# **Metastatic Profile of Thyroid Carcinoma: A Comprehensive Review of Regional and Distant Spread Across Histological Subtypes and Global Regions**

## **I. Introduction to Thyroid Cancer Metastasis**

### **A. Defining Regional and Distant Metastasis in Thyroid Cancer**

Thyroid cancer, a malignancy originating in the thyroid gland, exhibits diverse patterns of spread, broadly categorized into regional and distant metastasis. Regional metastasis signifies the cancer's extension to anatomical sites proximal to the thyroid, primarily encompassing the lymph nodes within the neck and upper chest.1 Conversely, distant metastasis refers to the dissemination of cancer cells to organs and tissues remote from the primary tumor, such as the lungs, bones, liver, or brain.1 This distinction is of paramount clinical importance as it fundamentally influences the staging, therapeutic approach, and prognostic outlook for patients with thyroid cancer. Generally, regional spread is associated with a more favorable prognosis compared to distant metastatic disease.

The staging systems for the principal histological types of thyroid cancer—differentiated (papillary or follicular), anaplastic, and medullary—explicitly incorporate these definitions of spread. For instance, in papillary or follicular thyroid cancer patients aged 55 years and older, the designation of Stage IVB indicates the presence of distant metastasis.2 Similarly, Stage IVC in anaplastic thyroid cancer and Stage IVC in medullary thyroid cancer are defined by the cancer having spread to distant parts of the body.2

The differentiation between regional and distant metastasis is a critical determinant in prognostic stratification across all thyroid cancer subtypes. However, the precise anatomical boundaries defining "regional" lymph node basins (e.g., central compartment, lateral cervical levels) can be subject to nuanced interpretation. Variations in how different studies or cancer registries define or group these regional nodes could potentially lead to slight differences in reported regional metastasis rates, even for the same cancer subtype. This highlights the importance of standardized anatomical definitions and meticulous pathological assessment in reporting regional lymph node involvement to ensure the accuracy and comparability of metastasis data across diverse clinical studies and geographical contexts.

### **B. Overview of Thyroid Cancer Histological Classification (Focus on WHO 2022)**

The accurate classification of thyroid neoplasms is essential for understanding their biological behavior, including metastatic potential. The World Health Organization (WHO) classification of endocrine and neuroendocrine tumors serves as the global standard. The 5th edition, released in 2022, introduced significant refinements to the categorization of thyroid tumors, building upon previous editions to better align histological features with molecular profiles and clinical outcomes.3

The main histological types of thyroid cancer remain Papillary Thyroid Carcinoma (PTC), Follicular Thyroid Carcinoma (FTC), Medullary Thyroid Carcinoma (MTC), and Anaplastic (Undifferentiated) Thyroid Carcinoma (ATC).6 The 2022 WHO classification further elaborates on follicular cell-derived neoplasms, dividing them into benign tumors (e.g., follicular adenoma, oncocytic adenoma), low-risk neoplasms (e.g., Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features - NIFTP), and malignant neoplasms.4

Key changes relevant to metastatic potential in the 2022 WHO classification include:

* **Detailed Subtyping of PTCs**: While many morphological subtypes of PTC are recognized, the 2022 classification emphasizes detailed subtyping of papillary microcarcinomas similar to their larger counterparts and advises against designating them merely as a "subtype" of PTC.4
* **Reclassification of Follicular Thyroid Carcinoma (FTC) and Oncocytic Carcinoma (OTC)**: Oncocytic carcinoma (previously often termed Hürthle cell carcinoma) is firmly established as a distinct entity separate from FTC.4 Both FTC and OTC are now categorized based on the degree of capsular and vascular invasion into minimally invasive (MI), encapsulated angioinvasive (EA), and widely invasive (WI) tumors.8 This reclassification has demonstrated improved risk stratification for outcomes like disease-specific survival (DSS) and radioactive iodine (RAI)-refractory disease, which are intrinsically linked to metastatic behavior.8
* **High-Grade Follicular Cell-Derived Malignancies**: This category now includes both the traditional Poorly Differentiated Thyroid Carcinoma (PDTC) and the newly defined Differentiated High-Grade Thyroid Carcinoma (DHGTC). DHGTC encompasses PTC, FTC, or OTC that exhibit high-grade features (tumor necrosis and/or increased mitotic activity, specifically ≥5 mitoses per 2 mm2) but otherwise retain their differentiated architecture.3 These high-grade features are associated with more aggressive behavior and higher metastatic potential.
* **Anaplastic Thyroid Carcinoma (ATC)**: Remains the most undifferentiated form. Notably, squamous cell carcinoma of the thyroid is now considered a pattern of ATC.4
* **Other Entities**: Cribriform-morular thyroid carcinoma is no longer classified as a PTC subtype but as a distinct entity.4 Salivary gland-type carcinomas of the thyroid (e.g., mucoepidermoid carcinoma, secretory carcinoma) and thymic tumors within the thyroid are also distinctly classified.3

The evolution of WHO classifications, culminating in the 2022 update, reflects a more profound understanding of tumor biology. This progression moves beyond simple histological pattern recognition to incorporate critical parameters like the extent of invasion and specific molecular features, which are more direct and reliable predictors of metastatic potential than some older, broader categorizations. Consequently, future epidemiological studies and clinical trial reports on thyroid cancer metastasis should adhere to the 2022 WHO classification to ensure accuracy, comparability, and relevance to current clinical practice. Historical data based on previous classifications may require careful re-evaluation when considering the metastatic rates of newly defined or reclassified entities.

**Table 1: Overview of Selected Malignant Thyroid Neoplasms (WHO 2022 Classification Relevant to Metastasis)**

| **Category** | **Key Malignant Neoplasms/Subtypes Discussed for Metastasis** |
| --- | --- |
| **Follicular Cell-Derived Neoplasms - Malignant** | Papillary Thyroid Carcinoma (PTC) and its variants (Classical, Invasive Encapsulated Follicular Variant, Tall Cell, Hobnail, Diffuse Sclerosing, Solid, Columnar Cell, Oncocytic Variant) |
|  | Follicular Thyroid Carcinoma (FTC) (Minimally invasive, Encapsulated angioinvasive, Widely invasive) |
|  | Oncocytic Carcinoma of the Thyroid (OTC) (Minimally invasive, Encapsulated angioinvasive, Widely invasive) |
|  | Follicular-Derived Carcinomas, High-Grade (Poorly Differentiated Thyroid Carcinoma, Differentiated High-Grade Thyroid Carcinoma) |
|  | Anaplastic Follicular Cell-Derived Thyroid Carcinoma (ATC) |
| **Thyroid C-Cell-Derived Carcinoma** | Medullary Thyroid Carcinoma (MTC) |
| **Mixed Medullary and Follicular Cell-Derived Carcinomas** | Mixed Medullary-Follicular Carcinoma (MMFC) |
| **Salivary Gland-Type Carcinomas of the Thyroid** | Mucoepidermoid Carcinoma (TMEC), Secretory Carcinoma of Salivary Gland Type (SC) |
| **Thyroid Tumors of Uncertain Histogenesis** | Cribriform Morular Thyroid Carcinoma |

*Source: Adapted from.3 Note: This table focuses on malignant entities for which metastasis data is pertinent to the report's scope.*

## **II. Metastasis in Papillary Thyroid Carcinoma (PTC) and its Subtypes**

Papillary Thyroid Carcinoma (PTC) is the most prevalent form of thyroid cancer, accounting for approximately 75-85% of all cases.6 While PTC generally carries a favorable prognosis, its metastatic behavior, particularly its propensity for lymphatic spread, is a defining characteristic.

General PTC Metastasis Profile

PTC frequently metastasizes to regional lymph nodes. Reports indicate that around 30% of individuals present with metastatic PTC at the time of diagnosis, which can include regional or, less commonly, distant spread.13 Lymphatic dissemination is more characteristic than hematogenous spread.12 The prevalence of distant hematogenous metastasis at presentation is estimated to be between 5-10%.12 A comprehensive autopsy study conducted in the Netherlands revealed distant metastases in 17.3% of PTC patients, offering a perspective on the ultimate metastatic burden.14

* **Regional Metastasis**: A significant proportion of PTC patients, estimated between 39% and 90% (with a general figure around 50%), exhibit regional lymph node involvement at presentation.12 These metastases commonly occur in the ipsilateral jugular chain of lymph nodes (approximately 88% of nodal cases), with levels III and IV being the most frequently affected (73%).12 In some instances, approximately 20% of patients, palpable cervical lymph node metastases are the initial manifestation of the disease.12 A US-based study utilizing the Surveillance, Epidemiology, and End Results (SEER) database indicated that cervical lymph node involvement in classic PTC was 51.2%.15
* **Distant Metastasis**: Distant spread at presentation is less common, occurring in 5-10% of PTC patients.12 The lungs are the most frequent site of distant metastasis.2 The Dutch autopsy series found lung involvement in 79.7% of PTC cases that had metastasized distantly.14 Bones are another significant site for distant spread, identified in 23.7% of metastatic PTC cases in the same Dutch study.14 The presence of distant metastases invariably worsens the prognosis.13

The notable frequency of regional lymph node metastasis in PTC, even in tumors that might otherwise be considered low risk based on primary tumor characteristics, underscores the necessity for thorough preoperative evaluation of the neck and meticulous intraoperative assessment. This high rate of regional spread, often occult, influences decisions regarding the extent of thyroidectomy and the appropriateness of adjuvant radioactive iodine therapy. While distant metastasis is less common than in more aggressive thyroid cancer histologies, its occurrence remains a critical factor for long-term outcomes.

