INTRODUCTION

Papillary thyroid cancer (PTC) is the most common endocrine cancer and its incidence has increased over the last three decades all over the world, including Korea. Although survival with PTC is excellent, substantial recurrence rates are problematic. Growth of thyroid cancer through a tissue barrier may be a feature of the primary cancer itself or of a metastatic deposit in a lymph node (LN), where it is described as extranodal extension (ENE). ENE is defined pathologically by tumor cells extending beyond the lymph-node capsule into the perinodal fibroadipose tissue. Thus, microscopic or gross disease beyond nodal capsule resulted in the diagnosis. ENE in thyroid cancer was first reported by Spires, et al. However, they did not identify this as a significant adverse prognostic feature. They initially suggested that the presence of extrathyroidal extension (ETE) and ENE was associated. Since then, ENE in PTC has been associated with an increased risk of distant metastases, disease persistence, and disease-specific mortality. Recently, the prognostic significance of histologic features of the involved LN rather than simply the presence of metastatic deposits has been highlighted.

Even though ENE is common in PTC, death is not, and this lack of clear prognostic indication led to controversy regarding

Prognostic Value of Extranodal Extension in Thyroid Cancer: A Meta-Analysis

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Purpose: Thyroid cancer is the most common endocrine cancer and its incidence has continuously increased in the last three decades all over the world. We aimed to evaluate the prognostic value of extranodal extension (ENE) of thyroid cancer.

Materials and Methods: We performed a systematic search of MEDLINE (from inception to June 2014) and EMBASE (from inception to June 2014) for English-language publication. The inclusion criteria were studies of thyroid cancer that reported the prognostic value of ENE in thyroid cancer. Reviews, abstracts, and editorial materials were excluded, and duplicate data were removed. Two authors performed the data extraction independently.

Results: 6 studies including 1830 patients were eligible for inclusion in the study. All patients included in the meta-analysis had papillary thyroid cancer (PTC). Recurrence-free survival was analyzed based on 3 studies. The pooled hazard ratio for recurrence was 2.01 [95% confidence interval (CI) 1.19–3.40, p=0.009]. Disease-specific survival was analyzed based on 3 studies with 973 patients. Patients of PTC with ENE showed 3.37-fold higher risk of death from the disease (95% CI 1.55–7.32, p=0.002).

Conclusion: ENE should be considered to be a poor prognostic marker in thyroid cancer; such knowledge might improve the management of individual patients. This might facilitate the planning of appropriate ablation therapy and tailored patient follow-up from the beginning of treatment.

Key Words: Thyroid carcinoma, lymph nodes, prognosis
the effect of ENE on survival. Therefore, ENE is not recognized in any staging system, while ETE of the primary tumor increases primary tumor stage.7 LN continues to be staged solely on location and pathologic evidence of involvement. As LN metastases do not all affect prognosis equally, there is a need for risk stratification of LN metastasis.7 Therefore, we evaluated the prognostic value of ENE in thyroid cancer patients.

MATERIALS AND METHODS

Data search and study selection
We performed a systematic search of MEDLINE (from inception to June 2014) and EMBASE (from inception to June 2014) for English-language publications using the keywords “thyroid cancer,” “extranodal extension”, “lymph node,” “metastasis,” and “prognosis.” All searches were limited to human studies. The inclusion criteria were studies of thyroid cancer that reported the prognostic value of ENE in thyroid cancer. Reviews, abstracts, and editorial materials were excluded, and duplicate data were removed. Two authors performed the searches and screening independently, and resolved the discrepancies by consensus.

Data extraction and statistical analysis
Data were extracted from each publication independently by two reviewers, and the following information was recorded: first author, year of publication, country, definition of ENE, number of patients, and endpoints. The primary outcome was recurrence-free survival (RFS), and the secondary endpoint was disease-specific survival (DSS). Only deaths from disease were included in DSS.

