Ann Surg Oncol (2019) 26:3593–3599
https://doi.org/10.1245/s10434-019-07451-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Risk of Distant Metastasis in Parathyroid Carcinoma and Its Effect on Survival: A Retrospective Review from a High-Volume Center

Elliot A. Asare, MD, MS[1], Angelica Silva-Figueroa, MD[2,3], Kenneth R. Hess, PhD[4], Naifa Busaidy, MD[5], Paul H. Graham, MD[1], Elizabeth G. Grubbs, MD[1], Jeffrey E. Lee, MD[1], Michelle D. Williams, MD[6], and Nancy D. Perrier, MD[1]

[1]Department of Surgical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX; [2]Universidad Finis Terrae, Santiago, Chile; [3]Department of Head and Neck Surgery, Hospital Barros Luco-Trudeau, Santiago, Chile; [4]Department of Biostatistics, University of Texas M. D. Anderson Cancer Center, Houston, TX; [5]Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas M. D. Anderson Cancer Center, Houston, TX; [6]Department of Pathology, University of Texas M. D. Anderson Cancer Center, Houston, TX

ABSTRACT

Background. Development of distant metastases (DM) is associated with markedly decreased survival in parathyroid carcinoma (PC). We sought to identify factors associated with development of DM and to quantify the effect that development of DM had on overall survival (OS).

Methods. Patients with surgically resected local/regional PC treated or surveilled at a tertiary-referral cancer hospital from 1980 to 2017 were included. We assessed the association between biochemical and clinicopathologic factors (preoperative parathyroid hormone (PTH) levels, sex, race, age, preoperative serum calcium levels, serum calcium levels at 6 months postop, tumor size, and extent of resection) with the development of DM. We also assessed the effect of development of DM on OS.

Results. Seventy-five patients with PC were assessed; 17 (22.7%) developed DM at a median follow-up of 77 months. The cumulative incidence of DM in the cohort was 20, 30, and 38% at 5, 10, and 20 years respectively. Tumor size > 3.2 cm based on recursive partitioning analysis was the only significant predictor for development of DM (hazard ratio (HR) = 3.51; 95% confidence interval [CI] 1.04–11.91; $p = 0.04$). Median OS for the entire cohort was 17 years compared with 40 months for the cohort who developed DM. The HR for death after distant metastasis was 9.6 (95% CI 4.2–22.3; $p < 0.0001$).

Conclusions. Development of distant metastasis during surveillance is associated with decreased OS, including late recurrences. Primary tumor size should be considered in future interval surveillance and development of treatment algorithms.

Parathyroid carcinoma (PC) accounts for less than 1% of primary hyperparathyroidism cases in the United States.[1] The preoperative diagnosis remains elusive, and definitive confirmation of disease is based on intraoperative assessment and postoperative histopathologic review of the resected specimen. The 5- and 10-year overall survivals (OS) for patients with PC have been estimated at between 78–85% and 49–70% respectively.[1–3]

Patients who develop distant metastasis (DM) have decreased survival and quality of life. Debilitating symptoms, including cardiac arrhythmias, renal failure, neuropsychiatric disturbances, and pathologic fractures, eventually result in death. Data regarding risk factors for DM after initial surgical resection are lacking. The National Cancer Data Base (NCDB) and Surveillance Epidemiology, and End Results (SEER) Program lack critical variables that would help to assess patterns of DM and determine factors predictive of DM.[4,5]

Delineating risk factors associated with DM will help clinicians tailor a surveillance strategy after initial curative resection. Patients at high risk for DM might be candidates for early systemic therapy. Also, aggressive treatment of

First Received: 14 September 2018;
Published Online: 20 May 2019

E. A. Asare, MD, MS
e-mail: eaasare@mdanderson.org

early metastasis may reduce the incidence and mitigate the implications of hypercalcemia-associated sequelae. Pertinent variables needed to enhance understanding of metastasis in patients with PC may be found in single or multi-institutional databases. Our institution is one of the highest volume centers in treating and surveilling patients with PC. The objectives of this study were to determine: (1) the cumulative incidence of DM in our cohort during surveillance, (2) factors predictive of DM during surveillance after curative resection, and (3) the effect of DM on OS.

