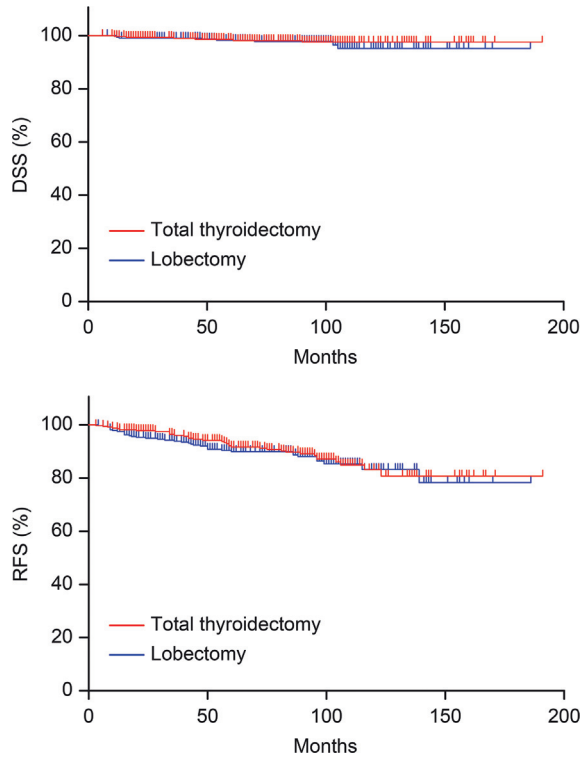

Fig. 1. Recurrent-free survival (RFS) and disease-specific survival (DSS) of total thyroidectomy (TT) and lobectomy groups after matched-pair. n = 341 in each group.

the TT group (p = 0.001), whereas regional and distant recurrence rates were similar in the two groups (Table 4) . No significant differences between the lobectomy and TT groups were observed with respect to 10-year RFS rate (77.4%% vs 80.2%, log rank = 0.244, p = 0.622) or 10-year DSS rate (97.2% vs 98.4%, log rank = 0.351, p = 0.554) (Fig. 1). Similar 10-year RFS and DSS rates were also detected in each primary size subgroups between lobectomy and TT cases (p > 0.05). After excluding pairs of cases who received RAI, 10-year RFS rates and DSS rates of lobectomy (n = 279) and TT (n = 279) groups were (81.2% vs 83.1%, log rank = 0.63, p = 0.42) and (97.3% vs 98.1%, log rank = 0.95, p = 0.33) respectively. In patients with lateral neck metastasis (pN1b, n = 416), the 10-year RFS rate was similar between lobectomy (80.8%) and TT patients (79.1%) (p = 0.612). In total, 6 and 2 disease-specific deaths occurred during follow-up in the lobectomy and TT groups, respectively, and the 10-year DSS rate was worse in the lobectomy group (93.2%) than in the TT group (97.8%), though without statistical significance (p = 0.128) (Fig. 2). For patients without lateral neck metastasis (n = 266), both 10-year RFS and DSS rates were similar between the lobectomy and TT groups (Fig. 3).

Discussion

In this study, we found thyroid lobectomy did not show any DSS- or RFS-related survival disadvantages relative to TT for intermediate-risk PTC. It was also observed that during the examined period, approximately 60% of intermediate-risk patients underwent lobectomy at our institute; this obviously conservative treatment strategy did not produce compromised long-term results compared with outcomes reported in the literature [6,10,11]. The main reason of these results may be this is a single institutional study from a tertiary cancer center, surgeon volume may have an influence on patient outcomes. Interestingly, similar situation could also be found in the literatures, lobectomy group from high volume hospitals is likely to achieve equal survival outcomes with TT than from population level analysis [9,12,13,14]. We also performed a power analysis was with PASS, Non-inferiority tests for the difference between two proportions were selected, when p1.0 was designed as 70%, power was 89% (N = 682, p2 = 77% p1.1 = 80%, p1.0 = 70%), which showed the sample volume of the study was enough to analysis the difference. Based on the evidences above, although selection bias may exist, our findings still call into question whether intermediate-risk group PTC should be an absolute determinant for TT.

