

Prediction of Nodal Metastasis by the AMES Scoring System in Patients with Papillary Thyroid Cancer

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Purpose: We assessed the prognostic value of AMES to determine the extent of surgery in PTC patients, and compared AMES score usefulness and accuracy with [¹⁸F] FDG PET/CT.

Methods: We conducted a review of data from a single center and a single surgeon, who treated 341 patients with PTC with total thyroidectomy and prophylactic bilateral CLN dissection at a tertiary referral center, Chungnam National University Hospital, between 2001 and 2012.

Results: In multivariate analysis, the rate of CLN metastasis was considerably higher in PTC patients with the higher AMES score (odds ratio [OR], 1.718; 95% confidence interval [CI], 1.073 ~ 2.752), higher SUV of the CLN (>0) (OR, 6.525; CI, 3.184 ~ 13.371), higher SUV of the tumor (>4.3) (OR, 1.855; CI, 1.065 ~ 3.231).

Conclusion: The AMES score is helpful in deciding whether to perform a CLN dissection, as there is a strong association between the AMES score and CLN metastasis. This high predictive value of CLN metastasis can help determine the extent of PTC surgery while considering the cost and effort.

Key Words: Papillary thyroid carcinoma, Central lymph node, AMES, Lymph node metastasis, Positron emission tomography-computed tomography

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INTRODUCTION

When used as an adjunct to total thyroidectomy, prophylactic central lymph node (CLN) dissection can provide accurate staging, more appropriate adjuvant therapy and establish a long term follow-up for patients with papillary thyroid carcinoma (PTC).⁽¹⁾ Also because of the high incidence of CLN metastasis in PTC even in clinically N0 patient group, many authors who claim that CLN metastasis significantly affect recurrence⁽²⁾ and survival in PTC strenuously insist on performing a prophylactic CLN dissection in order to reduce a locoregional recurrence rate.^(3,4)

However, there may be a significant risk of compli-

cations such as transient or permanent vocal cord palsy, due to unintentional recurrent laryngeal nerve palsy and permanent hypoparathyroidism after prophylactic CLN dissection.⁽⁵⁾ There are more side effects after total thyroidectomy associated with CLN dissection compared with total thyroidectomy alone.^(6,7)

For the reasons above, the role of prophylactic CLN dissection and the extent of surgery for PTC remain controversial.⁽⁸⁾ Thus the standard treatment of PTC has not yet been established. It demonstrates that it would be better to carry out the CLN dissection if CLN metastasis is highly suspected in selective PTC patients.

[¹⁸F] Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT) has been widely

used to discriminate between malignant and benign tumors and to detect CLN metastasis in the preoperative PTC patients in Korea until last year.⁽⁹⁾ It is an indication of the total thyroidectomy and CLN dissection if there is increased glucose metabolism in [¹⁸F] FDG PET/CT. In addition to showing reduced survival in those with FDG-avid disease, there is a significant correlation with the maximum SUV, suggesting that tumors with the highest metabolic activity might be those with the most rapid growth potential.⁽¹⁰⁾

However, we often observe that of tracer is not detected in the primary cancer focus in patients with histologically proven PTC on preoperative [¹⁸F] FDG PET/CT. Tumor size and perithyroidal and lymphovascular invasion of PTC can influence [¹⁸F] FDG PET/CT false negatives.

The MACIS and AMES scoring systems are well known prognostic staging systems for thyroid carcinoma.⁽¹¹⁾ Under MACIS, patients were categorized into 4 risk groups. Twenty-year cause-specific survival rates for PTC patients with MACIS less than 6, 6 to 6.99, 7 to 7.99, and above 8 were 99%, 89%, 56%, and 24%, respectively. Meanwhile twenty-year cause-specific survival rates for PTC patients with AMES low, high risk were 99.2%, 46%.⁽¹²⁾

We could figure out the individual prognostic score with the AMES and, MACIS scoring systems. They are available before and during surgery unlike other predictive system such as the TNM system, which is only available after surgery requiring a pathological report.^(13,14)

We formulated a hypothesis that the AMES and, MACIS scoring systems are related to CLN metastasis in PTC patients.

The purpose of this article is to know whether these prognostic scores could determine the extent of surgery in PTC patients. We also assessed their usefulness and accuracy compared with [¹⁸F] FDG PET/CT in PTC patients.

