Original Article

# Clinical and pathologic features for predicting malignancy in thyroid follicular neoplasms

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**Background:** The cytologic findings of follicular neoplasm do not distinguish between benign follicular adenoma and follicular thyroid carcinoma (FTC). The objective of this retrospective study was to identify clinical and cytologic/pathologic features to predict malignancy in patients preoperatively diagnosed with follicular neoplasms.

**Methods:** In total, 416 patients with follicular neoplasms who underwent thyroidectomy were reviewed at Seoul St. Mary's Hospital (Seoul, Korea) from January 2010 to June 2018. Clinicopathological features were analyzed retrospectively by complete medical chart review and pathologic slide review.

**Results:** Thyroid malignancy/noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was diagnosed in 209 patients (50.2%). In total, 59 patients (14.2%) were diagnosed with FTC, 55 patients (13.3%) were diagnosed with follicular variant papillary thyroid carcinoma (fvPTC). The number of patients with PTC-related nuclear changes was higher in the malignancy/NIFTP group than in the benign group (16.3% *vs.* 1.9%, P<0.001). Multivariate analysis indicated that the significant risk factors for the diagnosis of malignancy/NIFTP include cytologic or pathologic diagnosis with PTC-related nuclear changes, NRAS mutation, and male sex.

**Conclusions:** The prevalence of malignancy in patients with a preoperative diagnosis of follicular neoplasm was much higher in our study than in previous reports. Cytologic or pathologic PTC-related nuclear changes is a useful predictor of the presence of malignancy. Further studies must be conducted to support our results.

**Keywords:** Follicular neoplasm; atypia; thyroidectomy; thyroid carcinoma

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## Introduction

Thyroid nodules are one of the most common diseases in clinical practice. Worldwide, approximately 5% of women and 1% of men have palpable nodules (1-3). Recently, high-resolution ultrasound (US) has been used for screening tests, and the diagnosis of thyroid nodules has greatly increased (2,4). Thyroid nodules are very common, and most are benign, but approximately 5% to 10% are diagnosed as malignant (5).

Fine-needle aspiration cytology (FNAC) is the gold standard for diagnosing thyroid nodules with a simple procedure and high accuracy (6,7). Although US-guided FNAC is significantly accurate in distinguishing between

papillary thyroid carcinoma (PTC) and benign disease, it is difficult to distinguish follicular thyroid carcinoma (FTC) and follicular variant papillary thyroid carcinoma (fvPTC) from benign follicular adenoma (8,9). FTC is distinguished from a follicular adenoma based on capsular invasion, extrathyroidal extension (ETE), vascular invasion, lymph node metastasis, or distant metastasis (10,11).

Because of the risk of malignancy, with approximately 10% to 30% being follicular neoplasm or suspicious for follicular neoplasm (12,13), diagnostic surgical resection is the long-established standard of management according to the American Thyroid Association (ATA) guidelines (14). This standard causes many patients to undergo unnecessary surgery of benign disease. In contrast, some patients who are diagnosed with FTC in surgical pathology should undergo completion thyroidectomy. Therefore, it is quite important to determine whether follicular neoplasm is benign or malignant before surgery.

Several studies have validated clinical or pathologic features for predicting malignancy in follicular neoplasms. Age, male sex, large nodule size, US features, and cytologic features have been reported as the main risk factors to define patients at risk for malignancy. However, there are still controversial predictors of malignancy in follicular neoplasms.

The objective of this retrospective study was to identify the clinical and cytologic/pathologic features to predict malignancy in patients preoperatively diagnosed with follicular neoplasm. We present the following article in accordance with STROBE reporting checklist (available at http://dx.doi.org/10.21037/gs-20-500).

## Methods

### *Patients*

In total, 425 patients preoperatively diagnosed with follicular neoplasm or suspicious for follicular neoplasm who underwent a thyroid operation, including total or less than total thyroidectomy, were retrospectively reviewed at Seoul St. Mary's Hospital (Seoul, Korea) from January 2010 to June 2018. Nine patients were excluded as they had inappropriate data. A total of 416 patients were analyzed by a complete review of medical charts and pathologic slide review. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board at Seoul St. Mary's Hospital, the Catholic University of Korea (IRB No. KC19RESI0264) and the need for informed consent was waived due to the retrospective nature of this study.

