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Review

MiRNAs as Promising Therapeutic Targets for Breast Cancer

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Abstract

Breast cancer (BC) is the most common cause of cancer-related death and is the malignancy most frequently diagnosed in females worldwide. BC incidence is predicted to continue increasing worldwide. Without interventions, annual new cases will reach over 3 million by 2030. Genetic abnormalities account for almost 70% of all BC cases worldwide. Biological pathways implicated include non-coding RNAs (ncRNAs). MiRNAs are small non-coding RNA molecules that play a role in post-transcriptional regulation of gene expression. They can function as either tumor suppressors or oncogenes, and their role depends on the specific miRNA and target genes affected. The research on miRNA-based cancer treatments has yielded promising results. Depending on recent data, the goal of this review was to summarize the mechanisms that explain the role of some miRNAs in BC pathogenesis and drug resistance.

However, highlighting the areas needing further exploration and more research is required before using microRNAs in clinical settings.

Keywords
miRNA; clinical; cancer; drug resistance; breast; pathways; death

1. Introduction

Cancer is characterized by uncontrollable cell growth and invading other body tissues. Malignant tumors are another name for cancerous tumors. Benign tumors do not spread or invade near tissues. In the case of benign tumor removal, they rarely reoccur, whereas cancerous tumors do on occasion. Benign tumors can grow to be quite large at times, but some can cause severe symptoms or be fatal, such as benign tumors in the brain [1, 2].

Breast cancer (BC) is known as a type of cancer that starts in the breast. It starts in one or both breasts and occurs almost entirely in women, but men can get BC, too. Breast cancers can develop in many locations within the breast [3]. Breast cancer remains the most commonly diagnosed cancer in women worldwide. In 2020, an estimated 2.3 million new cases of BC were diagnosed globally [4, 5]. Younger women are being diagnosed at increasing rates, potentially attributed to factors such as obesity, alcohol consumption, and reproductive patterns [6, 7]. In the present time, many therapeutic regimens for BC were developed can be enumerated as the following:

- Surgery, which is the primary treatment for localized BC, is the surgical removal of the tumor via lumpectomy or mastectomy. It aims to remove all cancer from the breast and nearby lymph nodes [8, 9].
- Chemotherapy is used to treat many types of BC, especially when cancer has spread. Common chemodrugs include anthracyclines, taxanes, 5-FU, and cyclophosphamide, which are given before or after surgery [10, 11].
- Radiation therapy is given after lumpectomy to destroy any remaining cancer cells and reduce the risk of recurrence. External beam radiation is directed at the breast or chest wall [12, 13].
- Hormonal therapy is used for hormonally-responsive cancers like ER^+ or PR+, for example, tamoxifen and aromatase inhibitors (e.g., anastrozole, letrozole, exemestane). Given for 5-10 years after initial treatment [14].
- Targeted therapy that targets specific molecules involved in cancer growth. Examples are trastuzumab for HER_2^+ cancer, palbociclib, and ribociclib for ER^+/HER_2^- metastatic disease [15].
- Immunotherapy is a treatment approach that uses drugs, such as atezolizumab and pembrolizumab, to help the immune system better recognize and destroy cancer cells [16, 17].
- Combination therapy uses multi-modality treatment involving a combination of the above approaches depending on cancer stage, grade, and receptor status. The goal is to achieve the highest possible effectiveness in treatment while keeping the side effects within acceptable limits [18].

Our understanding of the biological regulation of genetic material has advanced significantly over the last two decades. The genome has 2% protein-coding genes and more than 90% non-coding

protein genes. Protein-coding genes undergo translation into proteins following transcription to RNA. Non-coding protein genes are transcribed but not translated into proteins [19]. Non-coding RNA is essential for genetic regulation. miRNAs are non-coding RNAs that are crucial in numerous diseases [20].

MicroRNA, regarded as a non-coding RNA, was discovered in 1993 in the nematode Caenorhabditis elegans. It is a member of the endogenous small non-coding RNA family. It is composed of ~22 nucleotides [21]. They participate in the posttranscriptional regulation of gene expression through one of two mechanisms: mRNA translation suppression or mRNA degradation. miRNA target sites are found in the 3'-UTR of more than 60% of human protein-coding genes. As a result, those genes are regulated by miRNA [22]. According to the miRNA database, over 1000 miRNAs have been identified in the human genome. Those miRNAs regulate 1 to 5% of human gene expression. As a result, miRNAs are one of the most numerous classes of genomic regulators [23].

One of the earliest studies discussing the relation of miRNAs and breast cancer is the work by Costinean, Sandhu, and colleagues from the Croce lab, who reported the first in vivo evidence implicating the overexpression of a miRNA in cancer. They found that miR-155 directly caused a leukemic phenotype. The following year, the Slack group reported that a single oncogenic miRNA, miR-21, was enough to cause neoplastic development in a mouse model with no predisposing mutations. These findings suggested that tumors could become addicted to miR-21, similar to the phenomenon of addiction to oncogenic proteins [24-26].

