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**REVIEW**

# Collision Tumors of the Thyroid

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**Abstract**: *Collision tumors, rare neoplasms underlying two distinct histological types of carcinomas (with different origins) separated by normal tissue, are described in many organs including the thyroid gland, but to a lesser extent. We aim to overview the current published data concerning collision tumors of the thyroid (CTT). This is a narrative review considering papers published on PubMed through a search starting from the terms "collision" and "thyroid". Inclusion criteria are full-length articles, the English language, the timeline from inception to December 2022, and original studies with different levels of statistical evidence. We followed the main types of thyroid carcinomas: differentiated thyroid carcinoma of papillary and follicular type, anaplastic/ undifferentiated/poorly differentiated carcinoma, respectively medullary thyroid carcinoma. We identified 92 papers based on the mentioned key words criteria. We excluded 54 papers (reviews or non-thyroid CTT or other topics outside our purpose). We included in the final analysis 38 papers: 34 case reports (1 patient per paper), 2 case series (2 individuals per each article), one case series of 3 subjects, and a single study of retrospective type (including 21 subjects) – a total of 62 patients on published cases which represents the largest study on published cases to our knowledge (according to our methodology).*

**Keywords**: *collision, thyroid, thyroid cancer, papillary carcinoma, follicular carcinoma, medullary thyroid cancer, thyroidectomy, pathological report*

## INTRODUCTION

Collision tumors, rare neoplasms underlying (at least) two distinct histological types of carcinomas (with different origins) separated by normal tissue (and no mixture areas), are described in many organs (for instance, lung, stomach, breast, and ovary, etc.) including the thyroid gland, but to a lesser extent than seen in others sites (affecting less than 1% of all thyroid malignancies) [1-3]. The most common combination is papillary and medullar carcinomas, but any type of primary thyroid malignancy is reported in collision with a secondary spreading to the thyroid from a non-thyroid primary cancer or another primary type [4-6].

Collision tumors of the thyroid (CTT) are regarded as challenging in terms of recognition, poor outcome elements, and particular behavior in addition to the fact that there are still areas of the unknown regarding this chapter on thyroid neoplasms [7-9]. A distinction with composite tumors should be done (where the same mutation causes histologically different entities) [10-12]. Also, metachronous tumors (syndromic or not) represent a different category [13-14].

We aim to overview the current published data concerning CTT.

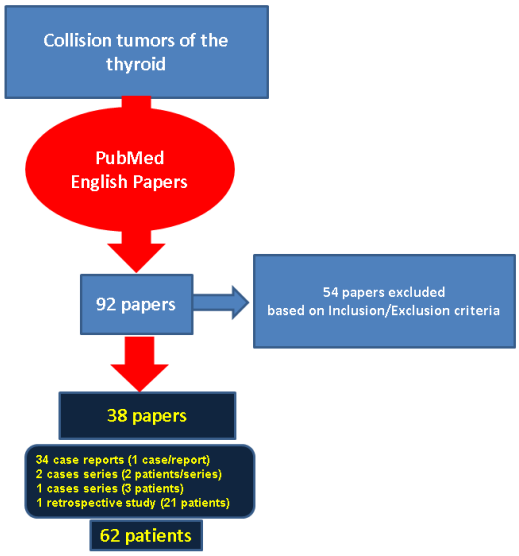
## MATERIALS AND METHODS

This is a narrative review considering papers published on PubMed through a search starting from the terms "collision" and "thyroid". Inclusion criteria are full-length articles, the English language, the timeline from inception to December 2022, and original studies with different levels of statistical evidence. Exclusion criteria are non-thyroid collision tumors, non-English papers, and reviews. We followed the main types of thyroid carcinomas: differentiated thyroid carcinoma of papillary and follicular type, anaplastic/undifferentiated/ poorly differentiated carcinoma, respectively medullary thyroid carcinoma.

## RESULTS

We identified 92 papers based on the mentioned key words criteria. We excluded 54 papers (reviews or non-thyroid CTT or other topics outside our purpose). We included in the final analysis 38 papers including 34 case reports (1 patient per paper), 2 case series (2 individuals per each article), one case series of 3 subjects, and a single study of retrospective type (including 21 subjects) – a total of 62 patients on published cases which represents the largest study on published cases to our knowledge (according to previously mentioned methodology) (Figure 1).

