

Sarcopenia Increases the Risk of Major Organ Invasion in Patients with Papillary Thyroid Cancer

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Abstract

While sarcopenia is associated with poor overall survival and cancer-specific survival in solid cancer patients, the impact of sarcopenia on clinicopathologic features that can influence conventional papillary thyroid cancer (PTC) prognosis remains unclear. To investigate the impact of sarcopenia on aggressive clinicopathologic features in PTC patients, prospectively collected data on 305 patients who underwent surgery for PTC with preoperative staging ultrasonography and bioelectrical impedance analysis were retrospectively analyzed. Nine sarcopenia patients showed more patients aged 55 or older ($p = 0.022$), higher male proportion ($p < 0.001$), lower body-mass index ($p = 0.015$), higher incidence of major organ invasion ($p = 0.001$), higher T ($p = 0.002$) stage, higher TNM ($p = 0.007$) stage, and more tumor recurrence ($p = 0.023$) compared to the non-sarcopenia patients. Unadjusted and adjusted logistic regression analyses showed that sarcopenia (odds ratio (OR) 9.936, 95% confidence interval (CI) 2.052–48.111, $p = 0.004$), tumor size (OR 1.048, 95% CI 1.005–1.093, $p = 0.027$), and tumor multiplicity (OR 3.323, 95% CI 1.048–10.534, $p = 0.041$) significantly increased the risk of major organ invasion. Therefore, sarcopenia in PTC patients should raise suspicion for a more locally advanced disease and direct appropriate management.

Introduction

Sarcopenia is the age-related loss of skeletal muscle mass and function, which is associated with metabolic, physiologic, and functional impairments.^{1,2} Clinically, sarcopenia is identified by low muscle strength as well as low muscle quantity and quality.² Such changes in body composition can impact an extensive variety of disease processes, such as cardiac disease, respiratory disease, as well as some malignancies.^{3–6}

In oncology, severe sarcopenia may occur in cancer patients with profound weight loss, particularly of the skeletal muscle.^{7,8} A high prevalence of sarcopenia has been reported in gastric cancer (57%), advanced hepatocellular carcinoma (HCC) (27.5%), and in metastatic renal cell carcinoma (RCC) (29%).^{9–11} Poor overall survival and poor cancer-specific survival have been associated with sarcopenia in breast cancer, HCC, RCC, and gastrointestinal tract cancer, as well as increased chemotherapy toxicity and post-operative complications in various solid cancers.^{4,12–14} However, sarcopenia has not been associated with poor survival in soft tissue sarcoma,¹⁴ suggesting that these associations may vary according to the specific cancer type.

In thyroid cancers, the DECISION trial showed a significant association between sorafenib and reduced muscle mass in advanced differentiated thyroid cancer.¹⁵ However, past studies have not explained whether sarcopenia can act as an aggressive clinicopathologic feature that potentially affects the prognosis of conventional papillary thyroid cancer (PTC).

Therefore, this study aimed to investigate the potential implications of sarcopenia on aggressive clinicopathologic features in PTC patients.

Results

Baseline characteristics

Baseline clinicopathologic characteristics of the 305 patients with conventional PTC are summarized in Table 1. The mean age was 43.6 ± 12.5 years [range, 19 – 75 years] with 231 women (mean age, 43.2 ± 12.5 years [range, 19 – 75 years]) and 74 men (mean age, 43.0 ± 12.8 years [range, 19 – 75 years]). Based on the bioelectrical impedance analysis (BIA) measurements of skeletal muscle index (SMI), nine patients (3.0%) were diagnosed with sarcopenia. There were 234 patients (76.6%) with no or minimal extrathyroidal extension (ETE), 55 patients (18.0%) with gross strap muscle invasion, and 16 patients (5.3%) with major organ invasion involving the trachea, esophagus, or recurrent laryngeal nerve. There were no cases of major vessel invasion or distant metastasis. The overall mean and standard deviation of body mass index (BMI) was 23.5 ± 3.4 kg/m² [range, 16.4 – 33.9 kg/m²] and there were 92 obese patients (30.2%). The mean primary tumor size was 16.9 mm [range, 11.0 – 130.0 mm]. Disease-free survival was 62.3 ± 13.7 months [range, 3.1–84.6 months], and tumors recurred in five patients (1.6%).

