Is central lymph node dissection necessary for parathyroid carcinoma?

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Background. *Parathyroid carcinoma is a rare cancer. Unlike other more common malignancies, the importance of lymph node (LN) status remains controversial. The purpose of this study was to determine the relative importance of LN metastases in disease-specific survival (DSS).*
Methods. *A retrospective review of the Surveillance, Epidemiology, and End Result database was performed on parathyroid carcinoma cases diagnosed between 1988 and 2010.*
Results. *We identified 405 parathyroid carcinoma patients. Among 114 patients with LNs examined at operation, only 12 (10.5%) had positive LNs. Sensitivity analysis found that a tumor size threshold of 3 cm best divided the cohort by DSS. Only tumors ≥3 cm and distant metastasis but not LN metastases were independent prognostic factors on multivariate analysis. When examining factors associated with LN status, only tumors ≥3 cm predicted LN metastasis. LN metastases were 7.5 times more likely in patients with tumors ≥3 cm than those with tumors <3 cm.*
Conclusion. *Tumors ≥3 cm were associated with LN metastases in parathyroid carcinoma, but positive LN status was not associated with DSS. Tumor size can potentially risk stratify patients by their risk of LN metastases. (Surgery 2014;156:1336-41.)*

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PARATHYROID CANCER IS A RARE DISEASE with major morbidity and mortality attributed to metabolic complications from hypercalcemia, including bone disease, nephrolithiasis, pancreatitis, and peptic ulcer disease, accounting for 0.005% of all malignancies[1] and 0.74–4.7% of hyperparathyroidism.[2-4] Unlike parathyroid adenoma, where the female to male ratio is approximately 4:1, parathyroid carcinoma affects both sexes equally.

Several studies in the past have used population data to analyze the prognostic factors of parathyroid carcinoma. The earliest United States population based study was performed by Hundahl et al[1] using the National Cancer Data Base (NCDB) with 286 patients diagnosed with parathyroid cancer between 1985 and 1996. The survey reported relative 5-year overall survival of 85.5% and 10-year survival of 49.1%. A second study by Lee et al,[5] using the Surveillance, Epidemiology, and End Results (SEER) database, with 224 patients diagnosed between 1988 and 2003 reported 5-year cancer-related survival of 91% and 10-year cancer-related survival of 87.6%.[5] There was a 60% increase in incidence between the periods of 1988–1991 and 2000–2003, but an improvement in survival was observed between the 2 population studies.[1,5] Potential explanations for the increase in parathyroid carcinoma incidence include increased screening, changes in diagnostic techniques, an increase in referral for surgery owing to availability of minimally invasive procedures, and possibly a true increase in the incidence.[6] Although younger age, female sex, absence of distant metastasis at diagnosis, and recent year of diagnosis were associated with improved survival, tumor size and LN status did not influence disease-specific survival (DSS).[1,5] The incidence of regional LN involvement at initial diagnosis varied widely, ranging between 6.5% and 32.1%.[7]

The therapy that offers the best outcome remains operative resection. The current standard of treatment dictates parathyroidectomy and en bloc resection with surrounding tissues, including the ipsilateral thyroid lobe, isthmus, and central neck lymph node (LN) compartment,[3,8-11] but even with resection, recurrence rate has been reported to be between 42 and 72%,[8,9,12-14] frequently

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requiring ≥1 reoperations. In addition, central neck dissection carries added risks, such as injury to the recurrent laryngeal nerve affecting voice and swallow function, bleeding, and inadvertent damage or removal of the other normal parathyroid glands.[15,16]

The purpose of this study was to determine how metastatic LNs impact DSS in parathyroid carcinoma. Because of the rare nature of parathyroid carcinoma, a population-based database allowed us to have a large enough sample size to answer the question of whether the regional LN status necessarily affected DSS.

