Original Article

The role of prophylactic central compartment neck dissection in patients with T1–T2 cN0 papillary thyroid carcinoma

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Background: It remains controversial whether prophylactic central compartment neck dissection (pCCND) is necessary in cases of stage T1–T2 cN0 papillary thyroid carcinoma (PTC). Some studies have demonstrated the benefits of pCCND on oncologic outcomes, whereas others reported that any advantages were insignificant. The purpose of this study was to investigate the effects of pCCND on cancer recurrence and its pattern in patients with T1–T2 cN0 PTC.

Methods: We retrospectively reviewed 2,902 patients with PTC who had undergone thyroidectomy between 2006 and 2012 at Seoul St. Mary's Hospital: 2,099 patients had undergone pCCND and thyroidectomy (pCCND group), whereas 803 did not undergo pCCND (non-pCCND group). We investigated the effects of pCCND on cancer recurrence by comparing these two groups. Recurrence was classified according to the location of the recurrence.

Results: The mean follow-up period was 112 months. The mean patient age was significantly younger in the pCCND group than in the non-pCCND group. There were no statistically significant differences in the distribution of sex, tumor size, or thyroidectomy extension between the groups. In the pCCND group, 883 (42%) patients showed evidence of N1a disease, and the mean number of metastatic lymph nodes was 1.26±2.2. Recurrence occurred in 67 (2.3%) patients in the total cohort. Recurrence was observed in 20 (2.5%) and 47 (2.2%) patients in the non-pCCND and pCCND groups, respectively, but there were no significant differences between the groups (P=0.687). When analyzed by the site of recurrence, 50% and 4.3% of recurrent disease in the non-pCCND and pCCND groups, respectively, occurred in the central compartment (P<0.001). There were no differences between the two groups in recurrent disease at other sites. The 15-year cumulative central compartment recurrence-free survival (RFS) rates of patients in the non-pCCND and pCCND groups were 99% and 100%, respectively (P<0.001). In the multivariate analysis, not performing pCCND was the only independent risk factor related to central compartment RFS, and the hazard ratio was 13.362 [95% confidence interval (CI): 2.928–60.986; P<0.001].

Conclusions: The omission of pCCND was found to be an independent risk factor for recurrence in the central compartment in patients with T1–T2 cN0 PTC.

Keywords: Papillary thyroid carcinoma (PTC); thyroid cancer; central compartment neck dissection (CCND); prophylactic CCND (pCCND)

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Introduction

Complete surgical resection of both the primary tumor and clinically significant lymph node metastases is the basic goal of cancer therapy and an important determinant of outcomes in patients with differentiated thyroid cancer (1). Central compartment neck dissection (CCND) is the surgical excision of all lymph nodes from the hyoid bone to the sternal notch between each side of carotid arteries (1). In cases of papillary thyroid carcinoma (PTC), it is known that central lymph node metastases are very common, and these malignant foci are discovered in 24–82% of patients with PTC without clinical evidence of central lymph node involvement during the preoperative evaluation (2-8). Lymph node metastases contribute to more frequent locoregional recurrence (LRR), and many studies suggest that the lymph node ratio (LNR) or the number of metastatic lymph nodes in the central compartment is a prognostic factor for PTC (6,9-11).

Although CCND is recommended in patients with clinically node-positive or invasive PTC, it is still debatable whether prophylactic CCND (pCCND) should be performed alongside thyroidectomy in patients with noninvasive and cN0 PTC (1,12). In studies favoring lymph node dissection, pCCND was thought to reduce LRR and improve disease-free survival (2,5,13-17). Some studies have demonstrated that the complications after the procedure were comparable in experienced surgeons (5,16,18). However, in studies skeptical of pCCND, the advantages of pCCND were vague (8,19-22) and significantly more complications occurred, such as permanent hypoparathyroidism or recurrent laryngeal nerve injury (8,21,22).

The purpose of this study was to investigate the effects of pCCND on cancer recurrence and its pattern in patients with T1–T2 cN0 PTC in a large patient cohort with an extensive follow-up period. We present the following article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-550/rc).

Highlight box

Key findings

- The effects of pCCND on recurrence pattern in PTC.

