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Is biopsy enough for papillary thyroid microcarcinoma?

An analysis of the SEER database 2004 to 2013 with propensity score matching

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Abstract

The treatment of papillary thyroid microcarcinoma (PTMC) remains deeply controversial. In this study, we investigated the prognosis of patients who underwent biopsy alone, as compared with other forms of thyroidectomy approaches. We sought to provide reference information for treatment selection in cases of PTMC.

The analysis included a large cohort of 34,972 PTMC patients from the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2013. Survival was examined by Kaplan-Meier analyses with log-rank tests, Cox proportional-hazards regression analyses, and propensity score matching analyses.

In the study cohort, the rate of cancer-specific mortality per 1000 person-years was higher for patients who underwent biopsy alone than for those who underwent other surgical approaches. According to multivariate Cox regression analyses, patients undergoing biopsy had similar cancer-specific survival rates and higher all-cause survival rates in comparison with patients undergoing other surgical approaches. After matching for influential factors using propensity scores, Kaplan-Meier analyses also showed that patients undergoing biopsy had similar cancer-specific survival rates and lower all-cause survival rates in comparison with patients undergoing other surgical approaches.

Our results provided helpful implications for the treatment of patients with PTMC.

Abbreviations: CSM = cancer-specific mortality, PSM = propensity score matching, PTMC = papillary thyroid microcarcinoma, SEER = Surveillance, Epidemiology, and End Results.

Keywords: biopsy, papillary thyroid microcarcinoma, propensity score matching, SEER

1. Introduction

The incidence of differentiated thyroid cancer has increased greatly in recent decades.[1,2] Roughly, 50% of this increase is attributable to the identification of intrathyroidal papillary thyroid microcarcinomas (PTMCs).[3] According to the World Health Organization classification, PTMCs are small thyroid cancers measuring 1 cm or less at their maximal diameter.[4,5] At least part of the increased incidence of thyroid cancer can be attributed to preoperative imaging tests, such as high-resolution ultrasonic testing.[6]

Papillary thyroid microcarcinoma has an excellent prognosis and is often regarded as an indolent disease. Nonetheless, it does pose risks of lymph node metastasis and local recurrence. The treatment of PTMC remains deeply controversial.[7–9] Overdiagnosis and overtreatment of PTMC have become a subject of substantial concern because some researchers have suggested that many low-risk PTMC lesions would not cause any harm if they were left untreated.[10–13]

Furthermore, the new version of American Thyroid Association guidelines introduced management by active surveillance as an alternative to immediate thyroid surgery in patients with very-low-risk tumors.[14] In this study, we investigated the prognosis of patients who underwent biopsy alone, as compared with other forms of thyroidectomy approaches. We sought to provide a reference for treatment selection in cases of PTMC.

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ZL and QZ contributed equally to this work.

The author(s) of this work have nothing to disclose.

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2. Material and methods

2.1. Ethical considerations and study population

This study's retrospective protocol was approved by our institution's ethical review board and complied with the ethical standards of the Declaration of Helsinki, and also the relevant national and international guidelines. We investigated a large number of thyroid cancer patients from the Surveillance, Epidemiology, and End Results (SEER) program. The SEER project is a US population-based cancer registry that began in 1973, and is supported by both the Centers for Disease Control and Prevention and National Cancer Institute. It contains cancer data from across multiple geographic regions on the incidence, prevalence, mortality, population-based variables, primary tumor characteristics including histological subtype, and more.

2.2. Data collection and analysis

We examined SEER data from 2004 to 2013, and selected patients with a diagnosis of PTMC, as defined by a combination of ICD-O site code of C73.9 (ie, thyroid, papillary, and/or follicular histology). The diagnosis codes were included in the study: "papillary carcinoma," "papillary adenocarcinoma," "Papillary microcarcinoma," and "Papillary carcinoma, follicular variant." To compare the survival rate among different surgical approach, 34,972 patients were included for analysis. Age, sex, race, N/M stage, multifocality, extension, and radiation treatment (none or refused, external beam radiation therapy, and radioactive I-131 ablation) were evaluated in patients with different surgical approaches. Rename of different surgical approaches: group A for biopsy; group B for lobectomy; group C for subtotal or near-total thyroidectomy; group D for total thyroidectomy.