Clinicopathologic features of PTC in the sarcopenia group

Compared to the non-sarcopenia group, the sarcopenia group showed more patients older than 55 years of age ($p = 0.022$), higher male proportion ($p < 0.001$), lower BMI ($p = 0.015$), and more tumor recurrence ($p = 0.023$) (Table 2). The sarcopenia group showed more major organ invasion ($p = 0.001$), high T stage ($p = 0.002$), and high overall TNM stage ($p = 0.007$) than the non-sarcopenia group. There were no significant differences in LN metastasis and disease-free survival between the two groups.

Unadjusted and adjusted logistic regression models between patient body composition and aggressive tumor features

Unadjusted logistic regression analysis between sarcopenia and various clinicopathologic features revealed that sarcopenia was significantly associated with major organ invasion (odds ratio (OR) 10.885, 95% confidence interval (CI) 2.445–48.453, $p = 0.002$) and high TNM stage (OR 12.208, 95% CI 1.142–130.552, $p = 0.038$) (Table 3). Sarcopenia was not significantly associated with high T stage (T3 or T4), lymph node (LN) metastasis, or tumor recurrence (Table 3).

On the unadjusted logistic regression analysis for clinicopathologic features and major organ invasion, sarcopenia, tumor size, tumor multiplicity, and LN metastasis showed significant associations with major organ invasion (Table 4). On adjusted logistic regression including these variables, patients with sarcopenia (OR 9.936, 95% CI 2.052–48.111, $p = 0.004$), larger tumor size (OR 1.048, 95% CI 1.005–1.093, $p = 0.027$), and tumor multiplicity (OR 3.323, 95% CI 1.048–10.534, $p = 0.041$) showed significantly higher risk of major organ invasion.

Unadjusted logistic regression analysis for clinicopathologic features and high TNM stage showed that age (OR 1.157, 95% CI 1.032–1.299, $p = 0.013$) and sarcopenia (OR 12.208, 95% CI 1.142–130.552, $p = 0.038$) were significantly associated with high TNM stage. However, adjusted regression analysis revealed that only older age (OR 1.148, 95% CI 1.018–1.294, $p = 0.024$) and not sarcopenia (OR 6.099, 95% CI 0.478–77.874, $p = 0.164$) was a significant risk factor for high TNM stage (Supplementary Table 1).

Discussion

In this study, sarcopenia was a significant risk factor for major organ invasion in PTC, and consequently a significant risk factor for more locally advanced disease. Sarcopenia was not significantly associated with disease-free survival in PTC.

Although significant associations between sarcopenia and adverse cancer outcomes have been suggested,⁴ published literature about the potential impact of sarcopenia on PTC is scarce. Our study showed that despite the higher risk of locally advanced disease in PTC patients with sarcopenia, sarcopenia by itself was not significantly associated with disease-free survival. This may be explained in part by advancements in surgical techniques that increase the rate of complete resection, even in advanced ETE.^{16,17} The low incidence of tumor recurrence in our study may also be a contributing factor.

Our results showed that sarcopenia was significantly associated with major organ invasion, but not with LN metastasis. The association between sarcopenia and potential LN metastasis in various types of cancers remains controversial.^{18–21} Sarcopenia has been shown to increase the risk of LN metastasis in colorectal cancer and advanced urothelial carcinoma, while no significant association has been found with resectable bile duct cancer or recurrent pancreas adenocarcinoma.^{18–21} As with the association between sarcopenia and adverse cancer outcomes, the association between sarcopenia and LN metastasis also seems to depend on the specific type of cancer. Preoperative diagnosis of sarcopenia may raise the suspicion of the clinician, radiologist, as well as the surgeon, for a more locally advanced disease and direct prompt and appropriate management.

In our study, BMI was not significantly associated with major organ invasion in PTC. While a previous Korean study suggested BMI as a significant risk factor for microscopic ETE and higher TNM stage,²² another Korean study suggested that higher BMI was a significant risk factor for tumor multiplicity, but not for higher T stage, positive LN metastasis, nor ETE.²³ In a United States study, higher BMI was significantly associated with higher incidence of PTC, but with less tumor invasion and LN metastasis.²⁴ Evidently, any potential association between BMI and aggressive clinicopathologic features of PTC is variable. Differences in ethnicity, culture, and lifestyle that may influence body composition,² as well as the application of previous versions of American Joint Committee on Cancer (AJCC) staging criteria may be the cause for these discrepant results.

