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The Rising Incidence Of Small Endocrine Cancers In The United States: Effects On Surgical Therapy In An Age Of Imaging

Eric Kuo

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Eric James Kuo

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ABSTRACT

The Rising Incidence of Small Endocrine Cancers in the United States: Effects on Surgical Therapy in an Age of Imaging

Eric J. Kuo[1], Ronald R. Salem[1], Sanziana A. Roman[2], Julie A. Sosa[2], [1]Department of Surgery, Yale School of Medicine, New Haven, CT, [2]Department of Surgery, Duke University School of Medicine, Durham, NC

The increasing utilization of imaging technology has led to the diagnosis of cancers earlier in their clinical course. When small tumor size is coupled with relatively indolent histology, excellent oncologic outcomes require the risks of surgery to be carefully considered. However, characteristics and outcomes of small cancers of the thyroid and endocrine pancreas remain poorly defined, and evidence to guide their management is sparse.

Patients with tall cell (mTCV) and diffuse sclerosing (mDSV) variants of papillary thyroid microcarcinoma (mPTC), follicular (mFTC) and Hurthle cell microcarcinoma (mHCC), parathyroid carcinoma (PC) and pancreatic neuroendocrine tumors (PNETs) ≤ 2 cm in size were selected from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, 1988-2009. Data regarding incidence, characteristics, and outcomes were extracted and analyzed with χ^2 tests, ANOVA, the Kaplan Meier method, log-rank tests, and Cox proportional hazards.

97 mTCV, 90 mDSV, 371 mFTC, 193 mHCC, and 263 PNETs ≤ 2 cm were identified. The incidence of mTCV, mDSV, and mFTC remained stable throughout the study period, while the incidences of mHCC and PNETs ≤ 2 cm increased by 400% and 710% over the study period, respectively. Although survival was similar, mTCV and mDSV were associated with higher rates of extrathyroidal extension and nodal metastasis in comparison to classic mPTC. mFHCC had over eight times the rate of distant metastases compared to mPTC and was associated with compromised 10-year disease specific survival (95.4 vs. 99.3%, P<0.001). Rates of extrapancreatic extension, nodal metastasis, and distant metastasis in PNETs ≤ 2 cm were 17.9%, 27.3%, and 9.1%, respectively.

The incidence of many endocrine cancers is increasing, presumably due to increased detection. All histologies studied were capable of exhibiting aggressive behavior despite small tumor size. Further studies that specifically examine the risks and benefits of surgical therapy in small tumors may clarify future surgical decision making.

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INTRODUCTION

While advances in molecular biology have revolutionized how we understand and treat cancer, and targeted pharmacologic therapy has dramatically changed outcomes for patients with breast cancer, lung cancer, and leukemia among others, surgery remains the mainstay of cancer therapy with curative intent and remains an essential component of a patient's hope for cure for those who present with localized disease.[1-3] While the goal of cancer surgery, namely the total resection of disease, has remained unchanged, trends in the manner in which cancer presents itself has had dramatic impacts on the extent of surgical resection necessary to maintain acceptable oncologic outcomes.

One of the most dramatic instances of this trend has been in the field of breast surgery. At the turn of the century, William Halsted established radical mastectomy as the standard of care for patients with breast cancer. A disfiguring procedure that involved resection of the entire breast along with the overlying skin, pectoralis major and minor muscles, and axillary lymphadenectomy, the Halsted radical mastectomy was developed in an era where many patients presented with bulky disease.[4] With the widespread use of screening mammography in the 1980s, however, breast cancer is being detected earlier in its clinical course and in 1985, a randomized clinical trial, the NSABP B-04, proposed that equivalent outcomes could be achieved with simple mastectomy.[5,6] Further still, the NSABP B-06 showed that in stage I and II breast cancers, lumpectomy in combination with radiation could also safely be performed without compromising oncologic outcomes.[7] Today, approximately 75% of patients with stage I or II breast cancer choose breast conserving surgery.[8]

The trend towards earlier detection of cancers is not limited to the breast. An analysis of cancer incidence rates in the United States from 1999-2008 revealed that the greatest increases in incidence in pancreatic, liver, thyroid, renal cancer, and melanoma have occurred in localized tumors.[9] Whereas the study of breast cancer has been facilitated by the social and statistical power afforded by its place as the most incident cancer in women, resulting in practice guidelines supported by randomized controlled trials, numerous barriers exist towards the optimal study of thyroid and pancreatic malignancies. The rarity of pancreatic cancer necessitates a collaborative multi-institutional effort towards the performance of randomized controlled trials. This need is only magnified with the more uncommon subtypes of pancreatic cancer such as pancreatic neuroendocrine tumors (PNETs), where the majority of evidence for management comes from institutional series. In differentiated thyroid cancers, almost universally excellent outcomes obscure the study of patients with compromised outcomes, rendering randomized clinical trials sometimes unfeasible.[10] Nevertheless, the possibility that small, localized tumors represent an increasing proportion of tumors as a whole deserves exploration, and a more precise characterization of these patients and their associated outcomes is necessary. This study seeks to accomplish these goals with respect to endocrine cancers of the thyroid and pancreas.

Thyroid cancer

The incidence of thyroid cancer has been rapidly increasing over the last 22 years, and notably, the largest rise in incidence has been observed in small tumors less than 1 cm in size, also referred to as microcarcinomas.[11] Much of this has been attributed to

increased detection, especially with respect to thyroid ultrasound.[10,12] To date, most of the research on thyroid microcarcinoma has focused on the papillary histology, which is the most common form of thyroid cancer. Papillary thyroid microcarcinoma (mPTC), defined as papillary thyroid carcinoma (PTC) ≤ 1cm in size, is rapidly rising in incidence, accounting for 49% of the increase in PTC incidence from 1973 to 2002; currently it represents 43% of PTC in patients older than 45 years.[13,14] These patients generally have an excellent prognosis, with 10- and 15- year disease specific survival in excess of 99%.[15]

Because of the excellent outcomes in these patients, the decision to expose patients to the risk of thyroid surgery has to be carefully considered. In Japan, out of 1,395 patients who were offered surgery or observation for mPTC, 340 chose observation. With a mean follow-up of 4 years, only 15.9% of observed tumors demonstrated enlargement, emphasizing the indolent nature of these tumors and calling into question the benefits of routine resection.[16]

However, a subpopulation of patients with mPTC carry increased risk of mortality and benefit from total thyroidectomy.[15] While risk factors such as age, race, nodal metastases, extrathyroidal invasion, and distant metastasis have helped characterize this population, the search continues for additional factors that can be used to identify patients with thyroid microcarcinoma who carry a poor prognosis.[15,17] In thyroid cancers of all sizes, both aggressive variants of PTC as well as the other forms of differentiated thyroid carcinoma (DTC), including follicular (FTC) and Hurthle cell (HCC) carcinomas, have been shown to have compromised outcomes in comparison to PTC. However, in these

histologies, tumors ≤ 1cm in size have not been exclusively studied, and therefore there is a paucity of evidence with which to guide their treatment.

Aggressive variants of papillary thyroid microcarcinoma

Several histologic variants of PTC have been identified as having aggressive behavior in comparison to classic PTC, including diffuse sclerosing (DSV) and tall cell variants (TCV). First described in 1985, DSV is characterized by papillary morphology, diffuse involvement of the thyroid gland, prominent fibrosis, abundant psammoma bodies, squamous metaplasia, and lymphocytic infiltration easily confused with thyroiditis.[18-20] It accounts for approximately 2-6% of PTC, classically occurs in young women, and is reported to have increased rates of multifocality, bilaterality, extrathyroidal extension, recurrence and nodal/distant metastasis.[20-29]

TCV, first described in 1976, accounts for 3-12% of all PTC, and is characterized by a population of cells at least twice as tall as they are wide, composing 30-70% of total tumor cells.[20,30-34] TCV has been reported to be larger than classic PTC on average, with higher rates of bilaterality, multifocality, extrathyroidal extension, recurrence, lymph node/distant metastasis, and decreased survival.[24,29,35-42]

While it appears clear that DSV and TCV are aggressive, the extent to which DSV ≤ 1cm (mDSV) and TCV ≤1cm (mTSV) exhibit aggressive behavior remains an open question, and the optimal management of these tumors is currently unclear. Studies of aggressive variants of PTC largely consist of case reports and single-center case series, and two population-level studies that have been performed on the topic of DSV and TCV do not specifically address tumors ≤1cm in size.[29,42] Similarly, in studies of mPTC, the

inclusion of aggressive morphologies is either variable or unclear, and it appears that no subset analysis of aggressive variants has been undertaken.[15,17,43]

This study represents the first population-level analysis of aggressive variants of mPTC in which the incidence, demographic, clinical, and pathologic characteristics of mDSV and mTCV are compared with classic mPTC.

Follicular and Hurthle cell microcaricnoma

Follicular thyroid carcinoma (FTC) and Hurthle cell carcinoma (HCC) arise from the follicular cells of the thyroid and account for approximately 10% and 4% of thyroid malignancies, respectively.[44] They are more likely than papillary thyroid carcinoma (PTC) to present with distant metastases, but nodal metastases are rare, which is consistent with the likely hematogenous dissemination of these tumors.[45] Patients with a finding of follicular or Hurthle cell neoplasm on cytology generally have a 20-30% risk of malignancy, and definitive diagnosis requires histopathologic examination after surgical excision documenting capsular or vascular tumor invasion.[46,47]

Follicular and Hurthle cell carccinomas less than 1 cm in size (mFTC and mFHCC, respectively) however, have not been exclusively studied. Just as with aggressive variants of papillary microcarcinoma, it is unknown whether these cancers have comparable outcomes, and evidence to guide their management is scarce. Therefore, their natural history is poorly understood and optimal treatment remains unclear.

This study is the first to focus on follicular and Hurthle cell microcarcinoma (mFHCC) and examine the incidence, characteristics, and outcomes of mFHCC in comparison with mPTC. We also evaluate the independent effect of tumor histology on

survival, identify prognostic factors associated with disease-specific mortality, and determine whether patients benefit from total thyroidectomy and radioactive iodine (RAI).