### **A. Classical/Conventional Papillary Thyroid Carcinoma (cPTC)**

Classical Papillary Thyroid Carcinoma (cPTC), also known as conventional PTC, is the most common histological subtype, constituting approximately 50% 12 to 68% 17 of all PTCs. Its metastatic behavior serves as a benchmark for comparison with other PTC variants.

* **Regional Metastasis**: cPTC exhibits a high propensity for regional lymph node involvement, with rates at presentation ranging from 39% to as high as 90% in some series.12 Data from the US SEER program indicated that 27% of PTC patients (a category largely composed of cPTC) had lateral neck nodal metastases at presentation 18, while another SEER-based analysis focusing specifically on cPTC reported cervical lymph node involvement in 51.2% of cases.15
* **Distant Metastasis**: The rate of distant metastasis at presentation for cPTC is generally reported to be between 5-10%.12 However, some large database studies, such as from SEER, have reported lower rates of distant metastasis specifically for cPTC, around 1%.19 A European study (though based on data from a US academic institution, potentially reflecting a specific referral population) found lung metastases in 3.0% and bone metastases in 0.5% of classic PTC cases.15 An Indian study reported a distant metastasis rate of 3.4% in a cohort of 87 conventional PTC patients.20

Despite being termed "conventional" and generally associated with a favorable prognosis, a clinically relevant fraction of cPTC patients presents with or subsequently develops metastases. This observation suggests an underlying biological heterogeneity even within this common subtype, where factors beyond basic histology, such as specific molecular alterations or aspects of the tumor microenvironment, likely play a role in determining metastatic potential. Further research into molecular markers within cPTC is essential to better identify the subset of patients at higher risk for distant metastasis, which could pave the way for more personalized surveillance and treatment strategies.

### **B. Follicular Variant Papillary Thyroid Carcinoma (FVPTC)**

The Follicular Variant of Papillary Thyroid Carcinoma (FVPTC) is the most common variant of PTC, accounting for approximately 30-33% of PTC cases.12 It is characterized by a predominantly follicular growth pattern but with the nuclear features typical of PTC. The understanding and classification of FVPTC have evolved significantly, with the 2022 WHO classification distinguishing *Invasive Encapsulated Follicular Variant PTC* (IEFVPTC) as a malignant entity requiring specific attention, while non-invasive encapsulated forms are now largely categorized as NIFTP (Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features), a low-risk neoplasm.3 Metastasis data for FVPTC primarily pertains to its invasive forms.

* **Regional Metastasis**: Invasive forms of FVPTC are associated with frequent lymph node metastases.17 A US SEER study reported a 16% lymph node metastasis rate for FVPTC, which was less common than the 34% seen in cPTC.19 A study from a US academic institution (often reflecting European and North American referral patterns) indicated 30.5% cervical lymph node involvement for FVPTC.15 The metastatic behavior can vary significantly based on FVPTC subtypes; for example, a Dutch study found no central nodal metastasis in encapsulated FVPTC (EFVPTC) or non-encapsulated non-invasive FVPTC, but 100% central nodal involvement in diffuse FVPTC.21 An Asian study from Korea focusing on encapsulated PTC reported a lymph node metastatic rate of only 3% (2/63) for E-FVPTC, markedly lower than the 26% observed in encapsulated cPTC.22
* **Distant Metastasis**: US SEER data indicated a 2% distant metastasis rate for FVPTC.19 The European-based study (US institution) reported lung metastases in 2.7% of FVPTC patients.15 The Korean study on E-FVPTC found distant metastasis in 6.3% of cases (4/63); notably, all these cases had extensive capsular and/or vascular invasion and lacked nodal disease.22

The metastatic behavior of FVPTC is critically dependent on its sub-classification, particularly the presence and nature of invasion (capsular and/or vascular) and whether the growth pattern is encapsulated or infiltrative/diffuse. The broad term "FVPTC" is insufficient for accurately prognosticating metastatic risk without these crucial pathological distinctions. This underscores the clinical importance of the refined WHO 2022 classification, which specifically identifies IEFVPTC as a malignant entity with metastatic potential. Pathological reports must meticulously detail these characteristics to guide appropriate clinical management. Older studies that aggregated all FVPTC subtypes may have obscured the true metastatic risk associated with the more aggressive forms like IEFVPTC and diffuse/infiltrative FVPTC.

### **C. Tall Cell Variant (TCV)**

The Tall Cell Variant (TCV) of PTC accounts for approximately 1-13% of all PTCs and is recognized as an aggressive variant.12 It is histologically defined by the presence of cells whose height is at least three times their width.23 TCV is often associated with older age at presentation, larger tumor size, a higher likelihood of extrathyroidal extension (ETE), and consequently, a poorer prognosis compared to cPTC.23

* **Regional Metastasis**: TCV demonstrates an increased incidence of regional lymph node metastases.24 Specific studies have reported cervical lymph node metastasis rates of 39.6% 24 and 56.3% 23 for TCV.
* **Distant Metastasis**: Distant metastases are more common in TCV than in classical PTC.25 Reported rates include 8.3% from a large US SEER database analysis 24 and 6.2% in a smaller Korean series.23 While rare, brain metastases from TCV have also been documented.26

Data from various geographical regions, including North America (SEER data 24), Asia (Korean study 23, Turkish case report review 26), and Europe (Italian case reports 25), consistently indicate that TCV exhibits more aggressive clinicopathological features. These include higher rates of both regional and distant metastasis compared to cPTC, thereby solidifying its classification as a high-risk PTC variant. This consistent aggressive profile, irrespective of geographical location, mandates that patients diagnosed with TCV receive consideration for more aggressive initial treatment strategies and are enrolled in more intensive long-term surveillance protocols to monitor for recurrence and metastasis.

### **D. Hobnail Variant (HVPTC)**

The Hobnail Variant of Papillary Thyroid Carcinoma (HVPTC) is a rare but particularly aggressive subtype of PTC, with a reported prevalence ranging from 0.3% to 2.7% of PTC cases.12 It is characterized histologically by cells featuring apically placed nuclei, which create a "hobnail" or "micropapillary" appearance.27 This variant is associated with aggressive clinical behavior, frequent local recurrences, and notably high rates of metastasis.27

* **Regional Metastasis**: HVPTC exhibits a very high rate of regional lymph node metastasis, with reported figures ranging from 60% to 75%.28 A systematic review and meta-analysis corroborated these findings, reporting an overall lymph node metastasis rate of 66% for HVPTC.29
* **Distant Metastasis**: The rate of distant metastasis in HVPTC is also alarmingly high, reported to be in the range of 25% to 40%.28 Common sites for distant spread include the lungs, brain, and bones. The aforementioned systematic review and meta-analysis found a pooled distant metastasis rate of 23%.29

Due to its rarity, data on HVPTC metastasis rates are primarily derived from systematic reviews pooling smaller series and case reports from international literature, rather than from large, dedicated regional cancer registries.28 The aggressive behavior of HVPTC is often linked to the accumulation of multiple genetic alterations.27 The extremely high rates of both regional and distant metastasis, often at presentation, make HVPTC a significant clinical challenge. Prompt and accurate pathological recognition of this variant is crucial, typically warranting aggressive multimodal therapeutic approaches. Given its rarity and aggressive nature, management in specialized centers with experience in such thyroid cancer variants is often recommended.

### **E. Diffuse Sclerosing Variant (DSVPTC)**

The Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma (DSVPTC) is an uncommon subtype, accounting for 0.7% to 5.3% of all PTCs.16 Histologically, it is characterized by diffuse involvement of one or both thyroid lobes, prominent fibrosis (sclerosis), squamous metaplasia, abundant psammoma bodies, and extensive lymphocytic infiltration, often mimicking Hashimoto's thyroiditis, alongside areas of conventional papillary cancer.16 DSVPTC typically occurs in younger patients, particularly women, and often presents with larger tumor sizes compared to cPTC.16

* **Regional Metastasis**: DSVPTC is associated with a significantly higher incidence of cervical lymph node metastases.16 A meta-analysis comparing DSVPTC to cPTC found an odds ratio (OR) of 5.85 for the presence of metastatic lymph nodes in DSVPTC patients.30
* **Distant Metastasis**: This variant also shows a higher propensity for distant metastases, particularly to the lungs.16 The distant metastasis rate in DSVPTC has been reported to be as high as 28%, compared to approximately 10-12% in classical PTC.16 The same meta-analysis reported an OR of 3.83 for distant metastases at presentation and an OR of 2.70 for overall distant metastasis during the course of the disease for DSVPTC versus cPTC.30

The prognosis of DSVPTC is generally considered less favorable than that of cPTC, largely due to its extensive nature and higher rates of both regional and distant spread.16 The diffuse infiltrative growth pattern and the extensive stromal reaction characteristic of DSVPTC likely contribute to its increased metastatic potential. These features may facilitate easier access to lymphatic and vascular channels, and can also make complete surgical eradication more challenging, thereby increasing the risk of local and regional recurrence. Consequently, DSVPTC typically necessitates aggressive surgical management, often involving total thyroidectomy and comprehensive lymph node dissection, followed by vigilant and extended surveillance due to the heightened risk of recurrence and metastasis. Data on DSVPTC is primarily from meta-analyses and smaller institutional series, without large specific regional registry breakdowns of metastasis rates in the provided information.