**Figure 1:** The method of research considering collision tumors of the thyroid




### Papillary thyroid carcinoma

Papillary thyroid carcinoma is the most frequent histological type in CTT, but, generally as a single entity, it represents the most common thyroid neoplasia [15]. Apart from the most often association of medullary thyroid neoplasia, follicular malignancy is reported as well [16-19]. The combination with thyroid metastasis (typically from lung, breast, or renal cancers, etc.) is reported at the level of case reports (the spreading may be by local extension or via blood mainstream) [20-21]. For example, a case from 2007 introduced a CTT consisting of metastasis from lung adenocarcinoma and papillary thyroid cancer in a 63-year-old female [20]. A case report from 2021 included a 60-year-old female who was identified with the same carcinoma and metastasis from osteosarcoma within a CTT. This is the first case with bone origin as the primary source reported in a CTT [21]. The combination with a second primary cancer which is not originating from the thyroid is also reported. We identified a single case of a 67-year-old male who was diagnosed with a CTT associated a papillary thyroid cancer (with lymph node metastases) and parathyroid carcinoma clinically manifested with primary hyperparathyroidism [22]. The co-existence of a squamous cell carcinoma was reported, as well, originating from different sites or of unknown origin [23-27]. In 2004, a most unusual association with metastatic liposarcoma was published (this represents a most unique combination) [28].

### Follicular thyroid carcinoma

This is the case of a 62-year-old female with follicular carcinoma (with capsular and vascular invasion) in association with a mucoepidermoid carcinoma and distant metastasis. Immunohistochemistry report might identify the mucoepidermoid differentiation of follicular malignancy over a different histological type (like mucoepidermoid malignancy) [29]. Hürthle cell carcinoma (regarded as a type of follicular group of differentiated thyroid cancers) is reported in less than 3% of thyroid malignancies, with the same ratio (of 3%) being reported for medullary thyroid carcinoma, as well. Their combination was identified on a 70-year-old female as a CTT (of note, the medullary cancer was intra-thyroidal, while the lymph nodes extension was derivate from Hürthle cell carcinoma) [30].

Interestingly, one retrospective study on 8 patients diagnosed with a primary thyroid malignancy identified the co-presence of the second histological type, meaning a follicular thyroid adenoma in association with papillary thyroid carcinoma (7/8), respectively medullary thyroid carcinoma (1/8) [31]. However, the current definition of CTT includes two malignant tumors, either primary or secondary, not a benign one like a follicular adenoma (which cannot be differentiated from a follicular carcinoma through the cytological report and it requires histological assessment) or a non-tumor – related cyst [31,32].

### Medullary thyroid carcinoma

CTT may concern the thyroid gland and/or associated lymph nodes [33,34]. For instance, there is a case published in 2021 involving a 27-year-old male presenting CTT at lymph nodes (central compartment) from papillary thyroid cancer and non-syndromic medullary thyroid cancer. The growth speed was evaluated and the authors suggested that it may be similar to what we prior know concerning each of the two malignancies [35]. Generally, collision metastasis (mostly at cervical lymph nodes) is rarely reported in the absence of a thyroid tumor itself. We identified two papers concerning collision metastasis from papillary thyroid cancer and breast malignancy in female subjects [36,37]. In another case, a 73-year-old male was admitted for collision metastasis (cervical lymph nodes) from squamous cell carcinoma of nasal origin and B-cell lymphoma [38]. A previous report from 2009 included a lymph node spreading from a primary follicular

malignancy and a squamous cell carcinoma of unknown origin [39]. Moreover, we mention the case of a 47-year-old male with collision metastasis from oral tongue–related squamous cell carcinoma and accidentally detected thyroid papillary carcinoma [40].

However, we currently do not have enough statistical evidence to compare the evolution in CTT versus non – CTT cases. The largest study particularly addressing CTT is a retrospective analysis that included the experience from 2009 to 2019 (a 10-year experience) on a tertiary care cancer. CTT (medullary + papillary) represented 4.7% of the medullary cancer series (N=21 individuals, the sex ratio of 1; mean age of 45.33 years, range between 26 and 77 years). 66.66% of the papillary cancers were situated at the right thyroid lobe; 85.7% of them were of micro-papillary type. The mean size of medullary cancer was three times larger than differentiated thyroid tumors. The contribution to lymph node spreading (which was confirmed in 76.2% of cases) was done by medullary type (87.5%), papillary cancer (12.5%), respectively both malignancies (12.5%) [41].

**Anaplastic, undifferentiated, and poorly differentiated thyroid carcinoma**

In 2022 Gupta RK. et al. reported the case of a 55-year-old female with a most unusual CTT: anaplastic thyroid malignancy (osteoclastic variant) and primary squamous cell carcinoma, each affecting a different thyroid lobe in addition to distant metastases at the level of bone, muscle and lymph nodes. However, according to WHO (World Health Organization) 2022, these two types are parts of the same malignancy spectrum thus their combination is nowadays regarded as a CTT-like lesion [42].

The "late anaplastic shift" theory concerns the identification of anaplastic thyroid carcinoma on a subject with a long history of differentiated thyroid carcinoma (either papillary or follicular) [43]. However, the synchronous identification of a differentiated tumor in association with a poorly differentiated cancer respecting a border area between them is consistent with the current concept of CTT. Here we mention the case published in 2021 by Vlad M. et al. (a 56-year-old female admitted amid the COVID-19 pandemic with a post-thyroidectomy confirmation of anaplastic cancer on the left lobe and lymph nodes spreading and a papillary micro-carcinoma on the right lobe) [44].