Pancreatic neuroendocrine tumors

Pancreatic neuroendocrine tumors (PNETs) are rare pancreatic tumors that account for < 3% of pancreatic neoplasms.[48-50] PNETs may be functional or non-functional, and multiple grading systems have been proposed to predict their clinical behavior. According to the WHO classification, tumors can be designated as benign, of uncertain malignant potential, or malignant based on the presence of frank invasion or metastasis, vascular or perineural invasion, size, and proliferative activity.[51] Hochwald, et al. proposed a different system, classifying PNETs as low or intermediate grade based on the presence of necrosis and proliferative activity alone.[52] Regardless of the system used, however, the clinical behavior of PNETs remains unpredictable. Because tumors initially classified as benign may later display malignant behavior, there is a growing sentiment that all tumors greater than 0.5 cm in size have malignant potential.[53]

The increasing incidence of PNETs of all sizes over the last two decades is well-documented.[54] With increasingly sophisticated imaging technology, the incidental finding of small tumors has become more frequent. However, the incidence of small PNETs in the United States has yet to be reported on the population-level. Furthermore, studies of clinical outcomes in small PNETs have been limited to institutional series with mixed conclusions. Some authors advocate resection of all incidentally discovered, non-functioning PNETs, while others propose observation to be a reasonable alternative.[55,56]

None have been able to analyze predictors of survival due to small sample size.[56,57] Additionally, the significance of nodal metastasis in small PNETs is unclear. Nodal metastasis has not been shown to be significant in multivariate analyses of survival in population-level studies.[58,59] However, both AJCC and ENETS systems take nodal metastasis into account when staging PNETs and have been validated in PNETs of all sizes.[60,61] Reported rates of nodal metastasis in PNETs ≤ 2 cm in size are variable, at 0%, 9%, and 26%.[56,60,62]

To our knowledge, this study is the first to exclusively analyze small PNETs on a population-level and examine incidence in addition to demographic, clinical, and pathologic characteristics of PNETs ≤ 2 cm in a surgical population. Our purpose is to determine the extent of increase in incidence of small PNETs in the United States, evaluate predictors of survival, and clarify the frequency and significance of nodal metastases in PNETs ≤ 2 cm.

METHODS

Data Source and Study Participants

The data source for this study was the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, which provides population-based data on cancer incidence and survival from 18 registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska, Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia) and represents 28% of the United States population.[63]

Patients diagnosed with mTCV, mDSV, mFTC, mHCC, and mPTC, from 1988 to 2009 were selected from all 18 registries using ICD-O-3 codes 8350 (DSV), 8344 (TCV), 8330-8332 (mFTC), 8290 (mHCC), and 8050, 8260, 8341 (mPTC), in combination with "Extent of Disease" and "Collaborative stage" variables designating tumors ≤ 1cm in size. Of note, the ICD-O-3 code 8344 does not distinguish between tall cell and columnar cell variants of PTC, likely due to ambiguities in definition.[64,65] Because histology has not been shown to be a significant prognostic factor distinguishing the two entities, mFTC and mHCC were compared to mPTC as one group.[66]

Patients with PNETs diagnosed from 1988 to 2009 were selected from all 18 registries using ICD-O-3 codes 8150 (islet cell carcinoma), 8246 (neuroendocrine carcinoma), and 8240-8249 (carcinoid tumor). Functional PNETs (insulinomas, etc.) were excluded from our study, as were mixed islet cell and exocrine adenocarcinomas. Because the SEER database is restricted to tumors with an ICD-O-3 behavior code of 2 (in situ) or 3 (malignant), PNETs that were considered benign were unable to be included in our study. Our study was restricted to patients ≥ 18 years of age whose data were informed by active follow-up.

Incidence data were obtained over the period of 1988-2009 from SEER 9 registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah), which offers the most complete incidence data for this time period. Because TCV was first collected in the SEER database in 2001, incidence analysis of mTCV and mDSV was restricted to the years 2001-2009 to allow

for comparison. Rates were age-adjusted using the 2000 U.S. standard population. Annual percentage changes (APC) were calculated.

Demographic variables of interest included patient age at diagnosis, gender, and race. Clinical variables of interest included surgical therapy, lymph node examination, radiation therapy, and survival status as of December 31, 2009. Survival time was calculated as time in years from diagnosis until death, date last known to be alive, or December 31, 2009, whichever came first. Overall and disease-specific survival rates were calculated. Pathologic variables of interest included tumor size, multifocality (for thyroid cancers), extraparenchymal extension, nodal metastasis, and distant metastasis. Extraparenchymal extension was defined as tumor invasion beyond the thyroid capsule for thyroid cancers or into peripancreatic tissue or adjacent organs or vessels for PNETs. Location of nodal metastasis in thyroid carcinomas were grouped corresponding to American Joint Committee on Cancer (AJCC) stages N1a (level VI) and N1b (levels I, II, III, IV, V, VII).

With respect to surgery for PNETs, the SEER database did not distinguish between enucleation and partial pancreatectomy prior to 1997, and these patients were grouped under “enucleation/partial pancreatectomy, not otherwise specified.” Extrapancreatic extension was defined as tumor extension into peripancreatic tissue or adjacent organs or vessels. Pathology reports from patients diagnosed with non-functioning neuroendocrine tumors of the pancreas from 1996-2012 were reviewed after identification through keyword search in an institutional pathology database at Yale-New Haven Hospital. Data regarding relevant clinical and pathologic variables were collected.

Statistical Analysis

Summary statistics were used to describe baseline characteristics. Chi square tests and analysis of variance were used to analyze categorical and continuous variables, respectively. Fischer's exact test was used for analyze categorical variables with expected values less than 5. Survival was analyzed using the Kaplan-Meier method, and the log rank test was used to determine differences in survival that were statistically significant. Cox proportional hazards and stepwise binary logistic regression were used to identify factors independently associated with survival, extrathyroidal extension, nodal metastasis, and distant metastasis. Variables with a level of significance of $P<0.1$ on univariate analysis were included in the multivariate analysis. All tests were two-sided, and $P<0.05$ was considered statistically significant.

Incidence and trend analysis were performed by SEER*Stat version 8.0.1 obtained from SEER (Bethesda, MD). All other analysis was performed with SPSS version 19 (SPSS, Inc., Chicago, IL). Because SEER data is publicly available and institutional data was recorded without identifiers, our study was deemed to be exempt from institutional review board approval.

RESULTS

Aggressive variants of papillary thyroid microcarcinoma

There were 90 cases of mDSV, 97 cases of mTCV, and 18,260 cases of classic mPTC diagnosed during the study period. Patients with mTCV were followed for up to 9 years, while mDSV and classic mPTC patients were followed for up to 22 years. Mean

follow-up for mDSV, mTCV, and classic mPTC was 7.0 years, 3.8 years, and 5.3 years, respectively.

Incidence

Incidence of classic mPTC increased from 1.42 per 100,000 in 2001 to 3.47 per 100,000 in 2009, representing an annual percentage change (APC) of +11.8% (P_{trend}<0.001). mTCV increased in incidence from 0.010 to 0.019 per 100,000 (APC +5.7%, P_{trend}=0.153) and mDSV decreased in incidence from 0.0075 to 0.0067 per 100,000 (APC -4.7%, P_{trend}=0.315).

Characteristics

Clinical and pathologic characteristics are summarized in Tables 1 and 2. There were no significant demographic differences between patients with mDSV and mTCV compared to classic mPTC with respect to age, gender, or race. Patients with mTCV had lymph nodes examined more frequently compared to mPTC (63.9 % vs. 39.2%, P<0.001). Aggressive variants were more likely to receive radioiodine ablation (RAI) (40.0% mDSV vs. 39.2% mTCV vs. 29.1% mPTC, P_{mDSV}=0.013, P_{mTCV}<0.001); however, they were not statistically more likely to receive total thyroidectomy versus lobectomy compared to classic mPTC (70.0% mDSV vs. 78.4% mTCV vs. 71.8% mPTC, P_{mDSV}=0.655, P_{mTCV}=0.311).

Compared to classic mPTC, mDSV had significantly higher rates of extrathyroidal extension (6.1% vs. 13.3%, P=0.004) and nodal metastasis (33.1% vs. 57.1%, P=0.007). In patients with nodal metastasis, the ratio of N1a vs. N1b metastases was similar (50% vs. 50% mDSV, 59.0% vs. 41.0% mPTC, P=0.694). mDSV also tended

to be larger (5.8 mm vs. 5.3 mm, P=0.165), however the difference was not statistically significant. There were no differences between mDSV and mPTC with respect to rates of multifocality (33.3% vs. 14.0%, P=0.926) and distant metastasis (0.0% vs. 1.3%, P=0.519).

The mTCV tumors tended to be larger on average compared to mPTC (7.1 mm vs. 5.3 mm, P<0.001), with significantly higher rates of multifocality (47.2% vs. 34.0%, P=0.018) and extrathyroidal extension (27.8% vs. 6.1%, P<0.001). Patients with mTCV also had higher rates of nodal metastasis (43.5% vs. 33.1%, P=0.081) and over four times the rate of distant metastasis compared to those with mPTC (2.1% vs. 0.5%, P=0.076). In patients with nodal metastasis, patients with mTCV tended to metastasize to the central compartment more frequently than those with mPTC (N1a vs. N1b, 76.5% vs. 23.5% mTCV, 59.0% vs. 41.0% mPTC, P=0.145), although the trend was not statistically significant.

Survival

All-cause mortality occurred in 3.3% of mDSV (n=3), 1.0% of mTCV (n=1), and 3.0% of classic mPTC (n=541), while disease specific deaths occurred in 1.1% of mDSV (n=1), 1.0% of mTCV (n=1), and 0.4% (n=69) of classic mPTC. 10-year disease specific survival for mDSV, mTCV, and classic mPTC was 100.0%, 98.5%, and 99.4% respectively, and univariate analysis of survival revealed no association between histologic variant and overall or disease specific survival (Figures 1-2). Due to the limited number of deaths in the mTCV and mDSV cohorts, multivariate analysis could not be performed.

Predictors of extrathyroidal extension and cervical lymph node metastasis

No statistically significant predictors of extrathyroidal extension or cervical lymph node metastases in mDSV were observed. In mTCV, extrathyroidal extension was independently associated with size >7mm (odds ratio [OR] 4.4, 95% CI 1.5-13.6) and nodal metastasis with multifocality (OR 5.4, 95% CI 1.3-23.4) and extrathyroidal extension (OR 5.8, 95% CI 1.3-25.4).