### **F. Solid Variant**

The solid variant of PTC is recognized as an aggressive subtype, estimated to comprise about 3% of all PTCs.12 It is characterized by a predominantly solid growth pattern of tumor cells that retain the characteristic nuclear features of PTC.

* **Regional Metastasis**: There is some variation in reported regional metastasis rates. One abstract indicated a high frequency of regional metastases at 62%.32 In contrast, a smaller study focusing on 28 cases of solid variant PTC from Turkey reported regional lymph node metastases in 2 out of 28 patients (7.1%) at the time of diagnosis.33
* **Distant Metastasis**: Specific rates for distant metastasis for the solid variant were not detailed in the provided information, though it is generally categorized among the more aggressive PTC subtypes.12

The discrepancy in reported regional metastasis rates (62% vs. 7.1%) for the solid variant is notable. This variation could be attributable to several factors, including differences in study populations, the stringency of diagnostic criteria used to define the "solid variant" (e.g., the percentage of solid growth required for classification), the thoroughness of lymph node evaluation in each study, and whether metastases developing after initial diagnosis were included. The lower rate of 7.1% was specifically for metastases present *at diagnosis*.33 Given the limited and potentially conflicting data, further research employing standardized diagnostic criteria and comprehensive staging is necessary to accurately delineate the metastatic potential of the solid variant of PTC.

### **G. Columnar Cell Variant (CCV)**

The Columnar Cell Variant (CCV) of PTC is a rare, aggressive subtype, accounting for only 0.15% to 0.4% of PTC cases.17 It is characterized by cells with a columnar morphology and typically has a poor prognosis. CCV tumors are often large at presentation and show a higher incidence in males and older patients compared to cPTC.34

* **Regional Metastasis**: CCV is associated with a high frequency of regional lymph node metastasis. One report cited a rate of 71%.32 A more extensive study using the US SEER database found nodal metastasis in 49.41% of CCV cases, compared to 35.91% in classic PTC.35
* **Distant Metastasis**: While distant metastases are generally uncommon at presentation for PTC overall (around 5-7%), CCV exhibits a greater propensity for such spread.34 The US SEER study reported distant metastasis in 3.01% of CCV patients, significantly higher than the 0.77% observed in classic PTC.35 There is also a case report detailing synchronous lung and pancreatic metastases from a CCV PTC, highlighting its aggressive metastatic potential to unusual sites.34

The data, particularly from large population-based registries like SEER 35, confirms that CCV, despite its rarity, has a significantly higher propensity for extrathyroidal extension, regional lymph node involvement, and distant metastasis compared to classical PTC. This aggressive behavior justifies its classification as a high-risk variant. Diagnosis of CCV should prompt consideration for more aggressive initial treatment strategies and intensive, long-term surveillance for metastatic disease.

### **H. Oncocytic Variant of PTC (OVPTC)**

The Oncocytic Variant of Papillary Thyroid Carcinoma (OVPTC) is defined by the presence of more than 75% oncocytic cells (large, eosinophilic, granular cells, also known as Hürthle cells or oxyphilic cells) that exhibit the characteristic nuclear features of PTC.4 It is important to distinguish OVPTC from Oncocytic Carcinoma (OTC), which also consists predominantly of oncocytic cells but lacks the typical nuclear features of PTC. The metastatic behavior of OVPTC is an area of ongoing study.

* **Regional Metastasis**: The reported rates of regional metastasis vary. One study found malignant lymph nodes in 57% of OVPTC patients who underwent central compartment neck dissection, a rate comparable to the 62% found in classical PTC patients in the same study (p=0.75).36 Another abstract mentioned a high frequency (100%) of regional metastases in "PTCs of oxyphilic type" 32; however, this exceptionally high figure likely pertains to a specific, possibly small or uniquely defined, cohort and should be interpreted with caution.
* **Distant Metastasis**: A study encompassing 218 patients with oncocytic PTC reported a 5-year incidence of distant metastasis (DM) of 3.4% and a 10-year incidence of 4.5%.37 This rate is relatively low but appears somewhat higher than the approximately 1% distant metastasis rate reported for cPTC in some large SEER database analyses.19

The metastatic potential of OVPTC seems to be generally comparable to, or in some aspects perhaps slightly greater than, that of classical PTC, but less aggressive than some of the overtly aggressive PTC variants. However, the data is still emerging, and historical studies may have included heterogeneous populations under the umbrella of "oncocytic PTC" or "Hürthle cell variant of PTC." Clearer distinction based on the current WHO 2022 criteria, which separates OVPTC from OTC based on nuclear features, is crucial for accurately understanding and reporting its specific metastatic risk profile.

### **I. Other PTC Subtypes**

Several other rare variants of PTC have been described, some of which have been reclassified under the 2022 WHO system.

* **Cribriform-morular variant**: This variant was historically considered a subtype of PTC. Lymph node metastases have been reported in approximately 26% of cases.17 However, the 2022 WHO classification has re-categorized this entity as "Cribriform morular thyroid carcinoma" and placed it under the heading of "Thyroid tumors of uncertain histogenesis," rather than as a PTC variant.3 This reclassification implies that its metastatic behavior, while documented, should now be considered in the context of its new, distinct classification.
* **Warthin-like variant**: This is another uncommon PTC variant. One report indicated a moderate rate of regional metastasis at 44%.32

The reclassification of entities like Cribriform-morular carcinoma away from the PTC category underscores the ongoing refinement in our understanding of thyroid tumor biology. As distinct molecular pathways and clinical behaviors are identified, tumors are more accurately categorized, which in turn impacts how their metastatic rates are attributed and understood. Epidemiological data for such reclassified entities will need to be collated and analyzed under their new classifications to provide a clearer picture of their metastatic potential.

**Table 2: Metastasis Profile of Papillary Thyroid Carcinoma and its Key Malignant Variants**

| **PTC Variant** | **Reported Regional Metastasis Rate (%)** | **Reported Distant Metastasis Rate (%)** | **Common Distant Metastatic Sites** | **Key Geographical/Source Notes** |
| --- | --- | --- | --- | --- |
| **Classical (Conventional) PTC** | 39-90 (general); 51.2 (US study); 27 (lateral neck, SEER) | 1-10 (general); 1 (SEER); 3.0 (lung), 0.5 (bone) (US institution); 3.4 (India) | Lungs, Bones | US SEER 18; US institution 15; India 20; General 12 |
| **Follicular Variant (FVPTC) - Invasive Forms (incl. IEFVPTC)** | 16 (SEER); 30.5 (US inst.); 0 (EFVPTC/NFVPTC, Dutch) to 100 (Diffuse FVPTC, Dutch); 3 (E-FVPTC, Korea) | 2 (SEER); 2.7 (lung, US inst.); 6.3 (E-FVPTC, Korea) | Lungs, Bones | US SEER 19; US institution 15; Netherlands 21; Korea.22 Rates vary significantly by specific FVPTC subtype and definition of invasion. |
| **Tall Cell Variant (TCV)** | 39.6 (SEER); 56.3 (Korea) | 8.3 (SEER); 6.2 (Korea) | Lungs, Bones, Brain (rare) | US SEER 24; Korea 23; Europe (case reports) 25; Turkey (review).26 Consistently aggressive. |
| **Hobnail Variant (HVPTC)** | 60-75 (general reviews); 66 (meta-analysis) | 25-40 (general reviews); 23 (meta-analysis) | Lungs, Brain, Bones | Pooled international data from reviews/meta-analyses due to rarity.28 Extremely aggressive. |
| **Diffuse Sclerosing Variant (DSVPTC)** | High (OR 5.85 vs cPTC, meta-analysis) | Up to 28 (general); High (OR 3.83 at presentation, OR 2.70 overall vs cPTC, meta-analysis) | Lungs | Meta-analyses 30; General reviews.16 Prognosis controversial but generally aggressive. |
| **Solid Variant** | 7.1 (at diagnosis, Turkey); 62 (general abstract) | Data limited | Data limited | Turkey 33; General abstract.32 Data sparse and somewhat conflicting. |
| **Columnar Cell Variant (CCV)** | 49.4 (SEER); 71 (general report) | 3.0 (SEER) | Lungs, Pancreas (rare) | US SEER 35; General report 32; Case report (pancreas).34 Rare but aggressive. |
| **Oncocytic Variant of PTC (OVPTC)** | 57 (central neck, US study) | 3.4 (5-yr), 4.5 (10-yr) (US study) | Data limited | US studies.36 Distinct from Oncocytic Carcinoma. |
| **Cribriform-morular Thyroid Ca.** | 26 (general report) | Data limited | Data limited | General report.17 Now classified as a distinct entity, not a PTC variant by WHO 2022.3 |
| **Warthin-like Variant** | 44 (general report) | Data limited | Data limited | General report.32 |

*Rates are approximate and can vary based on study population, diagnostic criteria, and length of follow-up. OR = Odds Ratio. IEFVPTC = Invasive Encapsulated Follicular Variant PTC.*

## **III. Metastasis in Follicular Thyroid Carcinoma (FTC) and its Subtypes**

Follicular Thyroid Carcinoma (FTC) is the second most common type of differentiated thyroid cancer, constituting approximately 5-15% of all thyroid malignancies.6 Unlike PTC, which predominantly spreads via lymphatics, FTC has a greater propensity for hematogenous (bloodstream) spread, leading to a higher incidence of distant metastases, particularly to the lungs and bones, while regional lymph node involvement is less characteristic.6 The overall rate of distant metastasis in FTC patients has been reported to range from 7% to 28% in various series.39 An autopsy study from the Netherlands found distant metastases in a substantial 38.7% of FTC patients.14 According to SEER data (2012-2018), the 5-year relative survival rate for FTC with distant spread is 67%.41

The 2022 WHO classification has significantly refined the categorization of FTC based on the extent of invasion, distinguishing three main subtypes: Minimally Invasive FTC (MIFTC), Encapsulated Angioinvasive FTC (EAFTC), and Widely Invasive FTC (WIFTC).4 This classification is crucial for prognostication and management, as the metastatic potential varies considerably among these subtypes. The introduction of EAFTC as a distinct intermediate-risk category is a key development, as it helps to better stratify patients who were previously grouped into broader, less precise categories. This refined approach necessitates a re-evaluation of historical data on FTC metastasis and underscores the importance of applying the 2022 WHO criteria in current practice and future research to accurately report metastasis rates and guide treatment decisions, such as the extent of surgery and the use of radioactive iodine.