METHODS

After approval by the Institutional Review Board (IRB) of the University of Texas MD Anderson Cancer Center (MDACC), the tumor registry database of MDACC was queried for patients with a diagnosis of PC. All histopathologic slides have been independently re-reviewed by a head and neck pathologist at our institution and the diagnosis of PC confirmed according to the World Health Organization (WHO) diagnostic criteria described previously.[6] Patients treated or surveilled at MDACC between January 1, 1980 to December 31, 2017 were eligible for inclusion.

Data on demographic factors, preoperative biochemical factors, extent of resection, and postoperative serum calcium level at 6 months were captured for each patient. Postoperative surveillance data, including vital status, development of metastasis during surveillance, location of metastasis if present, and cause of death if deceased were recorded. Patients with serum calcium levels greater than 10.2 mg/dL during the initial 6 months following parathyroidectomy were considered to have persistent disease, and those who developed serum calcium levels greater than 10.2 mg/dL after a period of eucalcemia for at least 6 months were considered to have disease recurrence.

Statistical Analysis

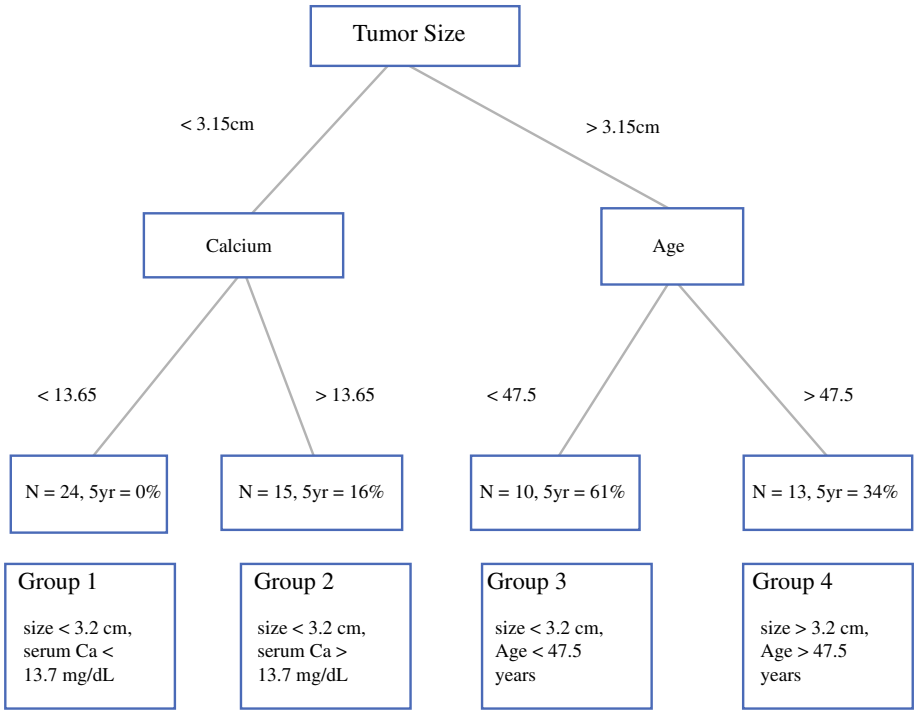
Data on continuous variables are reported as mean ± standard deviation (SD). Discrete variables are reported as frequency with corresponding relative frequency (percentage). Hazard ratios (HR) are presented as point estimates with 95% confidence intervals (CI). The primary objective was assessment of the factors predictive of development of DM. The effect of DM on OS was the secondary objective. Missing values [preoperative PTH (4), preoperative calcium levels (8), tumor size (8), serum calcium levels at 6 months post-surgery (1)] were excluded from analysis. The cumulative incidence of DM was estimated using the Aalen–Johansen method while treating death without DM as a competing risk; calculations were from date of surgery. Gray's test was used to test for differences between stratified cumulative incidence functions. A multivariable Fine-Gray proportional hazard regression model to predict risk of DM using the following variables was done: age, sex, race, preoperative serum calcium and PTH levels, tumor size, type of resection, and 6-month postoperative serum calcium. For purposes of analysis, the following continuous variables were dichotomized as: PTH $\leq$ 1200 pg/mL or $>$ 1200 pg/mL; age $\leq$ 65 years or $>$ 65 years; calcium $\leq$ 15 mg/dL or $>$ 15 mg/dL; and tumor size $\leq$ 3.2 cm or $>$ 3.2 cm. The cutoff points for analysis for age, PTH, and calcium levels were chosen to be consistent with our previous publication, whereas tumor size was based on the recursive partitioning analysis (RPA) from this study.[7] RPA also was employed to identify subgroups with different risks of DM (Fig. 1).[8]