Table 1. Clinical characteristics of classic mPTC vs. mTCV vs. mDSV (SEER, 1988-2009)

	Classic mPTC (n=18,260)	mDSV (n=90)	P value	mTCV (n=97)	P value
Age			0.699		0.144
Mean (SEM)	47.6 (0.1)	48.2 (1.4)		49.6 (1.4)	
Age 18-44	7,827 (42.9)	34 (37.8)		40 (41.2)	
Age 45-64	8,293 (45.4)	48 (53.3)		41 (42.3)	
Age ≥65	2,140 (11.7)	8 (8.9)		16 (16.5)	
Female gender	15,009 (82.2)	80 (88.9)	0.098	78 (80.4)	0.647
Race			0.093		0.172
White	13,430 (73.5)	57 (63.3)		82 (84.5)	
Hispanic	1,816 (9.9)	13 (14.4)		5 (5.2)	
Asian/Pacific Islander	1,761 (9.6)	13 (14.4)		7 (7.2)	
Black	919 (5.0)	7 (7.8)		3 (3.1)	
Other/Unknown	334 (1.8)	0 (0.0)		0 (0.0)	
Surgery			0.655		0.311
No surgery	117 (0.6)	0 (0.0)		0 (0.0)	
Lobectomy	4,993 (27.3)	27 (30.0)		21 (21.6)	
Thyroidectomy	13,114 (71.8)	63 (70.0)		76 (78.4)	
Other/Unknown	36 (0.2)	0 (0.0)		0 (0.0)	
Lymph nodes examined			0.113		<0.001
Not examined	11,503 (60.5)	62 (68.9)		35 (36.1)	
Examined	7,156 (39.2)	28 (31.1)		62 (63.9)	
Unknown	51 (0.3)	0 (0.0)		0 (0.0)	
Radiation			0.013		<0.001
None	12,339 (67.6)	52 (57.8)		50 (51.5)	
Radioiodine ablation	5,308 (29.1)	36 (40.0)		38 (39.2)	
External beam radiation	107 (0.6)	2 (2.2)		4 (4.1)	
Radioactive implant	123 (0.7)	0 (0.0)		0 (0.0)	
Other/unknown	383 (2.1)	0 (0.0)		5 (5.2)	
Overall survival			0.720		0.532
5 year	97.5	100.0		98.5	
10 year[a]	94.7	97.6		98.5	
Disease specific survival			0.410		0.173
5 year	99.6	90.9		98.5	
10 year[a]	99.4	90.9		98.5	

Values in parentheses represent percentages unless otherwise designated

[a]Represents 9 year survival for mTCV

Table 2. Pathologic characteristics of classic mPTC vs. mTCV vs. mDSV (SEER, 1988-2009)

	Classic mPTC (n=18,260)	mDSV (n=90)	P value	mTCV (n=97)	P value
Size			0.165		<0.001
Mean (mm) (SEM)	5.3 (0.02)	5.8 (0.3)		7.1 (0.3)	
Size ≤7 mm	12,427 (68.1)	63 (70.0)		49 (50.5)	
Size >7mm	5,341 (29.2)	27 (30.0)		43 (44.3)	
≤ 1cm, NOS	492 (2.7)	0 (0.0)		5 (5.2)	
Multifocality			0.926		0.018
Unifocal	7,452 (40.8)	30 (33.3)		38 (39.2)	
Multifocal	3,837 (34.0)	15 (16.7)		34 (35.0)	
Unknown	6,971 (38.2)	45 (50.0)		25 (25.8)	
Extrathyroidal extension			0.004		<0.001
Intrathyroidal	17,041 (93.3)	78 (86.7)		70 (72.2)	
Extrathyroidal	1,109 (6.1)	12 (13.3)		27 (27.8)	
Unknown	110 (0.6)	0 (0.0)		0 (0.0)	
Nodal metastasis[a]			0.007		0.081
No positive lymph nodes	4,785 (66.9)	12 (42.9)		35 (56.4)	
≥ 1 positive lymph node	2,365 (33.0)	16 (57.1)		27 (43.6)	
Unknown	6 (0.0)	0 (0.0)		0 (0.0)	
Median (IQR)	2 (1-3)	4 (1-12)		2 (1-3)	
Distant metastasis			0.519		0.076
No distant metastasis	17,948 (98.3)	90 (100.0)		95 (97.9)	
Distant metastasis	83 (0.5)	0 (0.0)		2 (2.1)	
Unknown	229 (1.3)	0 (0.0)		0 (0.0)	

Values in parentheses represent percentages unless otherwise designated

[a]Percentage reflects fraction of patients whose lymph nodes were examined

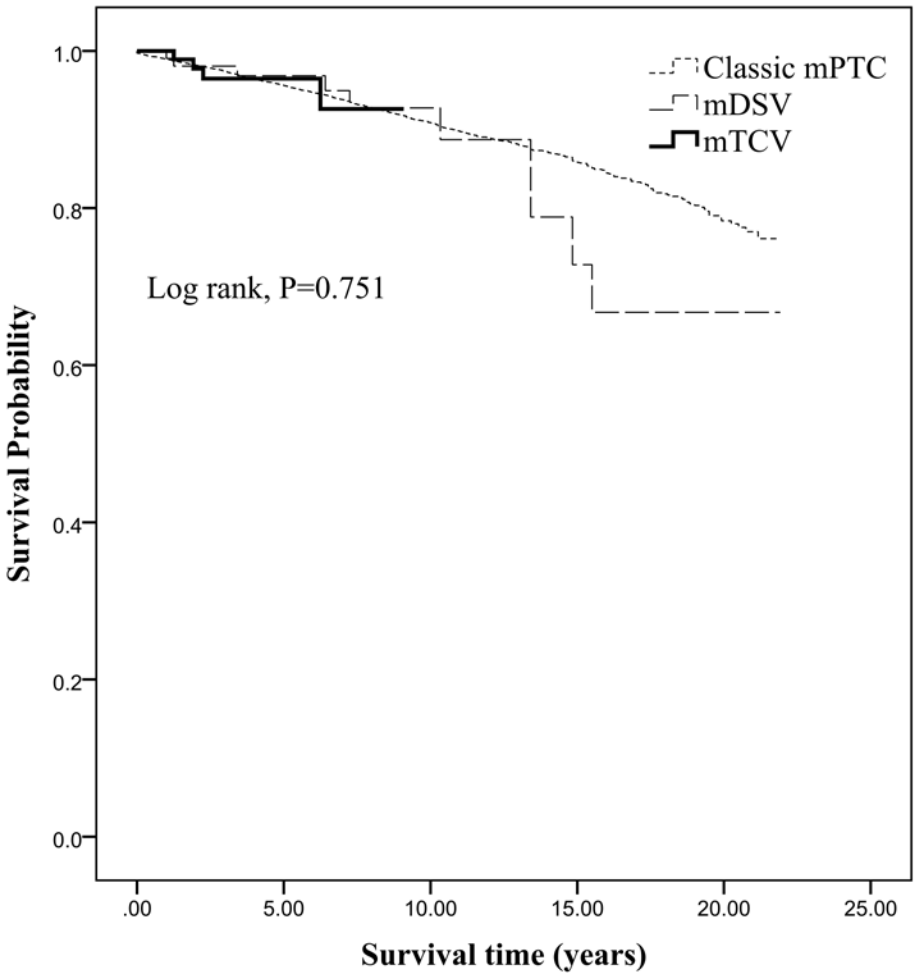

Figure 1. Kaplan-Meier analysis of overall survival.
Classic papillary thyroid microcarcinoma, mPTC; diffuse sclerosing variant ≤ 1cm, mDSV; tall cell variant ≤ 1cm, mTCV

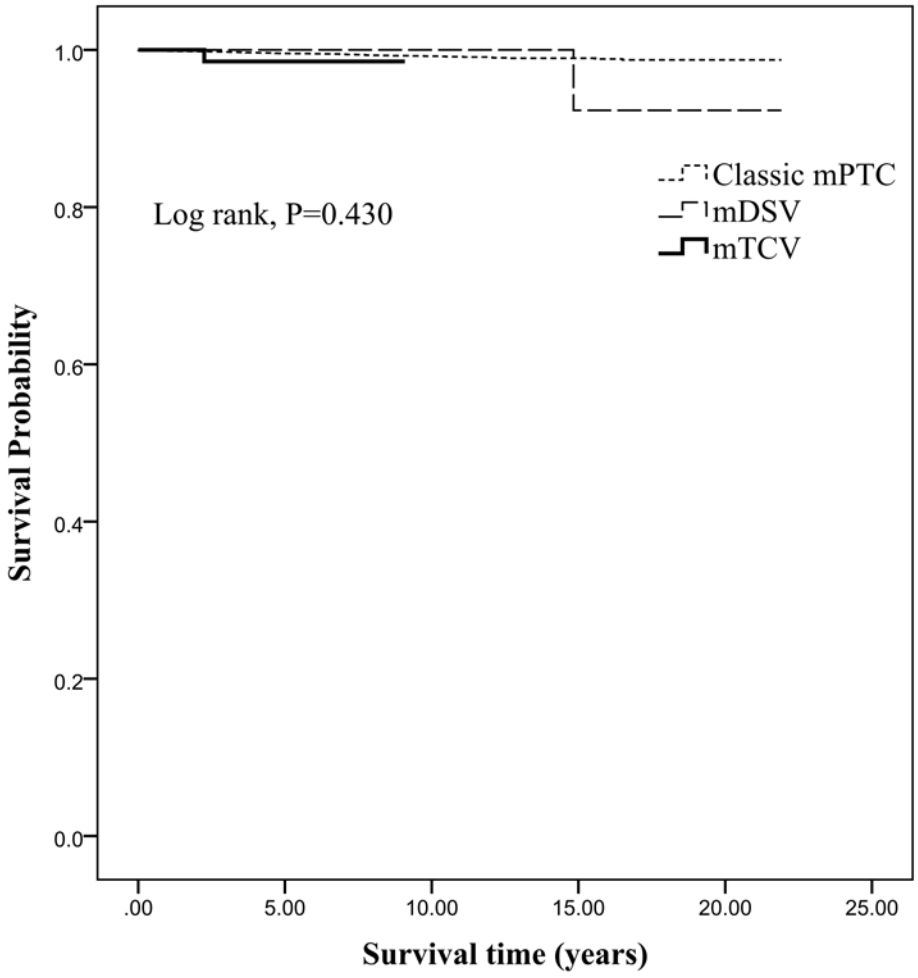

Figure 2. Kaplan-Meier analysis of disease specific survival. Classic papillary thyroid microcarcinoma, mPTC; diffuse sclerosing variant ≤ 1cm, mDSV; tall cell variant ≤ 1cm, mTCV

Follicular and Hurthle cell microcarcinoma

There were 564 cases of mFHCC (371 mFTC and 193 mHCC) and 22,174 cases of mPTC diagnosed during the study period. Patients with mFHCC and mPTC were followed for up to 22 years, with mean follow-up periods of 6.7 and 5.3 years, respectively.

