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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

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.[1,2] 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).[3] 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.[3] ENE in thyroid cancer was first reported by Spires, et al.[4] 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,[5] disease persistence,[3] and disease-specific mortality.[6,7] Recently, the prognostic significance of histologic features of the involved LN rather than simply the presence of metastatic deposits has been highlighted.[8]

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

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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 χ^2 tests and I^2 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

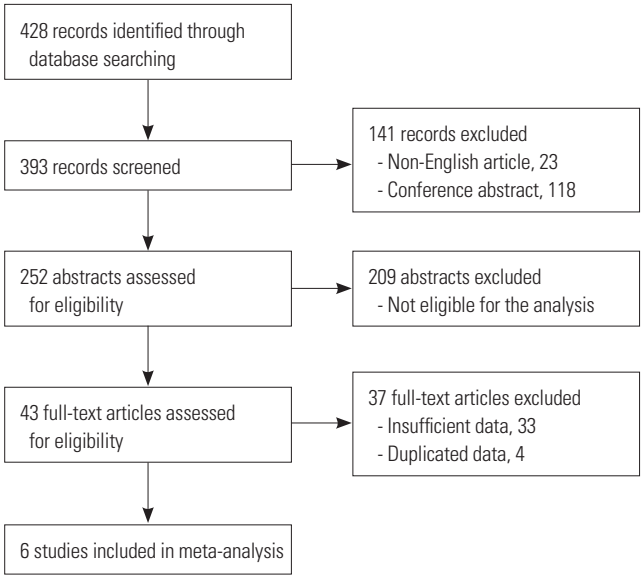

Fig. 1. Flowchart of the study selection process.

Table 1. Studies Included in Meta-Analysis

Author	Year of publication	Country	Institution	Period	Effect size	Endpoints
Ganly, et al.[13]	2014	USA	Memorial Sloan-Kettering Cancer Center	1985–2005	HR	DSS
Wang, et al.[17]	2015	USA	Memorial Sloan-Kettering Cancer Center	1986–2010	HR	RFS
Ryu, et al.[16]	2014	Korea	Asan Medical Center	2000–2006	HR	RFS
Lee, et al.[14]	2015	Korea	Asan Medical Center	2006–2010	HR	RFS
Wu, et al.[18]	2015	USA	University of California, San Francisco	1994–2004	HR	DSS
Moritani[15]	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[13,17] and Asan Medical Center[14,16] are included in this meta-analysis. Although the studies from Memorial Sloan-Kettering Cancer Center are duplicated, we extracted either DSS[13] or RFS[17] data from each study. In studies from Asan Medical Center, each included patients of PTC with either N1a[16] or N1b[14] metastases. ENE was not defined in four studies;[13,14,16,17] however, studies by Wu, et al.[18] and Moritani[15] explained the definition of ENE. RFS data were extracted in three studies,[14,16,17] those of DSS in 3 studies.[13,15,18] 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.[14,16,17] Wang, et al.[17] 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 (χ^2=3.26, p=0.35; I^2=8%) (Fig. 2).

Disease-specific survival

DSS was analyzed based on three studies[13,15,18] 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 (χ^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.[19] 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.[20] Neck LN metastases have increased and are found in up to 70% of cases of PTC.[21] 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.[7] 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

Table 2. Patient Characteristics

Author	Year of publication	No. of patients included in meta-analysis	Sex (M/F)	Follow-up (months)	Inclusion	Exclusion	Treatment	Definition of recurrence	Definition of ENE	Proportion of ENE (%)
Ganly, et al.[13]	2014	245	132/321	111*	PTC≥1 cm	-	-	Clinical and imaging data	-	32.2
Wang, et al.[17]	2015	121	-	65 (1–332)*	PTC+N1b	Distant metastasis within 6 months of presentation	-	-	-	41.3
Ryu, et al.[16]	2014	283	67/228	78 (63–137)*	PTC+N1a	Distant metastasis, tumors invading adjacent structures	TT+ND (central)+ RAI 80–150 mCi	-	-	14.6
Lee, et al.[14]	2015	136	40/96	62 (33–90)*	PTC+N1b	Distant metastasis, recurrent PTC	TT+ND (central/ lateral)+ RAI 150 mCi	Presence of tumors at local, regional, and/or distant sites	-	61.8
Wu, et al.[18]	2015	240	68/172	95*	PTC+N1	-	TT+RAI	Histological confirmation	Cancer cells invading beyond the capsule of the node	25.0
Moritani[15]	2014	488	114/374	126†	PTC	-	-	-	Gross invasion by LN metastasis or intraoperative cryosection analysis showing LN metastasis to the organ	12.3