2.3. Statistical analyses

Patients were followed up until December, 2013. Patient survival curves (thyroid cancer-specific mortality [CSM] and all-cause mortality) were examined by Kaplan-Meier analyses with the log-rank test. To further adjust for potential baseline confounding factors, a propensity score matching (PSM) analysis was conducted. Cox proportional-hazards regression analyses were performed to estimate the hazard ratios (HRs) with 95% confidence intervals (CIs), to show the magnitude of the effect of different surgical approach on CSM and all-cause mortality.[15] All P values were 2-sided, with $P < .05$ being considered significant. Analyses were performed using SPSS version 23.0, Stata/SE version 12 (Stata Corp.), and GraphPad Prism version 6 (GraphPad Software Inc.).

3. Results

3.1. Demographic and clinical features

In all, 34,972 patients who had PTMC and who underwent treatment with various surgical approaches were included in this study. The patients were divided into groups according to the treatment that they received: group A, biopsy (n = 214); group B, lobectomy (n = 7822); group C, subtotal or near-total thyroidectomy (n = 1490); and group D, total thyroidectomy (n = 25,447). The mean ages and follow-up times of patients are shown in Table 1, as stratified by surgical approach. Patients with biopsy had significantly fewer months of follow-up than did patients with other surgical approaches.

3.2. Cancer-specific and all-cause mortality rates for different surgical approaches

We investigated the CSM rate, which was defined as the rate of mortality attributed to thyroid cancer. The CSM rate per 1000 person-years was 3.87 (95% CI 0.97–15.46), 0.34 (95% CI 0.19–0.61), 0.54 (95% CI 0.20–1.43), and 0.53 (95% CI 0.41–0.70) in groups A, B, C, and D, respectively (Table 2). Furthermore, the all-cause mortality rate per 1000 person-years was 52.21 (95% CI 35.80–76.13), 9.12 (95% CI 8.14–10.22), 9.12 (95% CI 7.19–11.57), and 7.10 (95% CI 6.60–7.65) in groups A, B, C, and D, respectively (Table 2).

Table 1

Characteristics for patients with different surgery treatment.

		Surgery						
Covariate	Level	Biopsy (n = 214)	Lobectomy (n = 7821)	*P*	Subtotal or near-total thyroidectomy (n = 1490)	*P* value	Total thyroidectomy (n = 25447)	*P* value
Age		53.74 ± 16.66	52.35 ± 14.01	.493	51.43 ± 13.99	.151	50.29 ± 13.84	.011
Sex	Female	154 (72.0%)	6241 (79.8%)	.005	1210 (81.2%)	.002	20935 (82.3%)	<.001
	Male	60 (28.0%)	1580 (20.2%)		280 (18.8%)		4512 (17.7%)	
Race	White	158 (76.0%)	6568 (83.9%)	.005	1218 (82.3%)	.005	21303 (84.7%)	.001
	Black	17 (8.2%)	506 (6.6%)		131 (8.9%)		1547 (6.1%)	
	Other	33 (15.9%)	733 (9.5%)		130 (8.8%)		2314 (9.2%)	
Histology type	PTC	197 (92.1%)	5527 (70.7%)	<.001	1072 (71.9%)	<.001	18175 (71.4%)	<.001
	Other	17 (7.9%)	2294 (29.3%)		418 (28.1%)		7272 (28.6%)	
N stage	N0	185 (92.0%)	7648 (98.5%)	<.001	1419 (95.8%)	.017	21810 (86.7%)	.026
	N1	16 (8.0%)	118 (1.5%)		62 (4.2%)		3353 (13.3%)	
M stage	M0	210 (98.1%)	7813 (99.9%)	<.001	1483 (99.5%)	.017	25363 (99.7%)	<.001
	M1	4 (1.9%)	8 (0.1%)		7 (0.5%)		84 (0.3%)	
Multifocality	No	165 (86.4%)	6336 (81.7%)	.099	1050 (71.0%)	<.001	14912 (59.0%)	<.001
	Yes	26 (13.6%)	1417 (18.3%)		428 (29.0%)		10363 (41.0%)	
Extension	No	197 (98.5%)	7660 (98.0%)	.596	1431 (96.1%)	.088	23571 (92.7%)	.002
	Yes	3 (1.5%)	159 (2.0%)		58 (3.9%)		1857 (7.3%)	
Radiation	None or refused	206 (97.6%)	7188 (93.4%)	.007	1143 (78.2%)	<.001	15979 (64.0%)	<.001
	External beam radiation therapy	2 (0.9%)	28 (0.4%)		16 (1.1%)		240 (0.9%%)	
	Radioactive I-131 ablation	3 (1.4%)	476 (6.3%)		303 (20.7%)		8752 (35.1%)	
Survival		29.00 ± 29.18	50.11 ± 34.16	<.001	60.05 ± 34.03	<.001	46.86 ± 32.65	<.001