Incidence

No statistically significant change in incidence was observed in mFTC, which decreased over the study period by an annual percentage change of -1.1% (P_{trend}=0.241). Incidences of mHCC and mPTC increased significantly over the study period by 400.7% and 415.1% with annual percentage changes of 4.8% (P_{trend}=0.003) and 8.7% (P_{trend}<0.001), respectively.

Characteristics

Demographic, clinical, and pathologic characteristics are summarized in Table 3. There were no significant demographic differences between patients with mFHCC and mPTC with respect to average age or gender. Compared to mPTC, patients with mFHCC were more commonly of black race (5.1% vs. 8.3%, P=0.001) while less commonly Asian (9.2% vs. 6.6%, P=0.029). Rates of thyroidectomy for mFHCC and mPTC were not significantly different, but patients with mFHCC were less likely to have lymph nodes examined (27.8% vs. 38.5% mPTC, P<0.001) and more likely to receive radioactive iodine (33.0% vs. 28.4% mPTC, P<0.001).

Compared to mPTC, mFHCC had similar rates of multifocality and extrathyroidal extension. On average, mFHCC tumors tended to be larger than mPTC (6.3mm vs.

5.3mm, P<0.001), with more than eight times the rate of distant metastasis (4.1% vs. 0.5%, P<0.001). Nodal metastases were less frequent (9.6% vs. 33.5% mPTC, P<0.001), although the distribution between level N1a and N1b lymph nodes was similar.

Subset analysis comparing characteristics of mFTC and mHCC are summarized in Table 4. On average, patients with mHCC were older than those with mFTC (53.3 years vs. 49.3 years, P=0.004), had lower rates of distant metastasis (1.6% vs. 5.4%, P=0.030) and higher rates of lymph node examination (35.2% vs. 24.0%, P=0.005). There were no significant differences between mFTC and mHCC with respect to patient gender, race, tumor size, multifocality, extrathyroidal extension, nodal metastasis, extent of thyroid surgery, and radioactive iodine administration.

Survival

All-cause mortality occurred in 11.9% of patients with mFHCC and 5.2% of patients with mPTC; disease-specific mortality occurred in 3.5% of patients with mFHCC and 0.4% of patients with mPTC. Disease-specific survival (DSS) was decreased in mFHCC compared to mPTC at 5 years (97.0% vs. 99.6%), 10 years (95.4% vs. 99.3%), and 15 years (94.4% vs. 99.0%, P<0.001) (Figure 3). In a combined cohort of mFHCC and mPTC, follicular or Hurthle cell histology remained an independent risk factor of reduced survival (HR 5.30, P<0.001) after adjustment for patient age, type of surgery, type of radiation, extrathyroidal extension, nodal metastasis, and distant metastasis (Table 5).

In patients with mFHCC, patient age ≥ 65 years (HR 9.11, P=0.011), extrathyroidal extension (HR 9.55, P<0.001), and necessitating external beam radiation

(HR 35.62, P<0.001) remained independent predictors of decreased disease-specific survival after adjustment (Figures 4-5, Table 4). Patients with mFHCC were further stratified by independent predictors of survival as determined by multivariate analysis. 5-year disease-specific survival in patients with 0 risk factors (age < 65 years without extrathyroidal extension), 1 risk factor (age ≥ 65 years or extrathyroidal extension), or 2 risk factors (age ≥ 65 years and extrathyroidal extension) was 99.2%, 95.1% and 83.3%, respectively (P<0.001) (Figure 4).

Extent of thyroidectomy and radioactive iodine

In patients with mFHCC, no statistically significant benefit in disease-specific survival was observed with total thyroidectomy compared to lobectomy (10-year disease-specific survival 93.7% vs. 97.3%, respectively, P=0.523) or radioactive iodine compared to no radioactive iodine (10-year disease-specific survival 95.6% vs. 98.7%, respectively, P=0.097). Subset analysis of high risk patients with either 1 or 2 risk factors also revealed no benefit with total thyroidectomy (10-year disease-specific survival 80.5% vs. 90.5%, respectively, P=0.584), while survival was worse in patients who received radioactive iodine (5-year disease-specific survival 85.0% vs. 98.7%, respectively, P=0.027).

Predictors of extrathyroidal extension, nodal metastasis, and distant metastasis

After adjustment, tumor size >7mm remained the only independent risk factor for extrathyroidal extension in mFHCC (OR 2.45, P=0.020; reference, no extrathyroidal extension), and male gender remained the only independent risk factor for nodal metastases (OR 5.62, P=0.002; reference, female). Independent risk factors for distant

metastasis included patient age ≥ 65 years (OR 9.40, P<0.001; reference, age 18-44 years) and Asian race (OR 9.18, P<0.001; reference, White).

Table 3. Characteristics of patients with mFHCC vs. mPTC (SEER, 1988-2009)

		mFHCC (n=564)	mPTC (n=22,174)	P value
Demographic	Age (years)			0.011
	Mean (SEM)	50.7 (0.7)	49.2 (0.1)	
	18-44	37.4	38.8	
	45-64	41.1	46.3	
	≥65	21.5	14.9	
	Female gender	77.7	80.7	0.070
	Race			0.001
	White	76.2	74.7	
	Hispanic	7.8	9.5	
	Asian	6.6	9.2	
	Black	8.3	5.1	
	Other/Unknown	1.1	1.6	
Clinical	Surgery			0.183
	No surgery	1.2	0.9	
	Lobectomy	30.9	27.9	
	Thyroidectomy	67.7	71.0	
	Lymph nodes examined	27.8	38.5	<0.001
	Radiation			<0.001
	None	60.5	68.1	
	Radioiodine ablation	33.0	28.4	
	External beam radiation	1.8	0.7	
Pathologic	Size			<0.001
	Mean (mm) (SEM)	6.3 (0.12)	5.3 (0.02)	
	≤7mm	53.5	68.8	
	>7-10mm	42.4	28.5	
	≤ 10mm, NOS	4.1	2.7	
	Multifocal	28.6	33.9	0.071
	Extrathyroidal extension	5.7	6.0	0.837
	Nodal metastasis*			
	≥ 1 positive lymph node	9.6	33.4	<0.001
	Median (IQR)	2 (1-5)	2 (1-4)	
	Level			0.954
	N1a	57.1	58.1	
	N1b	42.9	41.9	
	Distant metastasis	4.1	0.5	<0.001
Survival	Overall survival			<0.001
	5 year	91.3	95.6	
	10 year	83.4	90.8	
	15 year	80.9	85.8	
	Disease-specific survival			<0.001
	5 year	97.0	99.6	
	10 year	95.4	99.3	
	15 year	94.4	99.0	

Values presented are percentages of given sample sizes unless otherwise designated. Unknowns were excluded from statistical analysis. Follicular and Hurthle cell microcarcinoma, mFHCC; papillary thyroid microcarcinoma, mPTC.

*Represents percentage of patients whose lymph nodes were examined.

Table 4. Characteristics of patients with mFTC vs. mHCC (SEER, 1988-2009)

	mFTC (n=371)	mHCC (n=193)	P value
Age (years)			0.004
Mean (SEM)	49.3 (0.8)	53.3 (1.1)	
18-44	42.0	28.5	
45-64	38.3	46.6	
≥65	19.7	24.9	
Female gender	79.0	75.1	0.298
Race			0.168
White	74.1	80.3	
Hispanic	7.3	8.8	
Asian	7.5	4.7	
Black	9.7	5.7	
Other/Unknown	1.3	0.5	
Surgery			0.054
No surgery	1.6	0.5	
Lobectomy	33.7	25.4	
Thyroidectomy	64.4	74.1	
Lymph nodes examined	24.0	35.2	0.005
Radiation			0.803
None	61.7	58.0	
Radioactive iodine	32.3	34.2	
External beam radiation	1.9	1.6	
Other/unknown	4.0	6.2	
Size			0.446
Mean (mm) (SEM)	6.2 (0.1)	6.4 (0.2)	
≤7 mm	54.4	51.8	
>7-10 mm	41.0	45.1	
≤ 10 mm, NOS	4.6	3.1	
Multifocal	26.3	32.3	0.297
Extrathyroidal extension	4.9	7.3	0.270
Nodal metastasis*			
≥ 1 positive lymph node	7.9	11.8	0.410
Distant metastasis	5.4	1.6	0.030

Values presented are percentages of given sample sizes unless otherwise designated. Unknowns were excluded from statistical analysis. Follicular thyroid microcarcinoma, mFTC, Hurthle cell microcarcinoma, mHCC

*Represents percentage of patients whose lymph nodes were examined.