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

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Study or subgroup	Log (hazard ratio)	SE	Weight	Hazard ratio IV, fixed, 95% CI
Lee, et al.[14]	1.1119	0.496	29.0%	3.04 (1.15, 8.04)
Ryu, et al.[16]	0.3716	0.4854	30.3%	1.45 (0.56, 3.75)
Wang, et al.[17]	0	0.6143	18.9%	1.00 (0.30, 3.33)
Wang, et al.[17]	1.2179	0.5727	21.8%	3.38 (1.10, 10.39)
Total (95% CI)			100.0%	2.01 (1.19, 3.40)

Heterogeneity: chi^2=3.26, df=3 (p=0.35); I^2=8%

Test for overall effect: Z=2.62 (p=0.009)

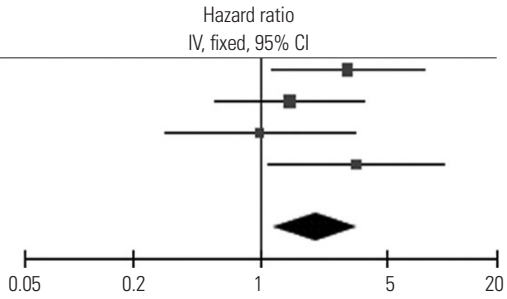

Fig. 2. Forest plots of the hazard ratios for recurrence. CI, confidence interval; SE, standard error.

Study or subgroup	Log (hazard ratio)	SE	Weight	Hazard ratio IV, fixed, 95% CI
Ganly, et al.[13]	1.8374	0.8935	19.6%	6.28 (1.09, 36.18)
Moritani[15]	1.0953	0.4701	71.0%	2.99 (1.19, 7.51)
Wu, et al.[18]	0.8154	1.2909	9.4%	2.26 (0.18, 28.38)
Total (95% CI)			100.0%	3.37 (1.55, 7.32)

Heterogeneity: chi^2=0.65, df=2 (p=0.72); I^2=0%

Test for overall effect: Z=3.07 (p=0.002)

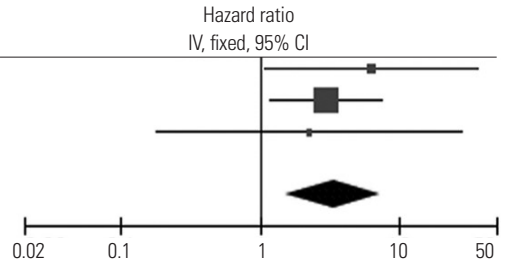

Fig. 3. Forest plots of hazard ratios for deaths from thyroid cancer. CI, confidence interval; SE, standard error.

with recurrent nodal disease. Ideally, the clinician should be able to use available information regarding the primary tumor to understand the potential severity of metastatic LNs. However, virtually all of the current staging systems for differentiated thyroid cancer are based on the presence of positive LNs. Recent literature has focused on the importance of specific features of the nodal metastases, including size, number of positive nodes, and presence of ENE.[7]

ENE is an important predictor of outcome in other head and neck cancers and is accepted as an indication for additional adjuvant therapy in squamous cell carcinoma.[22] However, research is limited on the effect of ENE on outcome in patients with thyroid cancer. Wang, et al.[17] noted that ENE was the LN characteristic most prognostic of nodal recurrence within the central neck compartment. A retrospective review by Clain, et al.[8] found the presence of ENE as a surrogate for more aggressive disease biology, and a strong association with minimal ETE. ENE is reported to diminish the probability of a biochemical complete response after treatment for regional metastatic PTC, and increase the probability of tumor persistence after initial resection, likely from abundant metastasis.[3] Several recent publications note that ENE is an indicator of poor prognosis and survival.[18,23] The development of ENE is presumably a late event in the progression pathway for PTC,[24] in contrast to BRAF mutation (recognized as a marker of enhanced potential for tumor invasion and metastasis[25]). In addition, ENE is associated with large tumor size.[17,26] The rate of ENE in PTC patients was also higher with younger age, where there was a higher number of central neck LN metastasis.[26] ENE is believed to be an independent manifestation of an aggressive thyroid cancer rather than a direct relationship between LN size and ENE.[8] 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.[27] 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 radioiodine 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.[24] 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,[18] 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.

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