What is known and what is new?

- It remains controversial whether pCCND is necessary in cases of stage T1–T2 cN0 PTC.
- The omission of pCCND was found to be an independent risk factor for recurrence in the central compartment in patients with T1–T2 cN0 PTC.

What is the implication, and what should change now?

- pCCND did not reduce the overall RFS, but appeared to prevent recurrence in the central compartment area. A careful follow-up strategy to look for recurrence in the central compartment may be necessary for patients who do not undergo pCCND.

Methods

Patients

We retrospectively reviewed the records of patients with PTC who underwent total thyroidectomy or unilateral thyroid lobectomy between 2006 and 2012 at Seoul St. Mary's Hospital, College of Medicine, the Catholic University of Korea. A total of 3,872 surgeries related to thyroid cancer were found in the database. The demographic information, surgical records, clinicopathological data, and recurrence status were collected for analysis. To minimize bias, we analyzed data from all cohorts who met the eligibility criteria and included all surgeries performed by multiple surgeons within our institution. The pathology report was revised according to the American Joint Committee on Cancer Staging Manual, 8th edition (23).

Patients with cN0 PTC on preoperative ultrasonography and stage T1 or T2 PTC on the pathology report were enrolled. Patients with a cancer stage greater than T3 or with lateral neck node metastases at the time of the initial diagnosis were excluded. We excluded tall cell, columnar cell, hobnail, and diffuse sclerosing PTC variants, which are known to have a poorer prognosis than classic PTC. Thirty-five patients with a follow-up period within 6 months after surgery were excluded. Finally, data from 2,902 patients were reviewed. The cohort was divided into two groups for comparison: 2,099 patients who had undergone pCCND with thyroidectomy (pCCND group) and 803 patients who did not undergo pCCND (non-pCCND group).

Five surgeons at our institution were involved with the patients in this study. Four are certified general surgeons (S.N. Kim, MD; B.J. Song, MD; S.S. Jung, MD; and B.J. Choi, MD) who performed the thyroid surgeries between 2006 and 2012 but did not dissect central lymph nodes routinely. The patients who perithyroidal lymph nodes were removed incidentally during the procedure were classified as non-pCCND group. The other surgeon, J.S. Bae, MD, is an endocrine surgeon who performed pCCND for all study patients with a thyroid malignancy.

Preoperative evaluations consisted of ultrasonography, neck computed tomography (CT), and other laboratory tests including thyroid function tests. After surgery, the patients were administered levothyroxine to suppress thyroid-stimulating hormone levels (TSH suppression), according to the guidelines issued by the American Thyroid Association (ATA) (24-26). All patients who underwent total thyroidectomy also underwent radioactive iodine (RAI) ablation 4–6 weeks after surgery.

Serum thyroglobulin level measurements and neck ultrasonography were regularly performed every 6 or 12 months. The patients whose recurrence was confirmed pathologically were considered as positive for recurrence. Recurrence in this cohort was classified by location: central compartment, lateral lymph node, remnant thyroid, and distant from the site of origin. Recurrence in the post-thyroidectomy bed or level VI area was considered central compartment recurrence. The recurrence in the remnant thyroid was evaluated only among patients who underwent unilateral thyroid lobectomy.

Statistical analysis

Variables were compared between the groups using the chi-square test, the Mann-Whitney U test, the Student's *t* test, or Fisher's exact test, considering the characteristics of each variable. The Cox proportional hazard model was used to identify factors associated with recurrence-free survival (RFS). Survival analysis and comparisons between groups were performed using the life table method. All P values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS software (SPSS Statistics for Windows, Version 24.0.; IBM, Armonk, NY, USA).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Seoul St. Mary's Hospital, the Catholic University of Korea (No. KC22WISI0219) and individual consent for this retrospective analysis was waived.