The effects of ENE on survival were assessed using hazard ratios (HRs). Survival data were extracted following a published methodology.9 A univariate HR estimate and 95% confidence intervals (CIs) were extracted directly from each study, if provided by the authors. Otherwise, p values of the log-rank tests, 95% CIs, numbers of events, and numbers of patients at risk were extracted to estimate the HR indirectly. Survival rates calculated from Kaplan-Meier curves were read using Engauge Digitizer version 3.0 (http://digitizer.sourceforge.net) to reconstruct the HR estimate and its variance, assuming that patients were censored at a constant rate during follow-up. An HR >1 implies worse survival for patients with ENE, whereas an HR <1 implies a survival benefit for patients with ENE. Heterogeneity among studies was assessed using χ2 tests and I2 statistics, as described.10 Funnel plots were used to assess publication bias.11 Null hypotheses of no difference were rejected if p-values were less than 0.05. Two authors reviewed each publication by the Cochrane risk of bias assessment tool (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting).12 The data from each study were analysed using Review Manager (RevMan, Version 5.2, Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

RESULTS

Study characteristics
The electronic search identified 428 articles, non-English-language articles (n=23), and conference abstracts (n=118). Two hundred and nine studies that did not meet the inclusion criteria based on their title and abstract were excluded. After reviewing the full text of 43 articles, six studies including 1830 patients were eligible for inclusion in the study (Table 1).13-18 All studies were judged to have a low or unclear risk of bias in

Table 1. Studies Included in Meta-Analysis

| Author         | Year of publication | Country | Institution                                | Period       | Effect size | Endpoints |
|----------------|---------------------|---------|--------------------------------------------|--------------|-------------|-----------|
| Ganly, et al.  | 2014                | USA     | Memorial Sloan-Kettering Cancer Center     | 1985–2005    | HR          | DSS       |
| Wang, et al.   | 2015                | USA     | Memorial Sloan-Kettering Cancer Center     | 1986–2010    | HR          | RFS       |
| Ryu, et al.    | 2014                | Korea   | Asan Medical Center                        | 2000–2006    | HR          | RFS       |
| Lee, et al.    | 2015                | Korea   | Asan Medical Center                        | 2006–2010    | HR          | RFS       |
| Wu, et al.     | 2015                | USA     | University of California, San Francisco    | 1994–2004    | HR          | DSS       |
| Moritani       | 2014                | Japan   | Kusatsu General Hospital                   | 1981–2008    | HR          | DSS       |

HR, hazard ratio; RFS, recurrence-free survival; DSS, disease-specific survival.
blinding of outcome assessment, incomplete outcome data, and selective reporting. The detailed procedure is shown in Fig. 1. Each of two studies from Memorial Sloan-Kettering Cancer Center and Asan Medical Center are included in this meta-analysis. Although the studies from Memorial Sloan-Kettering Cancer Center are duplicated, we extracted either DSS or RFS data from each study. In studies from Asan Medical Center, each included patients of PTC with either N1a or N1b metastases. ENE was not defined in four studies; however, studies by Wu et al. and Moritani explained the definition of ENE. RFS data were extracted in three studies, those of DSS in 3 studies. Visual inspection of the funnel plot suggested no evidence of publication bias. Patient characteristics are summarized in Table 2.

Extranodal extension

Recurrence-free survival
All patients included in the meta-analysis had PTC. RFS was analyzed based on three studies. Wang et al. divided their patients into two categories with patients of 45 or older (Wang 2015b) and those of less than 45 (Wang 2015a). The pooled HR for recurrence was 2.01 (95% CI 1.19–3.40, p=0.009), and the test for heterogeneity gave no significant results ($\chi^2 = 3.26$, p=0.35; $I^2 = 8\%$) (Fig. 2).

Disease-specific survival
DSS was analyzed based on three studies with 973 patients. PTC patients with ENE were at 3.37-fold higher risk of death from the disease (95% CI 1.55–7.32, p=0.002), and the test for heterogeneity gave no significant results ($\chi^2 = 0.65$, p=0.72; $I^2 = 0\%$). The forest plots for DSS are shown in Fig. 3.

DISCUSSION

This meta-analysis evaluated the prognostic value of ENE in patients with thyroid cancer. In combined results, PTC patients with ENE had a 2.01-fold higher risk of recurrence and a 3.37-fold higher risk of death than those without ENE.