Our results may not be entirely surprising since potentially similar findings have been obtained in previous studies. Several recent large-series studies have also indicated that lobectomy could achieve the same results as TT [15–17]. Accordingly, in these studies, intermediate- to high-risk cases have accounted for various proportions of lobectomy groups; for instance, certain groups had a maximum of 16% of cases involving extrathyroidal extension or 20% of cases treated using RAI, among other characteristics. Haigh et al. [15] analyzed 5432 PTC cases using a risk stratification system, and no differences were found between TT and lobectomy even in a lobectomy group in which 8% of patients were classified as high risk. In an analysis by Adam et al that included 61,775 patients in the National Cancer Database [16], certain patients with risk factors were also included in the lobectomy group (in which 7% of patients exhibited node positivity and 5% of patients exhibited extrathyroidal extension). Our study was also consistent with certain single-institution analyses. Shah et al. [18] previously performed a matched-pair analysis that included 931 patients at a single institute; the TT and lobectomy groups were matched based on patient age, histology, tumor size, extrathyroidal extension, nodal disease, and distant metastases. The results revealed no disease-specific survival difference between TT and lobectomy at 20 years. Other than surgical extent itself, adjuvant RAI is another reason given in support of TT. Ruel E et al [9], reported higher overall survival could be achieved by adjuvant RAI in intermediated risk group of PTC, however, nearly 20% percent of cases with positive surgical margin were included in the

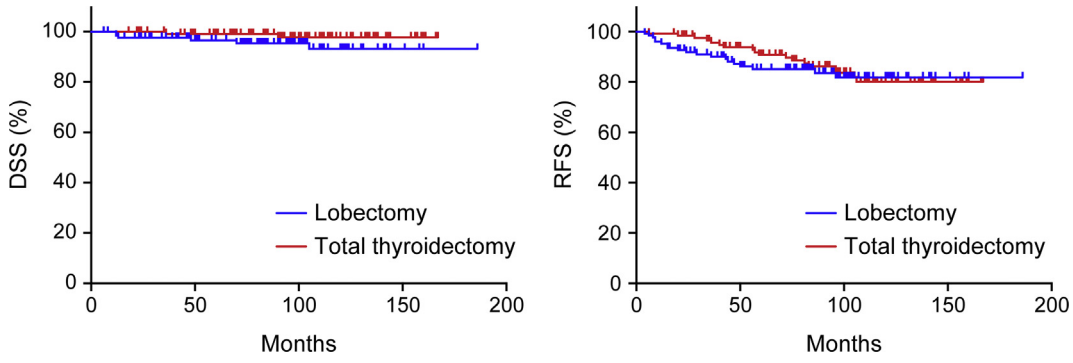

Fig. 2. Disease-specific survival (DSS) and recurrence-free survival (RFS) of the total thyroidectomy (TT) and lobectomy groups in patients with lateral neck metastasis (pN1b) (n = 208 in each group).