METHODS

1. Clinical data sources

We conducted a retrospective review of data from a single center, in which a single surgeon experienced a total of 341 patients with PTC who underwent total thyroid-

ectomy and prophylactic bilateral CLN dissection for treatment at a tertiary referral center, Chungnam National University Hospital, between 2001 and 2012. We excluded patients underwent lobectomy with any purpose, included patients underwent therapeutic total thyroidectomy and bilateral CLN dissection due to highly suspicious CLN metastasis with preoperative imaging. Written informed consent was obtained from all participants. All patients included in this study had a preoperative diagnosis of PTC by neck ultrasonography, fine needle aspiration biopsy and [¹⁸F] FDG PET/CT as well as a clinical examination.

2. Surgical procedures

All patients underwent total thyroidectomy and prophylactic bilateral CLN dissection. Central neck lymph nodes are Group VI lymph nodes surrounding both lobes of the thyroid; pretracheal, both paratracheal, and prelaryngeal lymph nodes. Pretracheal, prelaryngeal and bilateral paratracheal nodes were removed. Parathyroid glands and recurrent laryngeal nerves were identified and preserved. Parathyroid glands that could not be preserved were autotransplanted into the ipsilateral sternocleidomastoid muscle.

3. Prognostic staging systems

The MACIS staging system incorporates metastasis, age, completeness of resection, invasion, and size. The MACIS score was defined as 3.1 (if aged less than or equal to 39 years) or $0.08 \times \text{age}$ (if aged greater than or equal to 40 years), $+0.3 \times \text{tumor size}$ (in centimeters), $+1$ (if incompletely resected), $+1$ (if locally invasive), $+3$ (if distant metastasis is present).⁽¹⁵⁾

The AMES staging system incorporates age, distant metastasis, extrathyroidal invasion, and size. Both age and size were expressed as categorical variables; 5 cm was the cutoff point for size, but the cutoff point for age differed between the 2 sexes (41 years for men and 51 for women). Patients were classified into low-risk and high-risk groups by using the AMES risk classification. The low-risk group includes all younger (≤ 40 years for men and ≤ 50 years for women) patients with intrathyroidal carcinomas and all older patients with intrathyroidal carcinomas < 5 cm, the high risk group includes older (> 40 years for men and > 50

years for women) patients or extrathyroidal carcinomas.(16)

4. Statistical analysis

Statistical analysis was performed using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). Univariate analyses for the relationships between CLN metastasis and predictive staging systems were performed using the Pearson chi-square test or Fisher exact test. Variables with a P value of less than 0.05 were considered statistically significant and included multivariate logistic regression analysis.

RESULTS

We reviewed the medical records of 341 patients retrospectively with a preoperative diagnosis of PTC from 2001 to 2012. All patients had a total thyroidectomy with a routine prophylactic CLN dissection.

The clinicopathologic characteristics are presented in Table 1. Of the 341 patients, 149 had metastatic CLNs.

Univariate analysis suggested younger age (below 45 years old), greater tumor size, presence of capsular invasion or extrathyroidal extension, and lymphovascular invasion to be significant factors in CLN metastasis (Table 1).(17)

Associations of CLN metastasis with AMES scoring, MACIS scoring, and the maximum SUV of the CLN and the tumor is shown at Table 2. The number of patients with AMES low risk is 187 and that of AMES high risk is 154. Sixty six out of 187 patients had histologically positive lymph nodes following CLN dissection in the AMES low risk group and 83 out of 154 patients in the AMES high risk group. Among these patients, CLN metastasis were histologically detected in 43.7% (149/341). In this cross table, AMES high risk was a significant predictor of CLN metastasis in PTC (P=0.001). On the other hand, the relationship between MACIS score and CLN metastasis was not statistically significant (P=0.378) in this study (Table 2). [¹⁸F] FDG PET/CT scanning was performed on all the 341 patients who were included in this study. Patients were divided into two groups according to the SUV of the CLN (SUV=0 group, 279