Table 5. Multivariate analysis of factors independently associated with disease specific mortality for patients with differentiated thyroid microcarcinoma (mPTC, mFTC and mHCC combined) (SEER, 1988-2009)

	Hazard ratio	95% Confidence interval	P value
Histology			
Papillary histology	1.00		
Follicular or Hurthle histology	5.30	2.78-10.10	<0.001
Age (years)			
18-44	1.00		
45-64	4.84	2.33-10.07	<0.001
≥65	21.7	10.38-45.31	<0.001
Surgery			
No surgery	5.32	1.18-23.92	0.029
Lobectomy	1.00		
Thyroidectomy	1.13	0.67-1.95	0.624
Radiation			
No radiation	1.00		
Radioactive iodine	1.04	0.63-1.73	0.877
External beam radiation	5.44	2.45-12.10	<0.001
Extrathyroidal extension			
No	1.00		
Yes	4.63	2.77-7.74	<0.001
Nodal metastasis			
No	1.00		
Yes	3.36	1.93-5.82	<0.001
Distant metastasis			
No	1.00		
Yes	12.86	5.26-31.44	<0.001

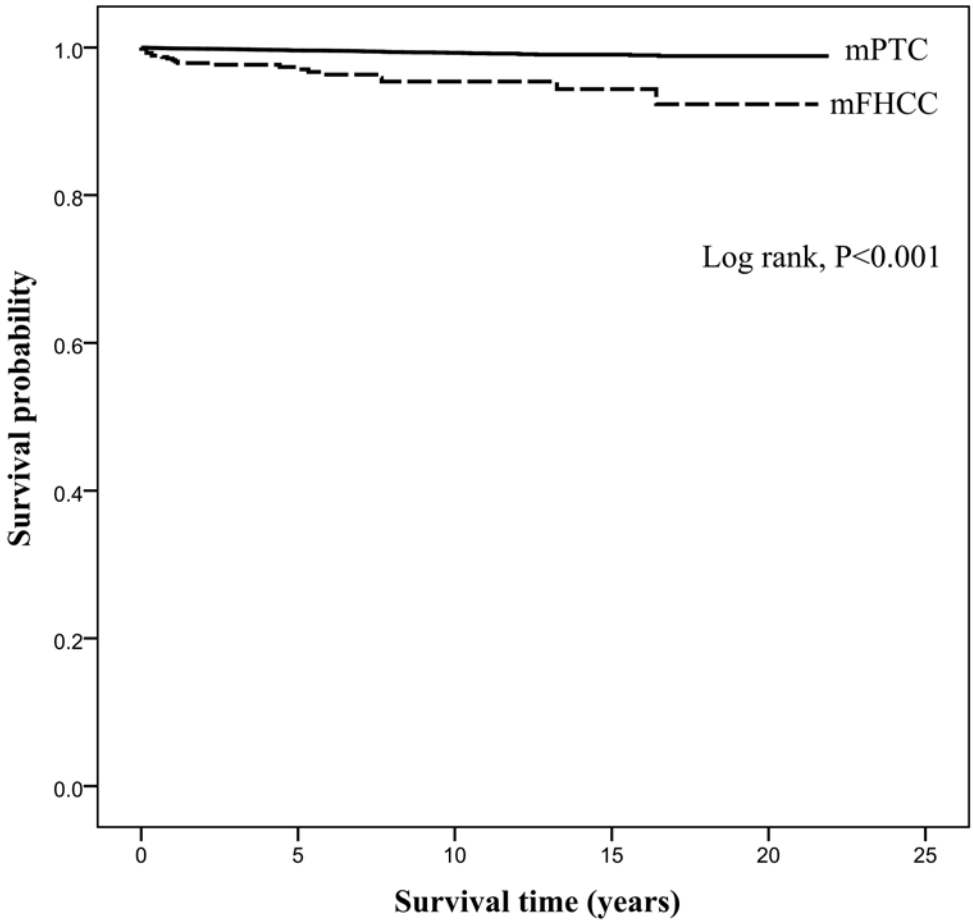

Figure 3. Disease-specific survival of mPTC and mFHCC (SEER, 1988-2009). Papillary thyroid microcarcinoma, mPTC; follicular and Hurthle cell microcarcinoma, mFHCC.

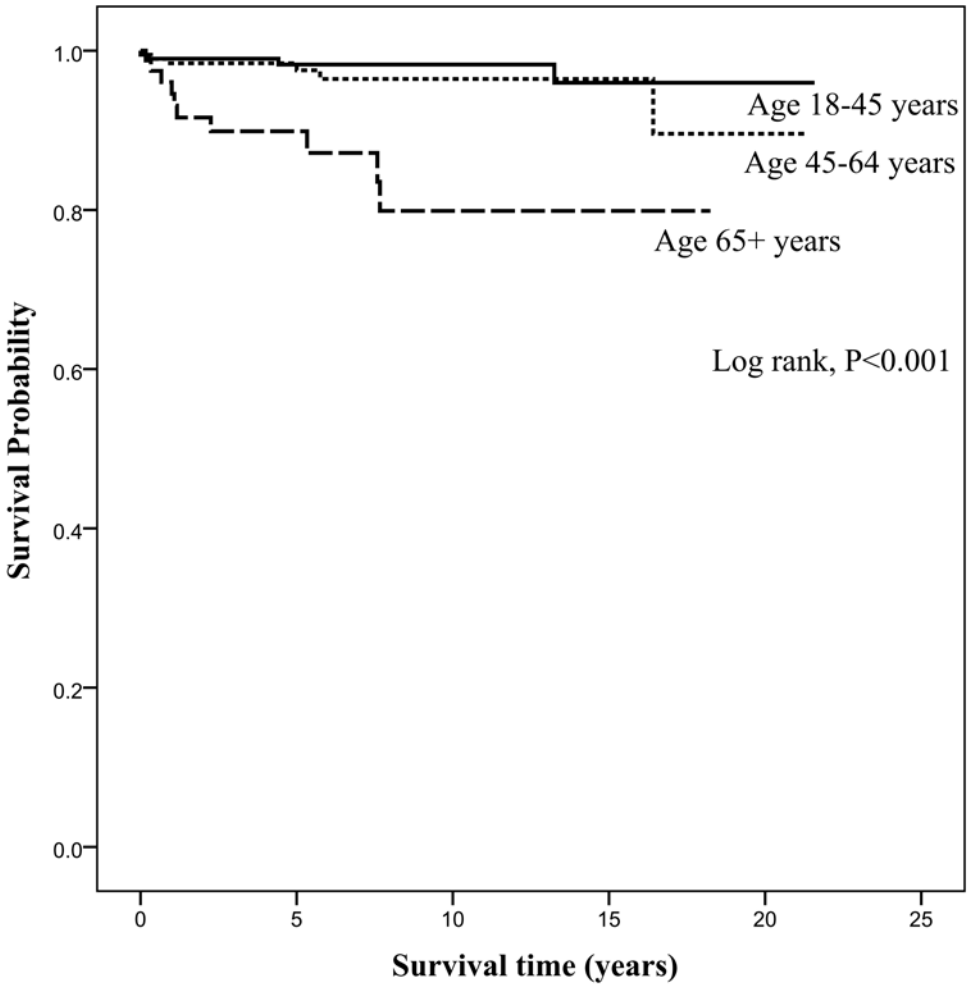

Figure 4. Disease-specific survival of follicular and Hurthle cell microcarcinoma by age (SEER, 1988-2009).

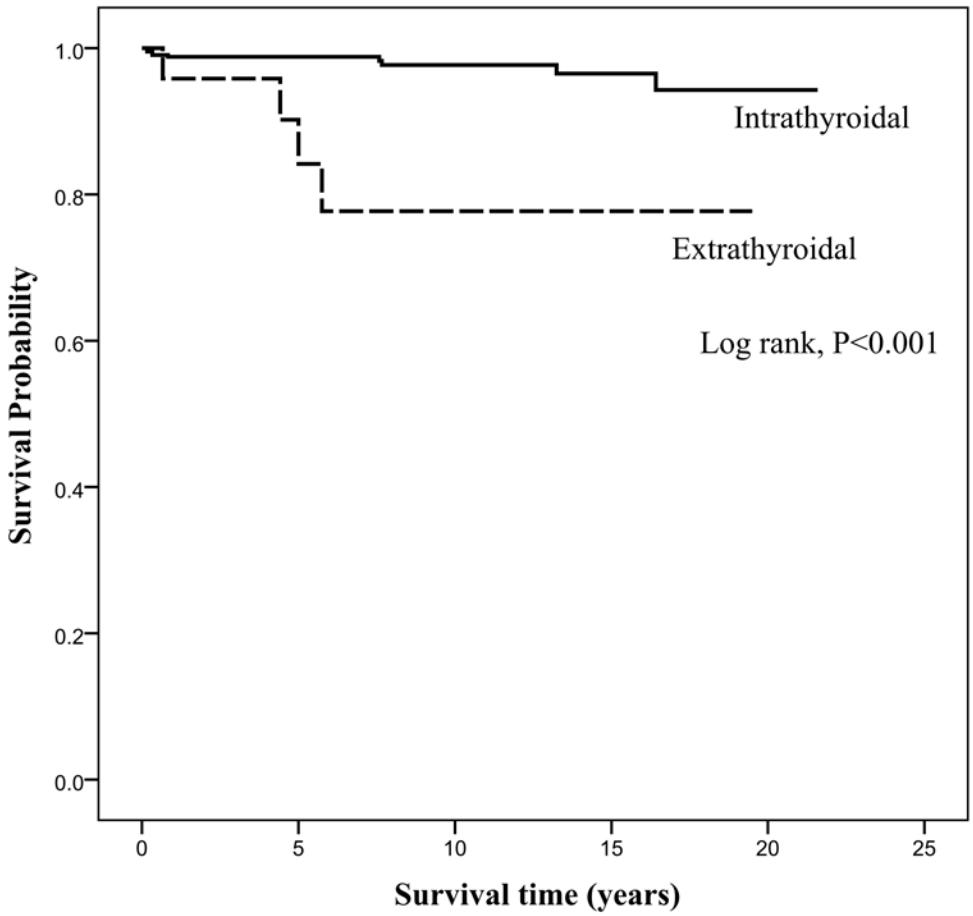

Figure 5. Disease-specific survival of follicular and Hurthle cell microcarcinoma by extrathyroidal extension (SEER, 1988-2009)

Pancreatic neuroendocrine tumors ≤ 2 cm in size

1,371 cases of non-functioning PNETs were identified in the SEER database, including 263 tumors ≤ 2 cm and 1,108 tumors > 2 cm; patients were followed for up to 21.7 years, with a mean follow-up of 4.2 years. In the institutional pathology database, 79 cases of non-functioning PNETs were identified, including 43 tumors ≤ 2 cm and 36 tumors > 2 cm.

Incidence

The annual incidence of PNETs ≤ 2 cm versus > 2 cm from 1988-2009 is shown in Figure 10. The incidence of PNETS ≤ 2 cm increased by 710.4% (annual percentage change [APC] 12.8%, P<0.0001) over the 22 year study period, while the incidence of PNETs > 2 cm in size increased by 343.6% (APC 7.5%, P<0.0001). PNETs ≤ 2 cm accounted for 20.2% of total PNET diagnoses in 2009, in contrast to 12.3% of total PNET diagnoses in 1988.