* **Regional Metastasis**: Regional lymph node involvement in FTC is relatively uncommon. SEER data from 2004-2018 indicated that 3.9% of FTC patients were N1 stage (regional lymph node metastasis).45 Another study analyzing FTC patients with distant metastases reported N1 stage in 3.4% of those with distant metastases at initial diagnosis and in 14.3% of those who developed distant metastases during follow-up.39 Prophylactic central lymph node dissection is generally not recommended for angioinvasive and widely invasive FTC due to the risk of complications and limited therapeutic benefit.39
* **Distant Metastasis**: The lungs and bones are the most common sites for distant metastasis from FTC.2 SEER data from 2010-2019, covering 5,116 FTC patients, revealed that 4.8% presented with distant metastases at diagnosis. Of these, bone metastases accounted for 3.6%, lung metastases for 2.4%, and brain metastases for a rare 0.37%.40

### **A. Minimally Invasive FTC (MIFTC)**

MIFTC is defined by limited capsular and/or vascular invasion that is not grossly apparent and can only be identified microscopically.42 This subtype is generally associated with an excellent prognosis.39

* **Regional Metastasis**: The risk is low, and prophylactic lymph node dissection is typically not indicated.39
* **Distant Metastasis**: The rate of distant metastasis is low. A global review suggested a 1–9% rate of distant metastasis at initial treatment for tumors broadly classified as "minimally invasive or encapsulated FTC".43 A study from Serbia (Europe) analyzing patients who developed distant metastases found that among 12 patients with metachronous (later-developing) distant metastases, 4 (33.4%) had an initial diagnosis of MIFTC. Among 3 patients with synchronous (at diagnosis) distant metastases, 2 (66.8%) were MIFTC.42 It is important to note these are proportions among metastatic cases, not overall rates for all MIFTC patients. In a Dutch study applying the 2022 WHO criteria, the 10-year disease-specific survival for the related category of MIOTC (Minimally Invasive Oncocytic Carcinoma) was 100%, suggesting very low lethal metastatic potential for minimally invasive tumors 8; similar favorable outcomes are expected for MIFTC. Asian data from Japan lists cohorts including MIFTC but does not provide specific metastasis rates for this subtype alone.43

### **B. Encapsulated Angioinvasive FTC (EAFTC)**

EAFTC is a more recently emphasized entity in the WHO 2022 classification, characterized by an encapsulated tumor with clear evidence of vascular invasion, with or without capsular invasion.4 It carries a higher risk of metastasis and recurrence compared to MIFTC but is generally less aggressive than WIFTC.39

* **Regional Metastasis**: Similar to MIFTC, prophylactic central lymph node dissection is not standard practice.39
* **Distant Metastasis**: EAFTC is associated with an intermediate risk of distant metastasis. In the Serbian study, among 12 patients who developed metachronous distant metastases, 1 (8.3%) was EAFTC. Among 3 patients with synchronous distant metastases, 1 (33.2%) was EAFTC.42 The Dutch study reported a 10-year disease-specific survival of 92.9% for the analogous EAOTC, indicating an intermediate prognosis 8, with similar trends anticipated for EAFTC. Asian data from Japan in reviewed literature lists EAFTC cases within cohorts but does not isolate specific metastasis rates for this subtype.43

### **C. Widely Invasive FTC (WIFTC)**

WIFTC is defined by extensive infiltration into the adjacent thyroid parenchyma and/or extrathyroidal tissues, often with prominent vascular invasion.42 This subtype carries the highest risk of recurrence and distant metastasis among FTCs.39

* **Regional Metastasis**: While hematogenous spread is dominant, regional nodes can be involved, though prophylactic dissection is not standard.39
* **Distant Metastasis**: WIFTC has the highest propensity for distant metastasis. A global review indicated that 8–45% of WIFTC patients present with distant metastasis at initial treatment.43 The Serbian study found that among 12 patients who developed metachronous distant metastases, 7 (58.3%) had WIFTC as their primary diagnosis.42 The Dutch study showed a 10-year disease-specific survival of only 56.5% for the analogous WIOTC, reflecting significant mortality likely attributable to metastatic disease 8; similar outcomes are expected for WIFTC. Asian literature from Japan includes WIFTC in cohort studies but does not provide specific metastasis rates for this subtype alone in the reviewed material.43

**Table 3: Metastasis Profile of Follicular Thyroid Carcinoma by Invasiveness (WHO 2022)**

| **FTC Subtype (WHO 2022)** | **Reported Regional Metastasis Rate (%)** | **Reported Distant Metastasis Rate (%)** | **Common Distant Metastatic Sites** | **Key Geographical/Source Notes** |
| --- | --- | --- | --- | --- |
| **Minimally Invasive (MIFTC)** | Low; Prophylactic CND not typical | Low (e.g., 1-9% for broad "minimally invasive/encapsulated" category at initial treatment) | Lungs, Bones | Europe (Serbia): 33.4% of metachronous DM & 66.8% of synchronous DM cases were MIFTC (proportion among metastatic cases).42 Netherlands: Excellent DSS for analogous MIOTC suggests low lethal metastasis.8 Global review.43 |
| **Encapsulated Angioinvasive (EAFTC)** | Low; Prophylactic CND not typical | Intermediate | Lungs, Bones | Europe (Serbia): 8.3% of metachronous DM & 33.2% of synchronous DM cases were EAFTC (proportion among metastatic cases).42 Netherlands: Good DSS (92.9% 10-yr for EAOTC) suggests intermediate metastatic impact.8 |
| **Widely Invasive (WIFTC)** | Higher than MIFTC/EAFTC but hematogenous spread predominates | High (8-45% at initial treatment) | Lungs, Bones | Europe (Serbia): 58.3% of metachronous DM cases were WIFTC (proportion among metastatic cases).42 Netherlands: Poorer DSS (56.5% 10-yr for WIOTC) suggests high lethal metastatic impact.8 Global review.43 |

*Rates are approximate and vary by study. CND = Central Neck Dissection. DM = Distant Metastasis. DSS = Disease-Specific Survival.*

## **IV. Metastasis in Oncocytic (Hürthle Cell) Carcinoma (OTC/HCC) and its Subtypes**

Oncocytic Carcinoma (OTC), historically often referred to as Hürthle Cell Carcinoma (HCC), is a relatively rare type of thyroid cancer, accounting for approximately 3-5% of differentiated thyroid carcinomas 8 and less than 5% of all thyroid cancers.7 It is generally considered more aggressive than many other differentiated thyroid cancers and has been reported to have the highest incidence of metastasis among them.47 Up to 34% of patients with OTC may develop metastatic disease during their clinical course.47 A 2020 US-based study found regional metastasis in 11.66% and distant metastasis in 4.24% of OTC patients at the time of diagnosis.48 It is estimated that approximately one in four individuals with OTC will develop metastatic disease at some point.48

According to the 2022 WHO classification, OTC is now recognized as a distinct entity, separate from FTC. It is defined as a follicular cell-derived neoplasm composed of more than 75% oncocytic cells that lacks the characteristic nuclear features of PTC.4 Crucially, similar to FTC, OTC is further sub-classified based on the extent of invasion into minimally invasive (MIOTC), encapsulated angioinvasive (EAOTC), and widely invasive (WIOTC) categories.4 This reclassification is vital for accurately assessing metastatic risk, as not all OTCs exhibit the same aggressive behavior. Data applying this new classification has shown significantly different prognoses for these subtypes, which directly correlates with their metastatic potential. For example, a Dutch study demonstrated 10-year disease-specific survival (DSS) rates of 100% for MIOTC, 92.9% for EAOTC, and only 56.5% for WIOTC.8 This improved risk stratification highlights that the metastatic potential of OTC is highly dependent on its invasive characteristics. Older studies on "Hürthle cell carcinoma" often grouped these distinct invasive subtypes, potentially obscuring the true metastatic risk of each.

