Liquid Biopsy-Derived Exosomal MicroRNAs

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Contributor: Eman Toraih

Circulatory tumor-derived exosomal microRNAs (miRNAs) play key roles in cancer development/progression. We aimed to assess the diagnostic/prognostic value of circulating exosomal miRNA in thyroid cancer (TC). A search in PubMed, Scopus, Web of Science, and Science Direct up to 22 May 2021 was performed. The true/false positive (TP/FP) and true/false negative (TN/FN) rates were extracted from each eligible study to obtain the pooled sensitivity, specificity, positive/negative likelihood ratios (PLR/NLR), diagnostic odds ratio (DOR), and their 95% confidence intervals (95%CIs). The meta-analysis included 12 articles consisting of 1164 Asian patients and 540 controls. All miRNAs were quantified using qRT-PCR assays. The pooled sensitivity was 82% (95%CI = 77–86%), pooled specificity was 76% (95%CI = 71–80%), and pooled DOR was 13.6 (95%CI = 8.8–21.8). The best biomarkers with high sensitivity were miR-16-2-3p (94%), miR-223-5p (91%), miR-130a-3p (90%), and miR182-5p (94%). Similarly, they showed high specificity, in addition to miR-34c-5p. Six panels of two to four exosomal miRNAs showed higher diagnostic values with an area under the curve (AUC) ranging from 0.906 to 0.981. The best discriminative ability to differentiate between cancer and non-cancer individuals was observed for miR-146b-5p + miR-223-5p + miR-182-5p (AUC = 0.981, sensitivity = 93.8% (84.9–98.3), specificity = 92.9% (76.5–99.1)). In conclusion, the expression levels of exosomal miRNAs could predict TC.

Keywords: thyroid cancer ; exosomal microRNAs ; miRNA ; liquid biopsy ; meta-analysis

1. Introduction

Thyroid cancer (TC) growth is one of the most common malignant tumors in the endocrine system [1]. The incidence of thyroid cancer increases with an annual rate of 5.4% in men and 4.6% in women [2]. Ultrasound imaging, positron emission tomography-computed tomography (PET-CT), and fine-needle aspiration biopsy (FNA) are widely conducted to determine the properties of the masses and confirm the diagnosis [3][4]. However, these strategies have their limitations of being expensive, invasive, time-consuming, or overly dependent on the medical staff's precise instruments and technical levels [5][6]. Financial distress and adverse financial events were common among thyroid cancer survivors and were associated with a more inferior health-related quality of life [7]. Moreover, about 10–40% of FNA cytology analysis cannot confirm the malignancy, and many patients undergo unnecessary thyroidectomy for benign lesions [8]. Therefore, novel non-invasive methods for diagnosis of TC have the potential to improve patient outcomes significantly.

MicroRNAs (miRNAs) are a group of small non-coding RNA molecules with a length of 21–23 nucleotides [9]. They regulate the expression of multiple protein-coding genes at the post-transcriptional level and are implicated in controlling signaling circuits within a cell [10]. Studies showed that miRNAs are dysregulated in human malignancies and play an essential role in the evolution and progression of cancer [11][12]. Furthermore, functional studies show that miRNAs affect TC cell proliferation, migration, and invasion [12][13]. In addition, studies showed that several of these miRNAs are related to prognosis and can serve as diagnostic markers [14].

Exosomes are vesicles with a size of 30–150 nm in diameter. They are essential for cells to communicate with neighboring cells or with distant cells [15]. All exosomes hold surface molecules that help them to target the recipient cells. Once attached to the recipient cells, the exosomes fuse with the cells' membranes to release their cargo into target cells, thereby changing the physiological state of the recipient cells. In addition to intra-cellular regulatory functioning, miRNA can be secreted by cells into interstitial spaces to shuttle the regulatory signal to neighboring and distant cells. Detection of tumor-derived miRNA in various bodily fluids may also be helpful for both early cancer diagnostic and therapeutic management [16]. Exosomal miRNAs are more stable than free miRNAs in circulation as they are more resistant to the proteolytic activity of ribonucleases [17][18]. Therefore, exosomal miRNA can serve as potential diagnostic and prognostic biomarkers. Previous studies suggest promising results of exosomal miRNA in diagnosing several human cancers, such as glioma and breast cancer [19][20]. In addition, studies report that expression levels of exosomal miRNAs in plasma of patients with TC were significantly different, suggesting that exosomal miRNAs have great potential to be biomarkers for

TC [21]. For example, plasma exosomal miR-146b-5p and miR-222-3p have been suggested as potential biomarkers for lymph node metastasis (LNM) in papillary TC (PTC) [20].

While prior studies have evaluated the novel use of exosomal miRNA in various cancers, the global profiling of exosomal miRNAs from plasma or serum of patients with TC has not been widely investigated. This systematic review and meta-analysis aimed to evaluate liquid biopsy-derived exosomal miRNAs from serum and plasma as diagnostic and prognostic tools in TC.

2. Current Insight on Exosomes and TC prognosis

Recently, research on exosomes and TC prognosis has become a medical hotspot. Many studies have found that exosomes play a vital role in the diagnosis/prognosis and treatment of TC, although the results remain controversial [22][23][24]. To our knowledge, this is the first systematic review and meta-analysis evaluating the diagnostic and prognostic value of exosomal miRNAs in thyroid cancer. Our meta-analysis consists of 12 articles, including 1164 patients and 540 controls. The pooled sensitivity was 82% (95%CI = 77–86%), pooled specificity was 76% (95%CI = 71–80%), and pooled DOR was 13.6 (95%CI = 8.8–21.8). The best biomarkers with high sensitivity were miR-16-2-3p (94%), miR-223-5p (91%), miR-130a-3p (90%), and miR182-5p (94%). Similarly, they showed high specificity, in addition to miR-34c-5p. This indicates that miRNAs can be potentially useful biomarkers when used as a diagnostic tool for thyroid cancer.