The presence of two highly aggressive malignancies in CTT makes the prognostic extremely severe. There is the case of a 63-year-old female confirmed with a triple CTT: poorly differentiated carcinoma, papillary carcinoma (classical and hobnail variant – this is the first case report underlying this subtype in CTT), and oncocytic (Hürthle cell) carcinoma. The hobnail pattern has been reported in anaplastic and poorly differentiated thyroid malignancies, representing a sign of a very aggressive profile with rapid evolution [45].

**DISCUSSION**

**Pathogenic loops in collision**

The field of thyroid surgery is extremely complex, while the domains of pathological reports underlying thyroid neoplasia are also extremely vast and dynamic [46-48]. The collision phenomenon has been described at many levels within multiple organs of the human body [49]. "Chance" theory is one pathogenic hypothesis [41]. CTT might be underdiagnosed, especially micro PTC [41]. Fine needle aspiration (cytological report) might not identify both tumors. However, immunohistochemistry and molecular studies might help the diagnostic [50].

Whether different immune or genetic co-morbidities might act as a trigger or epigenetic elements for CTT development there is still an open question. We mention a case of CTT (papillary and medullary neoplasia) in a 46-year-old female with multiple sclerosis and prior therapy with interferon. This is the first case of CTT on a patient with this neurologic condition (published in 2020) and there is still missing information about a potential pathogenic loop [51].

Common genetic background of both tumors underlying CTT is reported in some cases. For instance, there is the case of a 69-year-old woman with Hürthle cell carcinoma (on the right lobe) and multi-centric papillary cancer (on both thyroid lobes), associated with BRAF mutations (V600E gene) [52].

Also, in 2010, a case of non-multiple endocrine neoplasia medullary cancer in addition to papillary malignancy underlying CTT was reported in a female carrying a particular RET mutation (familial medullary thyroid cancer) [53]. A RET somatic point mutation in association with mixt medullary–papillary (including a follicular variant of papillary cancer) neoplasia was described in a 59-year-old male (a case published in 2007) [54]. Earlier data also suggest this theory [55]. Moreover, the co-presence of granulomatous inflammation in a case of papillary–medullary malignancy might represent the hallmark of common pathways [56].

**Early reports of CTT**

Of historical note, we identified the first report regarding CTT on PubMed in 1977 (non-English paper) [57]. The first English paper concerning a single case with medullary and papillary neoplasia is dated 1989 [58]. The first case series (2 out of 3 cases) on PubMed with the same mix of neoplasia is published in 1994 [59]. The first CTT with collision metastasis published in a PubMed – indexed journal dates from 1996 [60]. The first

triple CTT (on PubMed) was reported on a 27-year-old female with papillary, follicular, and medullary carcinoma [61].

**The literature-based analysis**

Overall, we identified 62 cases on published data concerning CTT, thus we may say that this particular entity remains at the level of case reports. However, paying attention to this most unusual neoplasia might improve the prognostic and help early detection of at least one of the tumors. With one exception, all cases included at least one differentiated thyroid malignancy, either papillary or follicular (including 3 cases of Hürthle cell/oncocytic carcinoma). Five reports were consistent with the concept of collision metastasis concerning local lymph nodes (near the thyroid). 16/38 articles included medullary thyroid cancers. Based on these data, following differentiated (papillary being the most frequent) and medullary types, elements of squamous cell carcinoma originating from different organs were more frequent than anaplastic/poorly differentiated carcinoma. As mentioned, the most uncommon elements in CTT were: metastatic liposarcoma and osteosarcoma, respectively, and parathyroid carcinoma. All reported cases are adults (we did not identify any pediatric cases). The age varied between 26 and 88 years. More than half of the papers included female patients, but the single study we have so far reported an equal prevalence between males and women (Table 1).

**Table 1:** Published cases on collision tumors of the thyroid according to our methodology; the cases are displayed from the most recent starting with 2022 (please see references in the text according to first column indices)