* **Regional Metastasis**: OTC can spread to regional lymph nodes, with some reports suggesting this occurs in about 20% of cases.50 The 2020 US study reported regional disease in 11.66% of patients at diagnosis.48
* **Distant Metastasis**: Hematogenous spread to distant sites such as the lungs, bones, and brain is characteristic of more aggressive OTCs.47 The 2020 US study found distant metastases in 4.24% of patients at diagnosis.48 A retrospective review from Taiwan indicated a distal metastasis rate of 12.2% for Hürthle cell cancer.51 OTC is also known for being less responsive to radioactive iodine (RAI) therapy compared to FTC, which can complicate the management of metastatic disease.8

### **A. Minimally Invasive OTC (MIOTC)**

As defined by the 2022 WHO classification, MIOTC exhibits limited invasion.

* **Metastasis**: MIOTC is expected to have a very low metastatic potential. The Dutch study reported a 10-year DSS of 100% for patients with MIOTC.8 This excellent survival rate strongly suggests a minimal risk of lethal metastasis. Specific metastasis rates for MIOTC are not yet widely reported under the new classification, but the survival data is a strong indicator of its indolent nature.
* **Geographical Notes**: The primary data supporting this favorable prognosis comes from the Netherlands.8

### **B. Encapsulated Angioinvasive OTC (EAOTC)**

EAOTC, according to the 2022 WHO classification, is an encapsulated tumor demonstrating vascular invasion, with or without capsular invasion.

* **Metastasis**: This subtype carries an intermediate metastatic potential. The Dutch study found a 10-year DSS of 92.9% for EAOTC.8 This indicates a better prognosis than widely invasive tumors but a higher risk than minimally invasive ones, implying a moderate risk of developing metastases that could impact survival.
* **Geographical Notes**: Data is primarily from the Netherlands.8

### **C. Widely Invasive OTC (WIOTC)**

WIOTC is characterized by extensive infiltration into the thyroid gland and/or adjacent tissues.

* **Metastasis**: This subtype possesses the highest metastatic potential among OTCs. The Dutch study reported a significantly poorer 10-year DSS of 56.5% for WIOTC 8, indicating a substantial risk of mortality, largely driven by metastatic disease. Supporting this, a US study focusing on oncocytic PTC (a related but distinct entity also characterized by oncocytic cells) found that widely invasive growth significantly increased the risk of distant metastasis (Hazard Ratio 17.1).38
* **Geographical Notes**: The Netherlands study provides key survival data.8 Data from a US study on oncocytic PTC with widely invasive growth also points to high distant metastasis risk.38

**Table 4: Metastasis Profile of Oncocytic Carcinoma by Invasiveness (WHO 2022)**

| **OTC Subtype (WHO 2022)** | **Reported Regional Metastasis Rate (%)** | **Reported Distant Metastasis Rate (%)** | **Common Distant Metastatic Sites** | **Key Geographical/Source Notes & DSS (as proxy for metastatic impact)** |
| --- | --- | --- | --- | --- |
| **Minimally Invasive (MIOTC)** | Low (expected) | Low (expected) | Lungs, Bones, Brain (if occurs) | Netherlands: 10-year DSS 100%.8 Specific metastasis rates sparse under new classification. |
| **Encapsulated Angioinvasive (EAOTC)** | Moderate (expected) | Moderate (expected) | Lungs, Bones, Brain | Netherlands: 10-year DSS 92.9%.8 Indicates intermediate metastatic impact. |
| **Widely Invasive (WIOTC)** | High (expected) | High (expected) | Lungs, Bones, Brain | Netherlands: 10-year DSS 56.5%.8 Indicates high lethal metastatic impact. US (oncocytic PTC study): Widely invasive growth linked to high DM risk.38 |

*General OTC: Regional metastasis ~11.7-20%; Distant metastasis ~4.2-12.2% at diagnosis/overall, up to 34% eventually develop DM.47 Rates vary by study and definition. DSS = Disease-Specific Survival. DM = Distant Metastasis.*

## **V. Metastasis in Medullary Thyroid Carcinoma (MTC)**

Medullary Thyroid Carcinoma (MTC) originates from the parafollicular C-cells of the thyroid gland and accounts for a small percentage (<5%) of all thyroid cancers. However, it is responsible for a disproportionately higher percentage of thyroid cancer-related deaths (up to 13%) due to its distinct biological behavior and metastatic potential.7 MTC can occur sporadically, which accounts for 75-80% of cases, or as part of hereditary syndromes, primarily Multiple Endocrine Neoplasia type 2 (MEN2A and MEN2B) and Familial MTC (FMTC), which constitute 20-25% of cases and are associated with germline mutations in the *RET* proto-oncogene.50

* **Regional Metastasis**: Regional lymph node involvement is a hallmark of MTC and often occurs early in the disease course. It is estimated that approximately 70% of patients presenting with a palpable thyroid nodule already have cervical lymph node metastases.52 Overall, 40-50% of MTC cases will present with regional lymph node involvement.52 Data from the US SEER database (2012-2018) indicates a 5-year relative survival rate of 92% for MTC with regional spread.41
* **Distant Metastasis**: Distant metastases are present in approximately 10-15% of MTC patients at the time of initial diagnosis.53 Common sites for distant spread include the liver, lungs, bones, and, less frequently, the brain.2 A Dutch autopsy study found the liver to be the most common site of distant metastasis in MTC, affecting 81.3% of metastatic MTC cases.14 A Korean study involving 46 MTC patients with distant metastases identified the lung (52.2%), bone (28.3%), mediastinum (19.6%), and liver (17.4%) as common metastatic locations.53 The 5-year relative survival rate for MTC with distant metastases is significantly lower, around 43%, according to SEER data.41
* **Influence of Genetic Subtype and Grading**: The metastatic potential and aggressiveness of MTC are significantly influenced by its genetic background. Sporadic MTCs with somatic *RAS* mutations are generally considered less aggressive than those with somatic *RET* p.Met918Thr mutations.52 Hereditary forms, particularly MEN2B, are associated with a very aggressive phenotype and early onset of metastases.52 A European study across five countries (EU5) found that among patients with advanced MTC, metastatic disease was present in 79% of the overall cohort and in 87% of patients confirmed to have *RET* mutations.54 Furthermore, the recently developed International Medullary Thyroid Cancer Grading System (IMTCGS), which classifies tumors into low- and high-risk categories based on histological features (necrosis, mitotic count, Ki-67 index), has shown that high-risk MTCs are associated with significantly lower distant metastasis-free survival (DMFS).57 This underscores that both genetic and histological features are critical in predicting metastatic risk. Serum biomarkers such as calcitonin and carcinoembryonic antigen (CEA) are crucial in MTC management, as their levels often correlate with tumor burden and the presence of metastases.52

**Geographical Notes on MTC Metastasis**:

* **Europe**: A Dutch autopsy study reported distant metastasis in 47.8% of MTC patients, with the liver being the predominant site (81.3% of those with DM).14 A study across five major EU countries (EU5) on advanced MTC indicated metastatic disease in 79% of patients overall, rising to 87% in those with *RET* mutations.54 Validation of the IMTCGS in a Dutch cohort confirmed its prognostic value for DMFS.57
* **North America**: SEER data (USA) provides 5-year relative survival rates of 92% for regional MTC and 43% for distant MTC.41
* **Asia**: A Korean study of 246 MTC patients found that 18.7% had distant metastasis; of these, 32.6% were synchronous and 67.4% metachronous. Common sites were lung (52.2%) and bone (28.3%).53 A large single-institution hospital-based cancer registry in China reported a 10-year overall survival rate for MTC of 85.61% 58; this reflects survival rather than direct metastasis rates but suggests a relatively better outcome in that specific cohort compared to some Western series with high distant disease rates.
* **Australia**: Reports suggest that 10% of MTC patients have distant metastases at presentation. The 10-year survival is around 70% for patients with regional node involvement and drops to 25% for those with distant spread.55

The wide spectrum of aggressiveness in MTC, influenced by its genetic underpinnings (sporadic vs. hereditary, specific *RET* mutations) and histological grade, highlights the necessity of comprehensive evaluation. Genetic testing for *RET* mutations is paramount for all MTC patients to identify hereditary cases, enable family screening, prognosticate metastatic risk, and potentially guide targeted therapies. Standardized histological grading using the IMTCGS should also be incorporated into routine pathological assessment.

