

## REVIEW ARTICLE

# Black Ink Thyroid Cancer Trilogy

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## Abstract

The trilogy of papers on thyroid cancer between 2017-2019 might be regarded as a milestone in the history of cancer research. Black Ink is a rare subgroup of thyroid cancer detected by Ultrasonography (US) and classified as papillary microcarcinoma. Nevertheless very small, there is the need to early diagnosis to avoid aggressiveness behaviour.

Tumor dimension associated with malignant cytology at FNAC (Fine-Needle Aspiration Cytology) represents as important biological risk factor and could be a predictor of the papillary thyroid microcarcinoma (PTMC).

Nowadays, focusing on the size, the cut-off for non-occult tiny tumors has dropped to 0.3 cm. This value is of great relevance because represents the smallest thyroid cancer identified by ultrasonography.

The purpose of this review paper is to attempt to provide a new optimal cut-off value of the PTMC size and foresee a risk for neck lymph node metastases (LNM).

**Keywords:** Ultrasonography; Black Ink; PTMC; Tumor size; FNAC; Lymph Node Metastasis

**Abbreviations:** LNM: Lymph Node Metastasis; PTMC: Papillary Thyroid Microcarcinoma; FNAC: Fine-Needle Aspiration Cytology; WHO: World Health Organization

## Introduction

Papillary thyroid microcarcinoma (PTMC) is defined by the World Health Organization (WHO) as papillary thyroid carcinoma that is <1 cm in the maximum diameter of the lesion [1].

In recent years, its incidence has gradually increased, attracting more attention from clinical physicians and researchers.

The data from the United States National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) show that from 1975 to date the incidence of thyroid cancer has been on the rise [2] and of all malignancies it has the fastest rate of increase [3].

According to the latest statistics, nearly 90% of cases of thyroid cancer are papillary carcinoma [4].

In addition, microcarcinoma accounts for 30% to 70% of cervical lymph node metastasis [5,6].

Some of these tiny size tumors (PTMC) are completely encapsulated, with papillary and follicular structures characterized histologically by overlapping cell nuclei with ground glass appearance and invaginations of cytoplasm into the nuclei [7].

These tumors are indolent and have a good prognosis, but others clearly infiltrate the thyroid parenchyma. Malignant behavior has been proven by several authors [8-10].

Ultrasonography represents the most sensitive imaging method for early diagnosis of thyroid lesion [11,12].

The diagnosis of tumors >0.5mm in diameter requires pathological evaluation. If an accurate diagnosis can be made before surgery, providers will then be able to select a reasonable surgical approach, avoiding the debate of whether to perform prophylactic central lymph node dissection. Therefore, preoperative determination of the characteristics and the metastasis risk of thyroid nodules are imperative.

Despite the tiny size of the lesion, the diagnostic image was strongly suspicious for malignancy and the FNAC procedure determined accurate detection of malignancy. Based on nuclear crowding and presence of prominent nuclear grooves and pseudoinclusions FNAC was classified TIR5 according to the Italian consensus [13] and Category VI according to the Bethesda Classification [14].

Black Ink is the smallest thyroid cancer by ultrasonography detected.

In the Thyroid Cancer Trilogy we proved this pattern Black Ink with ultrasonographic image and believe consistent with the infiltrating variant of papillary thyroid microcarcinoma if associated with malignant cytology after FNAC, characteristics that even with a size 0.3 cm still keep a high predictive score/value/index for malignancy ( $p < 0.001$ ) [15].

## Discussion

Clinical significance and recommendations for management of PTMCs is still evolving. In general the microcarcinomas is considered a clinically very low risk cancer type that uncommonly causes mortality with a greater than 90% disease-free survival [16,17]. Reported rates for distant metastases and mortality from PTMC are  $< 0.05\%$  [18].

PTMCs show a high incidence of regional lymph node metastasis, occurring in 12%–64% of patients [19,20]. Wada, *et al.* [21] reported that 64.1% and 44.5% of patients have central and ipsilateral node involvement respectively and two thirds of patients have lymph node metastasis (LNM) in at least one of the two compartments. It has been described that cases with positive lymph nodes have a higher risk of recurrence [22]. Kim, *et al.* [23] found that lateral cervical node metastasis was the most powerful independent predictor of clinical recurrence.

Some PTMCs exhibit aggressive behaviour, including the development of a regional and distant metastases, and even death [24,25].

The rising incidence of microcarcinoma and its associated morbidity requires risk stratification and guidelines for treatment. Currently treatment of PTM is based upon stratification of cancer risk for aggressive behaviour [26]. The clinical significance of PTMC tumors  $\leq 1$  cm is widely debated.

Management of PTMC ranges from observation alone to total thyroidectomy plus central lymph node dissection and postoperative radioiodine ablation therapy [27].

Currently no solid basis exists for establishing the most appropriate tumor size ( $\leq 1$ cm) as a criterion evaluation of these lesions.

Reason for the persistent controversy is our inability to accurately predict the aggressiveness of PTMC tumors and choose the optimal individualized management for those patients before surgery.

Some investigators proposed a further subdivision of PTMC to aid optimal treatment selection, such as microtumor [28] or tiny [29] for foci 5 mm in diameter or less.

According to prestigious authors, the optimal cut-off value of a tumor size which will enable to predict the risk of a lymph node metastasis (LNM) in a papillary thyroid microcarcinoma were the following: Lim *et al* indicated it would be 0.7 cm (Lim, *et al.*, 2009), Zhang, *et al* indicated it would be 0.6 cm (Zhang, *et al.*, 2012), Chang *et al* suggested it would be 0.5 cm (Chang, *et al.*, 2015) and finally Wang claims the value is 0.575 cm (area under the curve 0.721) according to the ROC curves (Wang, *et al.*, 2015).

Nowadays, thanks to the publication of three important researches focusing on the percentage of biological risk factors due to the non-occult tumors of very small size, the cut-off has dropped to 0.3 cm [30-34].

This value is of great importance because, the size of PTMC in ultrasound images are a fundamental data in order to predict the stage and aggressiveness of the tumors, it may also become an advantageous tools predictor for microcarcinomas prognosis and assist us to choose the right treatment.

A revision of the guidelines would be very useful of giving great importance to further lower the tumor size cut-off because to date it is a fact that microscopic neck lymph node metastases present in over 60% of PMC patients [35].

Thyroid cancer is generated by multi-step carcinogenesis in which long-existing PMCs show progression to acquire a more aggressive phenotype and finally turn into lethal cancers.

PMCs are not pre-cancers but true cancers. TRAPANESE *et al.* in this triad of studies have used very advanced and refined ultrasonography techniques including the BRAF molecular study, showing that very small tumors can be aggressive and important biological risk for neck lymph node metastases (LNM).

## Conclusion

The purpose of this current review is the attempt to provide a new reference value for PTMC by determining the optimal cut-off value of tumor size related to lymph node metastasis in PTC, which might be a preferable method to assess PTMC and assist individualized patient management decision.

Thyroid Cancer Trilogy might be regarded as a milestone in the history of cancer research, since they reported the existence of Black Ink the smallest thyroid cancer identified by ultrasonography which could provide valuable knowledge aggressive characteristics of Microtumors.

## Author Contributions

ET prepared the manuscript, conceived imaging, developed the concept and wrote most of the manuscript. GT contributed and supervised the manuscript.

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