Differentiated thyroid carcinoma tends to recur in 30% of patients, usually (in 66% of cases) within 10 years of initial therapy. Because prophylactic LN dissection is recommended and performed frequently, it is not surprising that the number of cases of pathologically proven, but clinically inapparent, LN metastasis is increasing. Neck LN metastases have increased and are found in up to 70% of cases of PTC. Not all types of nodal metastases have the same prognostic significance, and in particular, there is considerable controversy regarding the clinical importance of the spectrum of nodal metastases. If the clinician had information that would provide clues of the potential severity of those LNs, it could affect clinical decisions in primary treatment settings and when managing patients.

| Author | Year of publication | No. of patients included in meta-analysis | Sex (M/F) | Follow-up (months) | Treatment | Definition of recurrence | Definition of ENE | Proportion of ENE (%) | Definition of ENE | Definition of ENE |
|--------|---------------------|----------------------------------------|-----------|---------------------|----------|------------------------|-------------------|-----------------------|-------------------|-------------------|
| Ganly, et al. | 2014 | 245 | 132/321 | 111* | PTC≥1 cm | Clinical and imaging data | - | 32.2 | - | - |
| Wang, et al. | 2015 | 121 | 65 (1-321)* | PTCN1b | Distant metastasis within 6 months of presentation | - | - | 41.3 | - | - |
| Ryu, et al. | 2014 | 283 | 67/228 | 78 (63–137)* | PTCN1a | Distant metastasis, tumors invading adjacent structures | - | - | 14.6 | - | - |
| Lee, et al. | 2015 | 136 | 40/96 | 62 (33–90)* | PTCN1b | Distant metastasis, recurrent PTC | - | - | 61.8 | - | - |
| Wu, et al. | 2015 | 240 | 68/172 | 95* | PTCN1 | Presence of tumors at local, regional, and/or distant sites | - | - | 25.0 | - | - |
| Moritani | 2014 | 488 | 114/374 | 128 | PTC | Histological confirmation | - | - | 12.3 | - | - |

PTC, papillary thyroid cancer; TT, total thyroidectomy; ND, neck dissection; RAI, radioactive iodine ablation; LN, lymph node; ENE, extranodal extension.

*Median, †Mean.
The presence of ENE is associated with a higher number of central neck LN metastasis. Patients was also higher with younger age, where there was a potential for tumor invasion and metastasis to BRAF mutation (recognized as a marker of enhanced proliferation and survival). In conclusion, ENE should be considered a poor prognostic marker in thyroid cancer rather than a direct relationship between LN size and ENE. We proved, in accord with others, that the extent of ENE is a risk factor for recurrence and disease-related death. Recurrence is a stressful event for both patients and surgeons because of the difficulty of reoperation along the previously dissected planes, and high morbidity rates. Collectively, ENE categorizes patients with PTC into prognostically distinct groups, suggesting that ENE should be considered in the initial assessment of recurrence. We suggest that radioactive iodine ablation should be considered in patients with ENE as an adjuvant therapy after surgery. Furthermore, this prognostic effect of ENE has implications for the future update of the nodal classification of staging system.

This is the first study that meta-analyzed the prognostic value of ENE. However, using ENE as a prognostic factor raises the concern about interobserver variability because of lack of stringent criteria for the definition of ENE. In addition, some institutions do not routinely report the presence of ENE. These issues need to be addressed in future studies. As the number of metastatic nodes detected depends on both the extent of LN dissection by the surgeons and the scrutiny of pathologists, it may be less reliable than the examination for ENE, which cannot be detected preoperatively by imaging modalities such as ultrasound or computed tomography.