PTC = papillary thyroid cancer.

Table 2

Hazard ratios of different surgery for the cancer specific deaths and all-cause deaths of thyroid cancer.

Surgery	Cancer-specific deaths, n	%	Cancer-specific deaths per 1000 person-years	95% CI	All-cause deaths, n	%	All-cause deaths per 1000 person-years	95% CI
Biopsy	2	0.93	3.87	0.97–15.46	46	21.50	52.21	35.80–76.13
Lobectomy	11	0.14	0.34	0.19–0.61	311	3.98	9.12	8.14–10.22
Subtotal or near-total thyroidectomy	4	0.27	0.54	0.20–1.43	69	4.63	9.12	7.19–11.57
Total thyroidectomy	55	0.22	0.53	0.41–0.70	718	2.82	7.10	6.60–7.65

CI = confidence interval.

3.3. Risk factors for thyroid cancer-specific and all-cause mortality rates

The univariate Cox regression analyses showed that histological types, age, sex, lymph node metastasis, distant metastasis, thyroid capsular extension, radiation, and surgical approach were significant risk factors for CSM. Multivariate Cox regression analysis showed that CSM did not differ significantly between group A and groups B, C, and D after adjusting for relative risk factors (Table 3). The univariate Cox regression analyses confirmed that demographic data (age, sex, race), lymph node metastasis, distant metastasis, multifocality, radiation treatment, and surgical approach were found to be significant risk factors for all-cause mortality. It is verified that all-cause mortality differed significantly between group A and groups B, C, and D by multivariate Cox regression analysis (Table 3).

3.4. Adjusting for patient characteristics using propensity score matching

The CSM rate in group A was higher than that in groups B, C, and D ($P < .001$). Further, the all-cause mortality rate in group A was higher than that in groups B, C, and D ($P < .001$) (Fig. 1A–D). To minimize selection bias, a PSM analysis was performed, including age, sex, race, N/M stage, histologic subtype, multifocality, extension, and radiation treatment approaches.

After PSM for demographic data like age, sex, and race, cancer-specific survival analysis showed that the prognosis of patients in group A was similar to the prognoses of groups B, C, and D ($P = .353$, .904, and .663, respectively; Fig. 2A–C). After PSM for risk factors (age, sex, race, N/M stage, histologic subtype, multifocality, and extension), there were still no significant differences in CSM between group A and groups B, C, and D ($P = .422$, .926, and .434, respectively; Fig. 3A–C). Moreover, after matching for all influential factors (including radiation treatment), the prognosis of patients in group A remained similar to the prognoses of patients in groups B, C, and D ($P = .806$, .933, and .854, respectively; Fig. 4A–C).

In an all-cause survival analysis, the prognosis was poorer in group A than in groups B, C, and D after PSM for age, sex, and race (all $P < .001$; Fig. 5A–C). Similar results were obtained after PSM for age, sex, race, N/M stage, histologic subtype, multifocality, and extension (all $P < .001$; Fig. 6A and B). After matching for all

Table 3

Risk factors for survival (outcome is all-cause mortality and thyroid cancer-specific mortality).