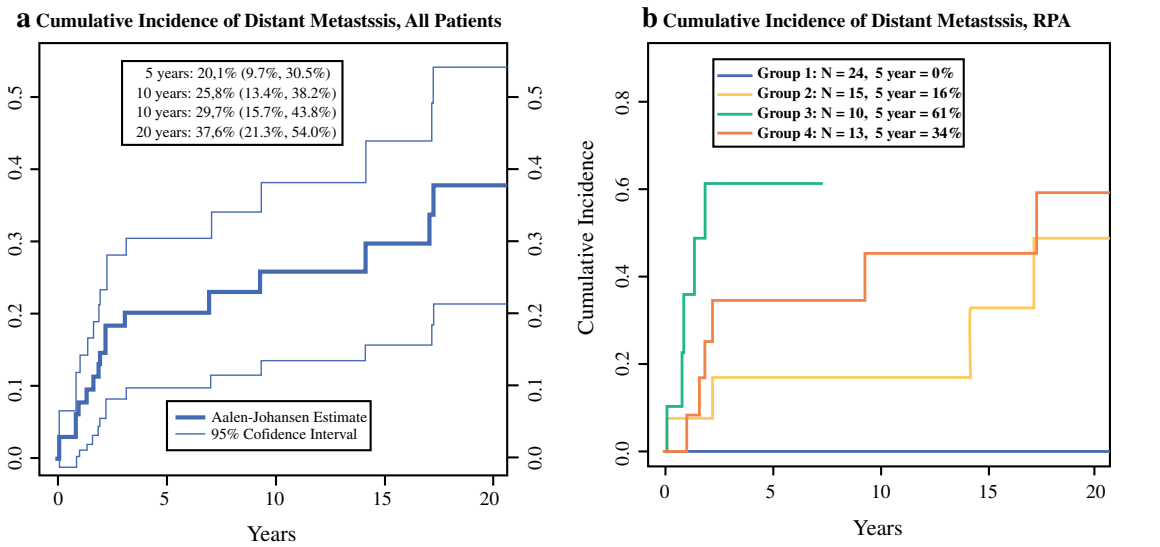
Overall survival from date of initial surgery was estimated using the Kaplan–Meier method. The effect of DM on OS was assessed by treating the survival data for patients who developed DM as left truncated for the Kaplan–Meier estimate and by treating the development of DM as a time-dependent indicator variable in a Cox proportional hazards regression model.

Statistical analysis was performed using S+Version 8.0 for Windows (TIBCO Software Inc) and R version 3.1.1 (R Foundation for Statistical Computing). Statistical significance was assumed for p values < 0.05.