MATERIAL AND METHODS

We used data from the SEER cancer registry between 1988 and 2010 because tumor size and LN status was reported beginning from 1988. Patients were first identified using primary site code of C750 (parathyroid) in combination with the *International Classification of Disease for Oncology, 3rd Edition*,[17] in combination with histology codes 800 (neoplasm), 801 (carcinoma, not otherwise specified), 802 (carcinoma, undifferentiated, not otherwise specified), and 814 (adenocarcinoma, not otherwise specified). We included all patients ≥18 years old with active follow-up and excluded patients without histology confirmation or autopsy-only cases. In addition, we obtained patient demographic information, tumor characteristics, treatment options, and survival information. We divided the patients into 2 age groups: <45 and ≥45 years old. Diagnostic years were grouped into 4 periods: 1988–1993, 1994–1999, 2000–2005, and 2006–2010. The last cutoff point for follow-up was December 31, 2009.

Statistics analysis was carried out using Stata (Stata 12 for Windows; StataCorp LP., College Station, TX). To evaluate potential factors affecting survival time, taking survival time and censoring into account, Cox proportional hazards regression was used to report hazard ratio (HR) with 95% CIs. Logistic regression was used to evaluate potential factors that predicted positive LN status. Factors with $P < .2$ in univariate analysis were included in multivariate analysis. Sensitivity analysis was performed to obtain the smallest tumor size threshold that differentiated survival. Unless otherwise stated, all tests were 2 sided. The study was approved by the Institutional Review Board of University of Wisconsin—Madison.

RESULTS

Patient characteristics. We identified 405 patients with parathyroid carcinoma meeting our inclusion criteria in the SEER registries between 1988 and 2010 with median follow-up of 68 months (interquartile range, 29–106). There was a slight male dominance with 52.3% of the patients being male and 47.7% of the patients being female (Table I); 75.8% of the patients were white, followed by black (15.8%), Asian (7.4%), and others (0.9%). The median patient age was 56 years (interquartile range, 46–66) within this time range. Of the cases, 47.2% were diagnosed in the third diagnostic period (2000–2005), following by the 27.2% of the cases in the last diagnostic period (2006–2010); 329 patients underwent parathyroidectomy, 42 patients had en bloc resection, and 7 patients had debulking procedures.

Tumor characteristics. Histology was recorded as neoplasm in 10 patients (2.5%), carcinoma not otherwise specified in 385 (95.1%), and adenocarcinoma not otherwise specified in 10 (2.5%). All tumors in the study were malignant. Tumor grades were recorded in 52 patients, including grade I in 39 (9.6%), grade II in 10 (2.5%), and grade III in 3 (0.7%). Median tumor size removed was 2.8 cm (interquartile range, 1.9–3.8). Regional LNs were examined in 114 patients, 12 of whom (10.5%) were found to have positive LN. The parathyroid carcinoma was confined to the gland in 318 patients (78.5%), locally invasive in 60 (14.8%), and metastatic in 7 (1.7%).

Prognostic factors. The DSS rates were 94.1% at 5 years and 89.9% at 10 years; however, the DSS remained stable between 10 and 20 years. The overall survival rates were 82.5% at 5 years and 65.4% at 10 years. Sensitivity analysis revealed that 3 cm tumor size cut off was the threshold that best divided he cohort by DSS (HR, 3.62; $P = .03$; Fig 1). On multivariate Cox proportional hazards analysis, controlling for sex, age, and diagnostic year, tumor size ≥3 cm (HR, 5.35; $P = .01$), and distant metastasis (HR, 45.10; $P < .01$) remained significant prognostic factors of DSS (Table II). Importantly, metastatic LNs did not independently predict worse DSS (HR, 3.72; $P = .19$).

LN status. LN metastasis were 7.5 times more likely in patients with tumors ≥3 cm (21% vs 2.8%; $P = .02$; Fig 2). On multivariate logistic regression, a tumor ≥3 cm (HR, 27.78; $P = .02$) was an independently predictive factor of positive LNs after controlling for sex, age, and diagnostic year (Table III). When we compared patients with LN data to those without LN data, there were no differences in distributions of sex, age ≥45 years, tumors ≥3 cm, diagnostic period, local invasion, or distant metastasis (Table IV). In both groups, most patients were white: 94 patients with LN examination (82%) and 200 without LN examination