		Thyroid cancer-specific mortality				All-cause mortality			
		Univariate Cox regression		Multivariate Cox regression		Univariate Cox regression		Multivariate Cox regression	
Covariate	Level	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age		1.075 (1.056–1.095)	<.001	1.074 (1.053–1.094)	<.001	1.082 (1.077–1.087)	<.001	1.076 (1.071–1.081)	<.001
Sex	Female	Ref		Ref		Ref		Ref	
	Male	3.846 (2.419–6.115)	<.001	1.454 (0.854–2.475)	.168	2.422 (2.145–2.736)	<.001	1.639 (1.441–1.866)	<.001
Race	White	Ref		Ref		Ref		Ref	
	Black	0.449 (0.110–1.837)	.265	0.962 (0.231–4.004)	0.957	1.362 (1.102–1.683)	.004	1.507 (1.212–1.873)	<.001
	Other	1.237 (0.592–2.584)	.571	0.907 (0.376–2.189)	0.828	0.697 (0.547–0.888)	.004	0.747 (0.581–0.96)	.022
Histological types	PTC	Ref		Ref		Ref		Ref	
	Other	0.855 (0.501–1.457)	.564	0.913 (0.509–1.638)	0.761	1.128 (0.995–1.28)	.06	1.071 (0.941–1.219)	.298
N stage	N0	Ref		Ref		Ref		Ref	
	N1	8.544 (5.289–13.803)	<.001	4.916 (2.698–8.957)	<0.001	1.352 (1.133–1.614)	.001	1.656 (1.354–2.027)	<.001
M stage	M0	Ref		Ref		Ref		Ref	
	M1	112.66 (65.372–194.157)	<.001	21.039 (10.28–43.058)	<0.001	8.786 (5.955–12.962)	<.001	4.605 (2.827–7.5)	<.001
Multifocality	No	Ref		Ref		Ref		Ref	
	Yes	1.426 (0.886–2.295)	.144	0.713 (0.411–1.237)	0.229	0.894 (0.789–1.013)	.079	1.017 (0.89–1.163)	.801
Extension	No	Ref		Ref		Ref		Ref	
	Yes	9.505 (5.898–15.317)	<.001	2.227 (1.185–4.186)	0.013	1.196 (0.953–1.501)	.123	1.058 (0.818–1.368)	.669
Radiation	None or refused	Ref		Ref		Ref		Ref	
	Radiation beam or radioactive implants	41.453 (21.629–79.445)	<.001	13.705 (5.926–31.698)	<0.001	2.458 (1.698–3.560)	<.001	2.001 (1.336–2.998)	.001
	Radioisotopes or radiation beam + isotopes/implants	2.638 (1.560–4.461)	<.001	1.937 (1.002–3.744)	0.049	0.654 (0.568–0.753)	<.001	0.792 (0.672–0.932)	.005
Surgery	Biopsy	Ref		Ref		Ref		Ref	
	Lobectomy	0.095 (0.021–0.431)	.002	0.417 (0.077–2.271)	0.312	0.104 (0.076–0.142)	<.001	0.195 (0.137–0.277)	<.001
	Subtotal or near-total thyroidectomy	0.157 (0.029–0.857)	.032	0.325 (0.054–1.968)	0.221	0.1 (0.069–0.145)	<.001	0.202 (0.134–0.306)	<.001
	Total thyroidectomy	0.154 (0.038–0.632)	.009	0.44 (0.089–2.163)	0.312	0.08 (0.059–0.108)	<.001	0.175 (0.124–0.247)	<.001

CI = confidence interval, PTC = papillary thyroid cancer.