### *FNAC and core needle biopsy (CNB)*

All FNAC or CNB procedures were performed by US guidance by experienced radiologists. US-guided CNB was performed according to the following indications: (I) thyroid nodules with macrocalcifications, hypervascularity, or scanty aspirates by FNAC; (II) thyroid nodules with prior non-diagnostic/unsatisfactory FNAC; (III) thyroid nodules with suspicious features for malignancy on US but prior non-malignant FNAC. An 18-gauge, double-action, spring-activated needle was used for CNB.

### *Pathologic diagnosis using FNAC and CNB*

The diagnosis made using FNAC and CNB was based on the Bethesda system and included Bethesda category IV. The slides were examined by a single, blinded and experienced pathologist at our institution. Follicular neoplasms with more than 75% of Hürthle cell components were classified as Hürthle cell subtypes. Follicular neoplasms, other than the Hürthle cell subtype, were classified according to the type of atypia, namely, architectural (microfollicular formations, crowding, and isolated cells) or nuclear (nuclear enlargement, chromatin clearing, nuclear grooves, and nuclear membrane irregularity) (15). The nuclear atypia raised the concern for PTC, but was not diagnostic of malignancy. The specimen showing architectural atypia and nuclear atypia concerning for PTC was interpreted as follicular neoplasm with PTC-related nuclear changes. These findings were compared with the final surgical pathology.

### *Statistical analysis*

Continuous variables were reported as the mean with standard deviation (SD), and categorical variables were provided as numbers with percentages. Student's *t*-test was used to compare continuous variables. Pearson's chi-square test or Fisher's exact test was performed to compare categorical variables between the two groups. Univariate and multivariate logistic regression analyses were performed to identify which factors were associated with the diagnosis of malignancy. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated. A P value $<0.05$ was considered statistically significant. All statistical analyses

**Table 1** Baseline clinical characteristics of the study patients

| Variable | N=416 |
|---|---|
| Age (years) | 47.1±13.7 (range, 14–83) |
| Male:female | 1:3.2 |
| Male | 99 (23.8) |
| Female | 317 (76.2) |
| TSH (mIU/L) | 2.1±1.9 (range, 0.01–25.3) |
| Method of diagnosis | |
| FNAC | 138 (33.2) |
| CNB | 278 (66.8) |
| Follicular neoplasm subtype | |
| Conventional | 337 (81.0) |
| Architectural atypia | 299 (71.9) |
| PTC-related nuclear changes | 38 (9.1) |
| Hürthle cell | 79 (19.0) |

Data are expressed as patient's number (%), or mean ± SD. TSH, thyroid stimulating hormone; FNAB, fine needle aspiration biopsy; CNB, core needle biopsy; PTC, papillary thyroid carcinoma.

were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA).

## Results

### *Baseline clinicopathological characteristics of the study patients*

*Table 1* presents the baseline clinical characteristics of the study patients who underwent thyroidectomy due to follicular neoplasm or suspicious for follicular neoplasm. The mean age of the study patients was 47.1±13.6 years (range, 14–83 years), and 317 (76.2%) patients were female. The mean TSH was 2.1±1.9 mIU/L (range, 0.01–25.3 mIU/L). In total, 278 (66.8%) patients were diagnosed with thyroid nodules by CNB. There were 79 (19.0%) patients diagnosed with the Hürthle cell subtype by FNAC or CNB. PTC-related nuclear changes and architectural atypia were diagnosed in 38 (9.1%) and 299 (71.9%) patients, respectively.