In conclusion, ENE should be considered a poor prognostic marker in thyroid cancer. This might help plan the radioactive iodine ablation and the disease monitoring.

| Study or subgroup | Log (hazard ratio) | SE | Weight | Hazard ratio IV, fixed, 95% CI |
|-------------------|-------------------|----|--------|-------------------------------|
| Lee, et al.       | 1.1119            | 0.496 | 29.0%  | 3.04 (1.15, 8.04)             |
| Ryu, et al.       | 0.3716            | 0.4854 | 30.3%  | 1.45 (0.56, 3.75)             |
| Wang, et al.      | 0                 | 0.6143 | 18.9%  | 1.00 (0.30, 3.33)             |
| Wang, et al.      | 1.2179            | 0.5727 | 21.8%  | 3.38 (1.10, 10.39)            |
| Total             |                   |       | 100.0% | 2.01 (1.19, 3.40)             |

Heterogeneity: chi²=3.26, df=3 (p=0.35); I²=8% Test for overall effect: Z=2.62 (p=0.009)

Fig. 2. Forest plots of the hazard ratios for recurrence. CI, confidence interval; SE, standard error.

| Study or subgroup | Log (hazard ratio) | SE | Weight | Hazard ratio IV, fixed, 95% CI |
|-------------------|-------------------|----|--------|-------------------------------|
| Ganly, et al.     | 1.8374            | 0.8835 | 19.6%  | 6.28 (1.09, 36.18)            |
| Moritani          | 1.0953            | 0.4701 | 71.0%  | 2.99 (1.19, 7.51)             |
| Wu, et al.        | 0.8154            | 1.2909 | 9.4%   | 2.26 (0.18, 28.38)            |
| Total             |                   |       | 100.0% | 3.37 (1.55, 7.32)             |

Heterogeneity: chi²=0.65, df=2 (p=0.72); I²=0% Test for overall effect: Z=3.07 (p=0.002)

Fig. 3. Forest plots of hazard ratios for deaths from thyroid cancer. CI, confidence interval; SE, standard error.
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REFERENCES

1. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol 2013;2013:965212.
2. Kweon SS, Shin MH, Chung II, Kim YJ, Choi JS. Thyroid cancer is the most common cancer in women, based on the data from population-based cancer registries, South Korea. Jpn J Clin Oncol 2013;43:1039-46.
3. Lango M, Fiedler D, Arrangoiz R, Veloski C, Yu QJ, Li T, et al. Extranodal extension of metastatic papillary thyroid carcinoma: correlation with biochemical endpoints, nodal persistence, and systemic disease progression. Thyroid 2013;23:1099-105.
4. Spires JR, Robbins KT, Luna MA, Byers RM. Metastatic papillary carcinoma of the thyroid: the significance of extranodal extension. Head Neck 1989;11:242-6.
5. Yamashita H, Noguchi S, Murakami N, Kawamoto H, Watanabe S. Extracapsular invasion of lymph node metastasis is an indicator of distant metastasis and poor prognosis in patients with thyroid papillary carcinoma. Cancer 1997;80:2268-72.
6. Yamashita H, Noguchi S, Murakami N, Toda M, Uchino S, Watanabe S, et al. Extracapsular invasion of lymph node metastasis. A good indicator of disease recurrence and poor prognosis in patients with thyroid microcarcinoma. Cancer 1999;86:842-9.
7. Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid 2012;22:1144-52.
8. Clain JB, Scherl S, Dos Reis L, Turk A, Wenig BM, Mehra S, et al. Extrathyroidal extension predicts extranodal extension in patients with positive lymph nodes: an important association that may affect clinical management. Thyroid 2014;24:951-7.
9. Parmar MK, Torri V, Stewert L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815-34.
10. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
11. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
12. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
13. Ganly I, Ibrahimpasic T, Rivera M, Nixon I, Palmer F, Patel SG, et al. Prognostic implications of papillary thyroid carcinoma with tall-cell features. Thyroid 2014;24:662-70.
14. Lee CW, Roh JL, Gong G, Cho KJ, Choi SH, Nam SY, et al. Risk factors for recurrence of papillary thyroid carcinoma with clinically node-positive lateral neck. Ann Surg Oncol 2015;22:117-24.
15. Moritani S. Impact of invasive extranodal extension on the prognosis of patients with papillary thyroid carcinoma. Thyroid 2014;24:1779-83.
16. Ryu IS, Song CI, Choi SH, Roh JL, Nam SY, Kim SY. Lymph node ratio of the central compartment is a significant predictor for locoregional recurrence after prophylactic central neck dissection in patients with thyroid papillary carcinoma. Ann Surg Oncol 2014;21:277-83.
17. Wang LY, Palmer FL, Nixon IJ, Tuttle RM, Shah JP, Patel SG, et al. Lateral neck lymph node characteristics prognostic of outcome in patients with clinically evident N1b papillary thyroid cancer. Ann Surg Oncol 2015;22:3530-6.
18. Wu MH, Shen WT, Gosnell J, Duh QY. Prognostic significance of extranodal extension of regional lymph node metastasis in papillary thyroid cancer. Head Neck 2015;37:1336-43.
19. Mazzaferrri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-28.
20. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
21. Noguchi S, Noguchi A, Murakami N. Papillary carcinoma of the thyroid. I. Developing pattern of metastasis. Cancer 1970;26:1053-60.
22. Wang LY, Palmer FL, Nixon IJ, Thomas D, Shah JP, Patel SG, et al. Central lymph node characteristics predictive of outcome in patients with differentiated thyroid cancer. Thyroid 2014;24:1790-5.
23. Ito Y, Fukushima M, Tomoda C, Inoue H, Kihara M, Higashiyama T, et al. Prognosis of patients with papillary thyroid carcinoma having extranodal extension of regional lymph node metastasis in papillary thyroid cancer. Ann Surg Oncol 2014;21:277-83.
24. Lango M, Flieder D, Arrangoiz R, Veloski C, Yu JQ, Li T, et al. Extranodal extension of metastatic papillary thyroid carcinoma: correlation with biochemical endpoints, nodal persistence, and systemic disease progression. Thyroid 2013;23:1099-105.
25. Moritani S. Impact of invasive extranodal extension on the prognosis of patients with papillary thyroid carcinoma. Thyroid 2014;24:1779-83.
26. Ryu IS, Song CI, Choi SH, Roh JL, Nam SY, Kim SY. Lymph node ratio of the central compartment is a significant predictor for locoregional recurrence after prophylactic central neck dissection in patients with thyroid papillary carcinoma. Ann Surg Oncol 2014;21:277-83.
27. Wang LY, Palmer FL, Nixon IJ, Tuttle RM, Shah JP, Patel SG, et al. Lateral neck lymph node characteristics prognostic of outcome in patients with clinically evident N1b papillary thyroid cancer. Ann Surg Oncol 2015;22:3530-6.
28. Wu MH, Shen WT, Gosnell J, Duh QY. Prognostic significance of extranodal extension of regional lymph node metastasis in papillary thyroid cancer. Head Neck 2015;37:1336-43.
29. Mazzaferrri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-28.
30. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
31. Noguchi S, Noguchi A, Murakami N. Papillary carcinoma of the thyroid. I. Developing pattern of metastasis. Cancer 1970;26:1053-60.
32. Wang LY, Palmer FL, Nixon IJ, Thomas D, Shah JP, Patel SG, et al. Central lymph node characteristics predictive of outcome in patients with differentiated thyroid cancer. Thyroid 2014;24:1790-5.
33. Ito Y, Fukushima M, Tomoda C, Inoue H, Kihara M, Higashiyama T, et al. Prognosis of patients with papillary thyroid carcinoma having clinically apparent metastasis to the lateral compartment. Endocr J 2009;56:759-66.
34. Ricarte-Filho J, Ganly I, Rivera M, Katabi N, Fu W, Shaha A, et al. Papillary thyroid carcinomas with cervical lymph node metastases can be stratified into clinically relevant prognostic categories using oncogenic BRAF; the number of nodal metastases, and extranodal extension. Thyroid 2012;22:575-84.
35. Pak K, Suh S, Kim SJ, Kim II. Prognostic value of genetic mutations in thyroid cancer: a meta-analysis. Thyroid 2015;25:63-70.
36. Lee YS, Lim YS, Lee JC, Wang SG, Kim II, Son SM, et al. Nodal status of central lymph nodes as a negative prognostic factor for papillary thyroid carcinoma. J Surg Oncol 2013;107:777-82.
37. Ito Y, Miyachi A. Lateral and mediastinal lymph node dissection in differentiated thyroid carcinoma: indications, benefits, and risks. World J Surg 2007;31:905-15.