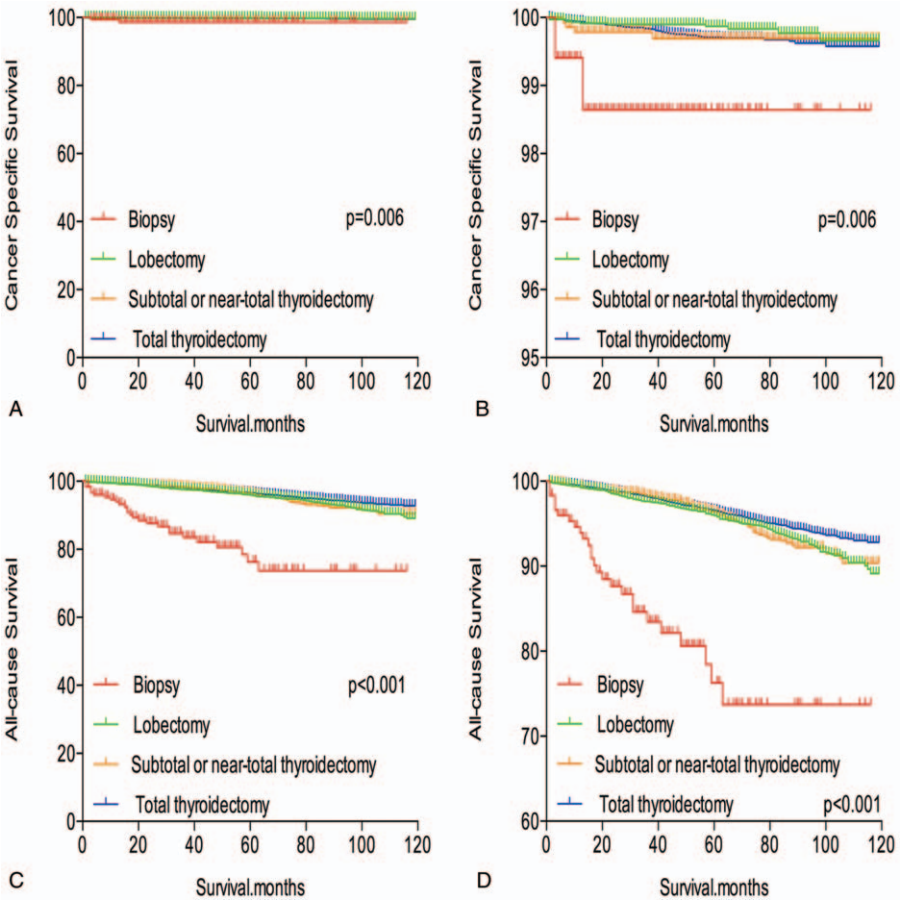

Figure 1. Kaplan-Meier curves among patients stratified by surgical approach for cancer-specific mortality (A, B: log-rank test, $P < .0001$) and all-cause mortality (C, D: log-rank test, $P < .0001$).

influential factors (including radiation treatment), patients in group A still showed a poorer all-cause prognosis than did patients in groups B, C, and D ($P < .001$ for all; Fig. 7A–C).

4. Discussion

In the literature on PTMC treatment, there have been many concerns about the balance between recurrence or mortality and the risk of permanent complications.[7,16–18] Overly aggressive surgical approaches are associated with more permanent complications, such as hypoparathyroidism and recurrent laryngeal nerve injury. On the contrary, inadequate treatment can result in elevated probabilities of recurrence and mortality.

In our study of SEER database, the PTMC-related CSM rates were similar for patients who underwent biopsy and for those who underwent other surgical approaches after PSM. However,

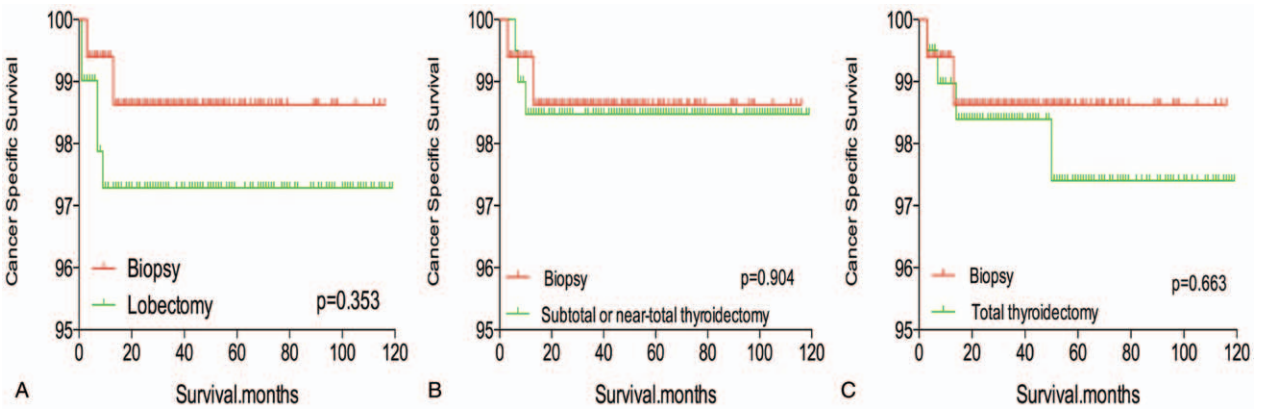

Figure 2. Kaplan-Meier curves of cancer-specific mortality for matched surgical approach pairs. Age, sex, and race matching between group A and group B (A), group A and group C (B), and group A and group D (C).

