



SYSTEMATIC REVIEW

Unusual Sites of Metastasis of Well-Differentiated Thyroid Cancer: A Systematic Review

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Abstract

Background: Thyroid cancer is one of the most common endocrine malignancies secondary to ovarian cancer. Its incidence has surged swiftly than that of any other malignancy in recent years. Well-differentiated thyroid cancers (WDTC) are relatively common and usually slow-growing tumors with a good prognosis, including three types: Papillary, follicular, and Hürthle cell carcinoma. The first metastatic sites of these types of cancer typically involve lymph nodes, lungs, brain, and bones.

Aim: To address the unusual sites of metastasis of well-differentiated thyroid cancer, which were not discussed in the literature before.

Methods: The PICOT included adult men and women of 18 years and above, with the primary WDTC metastasized to unusual sites. MEDLINE, CINAHL, Cochrane Library, PubMed, Web of Science, Scopus, NCBI/PUBMED, Google Scholar were systematically screened for English language citations on human studies from 1990 to 2016.

Results: The case reports found in literature were summarized in the form of tables including 8 cases of choroid plexus metastases, 22 cases of retropharyngeal node metastases, 5 cases of ovarian metastases, 22 cases of renal metastases, 6 cases of breast metastases, 8 cases of pancreatic metastases, 21 cases of choroid metastases, 10 cases of pituitary metastases, 54 cases of cardiac metastases, and one case of testicular metastases.

Conclusion: Rare metastases of WDTC have been reported on distant sites such as kidneys, ovaries, heart, eyes, pancreas, pituitary, and testes. Major cases of uncommon metastases have been reported after several years of diagnosis of WDTC. Careful clinical diagnosis, along with advanced imaging techniques and immune-histopathological assays, can help to diagnose the type of tumor cells in host organs, which is essential for the development of treatment strategies.

Keywords

Well-differentiated, Rare, Metastasis, Hürthle cell, Thyroid

Introduction

Thyroid cancer is the second most common endocrine malignancy after ovarian cancer. Well-differentiated thyroid cancers (WDTC) are slow growing that have a good prognosis with proper treatment. It includes three entities, namely, papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and Hürthle cell carcinoma (HCC) [1]. The common metastasis sites for these types of cancer usually involve lymph nodes with 80% occurrence, lungs (49%), brain (0.4-1.2%), and bones (25%). In this systematic review, the unusual sites of metastasis of WDTC were addressed, which were not discussed in the literature previously. We reviewed the relevant literature of rare metastases in WDTC according to the methodology, treatment strategies, disease burden, mechanism of metastasis, genetic predisposition/SNPs predisposing to early metastasis, and pharmacotherapeutic strategies aiming at targeting early metastasis [2].

Methodology

The designed PICOT consisted of adult men and women age 18 years and above with primary WDTC metastasized to unusual sites. MEDLINE, CINAHL, Cochrane Library, PubMed, Web of Science, Scopus, NCBI/PUBMED, Google Scholar were systematically screened for English language citations on human studies from 1990 to 2016. Complete case reports, clinical studies, reviews, and full-text articles were included.

Search strategy

We searched the electronic databases to identify relevant literature using the search terms: ‘Papillary thyroid carcinoma’, ‘follicular thyroid cancer’, ‘follicular thyroid carcinoma’, ‘follicular thyroid neoplasm’, ‘papillary thyroid cancer’, ‘unusual site of metastasis of well-differentiated thyroid cancer’, ‘Hürthle cell thyroid cancer’, ‘distal metastasis of well-differentiated thyroid cancer’, ‘rare metastasis’, ‘uncommon metastasis’ and ‘unusual course of well-differentiated thyroid cancer’ Bibliography of relevant papers was also searched. Studies were screened according to pre-defined inclusion and exclusion criteria. Adults with WDTC metastasizing to sites other than lungs, brain, and bones were included. Patients of pediatric age group, undifferentiated thyroid cancer, or well-differentiated types that metastasize to bone, brain, lung, and/or metastasize to rare lymph nodes were excluded from the review. Two investigators independently reviewed the extracted studies, and a third reviewer was consulted for disagreements, if any.