Characteristics—SEER

Demographic, clinical, and pathologic characteristics from the SEER database are summarized in Tables 10 and 11. PNETs ≤ 2 cm were more frequently well-differentiated (78.9% vs. 59.8%, P<0.001), with decreased rates of extrapancreatic extension (17.9% vs. 43.3%, P<0.001) and distant metastasis at presentation (9.1% vs. 24.2%, P<0.001) compared to PNETS > 2 cm.

PNETs ≤ 2 cm were less likely to have lymph nodes examined compared to PNETs > 2 cm (71.1% vs. 82.4%, P<0.001), and although the difference was not statistically significant, PNETs ≤ 2 cm also tended to have fewer nodes examined

(median[interquartile range] 6[3-14] vs. 8[3-14] nodes, P=0.282). PNETs ≤ 2 cm had lower rates of nodal metastasis compared to PNETs > 2 cm (27.3% vs. 54.1%, P<0.001). In patients with node positive disease, those with PNETs ≤ 2 cm had a smaller number of positive nodes (2[1-3] vs. 2[1-5], P=0.006) compared to PNETS > 2 cm. In tumors of all sizes, multivariate analysis revealed nodal metastasis to be less likely in PNETs ≤ 2 cm (hazard ratio [HR] 0.3, P<0.001; reference, 2.6-5.0 cm), but more likely in patients with poorly differentiated tumors (HR 2.2, P=0.010; reference, well differentiated) and extrapancreatic extension (HR 3.3, P<0.001). Subset analysis of PNETs ≤ 2 cm revealed nodal metastasis to be more likely in tumors with extrapancreatic extension (HR 6.7, P<0.001), but less likely in patients ≥ 65 years of age (HR 0.2, P=0.008; reference, age < 45 years).

Characteristics—Institutional series

Demographic, clinical and pathologic characteristics from the institutional pathology database are summarized in Table 12. Rates of nodal metastasis in PNETs ≤ 2 cm and > 2 cm were 5.7% (2 of 35) and 28.6% (10 of 35), respectively. Both nodal metastases in PNETs ≤ 2 cm were associated with tumors 2 cm in size; no nodal metastasis was observed in PNETs < 2 cm.

Survival—SEER

Review of SEER data showed the all-cause mortality rate to be 13.7% in patients with PNETs ≤ 2 cm and 30.8% in patients PNETs > 2 cm; disease-specific mortality occurred in 10.0% of patients with PNETs ≤ 2 cm and 24.9% of patients PNETs > 2 cm. Disease specific survival at 5, 10, and 15 years for PNETs ≤ 2 cm was 89.7%, 80.0%, and

70.6%, and for PNETs > 2 cm was 75.3%, 58.7%, and 44.9% (P<0.001). In PNETs ≤ 2 cm, decreased disease specific survival was associated with race, grade, and extrapancreatic extension on univariate analysis. After adjustment, decreased disease specific survival was associated with higher grade (moderately differentiated, HR 37.2, P=0.007; poorly differentiated, HR 94.2, P=0.003; reference group, well differentiated), and minority race (Asian, HR 30.2, 0.003; Black, HR 46.4, P=0.015; reference group, white) on multivariate analysis. Race was not a significant predictor of survival in PNETs > 2 cm on univariate analysis (P=0.187).

PNETs ≤ 2 cm were further subdivided into groups of 0.1-0.5 cm, 0.6-1.0 cm, 1.1-1.5 cm, and 1.6-2.0 cm, and nodal examination, nodal metastasis, and disease specific survival were analyzed (Table 13).

Table 10. Demographic and Clinical Characteristics of PNETs ≤ 2 cm vs. > 2 cm, SEER 1988-2009

	Size ≤ 2 cm (n=263)	Size > 2 cm (n=1,108)	P
Age			0.488
Mean [years] (SEM)	55.4 (0.8)	56.0 (0.4)	
Age 18-44	22.1	19.7	
Age 45-64	49.4	52.2	
Age ≥65	28.5	28.2	
Female gender	51.0	48.0	0.392
Race			0.512
White	72.6	75.3	
Hispanic	6.1	7.4	
Asian	8.0	6.0	
Black	11.4	10.1	
Other/Unknown	1.9	1.2	
Surgery			<0.001
Enucleation	9.5	2.5	
Partial pancreatectomy	44.1	40.7	
Enucleation/Partial pancreatectomy, NOS	3.4	3.2	
Pancreaticoduodenectomy	30.8	38.7	
Total pancreatectomy	6.1	9.7	
Other	6.1	5.1	
Nodal examination			<0.001
≥ 1 lymph node examined	71.1	82.4	
Median (IQR)	6 (3-14)	8 (3-14)	
Radiation			0.111
None	96.6	92.7	
External beam radiation	2.3	5.2	
Other	0.4	0.5	
Unknown	0.8	1.5	
Overall survival			<0.001
5 year	85.2	69.1	
10 year	75.2	51.8	
15 year	58.2	36.0	
Disease specific survival			<0.001
5 year	89.7	75.3	
10 year	80.0	58.7	
15 year	70.6	44.9	

Values presented are percentages of given sample sizes unless otherwise designated. Unknowns were excluded from statistical analysis. PNET, pancreatic neuroendocrine tumor; SEER, Surveillance, Epidemiology, and End Results database; SEM, standard error of the mean; IQR, interquartile range

Table 11. Pathologic Characteristics of PNETs ≤ 2 cm vs. > 2 cm, SEER 1988-2009

	Size ≤ 2 cm (n=263)	Size > 2 cm (n=1,108)	P
Mean size [cm], (SEM)	1.40 (0.03)	5.76 (0.10)	<0.001
Histology			0.001
Neuroendocrine carcinoma	27.4	34.0	
Islet cell carcinoma	61.6	60.7	
Carcinoid	11.0	5.2	
Location			0.018
Head	29.3	33.2	
Body	16.0	10.6	
Tail	30.0	35.9	
Other	24.7	20.2	
Grade			<0.001
Well-differentiated	41.1	34.4	
Moderately differentiated	6.8	14.2	
Poorly differentiated	1.9	6.9	
Undifferentiated	2.3	2.1	
Unknown	47.9	42.5	
Extrapancreatic extension	17.9	43.3	<0.001
Nodal metastasis			<0.001
≥ 1 positive lymph node[a]	27.3	54.1	
Median (IQR)	2 (1-3)	2 (1-5)	
Distant metastasis	9.1	24.2	<0.001

Values presented are percentages of given sample sizes unless otherwise designated. Unknowns were excluded from statistical analysis. PNET, pancreatic neuroendocrine tumor; SEER, Surveillance, Epidemiology, and End Results database; SEM, standard error of the mean; IQR, interquartile range

[a]Represents percentage of patients who underwent nodal examination

Table 12. Characteristics of PNETs ≤ 2 cm vs. > 2 cm, institutional series 1996-2012

	Size ≤ 2 cm (n=43)	Size > 2 cm (n=36)	P
Age			0.105
Mean [years], (SEM)	58.9 (1.4)	54.9 (2.2)	
Age 18-44	7.0	22.2	
Age 45-64	62.8	52.8	
Age ≥65	30.2	25.0	
Female gender	58.1	44.4	0.225
Surgery			0.051
Enucleation	4.7	0.0	
Partial pancreatectomy, NOS	7.0	5.6	
Distal pancreatectomy w/o splenectomy	30.2	8.3	
Distal pancreatectomy w/ splenectomy	30.2	55.6	
Pancreaticoduodenectomy	27.9	30.6	
Nodal examination			0.027
≥ 1 lymph node examined[a]	81.4	97.2	
Median (IQR)	10 (5-16)	13 (6-22)	
Extrapancreatic extension	7.0	36.1	0.001
Nodal metastasis			0.011
≥ 1 lymph node positive	5.7	28.6	
Median (IQR)	1.5 (1-2)	3.5 (2-7)	
Lymphovascular invasion	7.0	61.1	<0.001
Perineural invasion	11.6	19.4	0.335
Multifocal	4.7	5.6	0.855
Mitotic rate			0.008
<2 / 10 HPF	55.8	36.1	
2-5 / 10 HPF	2.3	19.4	
> 5 / 10 HPF	0.0	5.6	
Unknown	41.9	38.9	
Ki67			0.101
<2 %	27.9	13.9	
2-5 %	14.0	13.9	
> 5 %	4.7	16.7	
Unknown	53.5	55.6	

Values presented are percentages of given sample sizes unless otherwise designated. Unknowns were excluded from statistical analysis. PNET, pancreatic neuroendocrine tumor; SEM, standard error of the mean; IQR, interquartile range; HPF, high-powered field

[a]Represents percentage of patients who underwent nodal examination

Table 13. Nodal examination, nodal metastasis, and disease specific survival in PNETs ≤ 2 cm, SEER 1988-2009 (n=260)[a]

Tumor size	Nodal examination (%)	Nodal metastasis (%)[b]	Disease specific survival (%)		
			5-year	10-year	15-year
0.1-0.5 cm (n=16)	75.0	25.0	100.0	100.0	66.7
0.6-1.0 cm (n=51)	58.8	16.7	94.7	94.7	94.7
1.1-1.5 cm (n=94)	69.1	21.5	95.1	75.5	75.5
1.6-2.0 cm (n=99)	80.8	36.3	82.4	76.1	68.4

PNET, pancreatic neuroendocrine tumor; SEER, Surveillance, Epidemiology, and End Results

[a]Two patients with tumor size recorded as "2 cm, not otherwise specified" and one patient with unknown nodal status were excluded