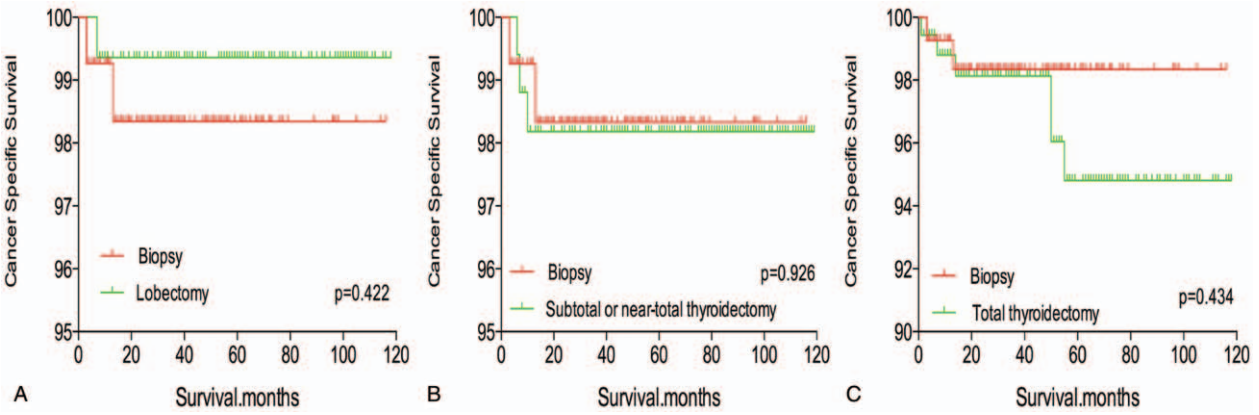

Figure 3. Kaplan-Meier curves of cancer-specific mortality for matched surgical approach pairs. Age, sex, race, N/M stage, histologic subtype, multifocality, and extension matching between group A and group B (A), group A and group C (B), and group A and group D (C).

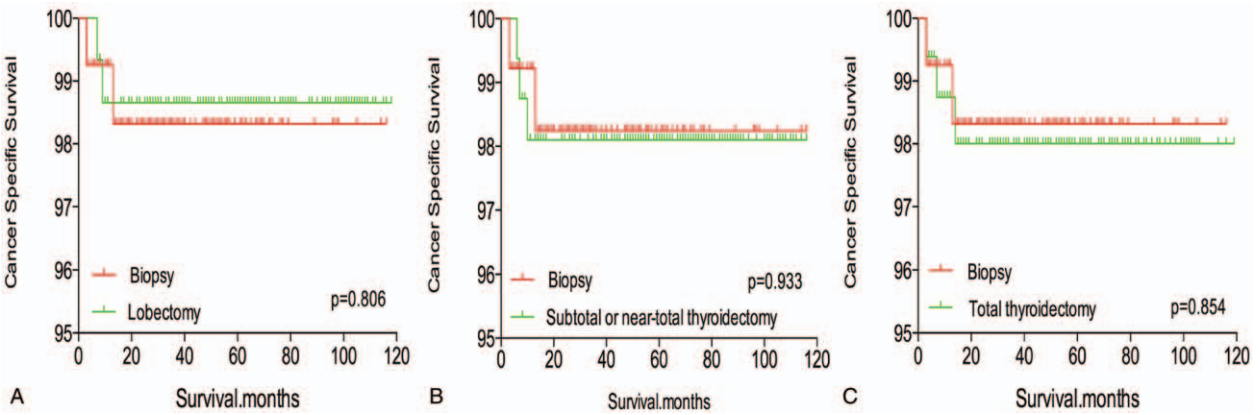

Figure 4. Kaplan-Meier curves of cancer-specific mortality for matched surgical approach pairs. Age, sex, race, N/M stage, histologic subtype, multifocality, extension, and radiation treatment matched between group A and group B (A), group A and group C (B), and group A and group D (C).

even after matching on several potential confounders, patients who underwent biopsy had significantly higher all-cause mortality rates than did patients in any of the other surgical approach groups.