We utilized BIA to assess body composition and to determine sarcopenia using SMI. BIA estimates skeletal muscle mass using whole-body electrical conductivity, and incorporates an affordable, widely available, and portable instrument with reproducible results.^{2,25} Unlike other malignancies in which abdomen and pelvic CT scans are often included during routine staging work-up, measuring SMI on CT scans to assess sarcopenia in thyroid cancer may unnecessarily burden patients with more radiation exposure. Alternatively, BIA may be an easier, more affordable tool to diagnose sarcopenia in PTC, as demonstrated in our study. In addition, the assessment of sarcopenia may be of importance in treatment decisions for advanced or refractory thyroid cancer because sarcopenia is considered a contraindication or discouraging factor in tyrosine kinase inhibitor treatment.^{15,26}

There are several limitations to this study. First, an inherent bias owing to the retrospective analysis of prospectively obtained data was inevitable. Second, the low incidence of sarcopenia in our study was a major limiting factor in statistical analysis. Last, body composition analysis by BIA may yield inconsistent or discrepant results depending on different instrument brands, as well as different population characteristics.² Our study utilized cutoff values previously obtained with identical equipment in young, healthy Korean subjects.²⁷ Therefore, the findings of this study may be limited to Korean patients. Further research that includes patients from more diverse populations may help clarify the potential impact of sarcopenia on the outcomes and clinicopathologic features of PTC patients.

In conclusion, sarcopenia is significantly associated with a higher risk of major organ invasion in conventional PTC. Sarcopenia in PTC patients should raise clinical, radiological, and surgical suspicion for a more locally advanced disease and direct appropriate management.

Methods

This prospective study was approved by the institutional review board at Severance Hospital (4-2013-0833), and was conducted in accordance with the Declaration of Helsinki as revised in 2013. Informed consent was obtained from all patients enrolled in this study.

Study population

From February 2014 to October 2015, a total of 2,717 patients aged 19 years or older underwent preoperative staging ultrasonography (US) at our institution. Patients who did not undergo preoperative BIA (n = 1,284) or thyroid surgery (n = 283) were excluded. Patients with benign pathology (including diffuse hyperplasia, adenomatous hyperplasia, follicular adenoma, Hurthle cell adenoma, Hashimoto's thyroiditis, lymphocytic thyroiditis, Grave's disease, hyalinizing trabecular tumor and branchial cleft cyst anomaly type II) (n = 98), PTC variants (follicular variant, oncocytic variant, diffuse sclerosing variant, and solid variant PTC) (n = 68), follicular carcinoma (n = 4), medullary carcinoma (n = 1), neuroendocrine tumor (n = 1), metastatic adenocarcinoma (n = 2), as well as papillary microcarcinoma (n = 671) were excluded. A total of 305 patients with a pathologically confirmed diagnosis of conventional PTC were

eligible for final analysis (Fig. 1). Disease-free survival was defined as the time interval from the date of diagnosis to the last follow-up visit or the date of tumor recurrence.

Preoperative staging ultrasonography (US)

Preoperative staging US was performed by one of 17 radiologists (12 fellows with 1 or 2 years of experience and 5 faculties with 6 to 18 years of experience in thyroid US) using a 5–12 MHz linear transducer (iU22, Philips Medical Systems, Bothell, WA). Primary tumor and cervical LNs were evaluated and reviewed based on the 8th AJCC TNM classification.²⁸ Any LN with at least one suspicious US feature (focal or diffuse hyperechogenicity, presence of internal calcification, cystic change, round shape, and chaotic or peripheral vascularity on Doppler US) was considered pathologic and was subsequently confirmed by either US-FNA or surgery.

Bioelectrical impedance analysis (BIA)