Table 1. Clinicopathological data in relation to CLN in PTC

	No. of patients (n=341)	Positive CLN (%)	Negative CLN (%)	P value
Age (years)				.000
<45	101	64 (63.4)	37 (36.6)	
≥45	240	85 (35.4)	155 (64.6)	
Sex				.488
Male	38	19 (50)	19 (50)	
Female	303	130 (42.9)	173 (57.1)	
Tumor size (cm)				.000
φ≤0.5 cm	117	29 (24.8)	88 (75.2)	
0.5<φ≤1 cm	131	50 (38.1)	81 (61.9)	
1<φ≤2 cm	70	51 (72.9)	19 (27.1)	
φ>2 cm	23	19 (82.6)	4 (17.4)	
Bilaterality				.714
Unilateral	247	106 (42.9)	141 (57.1)	
Bilateral	94	43 (45.7)	51 (54.3)	
Multiplicity				.174
Solitary	216	88 (40.7)	128 (59.3)	
Multiple	125	61 (48.8)	64 (51.2)	
Capsule invasion				.000
Yes	197	105 (53.3)	92 (46.7)	
No	144	44 (30.5)	100 (69.5)	
Extrathyroidal extension				.000
Yes	154	83 (53.9)	71 (46.1)	
No	187	66 (35.3)	121 (64.7)	
Lymphovascular invasion				.000
Yes	258	139 (53.8)	119 (46.2)	
No	83	10 (12.0)	73 (88.0)	

CLN = central lymph node; PTC = papillary thyroid cancer; φ = maximal tumor diameter.

Table 2. Associations of CLN metastasis with AMES, MACIS, SUV

Variables	Negative CLN (%)	Positive CLN (%)	Total	Univariate P value	Exp (β)	95% CI Lower	Exp (β) Upper
AMES score				.001	1.718	1.073	2.752
Low	121 (64.7)	66 (35.3)	187				
High	71 (46.1)	83 (53.9)	154				
MACIS score				.378			
<7	187 (56.8)	142 (43.2)	329				
≥ 7	5 (41.7)	7 (58.3)	12				
SUV of CLN				.000	6.525	3.184	13.371
0	181 (64.9)	98 (35.1)	279				
≥ 0	11 (17.7)	51 (82.3)	62				
SUV of tumor				.000	1.855	1.065	3.231
≤ 4.3	68 (73.9)	24 (26.1)	92				
> 4.3	124 (49.8)	125 (50.2)	249				

SUV = Standardized uptake values; CLN = central lymph node; AMES = Age, distant Metastasis, Extrathyroidal invasion, and Size; MACIS = Metastasis, Age, Completeness of resection, Invasion, and Size; CI = confidence interval.

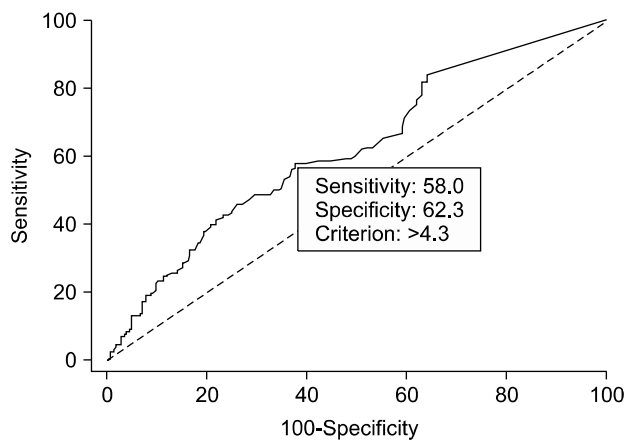


Fig. 1. Receiver operating characteristic curve of tumor SUVmax. With an SUVmax cutoff value of above 4.3, the surgeon can predict central lymph node (CLN) metastasis, and proceed total thyroidectomy and CLN dissection.

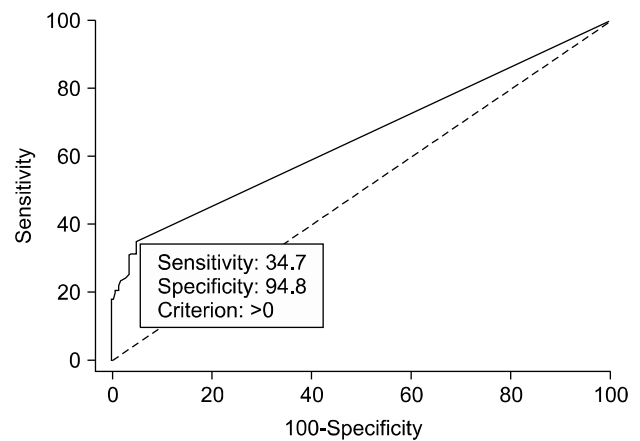


Fig. 2. Receiver operating characteristic curve of SUVmax. With an SUVmax cutoff value of above 0, the surgeon can predict central lymph node (CLN) metastasis, and proceed total thyroidectomy and CLN dissection.