[b]Reflects percentage of patients who underwent nodal examination

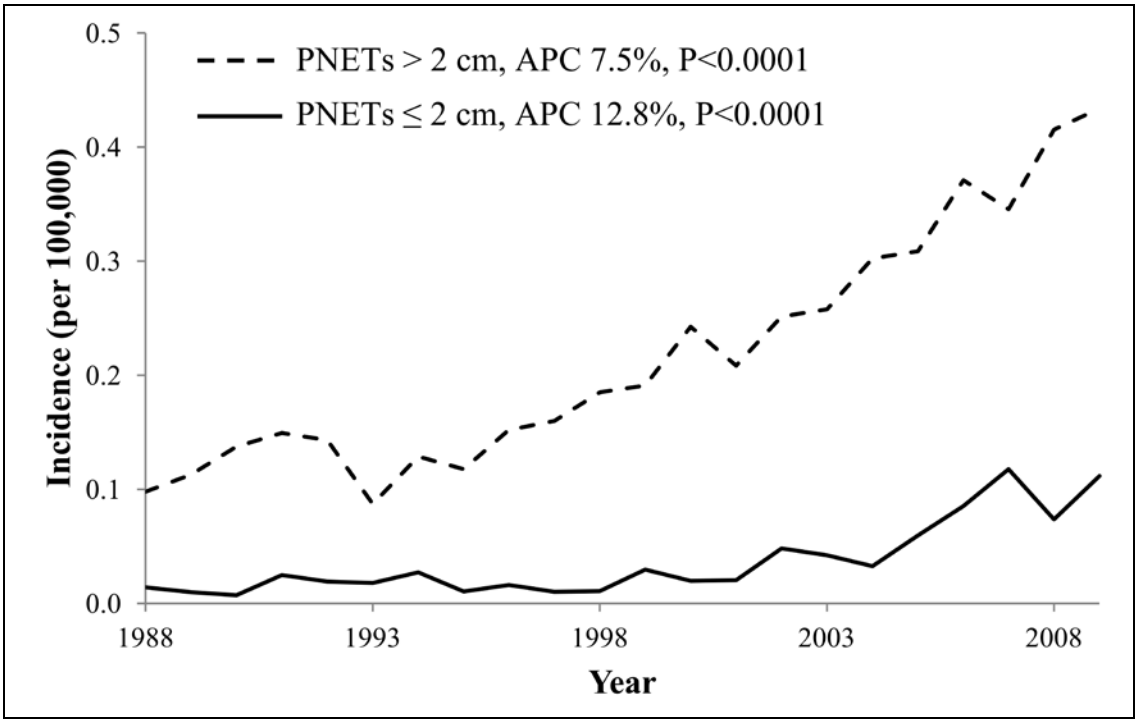

Figure 10. Incidence of pancreatic neuroendocrine tumors ≤ 2 cm and > 2 cm in size, SEER 1988-2009; PNET, pancreatic neuroendocrine tumor; SEER, Surveillance, Epidemiology, and End Results database; APC, annual percentage change

DISCUSSION

Aggressive variants of papillary thyroid microcarcinoma

To our knowledge, this study represents the first population-level analysis of aggressive variants of mPTC. We found the incidences of mTCV and mDSV are not increasing to the same degree as mPTC, and that mTCV and mDSV exhibit aggressive features despite their small size. In comparison to mPTC, mDSV was characterized by higher rates of extrathyroidal extension and nodal metastasis, while mTCV was characterized by higher rates of multifocality and extrathyroidal extension. Both multifocality and extrathyroidal extension predicted nodal metastasis in mTCV. While no association between histologic variant and overall or disease specific survival was found, our study was likely underpowered to detect such a difference.

The rapidly rising incidence of mPTC is well established, the most common type of PTC being microcarcinoma in patients older than 45 years.[11,13,14] However, no data on the incidence of aggressive variants of mPTC have been reported. In a population-level analysis of DSV and TCV of all sizes, Kazaure, et al. reported that the incidence of aggressive variants was outpacing that of PTC in the US, attributing the increase to improved detection and accuracy in the diagnosis of DSV and TCV.[29] A population-level analysis of thyroid cancers in Parma, Italy similarly showed a significant increase in TCV from 1998-2009g.[67] Therefore, the 79.9% increase in incidence of mTCV observed in our study is likely real, although limited by sample size. The incidence of mDSV appears to have been more level during the study period.

Management of aggressive variants is controversial, and current guidelines from the American Thyroid Association do not address the extent of thyroid surgery for patients with aggressive variants.[46] Overall, studies of DSV and TCV show that prognosis is worse, with increased recurrence and decreased survival.[26,29,40-42,68] Some authors have suggested that this difference should be attributed to higher rates of aggressive pathologic features rather than variant histology, and they do not recommend aggressive treatment based on histology alone.[39,68,69] Contrary studies that control for these aggressive features show that histology remains an independent risk factor for adverse outcomes, and many advocate total thyroidectomy with prophylactic central lymphadenectomy in aggressive variants regardless of tumor size.[20,28,40,42,70] None of these studies have examined mDSV and mTCV specifically, and it is unclear whether histology alone warrants more extensive surgery in tumors ≤ 1cm. In our study, no differences in survival were observed between the different histologies, suggesting histology alone may not warrant extensive surgery. However, because mDSV and mTCV appear to exhibit aggressive characteristics with increased rates of multifocality, extrathyroidal extension, and nodal metastasis, and we postulate that tumor recurrence is likely. As a result, in patients diagnosed pre- or intraoperatively with micro-aggressive variants of PTC, we recommend total thyroidectomy, central lymphadenectomy, and post-operative RAI, and for those diagnosed postoperatively after initial lobectomy, completion thyroidectomy and post-operative RAI. Performing a redo prophylactic ipsilateral central lymphadenectomy at the time of completion thyroidectomy is not

common practice, even though it has been shown to be safe if performed in a high-volume center with experienced surgeons.[71]

Preoperative diagnosis of DSV and TCV is difficult.[20,70] TCV and DSV have unique cytopathologic characteristics, and although diagnostic criteria have not been rigorously evaluated, several reports indicate that finding tadpole-shaped cells or inflammation and squamous metaplasia on FNA can raise preoperative suspicion of TCV and DSV, respectively.[31,32,34,72,73] Nevertheless, preoperative diagnosis of variant histologies on fine needle aspiration (FNA) is limited, and it is common for patients to be diagnosed post-operatively after histopathologic examination. Our study suggests that aggressive features found in DSV and TCV persist in tumors ≤ 1cm in size, and that therefore mDSV and mTCV are disproportionately represented in microcarcinomas presenting with size >7mm, multifocality, extrathyroidal extension, and nodal metastases.[21-29,35-42] Therefore, in patients with aggressive pre- or intraoperative findings, such as a high degree of sclerosis, obvious extrathyroidal extension or evidence of clinically positive lymph nodes, clinicians should have a high degree of suspicion for an aggressive variant and be prepared to perform a more aggressive operation with respect to the extent of thyroid surgery and possible lymphadenectomy.

The use of molecular tests is becoming more common, and may aid in the preoperative diagnosis of more aggressive variants of PTC. BRAF V600E has been shown in mPTC to be associated with tumor size, extrathyroidal extension, multifocality, nodal metastases, and advanced stage.[74-77] Furthermore, the mutation is highly prevalent in TCV, with reports ranging from 66-100%.[74,77-81]. While the molecular pathogenesis of

DSV is less well studied, RET/PTC rearrangements appear to predominate.[82] More work needs to be done on the molecular testing of these variants in order to provide valuable diagnostic, prognostic, and therapeutic information.[83]

The limitations of this study include those inherent to the SEER database, such as coding errors, limited data for variables where collection began only recently (for example, multifocality and location of cervical lymph node metastases), and lack of data on variables not collected by SEER (for example, BRAF/RET gene status, central vs. lateral lymphadenectomy, reoperation, and recurrence). Because mDSV and mTCV are rare tumors, our study, while the largest to date, may still be underpowered to document more subtle differences between mDSV, mTCV, and mPTC. The strengths of our study include its large relative sample size and the use of population-level data.

Overall, mDSV and mTCV are rare tumors that share many characteristics with histologically identical tumors > 1cm in size. They tend to be more aggressive compared to classic mPTC, and while they do not appear to differ with respect to survival, given our findings of higher nodal involvement and extrathyroidal extension, we postulate that they may have higher recurrence rates. Treatment with total thyroidectomy, possible central lymphadenectomy, and postoperative RAI may be indicated. Long term data on recurrence and more highly powered studies of survival will elucidate the prognosis of patients with mDSV and mTCV. Further understanding of the molecular pathogenesis of mDSV and mTCV will improve future diagnostic and prognostic power.

Follicular and Hurthle cell microcarcinoma

To our knowledge, this study represents the first population-level analysis of mFHCC. We found that more than 1 in 25 patients with mFHCC present with distant metastasis, and that patients with mFHCC had compromised survival compared to those with mPTC, which was most marked in older patients and those whose tumors exhibited extrathyroidal extension. Furthermore, no survival benefit was observed with total thyroidectomy over lobectomy.

Microcarcinomas of the thyroid have been rapidly rising in incidence, and while this increase is largely due to mPTC, changes in incidence of mHCC and mFTC remain undefined. With respect to HCC, Goffredo, et al. showed that the incidence of tumors of all sizes has increased; however, the incidence of mHCC and its relation to the rise in mPTC has not been previously reported.[84] In our study, we found that the incidence of mHCC increased dramatically over the last 25 years on an order similar to that of mPTC. Therefore, while mHCC represents a small fraction of thyroid microcarcinomas overall, its incidence is rapidly rising in parallel with mPTC, suggesting mHCC may be subject to similar epidemiologic factors. In contrast, the incidence of FTC, after decreasing in incidence likely due to the dissemination of iodine supplementation in the 1920-1930s, may be continuing to decline.[45] In a recent series of 258 patients treated over a 2 year period, FTC accounted for only 2.7% of thyroid carcinomas after pathologic review, which the authors attributed to increasing recognition of the follicular variant of PTC.[85] In our study, mFTC accounted for less than 2% of thyroid microcarcinomas and its incidence did not change significantly over the study period, confirming that mFTC is a

rare tumor with a stable incidence that is subject to epidemiologic factors distinct from mPTC and mHCC.

It is well known that FTC disseminates hematogenously; as a result, distant metastasis is relatively common, found in approximately 10% of patients at presentation, while nodal metastasis is rare.[86] Studies of HCC reveal similar rates of distant metastasis.[66] However, none of these studies exclusively analyzed tumors ≤ 1cm in size, and therefore the natural history of mFHCC is largely unknown. In our study, patients with mFTC and mHCC presented with distant metastasis eleven and three times more frequently than patients with mPTC, respectively, with the rate of distant metastasis in mFTC even surpassing that of medullary thyroid microcarcinoma.[87] Distant metastasis is therefore a unique feature of follicular and Hurthle cell histologies regardless of tumor size and can occur early in their natural history.