All included patients underwent preoperative BIA. Multifrequency bioimpedance data was measured using In-Body 720 (Biospace, Seoul, South Korea) in a standardized manner for all patients who underwent thyroid surgery. In-Body 720 employs a direct segmental multi-frequency bioelectrical impedance (MF-BIA) analysis method using a tetrapolar 8-point tactile electrode system with 30 impedance measurements taken at 6 frequencies (1 kHz, 5 kHz, 50 kHz, 250 kHz, 500 kHz, 1000 kHz) and reactance evaluated by 15 impedance measurements at 3 frequencies (5 kHz, 50 kHz, 250 kHz) for each of the 5 body segments (right arm, left arm, trunk, right leg, and left leg). All measurements were carried out prior to surgery in all patients. Body fat mass, body fat percentage, muscle mass, skeletal muscle mass, visceral fat surface, waist-hip ratio and basal metabolic rate were measured to assess body composition. Furthermore, the outer circumference and fat thickness of various body compartments (neck, chest, abdomen, hip, arm, and thigh) were measured. Finally, the SMI (skeletal muscle mass/height²) and BMI of each patient was analyzed using the aforementioned parameters. Sarcopenia was diagnosed according to sex-specific cutoff values (two standard deviations below the mean) for SMI that were suggested in a previous study of a healthy Korean population.²⁷ Obesity was categorized according to the BMI as follows: underweight (< 18.5 kg/m²), normal weight (18.5 – 22.9 kg/m²), overweight (23.0 – 24.9 kg/m²), obesity (25.0 – 29.9 kg/m²) and severe obesity (\geq 30 kg/m²) according to the World Health Organization guidelines for Asians.²⁹

Thyroid surgery and pathologic diagnosis

All total thyroidectomy at our institution routinely included bilateral central compartment LN dissection (CCND), which included the paratracheal, pretracheal, and prelaryngeal LNs. All hemithyroidectomy surgeries routinely included unilateral CCND. Selective lateral compartment LN dissection was performed only when lateral LN metastasis was suspected on either preoperative US and US-FNA, or during intraoperative observations. The lateral compartment included level II, III, IV, and V LNs. Pathologic tumor size, tumor multiplicity, ETE, and the presence of central and/or lateral LN metastasis on final surgical pathology reports were reviewed for analysis. T staging was as follows: 1) T1, tumor size smaller than 20

mm in greatest dimension limited to the thyroid; 2) T2, tumor size larger than 20 mm but equal to or smaller than 40 mm in greatest dimension limited to the thyroid; 3) T3a, tumor size larger than 40 mm but limited to the thyroid; 4) T3b, tumor of any size with gross strap muscle invasion; 5) T4, tumor of any size with invasion of major neck structures such as the larynx, trachea, esophagus, recurrent laryngeal nerve, prevertebral fascia or encasing major vessels. N staging was as follow: 1) N0, no evidence of regional LN metastasis; 2) N1a, metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal); 3) N1b, metastasis to unilateral, bilateral, or contralateral lateral neck LNs (levels I, II, III, IV, or V) or retropharyngeal LNs. T3 and T4 were considered high T stages, and the overall TNM stages III and IV were considered as high TNM stages.

Statistical analysis

All statistical analyses were performed with commercial software (IBM SPSS Statistics, version 25.0; IBM Corp., Armonk, NY). The independent t-test or Mann-Whitney U test was performed to compare clinical and pathological variables for parametric and non-parametric continuous variables, respectively. Categorical variables were compared using the chi square test or Fisher's exact test. Logistic regression analyses were performed to estimate unadjusted ORs with 95% CIs to elucidate the association between sarcopenia and aggressive tumor features (such as tumor multiplicity, ETE, LN metastasis, T stage, TNM stage, and tumor recurrence). Unadjusted logistic regression analysis was performed to explore the potential implications of sarcopenia on those aggressive tumor features. For variables that were significantly associated with sarcopenia on unadjusted analysis, a subsequent adjusted logistic regression analysis was performed that included the other clinicopathologic variables to obtain ORs and 95% CIs. A *p*-value of less than 0.05 was considered statistically significant.

Declarations

Competing Interests Statement

The authors declare no competing interests.

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None

Author contributions

Conception or design of the study was carried out by J.Y.K. and Y.J.K. All authors were responsible for data acquisition, analysis, interpretation as well as drafting or revising of the work. Y.J.K. and J.Y.K approved the final manuscript.