patients; SUV > 0 group, 62 patients). Ninety eight out of 279 patients had histologically positive CLN in SUV of CLN=0 group and fifty one out of 62 patients had histologically positive CLN in SUV of CLN > 0 group following CLN dissection. We deduced the cut off value with an ROC curve: > 0 for SUV of lymph node and > 4.3 for SUV of a tumor using the Medcalc program (Figs. 1 and 2). Patients number with an SUV of tumor ≤ 4.3 is 92 and > 4.3 is 249. Twenty four out of 92 patients had histologically positive lymph nodes following CLN dissection in SUV of tumor ≤ 4.3 group and 125 out of 249 patients in SUV of tumor > 4.3 group. There was a correlation between nodal status and the maximum SUV of tumor ($P < 0.001$) and between the nodal status and the maximum SUV of the lymph node ($P < 0.001$).

In multivariate analysis, the rate of CLN metastasis was considerably higher in the cases of PTC with the higher AMES score (odd ratio [OR], 1.718; 95% confidence interval [CI], 1.073 ~ 2.752), the higher SUV of the CLN (> 0) (OR, 6.525; CI, 3.184 ~ 13.371), the higher SUV of the tumor (> 4.3) (OR, 1.855; CI, 1.065 ~ 3.231) (Table 2).

In multivariate analysis, the rate of CLN metastasis was considerably higher in the cases of younger patients (< 45 years old) (OR, 2.743; CI, 1.535 ~ 4.901), large tumors (> 1 cm) (OR, 2.882; CI, 1.271 ~ 6.532), positive lymphovascular invasion (OR, 6.680; CI, 2.941 ~ 15.998), the higher SUV of the CLN (> 0) (OR, 4.519; CI, 2.000 ~ 10.212), and the higher SUV of the tumor (> 4.3) (OR, 1.217; CI, 0.637 ~ 2.327) (Table 3). (18)

Table 3. Associations of CLN metastasis with predictive values by multivariate logistic regression analysis

Variables	Exp (β)	95.0% CI Exp (β)	
		Lower	Upper
Age < 45	2.743	1.535	4.901
Tumor size			
0.5 < ϕ ≤ 1 cm	1.124	0.591	2.139
1 < ϕ ≤ 2 cm	2.882	1.271	6.532
ϕ > 2 cm	4.495	1.151	17.549
Capsular invasion	1.385	0.614	3.124
Extrathyroidal extension	0.747	0.347	1.608
Lymphovascular invasion	6.680	2.941	15.998
SUV of CLN > 0	4.519	2.000	10.212
SUV of tumor > 4.3	1.217	0.637	2.327

SUV = Standardized uptake values; CLN = central lymph node; ϕ = maximal tumor diameter; Exp (β) = odds ratio; CI = confidence interval.

The area under the ROC curve of tumor SUV max was 0.62 (CI, 0.567~0.672; P=0.000), while that of the CLN was 0.65 (CI, 0.599~0.699; P=0.000) (Figs. 1 and 2). In the other words, there is an accuracy in predicting lymph node metastasis about 62% with the SUV of the tumor and 65% with the SUV of the lymph node.

DISCUSSION

PTC is nearly unique among nondermatologic invasive malignancies because it is rarely lethal, regional metastatically-involved lymph nodes do not portend distant metastases and inevitable death, and the surgical treatment options do not differ radically in functional or cosmetic outcome.(19) Nevertheless, heated debate continues to rage regarding the appropriate extent of surgical resection, principally as it relates to low-risk patients. In the vast portion of PTC patients who are at a low risk state, unilateral lobectomy is sufficient surgical treatment. But, for all high-risk patients, near total or total thyroidectomy and CLN dissection should be performed since these patients will uniformly be given radioactive iodine in an attempt to improve their poor prognosis.(20)

For less aggressive treatment in low-risk patients, several scoring systems have been developed to identify low-risk patients. There are several criteria that will predict the prognosis for example, the MACIS and AMES

scoring system. However, CLN metastasis which is not accurate without a postoperative pathologic report was not incorporated in either prognostic staging systems, MACIS and AMES. If we can predict whether or not the CLN metastasis is occurring before surgery, it is helpful to determine the extent of the surgery in order to prevent an unnecessary operation and consequent complications. Then, we would like to verify the correlation between the AMES and MACIS scoring systems that can be obtained via preoperative clinical data and CLN metastasis for use in determining the operation range before surgery.