The baseline clinicopathological characteristics of the study patients are shown in *Table 2*. In total, 73 (17.5%) patients underwent total thyroidectomy, and 343 (82.5%) patients underwent lobectomy and/or contralateral

**Table 2** Baseline clinicopathological characteristics of the study patients

| Variable | N=416 |
|---|---|
| Extent of operation | |
| Less than total | 343 (82.5) |
| Total | 73 (17.5) |
| Malignancy/NIFTP | 209 (50.2) |
| Tumor size (cm) | 2.4±1.6 (range, 0.5–13.5) |
| ETE | 10 (6.8) |
| NRAS | 49/220 (22.3) |
| $BRAF^{V600E}$ | 14/193 (7.3) |
| Lymphatic invasion | 11/146 (7.5) |
| Vascular invasion | 31/146 (21.2) |
| Perineural invasion | 1/146 (0.7) |
| T category | |
| T1 | 74 (50.7) |
| T2 | 51 (34.9) |
| T3 | 21 (14.4) |
| N category | |
| N1a | 19 (13.0) |
| M category | |
| M1 | 2 (1.4) |
| TNM stage | |
| I | 135 (92.5) |
| II | 10 (6.8) |
| IVb | 1 (0.7) |

Data are expressed as patient's number (%), or mean ± SD. NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; ETE, extrathyroidal extension; T, tumor; N, node; M, metastasis.

partial thyroidectomy. In total, 209 (50.2%) patients were diagnosed with malignancy or noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). The mean tumor size was 2.4±1.6 cm (range, 0.5–13.5 cm), and ETE was diagnosed in 10 (6.8%) patients. The *NRAS* test was performed in 220 patients, of whom 49 (22.3%) patients were positive. Likewise, the $BRAF^{V600E}$ test was performed in 193 patients, of whom 14 (7.3%) patients were positive. In 146 patients diagnosed with malignancy, lymphatic, vascular and perineural invasion were diagnosed in

**Table 3** Surgical pathologic diagnosis of the study patients

| Variable | N=416 (%) |
|---|---|
| Non-malignant | 207 (49.8) |
| Nodular hyperplasia | 47 (11.3) |
| Follicular adenoma | 103 (24.8) |
| Hürthle cell adenoma | 57 (13.7) |
| NIFTP | 63 (15.1) |
| Malignant | 146 (35.1) |
| cPTC | 23 (5.5) |
| fvPTC | 55 (13.3) |
| FTC | 59 (14.2) |
| HCC | 5 (1.2) |
| Poorly DTC | 3 (0.7) |
| MTC | 1 (0.2) |

NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; cPTC, conventional papillary thyroid carcinoma; fvPTC, follicular variant papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; HCC, Hurthle cell carcinoma; DTC, differentiated thyroid carcinoma; MTC, medullary thyroid carcinoma.

11 (7.5%) patients, 31 (21.2%) patients and 1 (07%) patient, respectively. The numbers of patients with malignancy at each T stage were as follows: 74 (50.7%) at stage 1, 51 (34.9%) at stage 2, and 21 (14.4%) at stage 3. The numbers of patients diagnosed with N1a and M1 were 19 (13.0%) and 2 (1.4%), respectively. The numbers of patients at each TNM stage were as follows: 135 (92.5%) at stage I, 10 (6.8%) at stage II, and 1 (0.7%) at stage IVb.

### *Surgical pathologic diagnosis of study patients*

The final surgical pathologic diagnosis of the study patients is provided in *Table 3*. Of these, 207 (49.8%) patients were diagnosed with non-malignant disease, 47 (11.3%) patients were diagnosed with nodular hyperplasia, 103 (24.8%) patients were diagnosed with follicular adenoma, and 57 (13.7%) patients were diagnosed with Hürthle cell adenoma. Sixty-three (15.1%) patients were diagnosed with NIFTP. Of the 146 (35.1%) patients diagnosed with malignant disease, FTC was the most diagnosed with 59 (14.2%) patients, and fvPTC was the second most diagnosed with 55 (13.3%) patients. The 49 *NRAS* mutation patients comprised 13 (26.5%) fvPTCs and 2 (4.1%) FTCs, and the 19 N1a patients comprised 10 (52.6%) fvPTCs and 5 (26.3%) FTCs. Of 38 patients with PTC-related nuclear changes, fvPTC was the most diagnosed with 16 (42.1%) patients, and conventional PTC was the second most diagnosed with 7 (18.4%) patients.