RESULTS

Of the 75 patients with PC, 17 (22.7%) developed DM during the surveillance period with a median follow-up of 77 months. Nineteen (25.3%) patients had their initial surgery at MDACC, whereas 56 (74.7%) had their index surgery before referral. There were 38 males (50.1%). The median age at the time of first surgery was 51 years (range 43–61). Median tumor size was 2.7 cm (range 2.0–3.5), whereas median preoperative calcium levels and preoperative PTH levels were 13.4 mg/dL (range 11.85–14.6) and 620 pg/mL (range 256–1407) respectively. The cumulative incidence of DM for the entire cohort was 20.1, 25.8, and 37.6% at 5, 10, and 20 years, respectively (Fig. 2a). Stratification of preoperative serum PTH levels into terciles to predict the cumulative incidence of DM on univariate analysis did not show statistical significance (Table 1). Age was dichotomized into $\leq$ 65 or $>$ 65 years, but the cumulative incidence of DM was not statistically significant between the two groups. Neither sex, preoperative serum calcium levels, race, elevated serum calcium levels at 6 months after surgery, nor the extent of resection was associated with increased cumulative incidence of DM on





Group 1: size < 3.2 cm, serum Ca < 13.7 mg/dL; Group 2: size < 3.2 cm, serum Ca >13.7 mg/dL; Group 3: size > 3.2 cm, Age <47.5 years; Group 4; size > 3.2 cm, Age > 47.5 years

FIG. 1 Schema of recursive partitioning to determine groups at highest risk for distant metastasis

FIG. 2 **a** Cumulative incidence of distant metastasis for all patients with PC treated or surveilled at MDACC from 1980 to 2017 (n = 75). **b** Cumulative incidence of distant metastasis by recursive partitioning for patients with PC treated or surveilled at MDACC from 1980 to 2017 (n = 62)

univariate analysis (Table 1). Only tumor size stratified into terciles was associated with statistically significant increased cumulative incidence of DM at 5 and 10 years (Table 1). Patients with tumor size in the lowest tercile had the lowest cumulative incidence of DM of 6% at 5 years compared with 44% for patients in the third tercile.

Distant metastasis occurred in the lung, mediastinum, bone, and liver (Table 2). Among the cohort who developed DM, the median time to first DM was 23 months. The lung as a single site was the most common site of DM followed by bone (Table 2). All four patients with bone metastasis have since expired with an average time to death

TABLE 1 Univariate results of cumulative incidence for the development of distant metastasis for 75 patients with PC treated or surveilled at MDACC from 1980 to 2017

Variable	Minimum and maximum values	Group	*N*	5-year cumulative incidence for developing distant metastases [%, (95% CI)]	10-year cumulative incidence [%, (95% CI)]	*p* value
Preop-PTH (pg/ml)	72, 7200	All	75	20 (10, 30)	26 (13, 38)	–
		1st Tercile (72–351.2)	20	17 (4, 38)	17 (4, 38)	0.49
		2nd Tercile (351.2–1200)	22	19 (4, 42)	19 (4, 42)	
		3rd Tercile (1200–7200)	19	19 (4, 42)	30 (7, 56)	
Sex	–	Male	38	23 (10, 40)	30 (13, 50)	0.4
		Female	37	17 (6, 32)	21 (8, 38)	
Age (year)	13, 82	≤ 65	65	19 (10, 31)	23 (12, 36)	0.38
		> 65	10	26 (3, 60)	–	
Highest Ca	9.7, 24.0	≤ 15	50	22 (11, 37)	22 (11, 37)	0.22
Preop (mg/dL)		> 5	13	8 (0, 30)	24 (2, 59)	0.34
Type of resection	–	Parathyroidectomy	35	15 (4, 32)	28 (10, 49)	–
		En bloc (Parathyroidectomy + lobectomy or thyroidectomy)	21	10 (2, 29)	10 (2, 29)	
		En bloc + level VI dissection[b]	15	48 (15, 76)	48 (15, 76)	
		Modified lateral neck dissection	4	25 (0, 71)	–	
Tumor size (cm)	1.1, 8.0	1st Tercile (1.1–2.3)	24	6 (0, 23)	15 (2, 40)	0.01
		2nd Tercile (2.3–3.2)	23	10 (2, 28)	10 (2, 28)	
		3rd Tercile (3.2–8)	21	44 (21, 66)	54 (25, 76)	
Elevated Ca at 6 months[a]	–	Yes	12	18 (2, 44)	18 (2, 44)	0.47
		No	62	21 (11, 34)	25 (13, 40)	
Race	–	Other	25	15 (2, 40)	15 (2, 40)	0.85
		White	50	22 (1, 34)	28 (15, 42)	