**Table 5: Metastasis Profile of Medullary Thyroid Carcinoma (MTC)**

| **MTC Category/Aspect** | **Reported Regional Metastasis Rate (%)** | **Reported Distant Metastasis Rate (%)** | **Common Distant Metastatic Sites** | **Key Geographical/Source Notes** |
| --- | --- | --- | --- | --- |
| **Overall/Sporadic MTC** | 40-70 at presentation | 10-15 at diagnosis; up to 47.8 (autopsy series) | Liver, Lungs, Bones, Brain | Europe (Dutch): 47.8% DM (autopsy), liver most common (81.3% of DM).14 Australia: 10% DM at presentation.55 Korea: 18.7% DM in cohort.53 |
| **Hereditary MTC (e.g., MEN2A, MEN2B)** | High, often early | Higher in aggressive forms (e.g., MEN2B) | Liver, Lungs, Bones | EU5: 87% metastatic in RET+ advanced MTC.54 MEN2B very aggressive.52 |
| **High-Grade MTC (IMTCGS)** | Not specifically isolated | Lower DMFS in high-grade | Liver, Lungs, Bones | Netherlands: High-risk IMTCGS associated with lower DMFS (HR 5.651).57 |

*DMFS = Distant Metastasis-Free Survival. HR = Hazard Ratio. Rates are approximate and vary by study, definition, and patient cohort.*

## **VI. Metastasis in Anaplastic Thyroid Carcinoma (ATC)**

Anaplastic Thyroid Carcinoma (ATC) is the rarest, accounting for approximately 0.5% to 3% of all thyroid cancers, yet it is the most aggressive and lethal form.7 It is characterized by rapid local invasion of surrounding neck structures and a profound tendency for early and widespread distant metastasis.59 Due to its aggressive nature, all ATCs are considered Stage IV at diagnosis according to the American Joint Committee on Cancer (AJCC) staging system.2

* **Regional Metastasis**: Cervical lymph node involvement is common in ATC, with reported rates ranging from 40% 59 up to 84% in some series.63
* **Distant Metastasis**: A very high proportion of ATC patients, estimated between 50% and 75%, present with distant metastatic disease at the time of diagnosis.59 A Korean study involving 152 ATC patients found that 58% (88 patients) had distant metastases at diagnosis.63 The lungs are the most frequently affected distant site 2, followed by bones, brain, and liver.59 A Dutch autopsy series reported distant metastases in 75.4% of ATC patients, with lung involvement in 92.1% of these cases, distant lymph nodes in 43.8%, and liver in 30.3%.14 The 5-year relative survival rate for ATC with distant metastasis is extremely low, around 4% according to SEER data.41

ATC is an undifferentiated malignancy, and its histopathological appearance can be variable, with patterns including sarcomatoid, giant cell, and epithelial/squamoid features.59 However, specific metastasis rates broken down by these microscopic patterns are not extensively detailed in the available literature. The fulminant nature of ATC, characterized by its extremely high rates of both regional and distant metastasis often to multiple sites at diagnosis, explains its dismal prognosis and makes curative-intent treatment exceptionally challenging and rare. The metastatic profile necessitates a rapid diagnostic workup, including comprehensive staging for distant disease (PET/CT is often recommended 59), and a multidisciplinary approach that frequently focuses on palliative care or, in very select and rare cases of localized disease, aggressive multimodal therapy.

**Geographical Notes on ATC Metastasis**:

* **Global/General**: ATC accounts for 1-10% of all thyroid cancers globally, with distant metastasis rates at presentation between 50-75%.59
* **North America (US SEER)**: ATC comprises about 1.7% of thyroid cancer cases.59 The 5-year survival for distant ATC is a grim 4%.41
* **Europe**: The incidence is low, around 0.1-0.3 per 100,000 population in countries like Denmark, the Netherlands, and Wales.60 Metastatic disease (Stage IVc) is the presentation in approximately 55% of cases.60 The Dutch autopsy study found distant metastases in 75.4% of ATC cases.14
* **Asia**: A Korean study reported 58% distant metastasis at diagnosis, with 11% having brain involvement.63 In a Japanese cohort of advanced thyroid cancers, ATC constituted 23.6% of cases, and 89.2% of these ATC patients had metastases.67 Cardiac metastasis from ATC, though extremely rare, has been reported in India at an incidence of <2%.68
* **Australia**: Systemic metastases are reported in up to 75% of ATC patients, with the lungs being the most common site (80%).62
* **Africa**: Specific data on ATC metastasis rates from comprehensive African cancer registries is limited. One fact sheet referenced a study (likely from India, based on author affiliations in the source document 61) where 33% of an ATC cohort had metastatic disease extent.

**Table 6: Metastasis Profile of Anaplastic Thyroid Carcinoma (ATC)**

| **Metastasis Type** | **Reported Rate (%)** | **Common Sites** | **Key Geographical/Source Notes** |
| --- | --- | --- | --- |
| **Regional Metastasis (Lymph Nodes)** | 40-84 | Cervical, Intrathoracic Lymph Nodes | Global 59; Korea 63 |
| **Distant Metastasis (at presentation or overall)** | 50-75 (at presentation); 75.4 (autopsy series) | Lungs (most common, ~80-92% of DM cases), Bones, Brain, Liver, Distant Lymph Nodes | Global 59; Europe (Netherlands) 14; Korea 63; Australia 62; Japan 67 |

*DM = Distant Metastasis. Rates are approximate and reflect the aggressive nature of ATC, often with widespread disease at diagnosis.*

## **VII. Metastasis in Other and High-Grade Thyroid Carcinomas**

Beyond the four main types, several other rare thyroid carcinomas and newly defined high-grade categories exhibit distinct metastatic behaviors.

### **A. Poorly Differentiated Thyroid Carcinoma (PDTC)**

Poorly Differentiated Thyroid Carcinoma (PDTC) is an uncommon malignancy, with reported incidence figures varying from less than 5% to as high as 15% of all thyroid cancers, depending on the geographical region and diagnostic criteria utilized.7 It occupies an intermediate position in terms of aggressiveness and prognosis between well-differentiated thyroid carcinomas (DTC) and anaplastic thyroid carcinoma (ATC).69 The 2022 WHO classification includes PDTC under the umbrella of "Follicular-derived carcinomas, high-grade".3

* **Regional Metastasis**: PDTC has a significant tendency to spread to regional lymph nodes, with reports indicating that 50-85% of patients develop neck lymph node metastases.69 However, a study from Southeast Asia (Philippines) reported a lower rate of nodal metastasis at 27.8%.72
* **Distant Metastasis**: Distant metastases are also common in PDTC, with some series reporting rates up to 85%.69 The lungs and bones are frequent sites of distant spread.50 A European study from Poland found distant metastases in 14.3% of PDTC patients at diagnosis, with an additional 28.6% developing them during follow-up.70 The Southeast Asian study reported a 27.8% rate of distant metastasis (lung 16.7%, bone 11.1%).72 A small Canadian series of 21 PDTC patients noted distant metastasis in 19% (4 patients).71

The reported incidence and metastatic rates of PDTC show considerable geographic variation. This may be partly influenced by historical differences in diagnostic criteria (e.g., the Turin criteria versus the Memorial Sloan Kettering Cancer Center criteria) 69 and potentially by environmental factors such as iodine deficiency, which has been suggested to correlate with higher PDTC incidence in regions like Northern Italy.70 Standardization of diagnostic criteria, as promoted by the WHO 2022 classification, is crucial for obtaining more consistent global data on the metastatic behavior of PDTC.

**Geographical Notes on PDTC Metastasis**:

* **Global/General**: Prevalence varies (2-15%), with higher rates in some European regions (e.g., Northern Italy) possibly linked to iodine deficiency.69 General rates: Regional LN metastasis 50-85%; Distant metastasis up to 85%.69
* **Europe**: Poland: 14.3% DM at diagnosis, 28.6% developed later.70 Northern Italy: Higher prevalence noted, up to 15%.70
* **Asia**: Philippines: Regional LN 27.8%; Distant metastasis 27.8%.72 Japan: In an advanced thyroid cancer cohort, PDTC constituted 10%, and 98.2% of these PDTC cases had metastasis.67
* **North America**: Canada: 19% distant metastasis in a small series.71 US SEER: A study on DM from DTC (which would include some PDTC cases) found that 3.4% of 4470 thyroid cancer patients had DM, with common sites being lungs (91.9% of those with DM), skeleton (58.1%), and brain (9.3%).74

### **B. Differentiated High-Grade Thyroid Carcinoma (DHGTC)**

Differentiated High-Grade Thyroid Carcinoma (DHGTC) is a category formalized in the 2022 WHO classification. It applies to PTC, FTC, or OTC that retain their characteristic differentiated architecture but exhibit high-grade features, specifically tumor necrosis and/or a high mitotic count (≥5 mitoses per 2 mm2).3 The incidence of DHGTC is estimated to be less than 5% of all thyroid malignancies.27 This classification is critical because it identifies a subset of "differentiated" thyroid cancers that behave more aggressively and have a significantly higher metastatic risk than previously appreciated when they might have been grouped with their well-differentiated counterparts without high-grade features.

* **Regional Metastasis**: DHGTC is associated with a higher incidence of lymph node involvement.73 A Korean study reported regional node metastases in 12 out of 14 DHGTC cases.73
* **Distant Metastasis**: DHGTC also shows a higher incidence of distant metastases.73 One study found that the prevalence of DHGTC in a cohort of patients with poor prognosis thyroid cancer (fatal cases, metastatic, or radioiodine-refractory tumors) was 28.7%.75 A Korean study noted that 2 out of 14 DHGTC cases had organ/distant metastases.73 An Asian study focusing on advanced thyroid cancer reported that 10 out of 22 (45.5%) DHGTC cases had distant metastasis, compared to 17.9% in non-HGDTC cases.76 Another Korean study confirmed that DHGTC was associated with distant metastasis at the time of diagnosis.77

Pathologists must now specifically evaluate and report these high-grade features in otherwise differentiated thyroid carcinomas. This will lead to more accurate risk assessment and may necessitate more aggressive treatment and surveillance strategies for patients diagnosed with DHGTC, thereby altering management paradigms for tumors previously considered simply "differentiated."