Results

Clinicopathologic characteristics

Of 2,937 T1–T2 cN0 PTC patients, a total of 2,902 patients who met the inclusion criteria were analyzed (*Table 1*). The entire cohort was divided into two groups, according to whether CCND was performed, for comparison. The mean follow-up period for all patients was 112±36.9 months (7–192 months). The mean age of the total cohort was 46.8±11.6 years (12–79 years), and the mean tumor size was 0.83±0.52 cm. The mean age of patients in the non-pCCND group was greater than that of patients in the pCCND group (47.9 *vs.* 46.4 years, P=0.002). There were no statistical differences in the distribution of patients with regard to sex, thyroidectomy extension, or tumor size.

Comparison of overall recurrence between groups

Recurrence was then analyzed (*Table 2*). In terms of total recurrence, 20 (2.5%) cases of recurrence occurred in the non-pCCND group, and 47 (2.2%) cases occurred in the pCCND group. The 15-year cumulative RFS rates of patients in the non-pCCND and pCCND groups were 95% and 97%, respectively, but these values were not statistically different (P=0.687 and P=0.813, respectively).

Comparison of nodal recurrence pattern between groups

The two groups showed significant differences in nodal recurrence pattern, especially related to the central compartment (*Table 2*). Ten cases of central compartment recurrence (1.2%) occurred in the non-pCCND group, which is significantly higher than those in the pCCND group (0.1%, P<0.001). In the non-pCCND group, half of the cases of recurrence consisted of central compartment lesions, which was significantly greater than cases in the pCCND group (50% *vs.* 4.3%, P<0.001). In the non-pCCND group, the recurrence involving the central compartment, such as "central compartment only" (25% *vs.* 4.3%, P<0.001) or "both central and lateral lymph node" (25% *vs.* 0%, P<0.001) were significantly more frequent than pCCND group. In contrast, the most frequent site of

Table 1 Clinicopathologic characteristics of patients in non-pCCND and pCCND group

Variables	Non-pCCND (n=803)	pCCND (n=2,099)	P value
Age (years)	47.9±11.6 [17–78]	46.4±11.7 [12–79]	0.002
<55	568 (70.7%)	1,589 (75.7%)	
≥55	235 (29.3%)	510 (24.3%)	
Sex			0.092
Male	154 (19.2%)	347 (16.5%)	
Female	649 (80.8%)	1,752 (83.5%)	
Tumor size (cm)	0.80±0.5 [0.1–3.7]	0.84±0.5 [0.1–4.0]	0.084
≤1	634 (79.0%)	1,620 (77.2%)	
>1 to 2	146 (18.2%)	402 (19.2%)	
>2 to 4	23 (2.9%)	77 (3.7%)	
Nodal status			n/a
N0	n/a	1,216 (57.9%)	
N1a	n/a	883 (42.1%)	
No. of MLN	n/a	1.26±2.2 [0–20]	n/a
No. of MLN in N1a cases	n/a	3.0±2.6 [1–20]	n/a
≤5	n/a	1,973 (94.0%)	
>5	n/a	126 (6.0%)	
No. of lymph node retrieved	0.67±0.9 [0–3]	9.0±5.6 [3–41]	<0.001
Thyroidectomy			0.268
Unilateral lobectomy	169 (21.0%)	482 (23.0%)	
Total thyroidectomy	634 (79.0%)	1,617 (77.0%)	
Follow up period (months)	117.4±44.7 [9–191]	110.0±33.2 [7–192]	<0.001

Data were presented as Mean ± SD [Min–Max] or n (%). pCCND, prophylactic central compartment neck dissection; MLN, metastatic lymph node.

recurrence in the pCCND group was the "lateral lymph node only" (80.9%), which was significantly different from that in the non-pCCND group (35%, P<0.001). There were no cases in "both central and lateral lymph node" recurrence in the pCCND group.

The 15-year cumulative central compartment RFS in the non-pCCND group was significantly lower than that in the pCCND group (99% *vs.* 100%, respectively, P<0.001, *Figure 1*).

Central compartment recurrence status in 12 patients

The detailed status of central compartment recurrence is shown in *Table 3*. There were ten patients with recurrence in the non-pCCND group. Of these 10 patients, 4 patients underwent surgical treatment. During the re-operation of patient No. 1, only thyroid cartilage, and soft tissue with PTC on thyroidectomy bed were resected due to local adhesion. Two years later, second recurrence occurred at subcutaneous and trachea, and excision of tumor mass and reconstruction of trachea were performed. Single recurrent laryngeal nerve was sacrificed with this operation. For patients No. 2 to 4, CCND and lateral neck dissection were performed to the affected lesion. Ethanol ablation or radiofrequency ablation were attempted to 5 patients with recurrence (No. 5 to 9). One patient was lost to follow-up after the diagnosis of recurrence.