p value is from Gray's test for differences in cumulative incidence

[a]Elevated calcium at 6 months refers to serum calcium levels ≥ 10.2 mg/dL

[b]En bloc level VI dissection includes thyroid lobectomy or total thyroidectomy

of 27.6 months, whereas 8 of 12 patients with metastasis to the lungs are deceased with average time to death of 38.4 months (Table 2). The median follow-up time for patients with DM was 59 months. The average age at death for patients with bone metastasis and lung metastasis was similar 60 (range 49–71) compared with 59.8 (range 38–81) years, respectively. Of the 17 patients who developed DM, 13 (76.5%) occurred within 5 years from date of diagnosis. Four patients had recurrences at 10, 15, 17, and 18 years after initial diagnosis whose preoperative PTH levels were 1256 pg/mL, 7200 pg/mL, 620 pg/mL, and 1707 pg/mL respectively. These late recurrences had preoperative calcium levels that ranged from 15.3 to 18 mg/dL.

A multivariable, Fine-Gray proportional hazard regression analysis found tumor size greater than 3.2 cm to be predictive of increased risk of DM (HR = 3.51; 95% CI 1.04–11.91; $p = 0.044$). RPA identified four groups that differed with respect to risk of DM (Fig. 2b). The cohort with the lowest cumulative incidence of DM had a tumor size less than 3.2 cm and serum calcium levels less than 13.7 mg/dL, whereas the group with a tumor size greater than 3.2 cm and age less than 47.5 years had the highest cumulative incidence of DM ($p = 0.0005$; Fig. 2b).

The 5-, 10-, and 20-year OS for the entire cohort was 78, 61, and 39% respectively with a median OS of 17 years (95% CI 10 years to maximum not reached; Fig. 3a). The median OS for patients who developed DM was 40 months (95% CI 16 months to maximum not reached; Fig. 3b). Among the 12 patients with DM who are since deceased, the median time to death after DM was 25 (range 7.4–99.2) months. At 5 years, the OS for patients who developed DM within the first 5 years was 16% (95% CI 3–91%) compared with 87% (95% CI 77–97%) for those without DM (Fig. 3b).

There were 50 patients with documented capsular invasion and 24 patients in which capsular invasion was not reported. Lymphovascular invasion was present in 25 patients, absent in 26 patients, and not reported in 24 patients. Nineteen patients had ≥ 1 mitosis, 33 had < 1 mitosis, and mitotic count was unknown in 23 patients. The Ki-67 index was known in only 15 patients.

TABLE 2 Clinicopathologic course of patients with parathyroid carcinoma who developed distant metastases (n = 17)

Patient ID	Site of metastasis	Time from diagnosis to first distant metastasis (months)	Time from first metastasis to death (months)	Cause of death
1	Bone	38.8	40.4	Died of disease
2	Bone	1.1	48.5	Died-Unknown
3	Bone and lung	12.1	7.4	Died-Unknown
4	Bone	17.3	14.1	Died of disease
5	Mediastinum	210.3	33.0	Died of disease
6	Lung	5.5	7.8	Died of disease
7	Lung	86.3	16.4	Died of disease
8	Lung	27.2	NA	Alive
9	Lung	23.1	NA	Alive
10	Lung	27.1	NA	Alive
11	Lung	210.9	NA	Alive
12	Lung and liver	10.8	72.1	Died of disease
13	Lung	20.0	17.0	Died of disease
14	Lung	1.2	9.0	Died-Unknown
15	Lung	114.2	99.2	Died of disease
16	Lung	173.5	78.1	Died of disease
17	Liver	23.4	NA	Alive