**Geographical Notes on DHGTC Metastasis**:

* **Global**: Overall prevalence is low (<5% in the US, <1% in Japan), but it can be higher (>5%) in certain European regions like Northern Italy.73
* **Asia**: Korea: Regional nodes in 12/14 cases; distant metastasis in 2/14 cases.73 Another Korean study linked DHGTC with DM at diagnosis.77 A broader Asian study on advanced TC found 45.5% DM in DHGTC cases.76
* **Europe**: Higher prevalence (>5%) reported in Northern Italy.73
* **USA**: Prevalence <5%.73 One US study included in a multi-cohort table showed 5/32 DHGTC cases with organ/distant metastases.73

### **C. Mixed Medullary-Follicular Carcinoma (MMFC)**

Mixed Medullary-Follicular Carcinoma (MMFC) is an extremely rare thyroid malignancy characterized by the coexistence of both follicular cell-derived and C-cell-derived carcinomatous components within the same tumor.3 This dual differentiation poses unique diagnostic and therapeutic challenges.

* **Regional Metastasis**: Data on specific regional metastasis rates for MMFC are sparse. One case report mentioned the removal of 15 lymph nodes, implying regional involvement.79
* **Distant Metastasis**: MMFC exhibits a strikingly high rate of distant metastasis. Nearly 70% of patients present with distant metastases at the time of diagnosis.78 Common sites for distant spread include the lungs, bone, brain, and/or liver.78 This high rate of synchronous distant metastasis suggests an inherently aggressive biology, possibly arising from the complex interaction of two distinct malignant cell types or from a common progenitor cell that has undergone divergent differentiation with an aggressive potential.

**Geographical Notes on MMFC Metastasis**:

* **North America**: A study using the US National Cancer Database (NCDB) identified 153 MMFC patients and reported that nearly 70% presented with distant metastasis.78

Given its high metastatic propensity, MMFC requires careful pathological diagnosis and aggressive initial staging. Treatment strategies may need to consider therapies effective against both medullary and follicular components.

### **D. Salivary Gland-Type Carcinomas of the Thyroid**

This category includes rare primary thyroid tumors that histologically resemble carcinomas typically found in the salivary glands. The 2022 WHO classification lists Mucoepidermoid Carcinoma (TMEC) and Secretory Carcinoma (SC) of salivary gland type under this heading.3

* **Thyroid Mucoepidermoid Carcinoma (TMEC)**:
  + **Regional Metastasis**: Reported in 48% of cases.80
  + **Distant Metastasis**: Occurs in 20% of cases, with common sites being the lung (14%), bone (6%), and mediastinum (2%).80
* **Thyroid Secretory Carcinoma (SC)**:
  + **Regional Metastasis**: Reported in 64% of cases.80
  + **Distant Metastasis**: Occurs in 27% of cases. Common sites include the liver (27%), lung (18%), and rarely kidney, bone, or soft tissue (one case each reported in a review).80 It has been observed that SC arising in the thyroid appears to be more aggressive than its counterpart originating in the salivary glands.80

The data for these rare tumors are primarily based on reviews of reported cases rather than large regional registries, reflecting their infrequency.80 The observation that primary thyroid salivary gland-type carcinomas, particularly SC, can exhibit significant metastatic potential, sometimes exceeding that of their namesakes in the salivary glands, suggests a distinct biological behavior that may be influenced by the thyroid microenvironment or specific underlying molecular alterations. Clinicians should be aware of this potentially aggressive nature when these tumors are diagnosed in the thyroid.

**Table 7: Metastasis Profile of Other and High-Grade Thyroid Carcinomas**

| **Carcinoma Type** | **Reported Regional Metastasis Rate (%)** | **Reported Distant Metastasis Rate (%)** | **Common Distant Metastatic Sites** | **Key Geographical/Source Notes** |
| --- | --- | --- | --- | --- |
| **Poorly Differentiated (PDTC)** | 50-85 (general); 27.8 (Philippines) | Up to 85 (general); 14.3 at diagnosis, 28.6 later (Poland); 27.8 (Philippines); 19 (Canada); 98.2 (of advanced PDTC, Japan) | Lungs, Bones | Global/Europe 69; Asia 67; N. America.71 Incidence varies geographically. |
| **Differentiated High-Grade (DHGTC)** | High (e.g., 12/14 cases, Korea) | High (e.g., 45.5% in advanced TC cohort, Asia; 2/14 cases, Korea). Prevalence in poor prognosis TC 28.7%. | Lungs, Bones | Asia 73; Global prevalence data (US, Japan, Italy).73 Recently defined, data emerging. |
| **Mixed Medullary-Follicular (MMFC)** | Sparse data (LN removal in case report) | Nearly 70 at presentation | Lungs, Bone, Brain, Liver | N. America (NCDB).78 Rare, aggressive. |
| **Thyroid Mucoepidermoid Ca. (TMEC)** | 48 | 20 | Lung, Bone, Mediastinum | Case review data.80 |
| **Thyroid Secretory Ca. (SC)** | 64 | 27 | Liver, Lung, Kidney, Bone, Soft Tissue | Case review data.80 More aggressive than salivary gland SC. |

*Rates are approximate and based on available literature, which may be limited for rarer types.*

## **VIII. Global and Regional Perspectives on Thyroid Cancer Metastasis**

Understanding the global burden of thyroid cancer metastasis is complex due to variations in cancer incidence, diagnostic practices, healthcare systems, and the quality of cancer registration across different regions of the world.

### **A. Comparative Insights from Major Cancer Registries and Global Data**

Globally, thyroid cancer incidence has been rising, with an estimated 586,202 new cases in 2020.81 Asia bears the largest proportion of this burden, and the Western Pacific region reports the highest incidence rates.81 Despite the increasing incidence, thyroid cancer mortality remains relatively low compared to many other cancers.81 Detailed global data on stage at diagnosis by specific subtype is not uniformly available from large international databases like IARC/GLOBOCAN, which often provide overall incidence and mortality figures.83

* **North America (USA - SEER Program)**: The SEER database provides valuable population-based data. For 2012-2018, 5-year relative survival rates for distant metastatic thyroid cancer were: PTC 74%, FTC 67%, MTC 43%, and ATC 4%.41 A SEER cohort (2010-2019) of FTC patients showed 4.8% presented with distant metastases (bone 3.6%, lung 2.4%, brain 0.37%).40 For Oncocytic (Hürthle Cell) Carcinoma (2004-2018), SEER data indicated 11.7% presented with regional and 4.0% with distant metastases.85
* **Europe**:
  + **Netherlands (PALGA Registry)**: A nationwide autopsy study (1991-2010) of 650 thyroid cancer patients found distant metastatic disease in 35.1% overall. By subtype, distant metastasis rates were: PTC 17.3%, FTC 38.7%, MTC 47.8%, and ATC 75.4%. The most common distant site for PTC, FTC, and ATC was the lung, while for MTC it was the liver.14
  + **Poland**: A study on PDTC reported 14.3% with distant metastases at diagnosis, and an additional 28.6% developed them later.70
  + **Italy**: Higher prevalence of PDTC and DHGTC is noted in Northern Italy.70
  + **EU5 (France, Germany, Italy, Spain, UK)**: For advanced MTC, 79% were metastatic overall, and 87% of *RET* mutation-positive cases were metastatic.54
  + Other European registries (UK, Germany, Spain, Nordic countries) are mentioned in the literature, but specific metastasis rates by subtype are not consistently detailed in the provided snippets.86
* **Asia**:
  + **Taiwan**: A retrospective review indicated distal metastasis rates of 2.4% for PTC, 10.5% for FTC, and 12.2% for Hürthle cell cancer.51
  + **Korea**: In a cohort of 246 MTC patients, 18.7% had distant metastasis.53 For ATC, 58% presented with distant metastasis.63 A study on DHGTC found it was associated with distant metastasis at diagnosis.77 An institutional database of 3,145 DTC patients showed only 12 cases (0.38%) of distant metastasis, potentially reflecting a screened or earlier-stage population.91
  + **Japan**: In a cohort of advanced thyroid cancers, metastasis was present in 95.4% of PTC, 98.2% of FTC, 98.2% of PDTC, and 89.2% of ATC cases.67
  + **China**: General incidence and mortality data are available, with a low mortality-to-incidence (M/I) ratio for thyroid cancer (0.04), suggesting good data quality or low mortality relative to the high incidence.92
  + **India**: A smaller study (n=170) reported an overall metastasis rate of 1.8% (1.8% in PTC), with lymph node metastasis in 11.2%.20
* **Australia**: For MTC, 10% present with distant metastases.55 For ATC, systemic metastases occur in up to 75% of patients.62 General thyroid cancer incidence trends are also reported.93
* **Africa**: Data on specific metastasis rates by subtype from comprehensive African cancer registries is sparse. General thyroid cancer incidence for South Africa is available.94 One fact sheet 61 referenced a study where 33% of an ATC cohort had metastatic disease, but the study origin appears to be India. Pediatric PTC data from SEER (not an African registry) indicates higher distant metastasis rates in children.95
* **South America (Brazil)**: A study on 33 DTC patients (mostly metastatic cases) reported lung (69.7%) and bone (66.7%) as common distant metastatic sites, with 42.4% having distant metastasis at diagnosis.96

Significant geographical disparities are evident, not only in the overall incidence of thyroid cancer—which is partly attributed to varying intensities of diagnostic scrutiny leading to "overdiagnosis" of indolent tumors in some regions 81—but also critically in the availability and granularity of metastasis data categorized by specific histological subtypes. High-income countries with well-established, population-based cancer registries (e.g., SEER in the USA, PALGA in the Netherlands) provide more detailed and subtype-specific information on metastatic spread. In contrast, comprehensive data from many low- and middle-income countries, particularly within Africa and parts of Asia and South America, is often limited, derived from single-institution experiences, or focused on overall incidence rather than detailed metastatic patterns. This disparity significantly hampers the ability to construct a truly global and uniformly detailed picture of thyroid cancer metastasis across all subtypes and regions. Such limitations impact the global understanding of the burden of metastatic thyroid cancer and the effective allocation of resources for cancer control worldwide.