Review process

Our literature search resulted in 654 articles. Two levels of screening were done that resulted in the inclusion of 105 and exclusion of 549 studies. The studies reporting common metastases and reviews of common metastatic sites were excluded. The studies reporting sites with less than 2% frequency of metastases from WDTC, providing a direct reference of original case reports with sufficient data of uncommon metastasis,

were included in the review. Of the 549 excluded studies, 210 studies were excluded by the title, 305 by reading the abstract, and 34 were excluded after reading the full text (Figure 1).

A secondary reference was used to state cardiac metastases. Total studies cited were 105 that included 103 original case reports, one secondary reference for cardiac metastases, and one review article. The case reports found in the literature were summarized in the form of tables including eight cases of choroid plexus metastases, 22 cases of Retropharyngeal Node metastases, five cases of ovarian metastases, 22 cases of renal metastases, six cases of breast metastasis, eight cases of pancreatic metastases, 21 cases of choroid metastases, ten cases of pituitary metastases, 54 cases of cardiac metastases, and one case of testicular metastases.

Choroid plexus metastasis

Papillary carcinomas of thyroid origin are well-differentiated tumors, preferably using the lymphatic route for invasion, whereas vascular route for metastases and invasion is uncommon. Distant metastases in the case of PTC are rare and usually involve breasts and lungs, affecting the prognosis negatively [1]. Metastatic invaders use the hematogenous route to choroid plexus. The tumors reported for choroid plexus metastases are renal cell carcinomas and adenocarcinomas of lung [3]. Choroid plexus metastases from thyroid neoplasm especially in case of PTC are very rare. Eight cases of choroid plexus metastases have been reported by 2016. Table 1 sum-

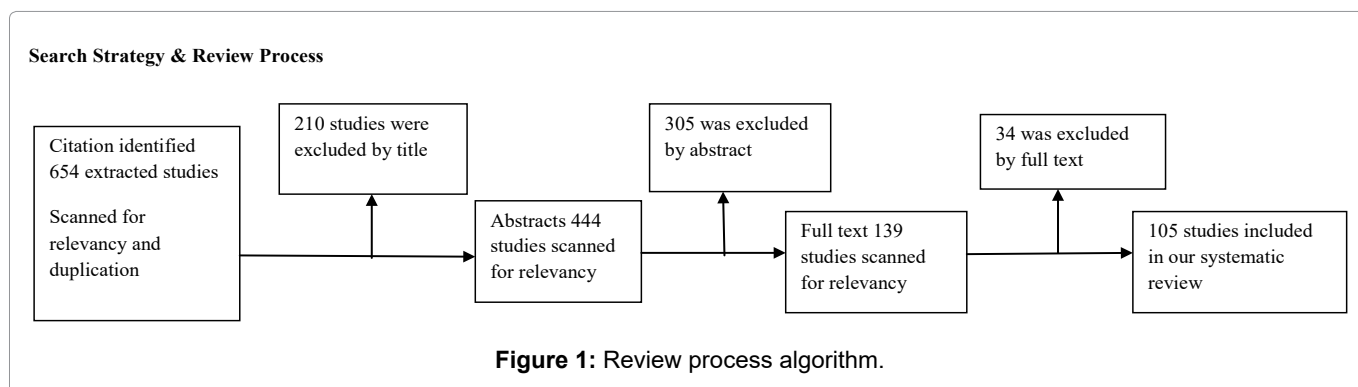


Table 1: Literature review of 8 cases of choroid plexus metastasis from thyroid cancer.

Study, year	Age/Sex	Histopathology of primary tumor	Location of metastasis
Ferrer, et al. [2]	NA	PTC (Tall cell variant)	Occipital horn
Wasita, et al. [3]	62/M	FTC and multifocal PTC (Follicular variant)	Right trigone
Wasita, et al. [3]	75/M	PTC (Conventional variant)	Right trigone
Heery, et al. [4]	88/M	PTC	Left occipital horn
Kitagawa, et al. [5]	74/F	Thyroid carcinoma	Right trigone
Manzil, et al. [6]	62/M	PTC	Left trigone
Healy, et al. [7]	70/F	PTC (Hürthle cell variant)	Left trigone
Sharifi, et al. [8]	52/F	PTC	Both lateral ventricles

FTC: Follicular thyroid carcinoma, NA: Not available, PTC: Papillary thyroid carcinoma

marizes the case reports reporting choroid plexus metastases from PTC.