1 month = 30 days

Twenty patients with metastatic disease and/or refractory hypercalcemia received systemic therapy, which included one or a combination of the following agents: Taxol, Ifosfamide, Carboplatin, Sensipar, Zometa, Sandostatin, Sirolimus, Cetuximab, Xgeva, Sorafenib, Pamidronate, Lenvatinib, Pembrolizumab, Everolimus, Vandentanib, Docetaxel, Gemcitabine, Erlotinib, Adriamycin, Lenalidomide. There were 18 patients treated with adjuvant XRT to the neck. The hazard ratio for the effect of systemic therapy and XRT on overall survival are 1.5 (95% CI 0.7–3.2, p = 0.34) and 1.4 (95% CI 0.6–3.1, p = 0.42) respectively.

DISCUSSION

Refractory hypercalcemia and its associated toxicities decrease the quality of life and survival among patients with metastatic PC. To our knowledge, this is the largest

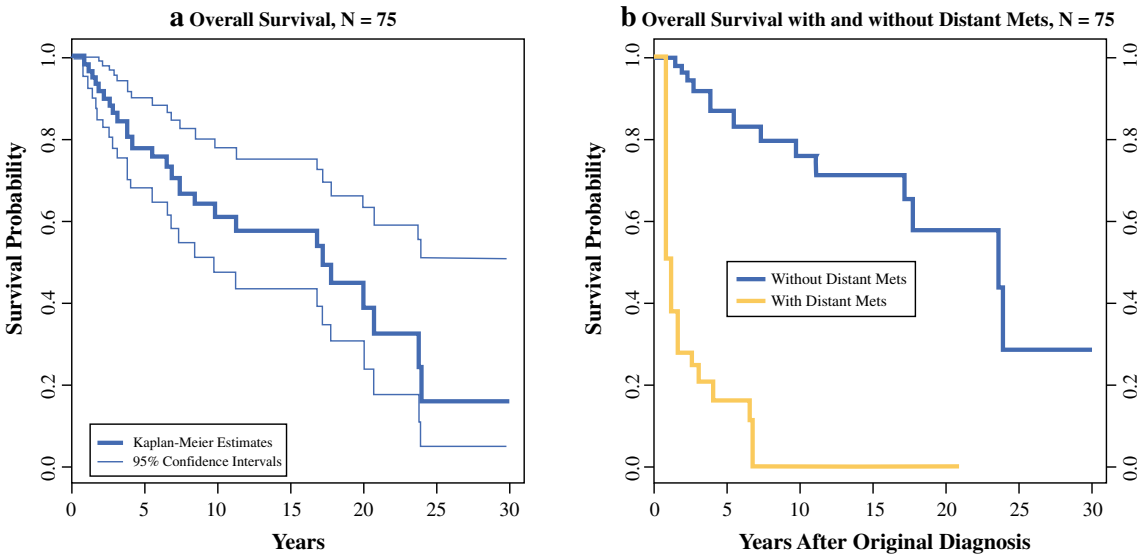


FIG. 3 **a** Overall survival (OS) for patients with PC treated or surveilled at MDACC from 1980 to 2017 (n = 75, deaths = 25). **b** Overall survival (OS) by distant metastasis status for patients with PC treated or surveilled at MDACC from 1980 to 2017 (n = 75, deaths = 25)

single institutional study to report on the risk of DM and its impact on OS for patients with PC. We found a 5-year OS of 16% for patients who developed DM compared with a 5-year OS of 87% for patients without DM and a HR for death of 9.6 (95% CI 4.2–22.3; $p < 0.0001$) associated with DM. RPA showed that patients with tumor size greater than 3.2 cm and age less than 47.5 years had the highest cumulative incidence of DM. Patients with late DM were in the highest category for preoperative PTH and calcium levels.