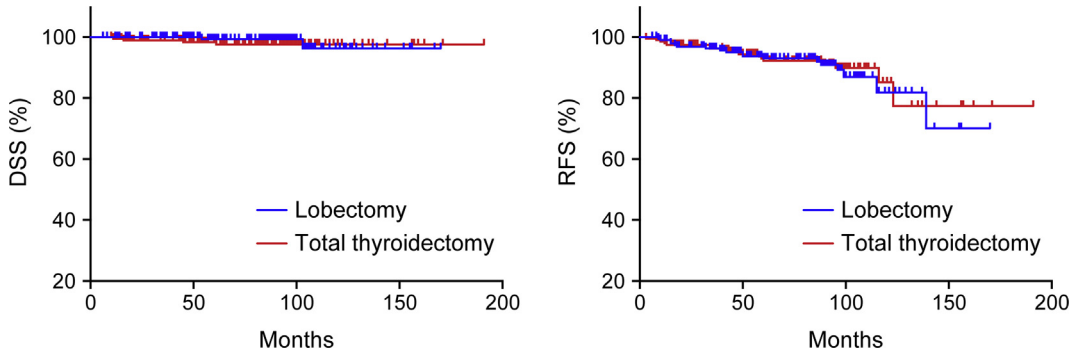

Fig. 3. Disease-specific survival (DSS) and recurrence-free survival (RFS) of the total thyroidectomy (TT) and lobectomy groups in patients without lateral neck metastasis (n = 133 in each group).

analysis, which strongly indicated of adjuvant therapy, so it was not sure whether TT and RAI could improve survival when clear margin had been achieved by lobectomy.

ETE and lateral neck metastasis constitute the main factors for categorizing patients into an intermediate-risk group. Compared with the formal factors, lateral neck metastasis is more likely to indicate TT, but in the stratified analysis of this study, lobectomy and lateral neck dissection did not result in statistically worse survival than TT did. However, the 10-year DSS rate of the lobectomy group was slightly lower than that of the TT group, indicating that TT may potentially improve long-term survival of patients with lateral neck metastasis, especially when compromised with other risk factors. Exact evaluation is still needed in the future.

Several factors may have influenced the results of this study. First, 80% of cases did not involve RAI treatment, which might have potentially influenced the survival results in the TT group; however, selectiveness in the use of RAI was also recommended in intermediate- patients, and all recurrences in our matched cohort were detected by regular neck US and enhanced CT, the influences of serum Tg measurement after TT and remnant ablation were minimized. Second, information regarding mutations in various genes (e.g., braf, ras, and tert promoter, among others) was not available in the study, which were potential prognostic factors. The strengths of our study lie in comparable proportion (TT:lobectomy 4:6) and matched cases of the two groups. Notably, this study is first to compare clinical outcomes concentrating on intermediate-risk PTC patients according to surgical extent applying a matched-pair method. For this certain risk group, although including large number of cohorts, previous population-level analyses may be influenced by some improperly operated cases [9].

In the detailed recurrence analysis, both local recurrence and regional recurrence were more common in the lobectomy group than in the TT group, whereas the total number of cases involving recurrence were similar in the two groups. This finding indicated that in the lobectomy group, multiregional surgery might be required for recurrent cases; this possibility should also be considered before the first determination of treatment. Given the aforementioned factors, we do not believe that there is sufficient evidence to recommend lobectomy for all intermediate-risk patients, but our study may call into question whether lobectomy is absolutely unsuitable for intermediate-risk patients; thus, in PTC management, the overall situation should be considered individually before decisions are made to ensure that an appropriate balance between survival benefit and quality of life is achieved.

Conclusions

In our cohort of intermediate-risk PTC patients, no differences in outcomes for the lobectomy and TT groups were detected.

Conflict of interest

None declared.

CRediT authorship contribution statement

Jie Liu: Conceptualization, Methodology, Writing - original draft. **Zongmin Zhang:** Conceptualization, Methodology. **Hui Huang:** Investigation, Writing - review & editing. **Siyuan Xu:** Formal analysis. **Yang Liu:** Investigation. **Shaoyan Liu:** Data curation, Supervision. **Xiaolei Wang:** Data curation, Visualization. **Zhengang Xu:** Conceptualization, Writing - original draft, Supervision.

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Author contributions

Conceptualization, Jie Liu, Zongmin Zhang and Zhengang Xu ; Methodology, Jie Liu, Zongmin Zhang; Formal Analysis, Siyuan Xu; Investigation, Hui Huang and Yang Liu; Data Curation, Xiaolei Wang and Shaoyan Liu; Writing – Original Draft Preparation, Jie Liu and Zhengang Xu; Writing – Review & Editing, Hui Huang; Visualization, Xiaolei Wang.; Supervision, Shaoyan Liu and Zhengang Xu.

The authors declare no conflict of interest.

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