### **B. Challenges and Limitations in Global Data Comparability for Metastasis Rates**

Directly comparing thyroid cancer metastasis rates across different geographical regions and over various time periods is fraught with challenges. Variations in diagnostic practices, including the intensity of screening programs, the utilization of fine-needle aspiration (FNA) cytology, and access to advanced imaging modalities, can significantly influence the detected incidence rates and the stage at which thyroid cancer is diagnosed.81 For instance, the well-documented "epidemic" of thyroid cancer observed in some countries is largely attributed to the increased detection of small, localized PTCs, which, if not properly stratified, would artificially lower the overall percentage of metastatic cases in those populations.84

Furthermore, histopathological interpretation and the application of classification criteria may vary between institutions and pathologists, and have certainly evolved over time, particularly with the updates to the WHO classification system.69 The adoption of new classifications, such as the 2022 WHO guidelines, is not instantaneous or uniform globally, meaning that historical data and even some contemporary reports might use older, less precise subtype definitions.

The completeness, quality, and coding standards of cancer registry data also differ substantially across countries.92 Not all registries capture the same level of detail regarding specific metastatic sites, the exact histological subtype according to the latest WHO criteria, or the nuances of tumor invasion. These heterogeneities in healthcare infrastructure, diagnostic approaches, pathological practices, and cancer registration systems collectively impair the ability to conduct robust global comparisons of metastasis rates. Therefore, caution is warranted when interpreting and comparing data from disparate sources, and efforts towards global harmonization of diagnostic criteria, staging protocols, and cancer registration practices are essential for achieving a more accurate and comparable understanding of international trends in thyroid cancer metastasis and outcomes.

**Table 8: Summary of Reported Distant Metastasis (DM) Rates for Major Thyroid Cancer Histotypes from Selected Population-Based Registries/Large Studies**

| **Histological Subtype** | **Region/Registry** | **Reported Distant Metastasis Rate (%)** | **Common Distant Sites** | **Source(s)** |
| --- | --- | --- | --- | --- |
| **Papillary (PTC)** | USA (SEER, survival proxy) | 74 (5-yr relative survival with DM) | Lungs, Bones | 41 |
|  | Netherlands (PALGA, autopsy) | 17.3 | Lungs (79.7% of DM), Bones (23.7% of DM) | 14 |
|  | USA (SEER, C-PTC) | 1 | Lungs, Bones | 19 |
|  | Taiwan (review) | 2.4 | - | 51 |
|  | Japan (advanced TC cohort) | 95.4 (of advanced PTC) | Lungs, Lymph Nodes, Bones | 67 |
| **Follicular (FTC)** | USA (SEER, survival proxy) | 67 (5-yr relative survival with DM) | Lungs, Bones | 41 |
|  | Netherlands (PALGA, autopsy) | 38.7 | Lungs (72.9% of DM), Bones (37.5% of DM) | 14 |
|  | USA (SEER, at diagnosis) | 4.8 (Bone 3.6, Lung 2.4, Brain 0.37) | Bones, Lungs, Brain | 40 |
|  | Taiwan (review) | 10.5 | - | 51 |
|  | Japan (advanced TC cohort) | 98.2 (of advanced FTC) | Bones, Lungs | 67 |
| **Oncocytic (OTC/HCC)** | USA (SEER) | 4.0 (at diagnosis) | Lungs, Bones, Brain | 48 |
|  | Taiwan (review) | 12.2 | - | 51 |
|  | Netherlands (WIOTC DSS proxy) | 56.5 (10-yr DSS for WIOTC) | Lungs, Bones, Brain | 8 |
| **Medullary (MTC)** | USA (SEER, survival proxy) | 43 (5-yr relative survival with DM) | Liver, Lungs, Bones | 41 |
|  | Netherlands (PALGA, autopsy) | 47.8 | Liver (81.3% of DM), Lungs (56.3% of DM) | 14 |
|  | EU5 (advanced MTC) | 79 (overall aMTC); 87 (RET+ aMTC) | - | 54 |
|  | Australia (at presentation) | 10 | - | 55 |
|  | Korea (cohort) | 18.7 | Lungs, Bones, Mediastinum, Liver | 53 |
| **Anaplastic (ATC)** | USA (SEER, survival proxy) | 4 (5-yr relative survival with DM) | Lungs, Bones, Brain, Liver | 41 |
|  | Netherlands (PALGA, autopsy) | 75.4 | Lungs (92.1% of DM), Distant LNs, Liver | 14 |
|  | Korea (at diagnosis) | 58 (Brain 11) | Lungs, Bones, Brain, Liver | 63 |
|  | Australia (overall) | Up to 75 | Lungs (80% of DM), Bones, Brain | 62 |
|  | Japan (advanced TC cohort) | 89.2 (of advanced ATC) | Lungs, Lymph Nodes | 67 |
| **Poorly Differentiated (PDTC)** | Poland (at diagnosis + follow-up) | 14.3 (at diagnosis) + 28.6 (later) | Lungs, Bones | 70 |
|  | Philippines (SE Asia) | 27.8 | Lungs, Bones | 72 |
|  | Japan (advanced TC cohort) | 98.2 (of advanced PDTC) | Lungs, Bones, Lymph Nodes | 67 |

*Rates are highly variable based on data source (e.g., clinical diagnosis vs. autopsy), patient selection (e.g., all cases vs. advanced cases), definition of distant metastasis, and follow-up duration. Survival data is used as an indirect proxy for the impact of distant metastasis where direct rates are unavailable. LN = Lymph Node.*

## **IX. Conclusion**

This report has synthesized available data on the regional and distant metastasis rates of thyroid cancer across its diverse histological subtypes, with consideration for geographical variations and the pivotal 2022 WHO classification.

A clear distinction exists in metastatic behavior among the main thyroid cancer types. Papillary thyroid carcinoma, the most common type, frequently metastasizes to regional lymph nodes (up to 90% in some PTC variant series), but distant metastasis is less common at presentation (typically 1-10% for classical PTC), primarily targeting the lungs and bones. However, aggressive PTC variants like Tall Cell, Hobnail, Diffuse Sclerosing, and Columnar Cell variants exhibit significantly higher rates of both regional and distant spread, underscoring the importance of accurate subtyping.

Follicular thyroid carcinoma preferentially spreads hematogenously, with distant metastasis (lungs and bones being common sites) reported in 4.8% to 28% of cases, depending on the study and definition of invasiveness. The 2022 WHO reclassification of FTC and Oncocytic Carcinoma (OTC) into minimally invasive, encapsulated angioinvasive, and widely invasive categories has substantially improved risk stratification. Widely invasive forms of both FTC and OTC demonstrate the highest metastatic potential and poorest prognoses, while minimally invasive forms are largely indolent. Encapsulated angioinvasive subtypes represent an intermediate-risk group. OTC, in general, tends to be more aggressive than FTC, with higher overall metastatic rates among differentiated carcinomas.

Medullary thyroid carcinoma often presents with regional lymph node involvement (40-70%), and distant metastases (liver, lungs, bones) occur in 10-15% of cases at diagnosis. Genetic factors, particularly *RET* mutations and associated MEN syndromes, as well as histological grading via the IMTCGS, significantly influence MTC's metastatic propensity. Anaplastic thyroid carcinoma remains the most aggressive form, with the vast majority of patients (50-75%) presenting with distant metastases, most commonly to the lungs, leading to a dismal prognosis.

Other rare and high-grade thyroid carcinomas, including Poorly Differentiated Thyroid Carcinoma (PDTC), the newly defined Differentiated High-Grade Thyroid Carcinoma (DHGTC), Mixed Medullary-Follicular Carcinoma (MMFC), and Salivary Gland-Type Carcinomas, generally exhibit aggressive behavior with high rates of regional and/or distant metastasis. The formalization of DHGTC is particularly crucial for identifying a subset of differentiated cancers with unexpectedly poor outcomes driven by high-grade features.

Geographically, data on metastasis rates is most robust from North American (SEER) and some European (e.g., Dutch PALGA) population-based registries. Asian countries like Korea and Japan also contribute significant cohort data, particularly for advanced cancers. However, comprehensive, subtype-specific metastasis data from many regions, including large parts of Africa, South America, and other areas of Asia, remains limited. This disparity, coupled with variations in diagnostic intensity, classification adherence, and registry quality, poses challenges for a truly global comparative analysis.

The evolution of the WHO classification, especially the 2022 update, marks a significant advancement in aligning histological categories with biological behavior and metastatic potential. Future research and cancer registration efforts should universally adopt these updated criteria to ensure more accurate and comparable global data. Continued investigation into the molecular drivers of metastasis across all subtypes is essential for developing targeted therapies and improving outcomes for patients with advanced thyroid cancer. Further population-based studies are particularly needed in underrepresented geographical regions to fully understand the global landscape of thyroid cancer metastasis.

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