### *Comparison of baseline clinicopathological characteristics between benign and malignant groups*

The results of the baseline clinicopathological characteristic comparisons between the benign and malignancy/NIFTP groups are shown in *Table 4*. There were no statistically significant differences in age, method of diagnosis and mean tumor size between the two groups. Malignancy/NIFTP was diagnosed in 71 (51.4%) and 138 (49.6%) patients with FNAC and CNB, respectively, but there was no statistically significant difference between the groups (P=0.755). However, the proportion of male patients was significantly higher in the malignancy/NIFTP group than in the benign group (P=0.038). PTC-related nuclear changes was higher in the malignancy/NIFTP group than in the benign group (P<0.001). PTC-related nuclear changes was diagnosed significantly more frequently with CNB than with FNAC (11.1%, 31/278 *vs.* 5.1%, 7/138; P=0.002; not shown in table). ETE was significantly more frequent in the malignancy/NIFTP group than in the benign group (P<0.001), and the proportion of *NRAS* mutations and $BRAF^{V600E}$ mutation were significantly higher in the malignancy/NIFTP group (P=0.013 and P<0.001, respectively).

### *Univariate and multivariate analyses of clinical parameters that influence the diagnosis of malignancy/NIFTP*

Univariate and multivariate logistic regression analyses were performed to determine the independent risk factors associated with the diagnosis of malignancy/NIFTP (*Table 5*). Male sex was a significant risk factor for the diagnosis of malignancy (OR, 2.027; 95% CI, 1.042 to 3.944; P=0.037). The *NRAS* mutation was confirmed as a significant risk factor in a multivariate analysis (OR, 2.483; 95% CI, 1.212 to 5.086; P=0.013). Among the various risk factors, PTC-related nuclear changes was identified as the most significant risk factor for the diagnosis of malignancy/NIFTP in both univariate and multivariate analyses (OR, 10.762; 95% CI, 3.002 to 38.575; P<0.001).

**Table 4** Comparison of baseline clinicopathological characteristics between benign and malignancy groups

| Variable | Benign (n=207) | Malignancy/NIFTP (n=209) | P value |
|---|---|---|---|
| Age (years) | 48.3±13.7 (range, 16–82) | 45.8±13.6 (range, 14–83) | 0.071 |
| Male | 40 (19.7%) | 59 (28.2%) | 0.038 |
| Method of diagnosis | | | 0.755 |
| FNAC | 67 (48.6%) | 71 (51.4%) | |
| CNB | 140 (50.4%) | 138 (49.6%) | |
| Follicular neoplasm subtype | | | <0.001 |
| Architectural atypia | 149 (72.0%) | 150 (71.8%) | |
| PTC-related nuclear changes | 4 (1.9%) | 34[†] (16.3%) | |
| Hürthle cell | 54 (26.1%) | 25 (11.9%) | |
| Tumor size (cm) | 2.2±1.4 (range, 0.5–7.5) | 2.5±1.7 (range, 0.5–13.5) | 0.152 |
| ETE | 0 (0%) | 10 (4.8%) | <0.001 |
| NRAS positive | 15/108 (13.8%) | 34/112 (30.4%) | 0.013 |
| $BRAF^{V600E}$ positive | 0/91 (0%) | 14/102 (13.7%) | <0.001 |

Data are expressed as patient's number (%), or mean ± SD. A statistically significant difference was defined as P<0.05. [†], the 34 PTC-related nuclear changes patients of malignant group comprised 7 (20.6%) cPTCs, 23 (67.6%) fvPTC and 4 (11.8%) FTCs. NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; FNAB, fine needle aspiration biopsy; CNB, core needle biopsy, ETE, extrathyroidal extension; cPTC, conventional papillary thyroid carcinoma; fvPTC, follicular variant papillary thyroid carcinoma; FTC, follicular thyroid carcinoma.