As a result of this study, AMES scoring showed a significant correlation with CLN metastasis; however, MACIS scoring was not able to prove the relevance despite there not being a big difference between the components of the two scoring systems. We had to decide the cut off value of MACIS, because it is represented by the number unlike AMES scoring which is only divided into two categories, high risk or low risk. However, it was difficult to decide the cut off value because of the insufficient number of patients with a MACIS score above 7.

On the other hand, we assessed usefulness and accuracy of [^{18}F] FDG PET/CT in PTC patients. FDG PET/CT has a role in the management of various thyroid cancers. Incidental focal thyroid uptake on PET/CT has a high risk of malignancy, 24~36%, necessitating further diagnostic workup with ultrasound and fine-needle aspiration biopsy. PET/CT has proven useful for the detection of recurrent or metastatic disease, as well as provision of prognostic information in patients with differentiated thyroid cancers and elevated thyroglobulin levels with negative iodine scintigraphy. FDG PET/CT has also been shown to have high sensitivity and specificity and to provide prognostic information. The higher the SUV value of [^{18}F] FDG PET/CT leads to the supposition that there is a high possibility of metastasis of CLN when considering the functional aspects of [^{18}F] FDG PET/CT.(10) It is also interesting that the CLN metastasis is significantly related to tumor SUVs, as well as CLN SUVs. According to this study, a tumor SUV is considered to be proportional to malignant cells. And we also assessed the usefulness of MACIS and AMES scoring compared with [^{18}F] FDG PET/CT in PTC patients. Based on these results, it is

helpful to determine the operation range if considering the value of tumor SUVs, CLN SUVs, and AMES scoring.

Some studies claim that the prognostic significance and optimal treatment of nodal metastasis are not known with certainty in thyroid carcinoma unlike other epithelial malignancies. They propose that lymph node metastasis at presentation do not adversely affect survival for PTC, and therefore extensive lymph node dissection at presentation offers no advantage and may cause increased morbidity in papillary carcinoma.(21-23) However, there are some opinions that the lymph node metastasis status significantly influenced recurrence and survival in PTC (24) and the survival of patients with well-differentiated PTC is adversely affected by lymph node metastasis.(25)

In this study, the AMES preoperative and intraoperative scoring system can be helpful to make more reasonable decisions regarding operation range about whether CLN dissection should occur along with total thyroidectomy or not. However even though the AMES score is low risk, intraoperative pathologic result of suspected lymph node or the maximum SUV of the [¹⁸F] FDG PET/CT should also be considered to plan the extent of surgery.

The limitation of our study is the limited number of cases and that there was no small categorized study between the size or number of CLN metastasis and the prognostic scoring systems. Another weakness in this study was multicenter and retrospective studies, makes the findings not highly generalizable. Nevertheless, it is meaningful to figure out the association between the AMES score and the SUV with CLN metastasis as a result of this study. More categorized prospective randomized controlled trial of prophylactic central lymph node dissection in PTC are required. Also large sample sizes would be required for sufficient statistical power to demonstrate more significant differences in outcomes. It is thought possible to be able to provide more effective treatment strategies to PTC patients with a new scoring system that can determine the CLN metastasis more precisely has been established.

CONCLUSION

It will be reasonable to perform a total thyroidectomy

with CLN dissection if CLN metastasis is highly suspected. According to the above results, it is worth considering performing a total thyroidectomy with CLN dissection rather than a lobectomy in the cases of younger patients, a large tumor, positive lymphovascular invasion, a higher SUV of CLN, and a higher SUV of the tumor.

The AMES score also could be taken into account in the decision whether or not to perform a CLN dissection for a meaningful correlation between the AMES score and CLN metastasis.

Thus, it is also an available predictor of CLN metastasis which is used to determine the extent of PTC surgery especially considering the cost and effort.

The AMES score and [¹⁸F] FDG PET/CT are complementary but do not replace one another. The AMES scoring system along with other clinicopathological factors including [¹⁸F] FDG PET/CT are useful modalities to predict CLN metastasis which could affect the surgical therapeutic plan of PTC.