Few studies on PC have reported on the incidence of DM. In a retrospective review of 224 patients in the SEER database from 1988 to 2003, only 10 patients had DM.[5] An updated review of SEER database from 1988 to 2010 reported 7 cases of DM among a cohort of 405 patients.[9] Xue et al. found 3 cases of DM among a cohort of 40 patients from 2000 to 2015, while the Spanish Parathyroid Carcinoma Study Group (SPCSG) observed 3 cases of DM among 62 patients from 1980 to 2013.[10,11] In contrast, there were 17 patients who developed DM in our cohort of 75 patients between 1980 to 2017. The cumulative incidence of DM continued to increase with time with an observed rate of 37.8% at 20 years. The smaller number of cases ($n = 10$) in the SEER database compared with 17 in our study may be secondary to limited follow-up information of recurrences in cancer registries and possible challenges in the diagnosis of PC with possible inclusion of patients with atypical parathyroid neoplasms.[12,13]

There have been several conflicting reports on the role of tumor size as a prognostic factor in patients with PC.[4,5,9,14,15] Asare et al. found a 2% increase in the risk of death on multivariable analysis of patients with PC.[4] Among 405 patients with PC in the SEER database, tumor size ≥ 3 cm was associated with increased risk of death from PC, HR 5.35 (95% CI 1.47–19.5), $p = 0.01$.[9] Lee et al. categorized size into 0–1.9, 2–3.9, and ≥ 4 and found no differences in prognosis.[1] Talat et al. found size > 3 cm to increase the risk of recurrence but was not prognostic for death.[14] This study found the cumulative incidence of DM to be higher in patients in the upper tercile for tumor size (3.2–8 cm). Additionally, tumor size > 3.2 cm was associated with a greater than threefold increase in the risk of DM. The predictive effect of tumor size on DM was further supported by results of our RPA where patients with tumor size > 3.2 cm and age younger than 47.5 years had a 61% cumulative incidence of DM.

The study from SPCSG found margin status, tumor rupture, and degree of intraoperative PTH drop to be predictive of recurrence.[11] In a previous report, vascular invasion, age > 65 years, and calcium > 15 mg/dL were found to be predictive of any recurrence (distant or locoregional).[7] In contrast to this current study, which looked at DM only, the SPCSG study had three patients with DM, whereas the study by Silva-Figueroa et al. had any recurrence as the outcome of interest. Distinguishing between the risk for locoregional versus DM is important as re-resection of locoregional recurrence is usually an option but not readily feasible for DM. Additionally, the relatively poor survival of patients with DM compared with locoregional recurrence calls for a tailored surveillance strategy based on risks for distant recurrence.[1,2]

Most studies have had a very small number of patients with DM and thus did not distinguish between locoregional recurrence and DM during analyses. Some investigators have found that recurrence is associated with an increased risk of death. One study reported an OR for death of 7.76 (95% CI 1.5–40.1; $p = 0.014$) for patients with any recurrence, whereas another found a HR for death of 11.6 (no CI reported, $p < 0.0001$) for DM.[5,10] Similarly, a review of 37 patients from the UCSF from 1966 to 2009 found an increased risk of death for patients with DM, HR 3.5 (95% CI 1.6–7.64).[2] In an analysis of 405 patients with PC, the HR for disease-specific death for 7 patients with DM was 45.1 (range 2.7–77.6; $p < 0.01$).[9] Our results confirm that patients who develop DM have markedly decreased survival compared with those without DM. The median time to death among the cohort with bone metastasis was shorter than those with metastasis to other sites suggesting that bony metastasis may portend worse survival.

Limitations include the retrospective nature of this study and the limited number of events for correlation. There was not enough data on microscopic features to be able to assess their effect on distant metastases in this cohort. Subgroup analysis could not be performed for disease specific analysis, such as survival for cohorts based on site of DM. Additionally, only 19 patients had their index surgery at our institution and therefore limits our ability to draw conclusions on the impact of intraoperative suspicion for parathyroid carcinoma on the extent of surgical resection.