## Discussion

Preoperative diagnosis of malignancy for follicular neoplasm remains difficult. US-guided FNAC is the most commonly used safe method for evaluating thyroid nodules with high sensitivity and specificity, but it has limited accuracy with follicular lesions. In spite of various studies, the distinction between benign and malignant disease from follicular neoplasm is still difficult on cytologic testing. Therefore, surgery is recommended for the diagnosis and treatment of follicular neoplasms.

Various methods, such as pathologic testing by CNB, US features, and *NRAS* testing, have been investigated to differentiate benign and malignant disease from follicular neoplasm. Min *et al.* reported that preoperative CNB had no advantage over FNAC in predicting malignancy (16). Lee *et al.* also reported that follicular neoplasm was frequently diagnosed in CNB, but the rates of malignancy were equivalent to FNAC (17). In the present study, CNB was performed in 278 (66.8%) patients, but there was no significant difference from FNAC in the diagnostic rate of malignancy/NIFTP (51.4% *vs.* 48.6%, P=0.755). Another group reported that US features, such as solid echo structure, microcalcification, or hypoechoic pattern, were associated with malignancy (18), but US has the disadvantage of being a subjective method used by radiologists.

Bongiovanni *et al.* reported that the malignancy rate of follicular neoplasm was 26.1% (19), but 146 (35.1%) patients were diagnosed with malignancy in the final surgical pathologic results in this study. Our malignancy rate was higher than that of previous reports. The first reason for these different results is the difference in ethnicity. Previous studies have been conducted mostly in the United States, but Korea is one of the countries with the highest prevalence of thyroid carcinoma. Yim *et al.* reported that the malignancy rate is 48% in Korea (20). The second reason is that Korea is an iodine-sufficient region. Iodine deficiency is associated with FTC, but iodine sufficiency is associated with PTC. Of the malignant cases, PTC was the most frequently diagnosed (53.4%, 78/146), and FTC was the second most frequently diagnosed (40.4%, 59/146) in this present study. In addition, almost one third of the malignancy (37.7%, 55/146) was fvPTC, which could signify that we have misdiagnosed or underdiagnosed a significant number of fvPTCs as follicular neoplasms.

**Table 5** Univariate and multivariate analyses of clinical parameters which influence on the diagnosis of malignancy/NIFTP

| Variable | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| Gender | | | | |
| Female | ref. | | ref. | |
| Male | 1.642 (1.039–2.596) | 0.034 | 2.027 (1.042–3.944) | 0.037 |
| Age (years) | | | | |
| ≥55 | ref. | | | |
| <55 | 1.693 (1.116–2.569) | 0.013 | | |
| Follicular neoplasm subtype | | | | |
| Hürthle | ref. | | ref. | |
| Architectural atypia | 2.274 (1.286–3.678) | <0.004 | 1.515 (0.693–3.312) | 0.298 |
| PTC-related nuclear changes | 18.360 (5.876–57.371) | <0.001 | 10.762 (3.002–38.575) | <0.001 |
| $BRAF^{V600E}$ mutation* | | | | |
| Negative | ref. | | | |
| Positive | 5.933 (1.291–27.274) | 0.022 | | |
| NRAS mutation** | | | | |
| Negative | ref. | | ref. | |
| Positive | 2.703 (1.372–5.324) | 0.004 | 2.483 (1.212–5.086) | 0.013 |

Data are expressed as odds ratio (OR) and 95% confidence interval (CI). A P value <0.05 was considered statistically significant. *, $BRAF^{V600E}$ mutation test was performed in 193 patients; **, NRAS mutation test was performed in 220 patients. NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma.

We investigated the clinical, cytologic or pathologic features of 416 patients with preoperatively diagnosed follicular neoplasms or suspicious for follicular neoplasms to identify which features influence the diagnosis of malignancy. The results showed that three different factors, namely, male sex, PTC-related nuclear changes and NRAS mutation, are predictors of malignancy.