REFERENCES

1. Moo TA, McGill J, Allendorf J, Lee J, Fahey T 3rd, Zarnegar R. Impact of prophylactic central neck lymph node dissection on early recurrence in papillary thyroid carcinoma. *World J Surg* 2010;34:1187-91.
2. Shaha AR. Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer. *Laryngoscope* 2004;114:393-402.
3. Lee YS, Kim SW, Kim SK, Kang HS, Lee ES, et al. Extent of routine central lymph node dissection with small papillary thyroid carcinoma. *World J Surg* 2007;31:1954-9.
4. Sugitani I, Fujimoto Y. Symptomatic versus asymptomatic papillary thyroid microcarcinoma: a retrospective analysis of surgical outcome and prognostic factors. *Endocr J* 1999;46:209-16.
5. Hay ID, Grant CS, Bergstralh EJ, Thompson GB, van Heerden JA, Goellner JR. Unilateral total lobectomy: is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? *Surgery* 1998;124:958-64.
6. Dionigi G, Dionigi R, Bartalena L, Boni L, Rovera F, Villa F. Surgery of lymph nodes in papillary thyroid cancer. *Expert Rev Anticancer Ther* 2006;6:1217-29.
7. Pellegriti G, Scollo C, Lumera G, Regalbuto C, Vigneri R, Belfiore A. Clinical behavior and outcome of papillary thyroid cancers smaller than 1.5 cm in diameter: study of 299 cases. *J Clin Endocrinol Metab* 2004;89:3713-20.
8. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS, et al. Extent of surgery affects survival for papillary thyroid cancer. *Ann Surg* 2007;246:375-81.

9. Kim H, Na KJ, Choi JH, Ahn BC, Ahn D, Sohn JH. Feasibility of FDG-PET/CT for the initial diagnosis of papillary thyroid cancer. *Eur Arch Otorhinolaryngol* 2015. [Epub ahead of print]
10. Wang W, Larson SM, Fazzari M, Tickoo SK, Kolbert K, Sgouros G, et al. Prognostic value of [¹⁸F] fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. *J Clin Endocrinol Metab* 2000;85:1107-13.
11. Rossi RL, Cady B, Silverman ML, Wool MS, Horner TA. Current results of conservative surgery for differentiated thyroid carcinoma. *World J Surg* 1986;10:612-22.
12. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. *Surgery* 1988;104:947-53.
13. Cady B. Hayes Martin Lecture. Our AMES is true: how an old concept still hits the mark: or, risk group assignment points the arrow to rational therapy selection in differentiated thyroid cancer. *Am J Surg* 1997;174:462-8.
14. Shah JP, Loree TR, Dharker D, Strong EW, Begg C, Vlamis V. Prognostic factors in differentiated carcinoma of the thyroid gland. *Am J Surg* 1992;164:658-61.
15. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery* 1993;114:1050-7.
16. Haigh PI, Urbach DR, Rotstein LE. Extent of thyroidectomy is not a major determinant of survival in low- or high-risk papillary thyroid cancer. *Ann Surg Oncol* 2005;12:81-9.
17. Roh JL, Kim JM, Park CI. Central lymph node metastasis of unilateral papillary thyroid carcinoma: patterns and factors predictive of nodal metastasis, morbidity, and recurrence. *Ann Surg Oncol* 2011;18:2245-50.
18. Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. *Ann Surg* 2003;237:399-407.
19. Moo TA, Umunna B, Kato M, Butriago D, Kundel A, Lee JA, et al. Ipsilateral versus bilateral central neck lymph node dissection in papillary thyroid carcinoma. *Ann Surg* 2009;250:403-8.
20. Palestini N, Borasi A, Cestino L, Freddi M, Odasso C, Robecchi A. Is central neck dissection a safe procedure in the treatment of papillary thyroid cancer? Our experience. *Langenbecks Arch Surg* 2008;393:693-8.
21. Grebe SK, Hay ID. Thyroid cancer nodal metastases: biologic significance and therapeutic considerations. *Surg Oncol Clin N Am* 1996;5:43-63.
22. Schindler AM, van Melle G, Evequoz B, Scazziga B. Prognostic factors in papillary carcinoma of the thyroid. *Cancer* 1991;68:324-30.
23. Tubiana M, Schlumberger M, Rougier P, Laplanche A, Benhamou E, Gardet P, et al. Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. *Cancer* 1985;55:794-804.
24. Scheumann GF, Gimm O, Wegener G, Hundeshagen H, Dralle H. Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. *World J Surg* 1994;18:559-67.
25. Podnos YD, Smith D, Wagman LD, Ellenhorn JD. The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. *Am Surg* 2005;71:731-4.