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Tables

Table 1. Clinicopathologic characteristics of the study population

Characteristic	All patients
Age (years)	43.2 ± 12.5
≥ 55 years old	64 (21.0%)
Female	231 (75.7%)
Weight (kg)	62.5 ± 11.6
Height (cm)	162.9 ± 8.1
BMI (kg/m ²)	23.5 ± 3.4
Obesity (BMI ≥25 kg/m ²)	92 (30.2%)
Sarcopenia	9 (3.0%)
Mean tumor size (mm)	16.9 ± 9.9
Extrathyroidal extension (ETE)	
No or minimal ETE	234 (76.7%)
Gross strap muscle invasion	55 (18.0%)
Major organ or vessel invasion	16 (5.2%)
Tumor multiplicity	121 (39.7%)
LN metastasis	182 (59.7%)
Distant metastasis	0 (0.0%)
T stage (AJCC 8 th edition)	
T1	200 (65.6%)
T2	31 (10.2%)
T3	58 (19.0%)
T4a	16 (5.2%)
TNM staging (AJCC 8 th edition)	
Stage I	266 (87.2%)
Stage II	35 (11.5%)
Stage III	4 (1.3%)
Stage IV	0 (0.0%)
Tumor recurrence	5 (1.6%)
Disease-free survival	62.3 ± 13.7

Values given are mean ± standard deviation. *BMI*, body mass index; *AJCC*, American Joint Committee on Cancer; *LN*, lymph node.

Table 2. Clinicopathologic features of patients according to the presence of sarcopenia

Characteristic	Non-sarcopenia (n=296)	Sarcopenia (n=9)	p-value
Age (years)	43.0 ± 12.4	47.2 ± 17.5	0.494
≥ 55 years old	59 (19.9%)	5 (55.6%)	0.022
Male	66 (22.3%)	8 (88.9%)	<0.001
BMI (kg/m ²)	23.6 ± 3.4	20.8 ± 2.2	0.015
Obesity (BMI ≥ 25kg/m ²)	92 (31.1%)	0 (0.0%)	0.062
Tumor size (mm)	16.8 ± 9.9	20.3 ± 10.3	0.286
range	11.0 - 130.0	11.0 - 43.0	
Tumor multiplicity	117 (39.5%)	5 (55.6%)	0.744
Extrathyroidal extension (ETE)			0.001
No or minimal	229 (77.4%)	5 (55.6%)	
Gross strap muscle invasion	54 (18.2%)	1 (11.1%)	
Major organ invasion	13 (4.4%)	3 (33.3%)	
T stage (AJCC 8 th edition)			0.002
T1	196 (66.2%)	4 (44.4%)	
T2	30 (10.1%)	1 (11.1%)	
T3	57 (19.3%)	1 (11.1%)	
T4a	13 (4.4%)	3 (33.3%)	
LN metastasis	175 (59.1%)	0 (0.0%)	0.261
TNM staging (AJCC 8 th edition)			0.003
Stage I	261 (88.2%)	5 (55.6%)	
Stage II	32 (10.8%)	3 (33.3%)	
Stage III	3 (1.0%)	1 (11.1%)	
Tumor recurrence	4 (1.4%)	1 (11.1%)	0.023
Disease-free survival	62.1 ± 13.9	66.6 ± 6.2	0.336

Values given are mean ± standard deviation. *BMI*, body mass index; *AJCC*, American Joint Committee on Cancer; *LN*, lymph node.

Table 3. Unadjusted logistic regression analyses between sarcopenia and clinicopathologic features

	Tumor multiplicity	Any ETE	Major organ invasion	LN metastasis	High T stage (T3 or T4)	High TNM stage (III or IV)	Tumor recurrence
Sarcopenia							
OR	1.224	2.734	10.885	2.42	2.583	12.208	9.125
(95% CI)	(0.322 - 4.652)	(0.714 - 10.470)	(2.445 - 48.453)	(0.494 - 11.849)	(0.675 - 9.882)	(1.142 - 130.552)	(0.914 - 91.117)
<i>p</i> -value	0.767	0.142	0.002	0.273	0.166	0.038	0.060

OR, odds ratio; CI, confidence interval; ETE, extrathyroidal extension; LN, lymph node.

Table 4. Unadjusted and adjusted logistic regression analyses between clinicopathologic features and major organ invasion

	Unadjusted			Adjusted		
	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value
Age	1.023	0.983 - 1.065	0.265	-	-	-
Male gender	1.950	0.684 - 5.561	0.212	-	-	-
Obesity	1.928	0.536 - 6.935	0.315	-	-	-
Sarcopenia	10.885	2.445 - 48.453	0.002	9.936	2.052 - 48.111	0.004
Tumor size	1.055	1.014 - 1.099	0.009	1.048	1.005 - 1.093	0.027
Tumor multiplicity	3.477	1.177 - 10.272	0.024	3.323	1.048 - 10.534	0.041
LN metastasis	5.042	1.125 - 22.593	0.035	3.545	0.757 - 16.599	0.108

OR, odds ratio; CI, confidence interval; LN, lymph node.