A cytologic or pathologic pattern of architectural atypia was associated with follicular neoplasm (21). The architectural atypia was not significantly different between the benign and malignancy/NIFTP groups (72% *vs.* 71.8%). In contrast, cytologic or pathologic PTC-related nuclear changes was more common in malignancy/NIFTP (1.9% *vs.* 16.3%) and was identified as the most powerful predictor of malignancy/NIFTP in the multivariate analysis (OR 10.762, P<0.001). This finding emphasizes that PTC-related nuclear changes is more important than architectural atypia for predicting malignancy/NIFTP in patients with follicular neoplasms.

Several studies have examined the factors that help predict malignancy in preoperatively diagnosed follicular neoplasm. The first study analyzed 368 surgical thyroid specimens. The authors found that 60% of nodules with cytologic PTC-related nuclear changes were malignant. They concluded that cytologic PTC-related nuclear changes consistent with a follicular neoplasm conferred a high risk of malignancy (22). The other study investigated 98 follicular neoplasms. It showed that the malignant proportions of follicular neoplasms with atypia and without atypia were 44.4% and 6.8%, respectively. They reported that follicular neoplasms with atypia were predictive of malignancy, as well (9).

Among 38 patients with PTC-related nuclear changes, 16 (42.1%) patients were diagnosed with fvPTC. This result suggests that there might be a significant relative risk of fvPTC associated with cytologic or pathologic PTC-related nuclear changes over other types of thyroid carcinomas, such as FTC and conventional PTC. Several studies were

consistent with our results (23,24), but further work is required to establish the durability of the relationship between PTC-related nuclear changes and fvPTC.

Clinical variables have been investigated to predict malignancy from follicular neoplasms. Several studies demonstrated that male sex was significantly associated with a diagnosis of malignancy (25,26). The present study also showed that male sex was predictive of malignancy/NIFTP in the multivariate analysis (OR: 2.027, P=0.037).

Tuttle *et al.* reported that a tumor size greater than 4 cm was associated with the risk of malignancy (27). Schlinkert *et al.* also found that the risk of malignancy in follicular neoplasm was higher in larger tumors (28). Another study showed that a tumor size greater than 2.1 cm increased the risk of malignancy (23). However, our results showed no significant difference between the benign and malignant groups with tumor size.

Recently, molecular biomarkers, such as *BRAF*, *RAS*, *RET-PTC*, or *PAX8-PPARγ* mutations, have been investigated for the diagnosis of thyroid nodules. The *BRAF* mutation has been observed in up to 83% of PTC (29-31), whereas the *NRAS* mutation has been commonly observed in follicular neoplasms (32). In the current study, the *NRAS* mutation was observed in 49 (22.3%) of 220 patients, and there was a statistically significant difference between the benign and malignancy/NIFTP groups (13.8% *vs.* 30.4%, P=0.013). In the multivariate analysis, the *NRAS* mutation was identified as an independent risk factor for the diagnosis of malignancy/NIFTP, as well (OR: 2.483, P=0.013). Bae *et al.* reported that the overall malignancy rate was significantly higher in the *NRAS* mutation than with no mutation (33). Preoperative *NRAS* tests using FNAC or CNB specimens may help improve the prediction of malignancy in patients with follicular neoplasm.

This study has several limitations. First, this study was designed as a retrospective study in nature. In addition, there may have been selection bias, as all the patients were enrolled from a single tertiary institution, and they do not reflect the entire patient population. Third, the *NRAS* test was not performed in all patients and was performed using a surgical specimen. Finally, we conducted this study with a relatively small sample size. This limitation could be overcome by conducting a multicenter study in the future. The most important strength of this study is that because all the cytologic and pathologic slides were reviewed by a single, experienced pathologist, so there is uniformity of diagnosis.

## Conclusions

Based on the results of our study, the prevalence of malignancy in patients with a preoperative diagnosis of follicular neoplasm was much higher than in previous reports. Cytologic or pathologic PTC-related nuclear changes is a useful predictor for the presence of malignancy. Further studies must be conducted to support our results.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/gs-20-500

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of the Institutional Review Board at Seoul St. Mary's Hospital, the Catholic University of Korea (IRB No.: KC19RESI0264) and individual consent for this retrospective analysis was waived.

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