Only two cases of central compartment recurrence

Table 2 Comparison of recurrence status between non-pCCND and pCCND group

Variables	Non-pCCND (n=803)	pCCND (n=2,099)	P value
Recurrence (total), n (%)	20 (2.5%)	47 (2.2%)	0.687
Site, n (%)			
Central compartment	10 (1.2%)	2 (0.1%)	<0.001
Lateral lymph node	12 (1.5%)	38 (1.8%)	0.558
Remnant thyroid[†]	2/167 (1.2%)	6/482 (1.2%)	0.950
Distant organ (lung)	1 (0.1%)	0 (0.0%)	0.106
Nodal recurrent pattern in recurrence cases, n (%)			
Central compartment	10/20 (50.0%)	2/47 (4.3%)	<0.001
Central compartment only	5/20 (25.0%)	2/47 (4.3%)	<0.001
Lateral lymph node	12/20 (60.0%)	38/47 (80.9%)	0.073
Lateral lymph node only	7/20 (35.0%)	38/47 (80.9%)	<0.001
Both central and lateral lymph node	5/20 (25.0%)	0/47 (0.0%)	<0.001
RFS			
Cumulative RFS (10/15 years)	97%/95%	98%/97%	0.813
Cumulative central compartment RFS (10/15 years)	99%/99%	100%/100%	<0.001

[†], remnant thyroid recurrence was analyzed in lobectomy cases. One case of recurrence from remnant thyroid tissue occurred 27 months after initial surgery in patients with total thyroidectomy and pCCND. This case was included total recurrence, but not considered as 'remnant thyroid recurrence'. Central compartment: thyroidectomy bed or level IV. Remnant-contra lateral thyroid lobe was not included. pCCND, prophylactic central compartment neck dissection; RFS, recurrence free survival.

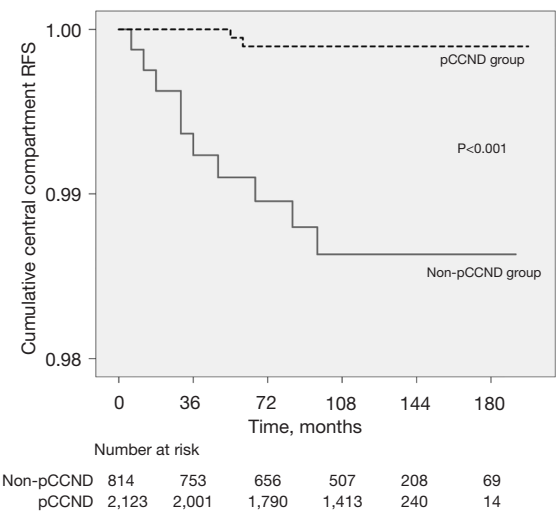

Figure 1 Cumulative central compartment RFS of non-pCCND and pCCND group. pCCND, prophylactic central compartment neck dissection; RFS, recurrence free survival.

occurred in the pCCND group. One patient (No. 11) underwent right thyroid lobectomy with ipsilateral pCCND for the initial procedure, no metastatic lymph node among the six lymph nodes removed at the initial surgery. The recurrence occurred in the operation bed in level VI, the patient underwent completion thyroidectomy with redo CCND and RAI ablation therapy. The other patient (No.12) initially underwent total thyroidectomy with bilateral CCND due to right thyroid cancer, the initial LNR was 11/16. The recurrence occurred at ipsilateral central compartment area, and he was followed without further treatment with active surveillance.