PTCs are characterized histopathologically based on the growth pattern, stromal attributes, and cell types. Brain metastases from PTC account for 0.1-5%, with a median survival rate of 12.4 months. Choroid plexus metastases are usually from the neoplasms that depict slow growth patterns, as shown by eight studies summarised in [Table 1](#). However, aggressive variants of PTC are more prone to metastasize in uncommon sites. The seed and soil hypothesis of metastases and biological nature of metastatic invaders seems to play a role in choroid plexus metastases from well-differentiated slow-growing PTC.

Retropharyngeal node (nodes of Rouvière) metastasis

Metastatic invaders prefer the lymphatic route for traveling to the distant sites from thyroid neoplasm. Therefore, lymph node invasion and metastasis are not rare, but metastasis to retropharyngeal node (RPN) is uncommon, with a total number of 94 cases reported. Of these, 31 have been reported in the literature as comprehensive case studies, since 1970 and four of the case reports were for RPN metastases originated from medullary and anaplastic thyroid neoplasms. The

majority of the cases reported papillary thyroid tumor mass as the primary tumor type. No clue was provided for RPN metastases either by the histopathological characterization or the size of the primary tumor. There were reports of microscopic tumors to aggressive papillary macro masses of thyroid tumors in the literature for RPN metastases. [Table 2](#) summarises the comprehensive case reports from the literature regarding RPN metastases from thyroid carcinomas of classical variance.

Ovarian metastasis

Papillary thyroid carcinomas rarely establish distant metastasis, and the ovarian metastasis is even rarer. Twenty cases have been reported in the literature, and among them, only four cases have been reported with detailed case reports and related information from 1929 to 2016. All the cases were unilateral in metastatic sites with only one exception. According to the seed and soil hypothesis, it is unusual for the follicular cancer cells to establish metastasis in ovaries compared to the papillary cells. The ovarian metastasis is usually reported decades after the primary tumor diagnosis leading to poor prognosis. Solitary ovarian metastasis is even rarer. Case reports of ovarian metastasis extracted from the literature are summarized in [Table 3](#).

Table 2: Review of published case series of RPN metastases from thyroid cancer.

Study	Number of cases and pathology	Age/Sex
Wang, et al. [9]	22 papillary 1 follicular 2 MTC	15-73/M, 20/F
Andrews, et al. [10]	5 papillary 1 follicular	35-87/M
Kainuma, et al. [11]	3 papillary	47-68/M
Kim, et al. [12]	5 non-anaplastic	NA
Kaplan, et al. [13]	8 papillary: 1 anaplastic	47-58/F, 74/M
Ma, et al. [14]	1 papillary	24/F
Laccourreye, et al. [15]	1 papillary	49/M
Le, et al. [16]	6 papillary	NA
Otsuki, et al. [17]	5 papillary	40-84/F
Shellenberger, et al. [18]	1 MTC	36/M
Tomoda, et al. [19]	1 papillary	58/F
Desuter, et al. [20]	3 papillary	NA
Lombardi, et al. [21]	2 papillary	40/M, 52/F
Erdem, et al. [22]	1 papillary	40/M
Aygenc, et al. [23]	2 papillary	47/M, 13/F
Thomas, et al. [24]	1 papillary	46/M
Ducci, et al. [25]	2 papillary	51,68/M
Leger, et al. [26]	4 papillary	29,39/M & 42,44/F
Imai, et al. [27]	1 papillary	72/M
Saydam, et al. [28]	1 papillary	54/F
Sirotnak, et al. [29]	1 papillary	53/F
Ferrario, et al. [30]	1 papillary	47/M
Carrau, et al. [31]	1 follicular	NA/F

MTC: Medullary thyroid carcinoma, NA: Not available

Table 3: Literature review of ovarian metastasis from thyroid carcinoma.