Figures

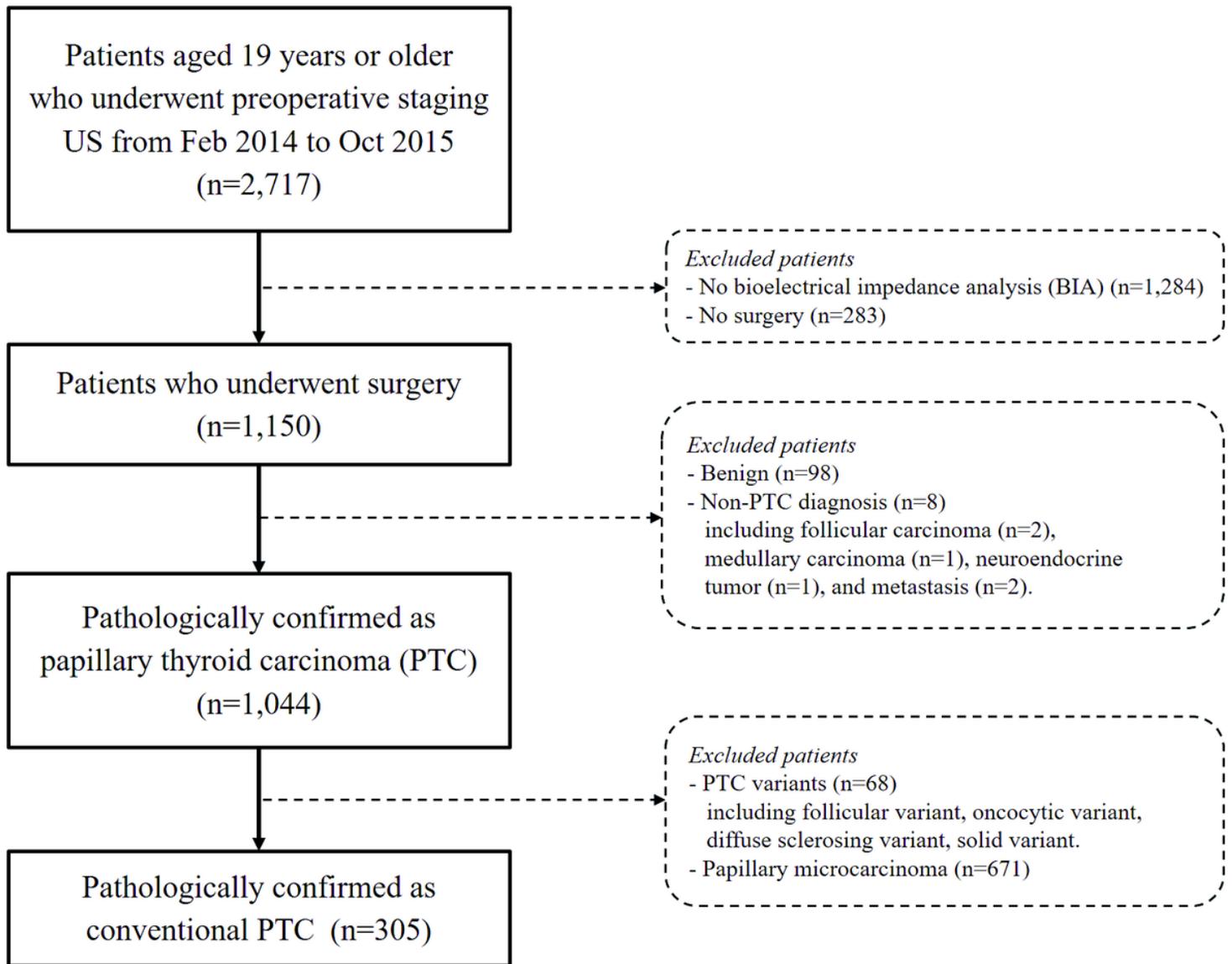


Figure 1

Patient selection diagram. A total of 2,717 patients were enrolled. Patients who did not undergo preoperative bioelectrical impedance analysis (BIA) or thyroid surgery were excluded. Only pathologic diagnosis of conventional PTC was included, resulting in a total of 305 patients eligible for final analysis.

Supplementary Files

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- [SupplementaryTable1.docx](#)