CONCLUSIONS

Compiling 37 years of patient management from a single institution, we found that patients with metastatic PC have significantly decreased survival compared with those without DM and that the lung is the most common site of DM. Patients with bony metastasis may have shorter survival compared with other sites of metastases. Our results support the use of Tumor, Node, Metastasis (TNM) as meaningful in PC as incorporated in the American Joint Committee on Cancer (AJCC) 8th Edition Cancer Staging System, with DM reflecting the highest risk factor impacting survival. Close surveillance of patients with PC is warranted in the long-term. While acknowledging

sample size limitations, our current results identify patients younger than 47.5 years old with tumors larger than 3.2 cm as having the highest cumulative incidence of DM. Closer surveillance should be considered in this cohort. The three cases of late metastasis (> 10 years after diagnosis) that were identified highlight the need for life-long follow-up in these patients. Future work will seek to assess the mutational profiles of patients with PC to look for molecular predictors of metastasis, with focus on potential targets for salvage therapies.

DISCLOSURES All authors have no financial disclosures.

REFERENCES

1. Lee PK, Jarosek SL, Virnig BA, et al. Trends in the incidence and treatment of parathyroid cancer in the United States. *Cancer*. 2007;109:1736–41.
2. Harari A, Waring A, Fernandez-Ranvier G, et al. Parathyroid carcinoma: a 43-year outcome and survival analysis. *J Clin Endocrinol Metab*. 2011;96:3679–86.
3. Sandelin K, Auer G, Bondeson L, et al. Prognostic factors in parathyroid cancer: a review of 95 cases. *World J Surg*. 1992;16:724–31.
4. Asare EA, Sturgeon C, Winchester DJ, et al. Parathyroid carcinoma: an update on treatment outcomes and prognostic factors from the National Cancer Data Base (NCDB). *Ann Surg Oncol*. 2015;22:3990-5.
5. Busaidy NL, Jimenez C, Habra MA, et al. Parathyroid carcinoma: a 22-year experience. *Head Neck*. 2004;26:716–26.
6. DeLellis R, Heitz PU. Pathology and genetics of tumours of endocrine organs. Lyon: IARC Press; 2004.
7. Silva-Figueroa AM, Hess KR, Williams MD, et al. Prognostic scoring system to risk stratify parathyroid carcinoma. *J Am Coll Surg*. 2017;224:980–7.
8. Zhang H, Singer B. Recursive partitioning in the health sciences. New York: Springer; 1999.
9. Hsu KT, Sippel RS, Chen H, et al. Is central lymph node dissection necessary for parathyroid carcinoma? *Surgery*. 2014;156:1336–41; discussion 1341.
10. Xue S, Chen H, Lv C, et al. Preoperative diagnosis and prognosis in 40 parathyroid carcinoma patients. *Clin Endocrinol (Oxf)*. 2016;85:29–36.
11. Villar-del-Moral J, Jimenez-Garcia A, Salvador-Egea P, et al. Prognostic factors and staging systems in parathyroid cancer: a multicenter cohort study. *Surgery*. 2014;156:1132–44.
12. In H, Bilimoria KY, Stewart AK, et al. Cancer recurrence: an important but missing variable in national cancer registries. *Ann Surg Oncol*. 2014;21:1520–9.
13. Christakis I, Bussaidy N, Clarke C, et al. Differentiating atypical parathyroid neoplasm from parathyroid cancer. *Ann Surg Oncol*. 2016;23:2889–97.
14. Talat N, Schulte KM. Clinical presentation, staging and long-term evolution of parathyroid cancer. *Ann Surg Oncol*. 2010;17:2156–74.
15. Shaha AR, Shah JP. Parathyroid carcinoma: a diagnostic and therapeutic challenge. *Cancer*. 1999;86:378–80.