Study	Age	Histotype	Site of metastasis
Young, et al. [32]	17	Follicular	Brain, ovaries
Logani, et al. [33]	34	Papillary	Ovaries
Brogioni, et al. [34]	38	Papillary	Thymus, lungs, ovaries, brain
Corrado, et al. [35]	26	Papillary	Lungs, ovaries
Corrado, et al. [35]	42	Papillary	Ovaries

Table 4: Characteristics and related data of patients with renal metastases from well-differentiated thyroid carcinoma.

Study	Age/Sex	Histopathology	Other synchronous distant metastases
Borde, et al. [37]	56/M	Papillary	-
Malhotra, et al. [38]	30/M	Papillary	Lungs, liver, bones, mediastinum, and adrenal
Djekidel, et al. [39]	75/M	Hurthle cell	Bone
Luo, et al. [40]	29/M	Papillary	Erector spinae
von Falck, et al. [41]	64/F	Follicular	Lungs and bone
Ahmed, et al. [36]	24/F	Papillary	-
Kumar, et al. [42]	66/F	Follicular	Adrenal
Iwai, et al. [43]	76/F	Follicular	Muscle, lung
Liou, et al. [44]	50/F	P/F	Lungs and bone
Inahara, et al. [45]	66/M	Papillary	-
Smallridge, et al. [46]	61/F	Papillary	Muscle
	53/F	Papillary	Lungs
Garcia-Sanchis, et al. [47]	65/F	Follicular	Lungs and bones
Benchekroun, et al. [48]	56/M	Papillary	-
Lam, et al. [49]	91/F	Papillary	-
Graham, et al. [50]	75/M	P/F	-
Ro, et al. [51]	47/F	Follicular	-
Tur, et al. [52]	72/F	P/F	Liver
Sardi, et al. [53]	53/M	Papillary	Lungs
Marino, et al. [54]	-/ F	Follicular	-
Johnson, et al. [55]	66/F	Follicular	Lungs
Davis, et al. [56]	49/F	Follicular	-
Takayasu, et al. [57]	44/F	Follicular	Bone

Renal metastasis

Twenty-six cases of renal metastasis of WDTC have been reported in the literature so far. However, data is not available for four patients. Ahmed, et al. reported only one case of kidney metastasis out of 3500 patients tested from December 1975 to September 2005 [36]. Multimodal imaging was used to detect renal metastases of WDTC. Table 4 summarizes 22 cases of renal metastases.

Breast metastasis

The occurrence of breast metastasis for WDTC is 1-2%. However; the solitary metastasis to the breast is very rare with one unusual case of the male patient, while all other cases were of female patients. In male patients, the breast metastasis, a rare occurrence has been diagnosed as invasive ductal carcinoma. To diagnose the cancer type before surgery, careful diagnosis

and complete immune-histochemistry analysis can be helpful. However, it was neglected in this unique case. Table 5 summarises the case reports of breast metastases in WDTC and related details.

Pancreatic metastasis

Pancreatic cancer is a rare manifestation of thyroid carcinoma, which is often asymptomatic and usually presented as an abdominal ache. Ten cases of pancreatic metastasis from WDTC were found in the literature. However, the data is available for eight cases only, which is mentioned in Table 6. Additionally, the follicular variant of PTC has been reported for pancreatic cancer so far.

Choroid metastasis

Metastasis of WDTC to choroid and orbit does not occur frequently and mostly presented as long-term disease-associated survival and synchronous metastasis

Table 5: Review of literature of breast metastasis from thyroid carcinoma.

Study	Age/Sex	Histology	Metastasis (time from primary diagnosis)
Al-Abed, et al. [58]	77/F	Hurtle cell carcinoma	10 months later
Angeles-Angeles, et al. [59]	58/F	Papillary carcinoma	20 years
Chisholm, et al. [60]	75/F	Follicular carcinoma	9 years
Vizcaino, et al. [61]	64/F	Papillary carcinoma	10 years
Farmer, et al. [62]	59/F	Tall cell variant-PTC	2 months
Cristallini, et al. [63]	57/F	Follicular carcinoma	15 years

Table 6: Cases of pancreatic metastasis secondary to papillary thyroid carcinoma reported from 1991 to 2016.