Factors associated with central compartment RFS

Results of a Cox regression analysis to determine factors affecting central compartment RFS are shown in *Table 4*. A univariate Cox regression analysis was performed for

Table 3 The status of central compartment recurrence in non-pCCND and pCCND group

Patients	CCND	LNY	MLN	Thyroidectomy	Age	Sex	Tumor size (cm)	ETE	Concurrent recurrence	Treatment (MLN/LNY)	Time to recurrence (months)
1*	No	0	n/a	Total thyroidectomy	68	F	3.5	Min	None	Excision (PTC was found in thyroid cartilage and soft tissue on level VI), RAI	91
2	No	3	2	Total thyroidectomy	25	F	1	None	LLN	CCND (2/4) with lateral neck dissection (1/13), RAI	25
3	No	0	n/a	Total thyroidectomy	51	F	0.7	Min	LLN	CCND (1/5) with lateral neck dissection (8/64), RAI	44
4	No	0	n/a	Total thyroidectomy	33	F	1.5	None	LLN	Transferred to CCND with lateral neck dissection	24
5	No	2	2	Total thyroidectomy	47	F	1.8	Min	None	RFA	81
6	No	0	n/a	Total thyroidectomy	49	M	1.5	None	None	RFA	64
7	No	0	n/a	Total thyroidectomy	50	F	0.4	Min	LLN	Ethanol ablation for level VI RFA for level IV	5
8	No	0	n/a	Total thyroidectomy	45	F	0.8	Min	None	RFA, RAI	13
9	No	0	n/a	Total thyroidectomy	26	F	0.6	None	None	RFA, RAI	10
10	No	0	n/a	Total thyroidectomy	38	F	1	None	LLN	Follow-up loss	31
11	Right CCND	6	0	Right thyroid lobectomy	48	F	0.6	None	None	Completion thyroidectomy with CCND (1/7), RAI	53
12	Bilateral CCND	16	11	Total thyroidectomy	49	M	2.8	Min	None	Active surveillance	58

*, second recurrence occurred at subcutaneous and trachea (thyroidectomy bed), 2 years after treatment of first recurrence. Excision of tumor mass and reconstruction of trachea were performed. pCCND, prophylactic central compartment neck dissection; CCND, central compartment neck dissection; LNY, lymph node yield; the total number of lymph node harvest; MLN, metastatic lymph node; the total number of metastatic lymph node; ETE, extrathyroidal extension; LLN, lateral lymph node; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; RFA, radiofrequency ablation.

each variable, including age group, sex distribution, thyroidectomy extension, tumor size, and pCCND group. The variables of non-pCCND and tumor size larger than 2 cm were the only factors that predicted a worse central compartment RFS (*Table 4*). In the multivariate analysis using the forward conditional method, non-pCCND remained the only independent risk factor related to central compartment RFS; the hazard ratio was 13.362 (95% CI: 2.928–60.986; P<0.001).

Discussion

The controversy associated with pCCND still remains. Weighing the risks and benefits of lymph node dissection is at the center of this controversy. However, results from different studies are conflicting.

The increase in complications, such as recurrent laryngeal nerve or parathyroid gland injury, associated with lymph node dissection is an important consideration

Table 4 Clinicopathological factors associated with central compartment recurrence free survival in Cox proportional hazard model

Variables	Hazard ratio [95% CI]	P value
Univariate analysis		
Age, years		
<55 *vs.* ≥55	0.262 [0.34–2.032]	0.2
Sex		
Male *vs.* female	1.045 [0.229–4.770]	0.955
Thyroidectomy		
Lobectomy *vs.* total thyroidectomy	3.094 [0.401–24.073]	0.278
Size, cm		
≤1	Ref.	
>1 to 2	1.764 [0.456–6.823]	0.411
>2 to 4	6.192 [1.286–29.804]	0.023
pCCND *vs.* non-pCCND	13.362 [2.928–60.986]	0.001
Multivariate analysis		
pCCND *vs.* non-pCCND	13.362 [2.928–60.986]	0.001

pCCND, prophylactic central compartment neck dissection.

when performing pCCND (8,21). Viola *et al.* reported that permanent hypoparathyroidism occurred more frequently in patients who underwent total thyroidectomy with pCCND compared to patients who underwent total thyroidectomy only, but the rate of recurrent laryngeal nerve injury did not differ between the two groups in this prospective randomized controlled study (22). Many studies that compared the complication rates between patients undergoing total thyroidectomy alone and those undergoing total thyroidectomy with pCCND reached similar conclusions (3,20,27). In another prospective randomized controlled study by Sippel *et al.*, there was no difference in patient complications between those undergoing total thyroidectomy only and those undergoing total thyroidectomy with pCCND (28). Other studies reported that CCND did not increase the risk of complications (5,16). The experience of the surgeon may contribute to this discrepancy. Complications related to thyroid surgery may be affected by the volume of surgery, which is determined by the number of surgeries performed by the surgeon per year (29).