MiRNAs play a key role in various processes, including cancer development, progression of the disease, and metastasis [25]. These highly conserved molecules are exceptionally stable in blood and urine due to their small size and resistance to nucleolytic cleavage by RNAse [26]. This feature allows miRNAs to be a reliable, non-invasive, and sensitive method of detecting tumors. Furthermore, miRNA exhibit unique “molecular signatures.” These mutations can be used to identify a wide range of malignancies, including hepatocellular, lung, and thyroid cancer [27][28][29]

More studies are emerging on circulating miRNA for detecting TC [18][21][30][31]. For instance, Liu et al. conducted a meta-analysis and found that circulating miR-222 and miR-146b had high diagnostic value for PTC in the Asian population [18]. Specifically, miR-222 had a sensitivity of 0.70%, specificity of 0.90%, and a diagnostic ratio of 22.55. Other miRNAs reported to be associated with thyroid cancer include miR-146b and miR-221, which are upregulated in benign and malignant thyroid nodules [32][33][34]. MiR-146b can serve as an independent risk factor for poor prognosis in PTCs. However, overexpression of miR-146b can be found in both PTCs and FTCs and cannot help differentiating between tumors [32]. Additionally, Samsonov et al. confirmed that plasma exosomal miR-21 could help differentiate benign tumors and FTC [22]. Our results add miR-21, miR-451a, miR-1290, and miR-638 to the existing repertoire of miRNAs that can be used as diagnostic tools for TC.

Our results support previous studies demonstrating that a panel of multiple miRNA assays has higher diagnostic accuracy than single miRNA assays [18][35][36]. The best discriminative ability to differentiate between cancer and non-cancer individuals was an miR-146b-5p + miR-223-5p + miR-182-5p panel. Thus, it is important to consider using a combination of miRNA rather than single miRNAs when using these biomarkers as a diagnostic tool.

The utility of miRNAs is extensive as they can serve as prognostic markers for TNM staging, tumor size, short-term survival, overall survival, and recurrence [23][37]. Our study adds to the existing literature by demonstrating that circulating exosomal miR-21, miR-451a, miR-1290, and miR-638 can be used to predict OS and DFS in these patients further. Jiang et al. described exosomal miR-146-5p and miR-222-3p to be upregulated in PTC with LNM [21]. Overexpression of these various miRNA may play a role in the migration and invasion of PTC. By further deciphering the roles of miRNAs in cancer outcomes, such as lymph node metastasis, surgical interventions can be limited. For instance, prophylactic neck dissection is controversial in patients with clinically LNM-negative PTC patients. Thus, non-invasive biomarkers can help prevent unnecessary surgery while providing information on prognosis [38].

The biomarkers with highest sensitivity in our study were miR-16-2-3p (94%), miR-223-5p (91%), miR-130a-3p (90%), and miR182-5p. Liang et al. similarly reported that miR-16-2-3p and miR-223-5p could be utilized for detecting PTC from benign nodules [30]. MiR130a-3p has been previously studied in glioblastoma, which regulates disease progression [39]. We found that miR-182-5p underexpression was associated with TC. MiR-182-5p has been studied in other cancers, including hepatocellular cancer and breast cancer, where it is proposed to be responsible for the proliferation and metastasis of cancer [40][41]. In thyroid cancer, other studies have shown that miR-182-5p can be a helpful marker for PTC, particularly metastasis, which agrees with our results [42].

The clinical advantages of miRNAs are multi-fold. First, miRNAs can be used as a screening tool for early detection of PTC, which would aid in early cancer prevention and improve patient survival. Secondly, the use of these biomarkers can

help prevent unnecessary diagnostic surgery. Using the Bethesda classification of thyroid nodule fine-needle aspiration, 20–30% of thyroid nodules are considered “indeterminate” (Bethesda Class III/IV), and approximately 15–30% of these that are surgically removed are malignant [43]. Therefore, most patients who undergo surgery under these classifications have benign diseases and do not require surgery. By using miRNA, we have the potential to save patients from the burden of surgery.

This study had some limitations. First, except for one study, all studies included in our analysis originated from China and included an Asian population. We recommend that future studies include other ethnicities to improve the generalization of the miRNAs panel. Secondly, studies involving biomarkers should expand their analysis to demonstrate comprehensive diagnostic accuracy measures. Thirdly, measures of test accuracy are not fixed properties of a test, and there are generally many contributing factors leading to variation. Variation between studies in following the MISEV guidelines [44] on the experimental methodology can add a further element of heterogeneity that also should be considered. Therefore, heterogeneity is a common feature of DTA reviews. Due to this wide variability or heterogeneity between studies, we suggest that future studies narrow their analysis to select the best miRNAs and follow the standard published methodology for reporting their results.

Future research should continue to evaluate the causative role of these miRNAs in thyroid cancer development. By understanding the underlying mechanisms in which miRNAs affect tumor progression or metastasis, we can better develop therapeutics using miRNAs. For instance, studies have shown that exosomal miRNA-423-5p secreted by PTC can, in turn, deliver the miRNA into PTC cells [45]. Thus, there is potential to use exosomal miRNAs as therapeutic targets in PTC. Furthermore, we recommend that a panel of exosomal miRNAs is tested and validated.

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