Study	Age/Sex	From the time of initial treatment	Variant
Zhu, et al. [64]	NA	NA	Tall cell
Sugimura, et al. [65]	53	7 years after TT + RAI	Classical
Jobran, et al. [66]	53/M	NA	Tall cell
Angeles-Angeles, et al. [59]	72/M	NA	Classical
Borschitz, et al. [67]	34/F	9 years after TT + RAI	Classical
	46/M	2 years after TT + RAI	Follicular
Chen, et al. [68]	82/M	5 years after TT + RAI	Classical
Alzahrani, et al. [69]	56/M	6 years after TT + RAI	Classical
Tunio, et al. [70]	67	7 years after TT + RAI	Tall cell

NA: Not available, RAI: radioactive iodine, TT: thyroid treatment

Table 7: Choroid metastasis from well-differentiated thyroid cancer.

Study	Age/sex	Primary tumor type	Other metastases
Ritland, et al. [71]	80/F	FTC	Lung, mediastinal tumor, bone
Scott, et al. [72]	50/M	FTC	Lung, bone
Slamovits, et al. [73]	64/F	FTC	Right and left paratracheal lesion, bone, lung
Arat, et al. [74]	83/M	FTC	Lung, bone, liver, skin (Widespread metastasis)
Seneviratne, et al. [75]	74/F	FTC	Bone, lung, abdominal wall
Dutton, et al. [76]	70/M	HCTC	Lung, right suprarenal metastasis
Biswas, et al. [77]	37/M	Clear-cell TC	No data available
Avram, et al. [78]	81/M	PTC	Neck recurrence, mediastinal LN, lung, bone, skin
Anteby, et al. [79]	55/F	PTC	Mediastinal LN, lung
Ahmadi, et al. [80]	43/F	PTC	Lung, bone, brain
Bucerius, et al. [81]	61/F	PTC	Mediastinal LN, lung, malignant pleural effusion, skin
Tran, et al. [82]	36/F	PTC	Multiple bone lesions, lung
Singh, et al. [83]	70/M	PTC occult microcarcinoma	No other metastases were detected
Yunta, et al. [84]	42/M	PTC (Tall-cell variant)	Bone, brain, skin
Søndergaard, et al. [85]	29/F	MTC (MEN 2B)	Bone
Shields, et al. [86]	36/F	MTC (MEN 2B)	Widespread metastases
Rosário, et al. [87]	43/M	MTC (Sporadic)	Cervical and mediastinal LN, lung, liver, bone
Bianciotto, et al. [88]	56/M	MTC (Sporadic)	Mass in the right upper eyelid, lung, cervical lymph node, liver
Yildiz, et al. [89]	63/M	MTC (Sporadic)	Widespread metastases: Bone, liver, lung, lymph nodes
Palm, et al. [90]	42/M	MTC (Sporadic)	Widespread metastases; mediastinal LN, lungs, bones, bilateral adrenals
Ozpacaci, et al. [91]	76/M	Insular TC	Left cervical LN, massive bilateral lung metastases
Puri, et al. [92]	46/M	Squamous TC	No data available

FTC: Follicular thyroid carcinoma, LN: Lymph nodes, MTC: Medullary thyroid carcinoma, PTC: Papillary thyroid carcinoma, TC: Thyroid carcinoma

to various body sites. Choroid metastasis is mostly associated with papillary carcinoma, followed by medullary and follicular carcinomas. Ultrasonography, transillumination, computed tomography (CT), and/or magnetic resonance imaging (MRI) scanning are the main techniques used to diagnose choroid metastasis clinically. A summary of case reports of choroid metastasis from WDTC is described in [Table 7](#).

Pituitary metastasis

Although lung cancer in men and breast cancer in women are associated with pituitary metastasis, yet pituitary metastasis is a rare complication of WDTC. Sufficient information about the use of imaging techniques for pituitary metastasis was not found in the literature. The diagnosis of this type of metastasis is generally delayed because the non-specific systemic symptoms (fatigue, nausea, and weight loss) of underlying malignancy and TSH suppression therapy hide hypopituitarism. Case reports have been summarized in [Table 8](#) from literature reporting pituitary metastasis with WDTC.