Cancer-specific mortality for PTMC is very low, reaching up to 0.3% in clinical series.[19,20] In other words, PTMC is associated with an excellent cancer-specific survival rate. However, in this study, the mean follow-up time for patients with biopsy was 29.0

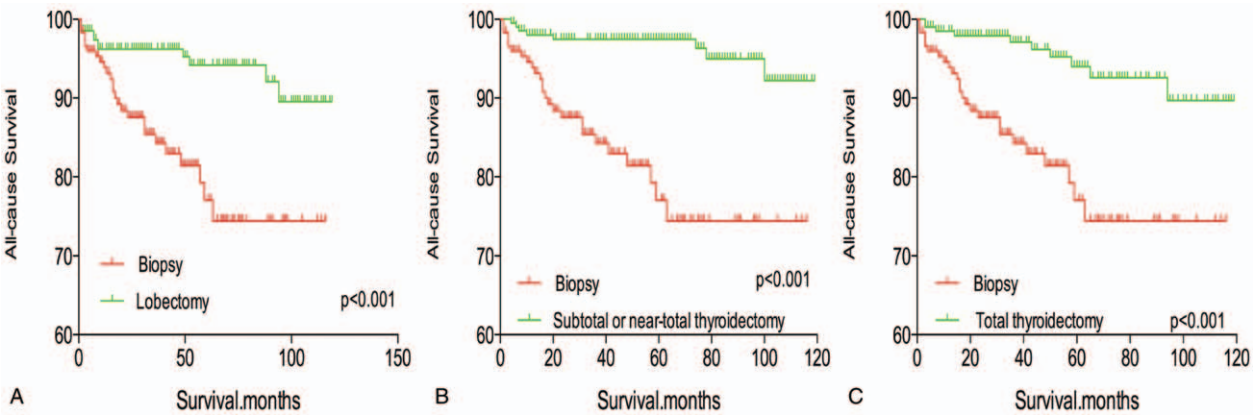

Figure 5. Kaplan-Meier curves of all-cause mortality for matched surgical approach pairs. Age, sex, and race matching between group A and group B (A), group A and group C (B), and group A and group D (C).

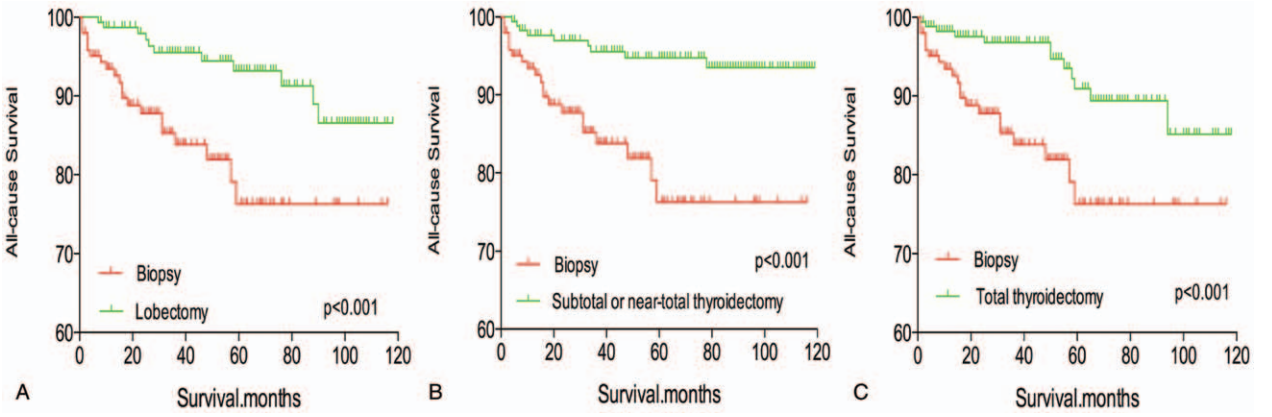

Figure 6. Kaplan-Meier curves of all-cause mortality for matched surgical approach pairs. Age, sex, race, N/M stage, histologic subtype, multifocality, and extension matching between group A and group B (A), group A and group C (B), and group A and group D (C).

months, which was shorter than the follow-up times in other groups. The differences in follow-up times and the low CSM rates made it difficult to detect any significant differences in cancer-specific survival between the biopsy group and other 3 groups after matching on influence factors.