| First author, Number, Reference number | Studied population | DTC | ATC | MTC | Other types of carcinoma |
|---|---|---|---|---|---|
| Vijayvergiya G., 1, [29] | 1 case (62-y, F) | FTC | | | mucoepidermoid carcinoma |
| Yeap ZH., 2, [30] | 1 case (70-y, F) | Hürthle cell carcinoma | | MTC | |
| Vlad M., 3, [44] | 1 case (56-y, F) | micro-PTC | ATC | | |
| Li H., 4, [35] | 1 case (27-y, M) | PTC | | sporadic MTC | |
| Toyoshima MTK., 5, [45] | 1 case (63-y, F) | oncocytic carcinoma classical and hobnail PTC | poorly differentiated carcinoma | | |
| Koufopoulos N., 6, [21] | 1 case (63-y, F) | PTC | | MTC | metastasis from osteosarcoma |
| Foppiani L., 7, [22] | 1 case (67-y, M) | PTC | | | parathyroid carcinoma |
| Thomas A., 8, [41] | retrospective (N=21, F/M=1) | PTC | | MTC | |
| Feng JW, 9, [16] | 1 case (40-y, F) | PTC + FTC | | | |
| Sirbu AM., 10, [51] | 1 case (46-y, F) | PTC | | MTC | |
| Pishdad R., 11, [17] | 1 case (79-y, M) | PTC + FTC | | | |
| Dikbas O., 12, [18] | 1 case (35-y, F) | PTC | | MTC | |
| Alhanafy AM., 13, [33] | 1 case (73-y, F) | PTC | | | moderately differentiated squamous cell carcinoma |
| Sinno S., 14, [52] | 1 case (69-y, F) | PTC + Hürthle cell carcinoma | | | |
| Fulciniti F., 15, [50] | 1 case (#) | PTC | | | mucoepidermoid carcinoma |
| Gao Q., 16, [36] | 1 case (59-y, F) | PTC | | | breast cancer ## |
| Ryan N., 17, [23] | 1 case (88-y, F) | PTC | | | squamous cell carcinoma |
| Gurkan E., 18, [6] | 1 case (44-y, M)<br>1 case (77-y, M) | PTC | | MTC | |
| Plauche V., 19, [19] | 1 case (62-y, F) | PTC + FTC | | | |
| Wang X., 20, [24] | 1 case (55-y, M) | PTC | | | laryngeal squamous cell carcinoma |
| Kataria K., 21, [56] | 1 case (35-y, M) | PTC | | MTC | |
| Zeng H, 22, [37] | 1 case (49-y, F) | PTC | | | breast cancer ## |
| Sadat Alavi M., 23, [34] | 1 case (25-y, M) | PTC | | MTC | |

| | | | | | |
|---|---|---|---|---|---|
| Kakarala K., 24, [38] | 1 case (73-y, M) | | | | squamous cell carcinoma low-grade B cell lymphoma ## |
| Warman M., 25, [25] | 1 case (84-y, F) | PTC | | | squamous cell carcinoma |
| Gul K., 26, [53] | 1 case (F, #) | PTC | | MTC | |
| Jacobson AS., 27, [26] | 1 case (#) | PTC | | | squamous cell carcinoma |
| Mattioli F., 28, [39] | 1 case ( #) | FTC | | | squamous cell carcinoma ## |
| Lim YC., 29, [40] | 1 case (47-y, M) | PTC | | | squamous cell carcinoma## |
| Rekhi B., 30, [54] | 1 case (59-y, M) | PTC | | MTC | |
| Nabili V., 31, [20] | 1 case (63-y, F) | PTC | | | metastasis from lung adenocarcinoma |
| Walvekar RR., 32, [27] | 1 case (65-y, F) | PTC | | | squamous cell carcinoma |
| Rossi S., 33, [55] | 1 case (61-y, F)<br>1 case (27-y, M)<br>1 case (34-y, M) | PTC | | MTC | |
| Brandwein-Gensler M., 34, [28] | 1 case (86-y, F) | PTC | | | metastatic liposarcoma |
| Wu CJ., 35, [61] | 1 case (27-y, F) | PTC + FTC | | MTC | |
| Pastolero GC., 36, [60] | 1 case (#) | PTC | | MTC | |
| Lax SF., 37, [59] | 2 cases (#) | PTC | | MTC | |
| Gero MJ., 38, [58] | 1 case (#) | PTC | | MTC | |

We currently do not know if any data concerning the age or the sex of the subjects should be regarded as risk factors. In addition to the lack of poor survival indices (which are relevant in metastatic cases, those with late diagnostic, and anaplastic/ poorly differentiated tumors), the underlying mechanisms are controversial and we need further histological, molecular, and genetic studies.

## CONCLUSIONS

The current limits of the CTT field are correlated with the small size of published data until the present time. We still need markers of poor prognostic. Awareness is essential for early detection with a consecutive potential improvement of the outcome.

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The authors declare no conflict of interest.

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None

**Authors' contribution**
Conceptualization, A.D., and M.C.; methodology, M.C.; software, A.P.C.; validation, A.D., E.P., and M.C.; formal analysis, D.T.; investigation, A.P.C., D.T.; resources, A.D., M.C.; data curation, E.P.; writing—original draft preparation, M.C.; writing—review and editing, A.D., A.P.C, D.T., M.C.; visualization, M.C.; supervision, A.D.; project administration, A.D., M.C.
All authors have read and agreed to the published version of the manuscript.

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