Cardiac metastasis

Cardiac metastasis from WDTC with a frequency of 0-2% has been associated with anaplastic thyroid carcinoma (ATC), closely followed by FTC, including HCC, & PTC. In the previous 130 years, 54 cases of WDTC have been reported with cardiac metastasis, which are summarized in [Table 9](#) [104]. Follicular carcinoma, followed by papillary carcinoma, presents the major types for direct tumor invasion involving heart via the venous system.

Testicular metastasis

Testicular metastasis is not a common complication of WDTC, with only a single case report presented in 2014. The invasion of the testis by medullary thyroid cancer has not been reported before or after 2016. A 73-year-old Caucasian man was recommended for uro-

Table 8: Pituitary metastases from thyroid malignancy.

Study	Age/Sex	Thyroid carcinoma type
Bell, et al. [93]	35/F	Papillary
Chrisoulidou, et al. [94]	60/M	Follicular
Palosi, et al. [95]	32/M	Papillary
Sziklas, et al. [96]	44/M	Papillary
Masiukiewicz, et al. [97]	56/M	Papillary
Trunnell, et al. [98]	42/F	Follicular
Johnson, et al. [99]	56/F	Papillary
Kistler, et al. [100]	69/F	Follicular
Ochiai, et al. [101]	62/F	Follicular
		Papillary
Yilmazlar, et al. [102]	43/F	Follicular
Simon, et al. [103]	33/F	Follicular

Table 9: Cardiac metastasis from thyroid malignancy.

Age	Sex	Tumor type	Year
58	M	Unknown (U)	1881
55	M	U	1898
U	U	U	1902
40	M	Adenocarcinoma	1919
52	F	Adenocarcinoma	1925
52	F	Adenocarcinoma	1933
48	F	ATC	1933
69	F	Adenocarcinoma	1936
U	U	Thyroid carcinoma-not specified	1968
U	U	U	1969
U	U	ATC	1971
U	U	Thyroid CA-not specified	1972
53	F	PTC (Well-differentiated)	1981
U	U	U	1981
U	U	Poorly differentiated thyroid carcinoma	1983
U	U	Adenocarcinoma	1985
44	F	Papillary adenocarcinoma	1985
U	U	ATC	1985
72	F	Undifferentiated thyroid carcinoma	1986
U	U	U	1986
41	M	PTC	1986
U	U	ATC	1986
62	U	Poorly differentiated FTC	1989
46	F	ATC	1990
73	F	Clear cell carcinoma	1991
87	F	FTC	1991
U	U	U	1992
61	M	ATC	1992
68	M	PTC	1994
40	M	FTC (Well-diff)	1996
U	U	PTC	1996
45	F	Follicular carcinoma of ectopic thyroid tissue in the heart	1997
70	U	Well-differentiated with undifferentiated foci	1998
62	M	FTC (Poorly differentiated)	1998
67	F	FTC (Poorly differentiated)	1999
40	M	FTC	1999
57	F	HTC	2000
62	M	PTC (Poorly differentiated)	2000
69	F	ATC (Spindle cell, undifferentiated)	2001
73	M	ATC	2001
85	M	ATC (Large cell)	2001
33	F	PTC (With follicular variant)	2003
19	F	PTC	2005
68	M	PTC	2008
74	M	MTC	2009
56	F	MTC	2010
57	F	Poorly differentiated thyroid carcinoma	2011

ATC: Anaplastic thyroid carcinoma, FTC: Follicular thyroid carcinoma, PTC: Papillary thyroid carcinoma, U: Unknown

logic surgery due to a nodule in the right testis. Histopathological and immune histopathological examinations revealed that lesions were due to WDTC metastasis [105].

Conclusion

Lungs and lymph nodes are usually overlooked as they are not the common sites of rare metastases. Therefore, major cases of rare metastasis are diagnosed late, which results in poor prognosis. Hence, it is essential to document and review the statistics, including their economic burden from time to time. The relevant data may be used to update guidelines for diagnosis and treatment. The rare metastases have been reported in kidneys, ovaries, eyes, pancreas, pituitary gland, heart, and testes in addition to the most common sites. It is imperative to look for the early clinical signs to rule out the involvement of the above-mentioned systems. Future research may help to predict rare instances of metastases and pave the way for early intervention.

Competing Interests Statement

Author declares no conflict of interest regarding this paper.

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