One of the surprising aspects of our study was that the percentage of patients with lymph node metastasis was even higher in the biopsy group than in the lobectomy and subtotal or near-total thyroidectomy groups. This may be a consequence of relatively rigorous preoperative screening for nodal metastases being conducted in patients who undergo biopsy alone. Lymph node metastasis plays an important role in mortality from thyroid cancer.[21,22] This may also help to explain why the cancer-specific survival rates did not differ significantly between the biopsy group and other groups after matching that included N stage.

Distant metastases at the time of diagnosis have an adverse effect on survival in thyroid cancer.[14,23] In our study, distant metastasis was recorded for 1.9% patients who underwent biopsy, which was more than observed for the other 3 surgical methods. The patients with distant metastasis may have contributed to the poorer all-cause survival that was observed in the biopsy group, although we did match for M stage.

Radiofrequency ablation and sonographically guided percutaneous ethanol injection were first developed for the treatment of benign nodules or distant metastases from thyroid cancer and locoregional recurrences of thyroid cancer.[24–27] Based on the information recorded in the SEER database, we were unable to determine whether patients who underwent biopsy also received ablation. However, we would only recommend this treatment for carefully selected cases of PTMC because supportive evidence is lacking from studies with long-term follow-up data.

There are several limitations in our study. Our study lacked strict inclusion criteria for patients who underwent biopsy. We were only able to include patients with maximum tumor sizes less than or equal to 1 cm, but were unable to exclude patients with total tumor sizes of more than 1 cm.[5,28] In addition, other limitation of this study is that family history, vascular invasion, and recurrence were not evaluated or included in our study. Molecular markers (such as *BRAF, RAS*, and *TERT* mutations) were not observed and adjusted for in our analyses in our study.

In conclusion, the results of our investigation demonstrated that patients who underwent biopsy alone for PTMCs had similar cancer-specific survival and worse all-cause survival than patients

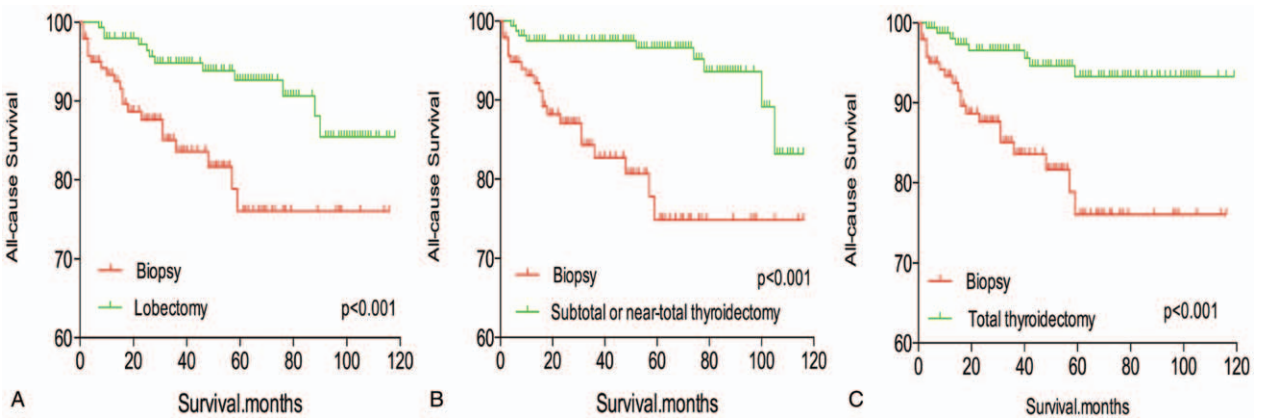

Figure 7. Kaplan-Meier curves of all-cause mortality for matched surgical approach pairs. Age, sex, race, N/M stage, histologic subtype, multifocality, extension, and radiation treatment matched between group A and group B (A), group A and group C (B), and group A and group D (C).

who received other surgical approaches. Our findings may provide a helpful reference for treatment decision-making in cases of PTMC.

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Validation: tao huang.
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Writing – original draft: Qiuyang Zhao, Chunping Liu, Yiquan Xiong.
Writing – review & editing: Zeming Liu, tao huang, Liang Guo.

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