Our study also found that compared to mPTC, patients with mFHCC have compromised survival. It is known that survival in FTC and HCC in general is decreased compared to that of PTC.[44,88] However, our finding that follicular or Hurthle cell histology was independently associated with mortality confirms that this difference persists even in small tumors. Additional predictors of increased mortality identified in FHCC tumors of all sizes include older patient age, male gender, large tumor size, extrathyroidal extension, nodal metastasis, and distant metastasis.[66,86,89-94] Our study found patient age ≥ 65 years and extrathyroidal extension to be the two factors most predictive of mortality in tumors ≤ 1cm in size, and notably, 5- and 10-year survival rates of patients with mFHCC and one risk factor approached survival rates in studies of FTC

of all sizes. Overall, the high rate of distant metastasis and compromised survival exhibited in mFHCC compared to mPTC refutes any notion that these tumors can be dismissed on account of their small size.

In contrast to mPTC, which frequently can be diagnosed on fine needle aspiration, a diagnosis of mFHCC cannot be made until capsular or vascular invasion is identified in a surgical specimen. The risk of malignancy in patients with a cytologic diagnosis of follicular or Hurthle cell neoplasm is 20-30%; however, large tumor size (> 4 cm), among other factors such as family history, history of irradiation, and marked atypia on biopsy, have been associated a higher risk of malignancy.[95] Patients with a follicular or Hurthle cell neoplasm and a small nodule ≤ 1 cm in size may therefore be more likely to be dismissed as having a lower risk of malignancy, which may result in delays in treatment. Given the higher rates of distant metastasis and compromised survival for mFHCC observed in this study, we recommend that the possibility of harboring mFHCC should be taken seriously, and definitive diagnostic surgery should be performed.

An improved understanding of the molecular biology of these tumors may help to raise suspicion of malignancy, especially in tumors ≤ 1 cm where suspicion is otherwise low. RAS point mutations and PAX8-PPARγ rearrangements are common in follicular and Hurthle histologies. In a series of 1056 consecutive fine needle aspiration samples, a panel of molecular tests including RAS and PAX8- PPARγ was able to predict malignancy in patients with a cytologic diagnosis of follicular or Hurthle cell neoplasm with a positive predictive value of 87%.[96] Molecular diagnostics may therefore have a

unique role in diagnosing malignancy in patients with follicular or Hurthle cell neoplasms ≤ 1 cm where the risk of malignancy is otherwise low.

The optimal extent of thyroid surgery to be performed in mFHCC is unclear. Guidelines from the American Thyroid Association suggest lobectomy to be the procedure of choice for mPTC in low-risk patients, but does not specifically comment on microcarcinomas with follicular or Hurthle histologies.[46] Therefore, the necessity of completion thyroidectomy if mFHCC is diagnosed post-operatively is unclear. In our study, no survival benefit was observed in patients undergoing thyroidectomy over lobectomy; therefore, lobectomy likely represents an adequate intervention for the purposes of diagnosis and treatment in patients with tumors ≤ 1 cm and a diagnosis of follicular or Hurthle cell neoplasm.

In regard to radioactive iodine administration, patients with FTC who have clinical indications for radio iodine treatment in the adjuvant setting have demonstrated some benefits; by convention, radioactive iodine also is administered to patients with HCC even though only a minority of these tumors demonstrates iodine avidity.[84] In our study, radioactive iodine treatment did not confer a survival benefit in patients with mFHCC, and therefore may not be necessary for tumors ≤ 1 cm in size.

The limitations of this study include those inherent to the SEER database, such as coding errors, limited data for variables where collection began only recently (for example, multifocality and location of cervical lymph node metastases), and lack of data on variables not collected by SEER (for example, molecular markers, central vs. lateral lymphadenectomy, reoperation, persistence of disease, and recurrence). Because the

study was retrospective, it is difficult to interpret the lack of survival benefit with total thyroidectomy and radioactive iodine administration, as treatments were not standardized. SEER also lacks a centralized review of pathologic specimens, and concern that FTCs are rare and may be overdiagnosed is well established.[45,66,85] However, the accuracy of SEER histology codes has been independently validated in a statewide registry, and SEER remains one of our strongest resources in the analysis of rare malignancies.[97] The strengths of our study include the use of population-level data and the largest sample size to date, with long follow-up.

Overall, our study shows that mFTC and mHCC are distinct clinicopathologic entities from mPTC which present more frequently with distant metastasis and are associated with compromised disease-specific survival. As a result, the possibility of mFHCC in patients with tumors ≤ 1cm in size and a cytologic diagnosis of follicular or Hurthle cell neoplasm should be strongly considered, and patients should undergo timely diagnostic lobectomy, which ultimately may be therapeutic as well.

Pancreatic neuroendocrine tumors ≤ 2 cm

To our knowledge, this study is the first population-level analysis to exclusively characterize PNETs ≤ 2 cm in a surgical population. In addition to determining that the proportion of PNETs ≤ 2 cm in comparison to PNETs of all sizes has nearly doubled over the last 22 years, we found that nodal metastasis was not predictive of disease specific mortality, which was rather associated with high grade and black or Asian race. Also, we observed the rate of nodal metastasis in PNETs ≤ 2 cm to vary greatly between SEER versus institutional data.

It is well documented that the incidence of PNETs has increased over the last three and a half decades. Lawrence et al. surveyed PNETs in the SEER database and found that their incidence rose from 1.7 per million in 1973-1977 to 4.3 per million in 2003-2007.[54] Vagefi et al. noted a trend towards smaller tumor size in incidentally diagnosed tumors in an institutional series of 168 PNETs, but the study was not sufficiently powered to establish statistical significance.[98] Our study supports that PNET incidence continues to rise, and that the incidence of small PNETs is growing disproportionately in comparison to larger tumors on a population level. Furthermore, because this rate only reflects the incidence of PNETs deemed to be malignant, the disproportionality of the increase is likely underestimated. Overall, these findings highlight the necessity to more precisely characterize and define therapeutic strategies for this increasingly common population of patients.

With respect to clinical outcomes, no population-based studies have analyzed PNETs with a focus on size in a surgical population. Bilimoria et al. examined a surgical population utilizing the National Cancer Database (NCDB) and yielded similar results in comparison to SEER data with respect to age, gender, race, tumor location, nodal metastasis, and distant metastasis.[58] Our study additionally highlights these characteristics in the context of tumor size. As expected, PNETs ≤ 2 cm were more likely to be lower grade, with lower rates of extrapancreatic extension, nodal metastasis, and distant metastasis compared to PNETs > 2 cm. Nevertheless, rates were still substantial, with 17.9% of PNETs ≤ 2 cm in the SEER database presenting with extrapancreatic extension, 27.3% with nodal metastasis, and 9.1% with distant metastasis. The

interpretation of this data, however, is complicated by the SEER database's exclusion of PNETs thought to be benign, which results in the selection of a population of aggressive tumors that is not representative of PNETs ≤ 2 cm as a whole. One may correctly argue that the rate of nodal metastasis reported here is artificially high. However, while the exact frequency of nodal metastasis may be unclear, it appears that PNETs ≤ 2 cm, even microadenomas ≤ 0.5 cm, indeed have malignant potential.

Rates of nodal metastasis in PNETs ≤ 2 cm have been reported at 0%, 9%, and 26% in various series.[56,60,62] In our institutional series, the rate of nodal metastasis in PNETs ≤ 2 cm was 5.7%. Nodal metastasis has not been shown to be a predictor of survival in population level analyses of PNETs.[58,59] However, this notion has recently been challenged. Parekh et al. argued that inadequate lymph node sampling precludes any conclusions about the prognostic power of nodal metastasis.[99] In their single center series, no lymph node examination was documented in pathology reports in 37% of patients, and when lymph nodes were examined, only a median of five nodes were evaluated. While a median of ten nodes were examined in PNETs ≤ 2 cm in our institutional series, a median of six nodes were examined in PNETs ≤ 2 cm in the SEER database, confirming that lymph nodes may not be adequately sampled in the US. Therefore, while nodal metastasis was not a significant predictor of survival in our population-level cohort, this may be a result of inadequate lymph node sampling.

The two staging systems proposed for PNETs include those of the European Neuroendocrine Tumor Society (ENETS) and the American Joint committee on Cancer (AJCC). Although both have been validated in an American series of 123 patients, a

European series of 1,072 patients showed the ENETS system to be superior and nodal metastasis to be significantly associated with disease specific survival on univariate analysis.[60,61] Our study emphasizes the prognostic significance of grade and race in tumors ≤ 2 cm. Black race been associated with lower rates of specialist consultation, chemotherapy, and resection in pancreatic adenocarcinoma.[100] Similar factors may be affecting prognosis in black and Asian patients with small PNETs as well.

The limitations of this study include those inherent to the SEER database, such as coding errors, limited data for certain variables (for example, tumor grade), and lack of data on variables not collected by SEER (for example, mitotic rates, Ki67, incidental diagnosis, and recurrence). As discussed, the SEER database is restricted to tumors with an ICD-O-3 behavior code of 2 (in situ) or 3 (malignant), which selects for a population with artificially high rates of aggressive features. Because it is increasingly recognized that all PNETs > 0.5 cm have malignant potential, inclusion of such tumors in SEER that would have previously been designated as benign may have contributed to the observed increase in incidence. The strengths of this study include its relatively large sample size and use of population-level data.

Overall, our study confirms on a population-level that the incidence of small PNETs is increasing at a rapid rate, and that this group of tumors can display malignant behavior despite small tumor size. Furthermore, grade as well as Asian or black race were independent predictors of disease specific survival in tumors ≤ 2 cm. Resection versus observation, however, remains controversial. Additional studies that evaluate the full spectrum of benign and malignant disease, as well as prospective studies assessing the

necessary extent of lymphadenectomy will improve our understanding of the natural history of these small tumors and allow for optimization of surgical therapy.

Conclusions

Imaging has fundamentally changed the way patients with cancer present for surgical consultation. While the adoption of screening protocols in breast cancer has increased the diagnosis of localized cancers, it is uncertain whether the increasing incidences of thyroid cancers and PNETs are similarly due to the increased frequency of imaging in the era of modern medicine. Nevertheless, the increased utilization of ultrasound in the evaluation of thyroid pathology as well as frequent use of endoscopic ultrasound and axial imaging in evaluating diseases of the pancreas have likely played a role in the observed increases in incidence of small thyroid and endocrine pancreatic cancers. Furthermore, in all histologies studied, small cancers were capable of exhibiting aggressive behavior despite small tumor size, and additional studies that specifically examine the risks and benefits of surgical therapy in small tumors may clarify future surgical decision making

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