It is not simple to demonstrate positive oncologic outcomes associated with pCCND in patients with PTC, as it is difficult to demonstrate reduced recurrence. Carling *et al.* proposed that 5,840 patients in a prospective trial would be necessary to have sufficient statistical power to prove positive effects on recurrence rate (30). Nevertheless, some studies have suggested that pCCND protects against recurrence (2,5,13-17). Liu *et al.* demonstrated that the addition of pCCND to total thyroidectomy reduces the risk of local recurrence compared to total thyroidectomy alone in their meta-analysis (14).

Because there are conflicting studies about the role of lymph nodes in cancer recurrence, there may also be disagreements about the need for lymph node resection. In several studies, lymph nodes may play a role as education centers of the immune system and anti-tumor immunity (31,32). According to these studies, it seems that the removal of lymph nodes has adverse effects on oncologic outcome. On the other hand, according to recent research, lymph node colonization can induce cancer metastasis (33). However, it is difficult to study the effect of occult lymph node metastasis on thyroid cancer recurrence because it is impossible to determine whether lymph node metastasis exists without pCCND in clinically N0 patients with thyroid cancer. Forty-two percent of patients in pCCND group had occult lymph node metastasis in this study and generally the rate of occult lymph node metastasis in PTC has been reported up to 82% (2-8). Considering this, we may estimate that undissected-occult lymph nodes induced local recurrence in central compartment in non-pCCND group.

Despite these controversies, pCCND is not recommended for noninvasive, T1–T2 cN0 PTC according to the ATA 2015 guidelines (1). In this study, we compared a large number of patients with PTC to investigate the benefits of pCCND during a relatively long follow-up period. The total recurrence rate and RFS of the non-pCCND group were not statistically different with pCCND group. Prophylactic CCND did not appear to have any effect on preventing the overall recurrence of T1–T2 cN0 disease. Considering these non-different results and the easier accessibility to the non-dissected central compartment lymph node during the re-operation rather than to the dissected area, it seems impossible to conclude that pCCND is necessary to patients with thyroid cancer to improve overall outcome.

However, it is clear that pCCND reduces recurrence in the central area and affects the distribution of the sites of recurrence. When pCCND was not performed, the risk

of central compartment recurrence was about 13 times higher than that of the pCCND group [13.362 (95% CI: 2.928–60.986)] (P<0.001). The elimination of central neck lymph nodes appears to prevent local recurrence around the site of the previous malignant tumor even at early stages (T1–T2 cN0, without ETE) of thyroid cancer. Performing of pCCND would have reduced unnecessary additional procedures due to recurrence. Considering the psychological adverse effects of local-regional recurrence of thyroid cancer (34) or expected complications followed by re-operation, pCCND can be applied depending on the surgeon's performance.

There are several limitations of our study. First, the study design was retrospective. Second, the incidence of complications due to pCCND was not investigated in this study due to a lack of data. In addition, a longer follow-up period could contribute to a more thorough investigation, considering that PTC is indolent, and cases in this study were all early stage.

Conclusions

In this study, pCCND did not reduce the overall recurrence rate or RFS in patients with T1–T2 cN0 PTC. However, the omission of pCCND was determined to be an independent risk factor for worse recurrence in the central compartment, which was the primary site of recurrence in this study. A careful follow-up strategy to look for recurrence in the central compartment may be necessary for patients who do not undergo pCCND.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-550/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-550/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-550/coif). The authors have no conflicts of interest to declare.

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 institutional review board of Seoul St. Mary's Hospital, the Catholic University of Korea approved the study (No. KC22WISI0219) and individual consent for this retrospective analysis was waived.

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