In a review by Lu et al. (2005), the authors reported the differential expression of miRNAs in breast cancer. They demonstrated that miRNAs could perform their function as oncogenes or tumor suppressors. They also discussed the potential of miRNAs as diagnostic and prognostic markers in BC therapy [27, 28]. So, in this review article, we will discuss some miRNAs' role in BC pathogenesis.

2. The Biogenic Pathway of miRNAs

Two main pathways exist for generating miRNAs from genetic sequences in the genome (see Figure 1).

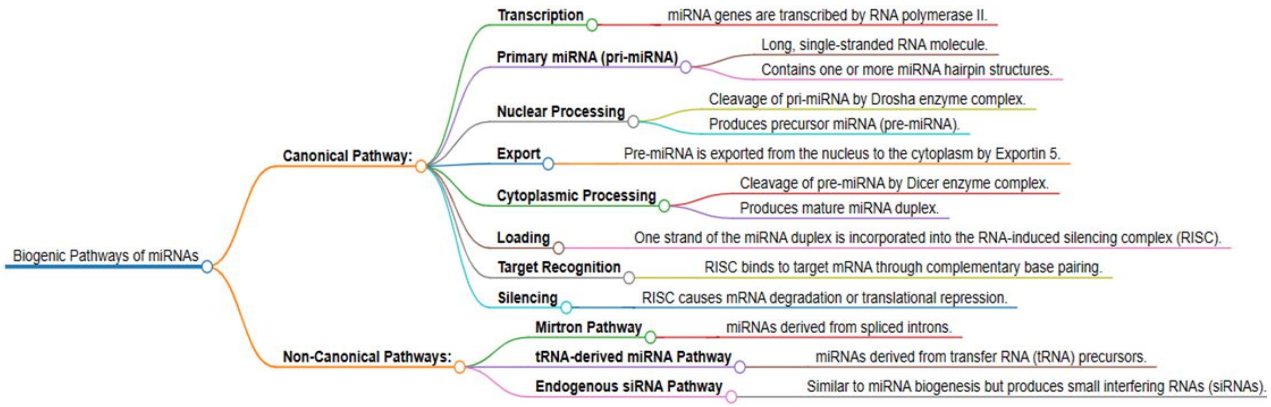

Figure 1 Biogenic pathways of miRNAs.

2.1 Canonical/non conical Pathways of miRNA Biogenesis

miRNA genes are transcribed by RNA polymerase II into long primary miRNA transcripts (pri-miRNAs) that can be several kilobases long. In the nucleus, the pri-miRNA is cleaved by the Drosha

RNase complex into a 60-70 nucleotide stem-loop precursor miRNA (pre-miRNA). The pre-miRNA is then exported from the nucleus into the cytoplasm by Exportin-5. Dicer cleaves off the loop in the cytoplasm, leaving a short double-stranded miRNA/miRNA* duplex around 22 nucleotides long. One strand of the duplex is associated with the RNA-induced silencing complex (RISC) to regulate target mRNAs [29, 30].

2.2 Non-Canonical/Mirtrons Pathways

Some miRNAs are situated within the introns of genes that encode proteins. The splicing machinery spliced and debranched the intron, generating a pre-miRNA-like structure without the involvement of Drosh. This pre-miRNA is then exported and processed similarly by Dicer/RISC [31].

So, miRNAs predominantly undergo canonical nuclear processing by Drosha and Dicer, but a minor fraction uses the non-canonical mirtron pathway dependent on splicing alone. Both ultimately produce mature functional miRNAs incorporated into RISC.

3. Breast Cancer and Micro-RNAs

Because of their stability in blood and differential expression in different tissues and diseases (Table 1), miRNAs have received much attention as cancer biomarkers. There is also the option of repeating measurements in a non-invasive manner. The underlying miRNA's mechanisms of high stability in an RNAase-rich environment are still unidentified. Two hypotheses about how miRNAs in circulation protect themselves against degradation are reported. The first hypothesis proposes that miRNAs are found in apoptotic bodies, microvesicles, lipoproteins, lipids, or exosomes [32, 33]. The second hypothesis proposes that miRNA is present in protein complexes. Almost all circulating miRNAs were recently discovered with protein complexes co-fractionated and bound to Argonaute proteins, indicating that they remain stable in circulation even when removed from the exosome [34, 35].

Several studies have discovered differences in miRNA expression in BC patients versus healthy subjects in blood or tissue. They suggested they could be used as predictive, prognostic, or diagnostic biomarkers. miRNA profiling in circulation has been proposed as a novel technique for detecting BC in the early stages [36]. A pilot study proposed that changes in circulating miRNA concentrations (up-or-down-regulation) could be used as markers in early detection of BC [37]. Furthermore, some miRNAs, such as miR-21 overexpression, have been linked to an advanced stage of the tumor, lymph node metastasis, and poor survival [38]. Some miRNA expression levels, such as miR-375 and miR-9, were strongly associated with ER+ BC. Other miRNAs' expression levels changed after treatment [39-41]. A different type of cancer was found to have higher miR-21 expression levels. When comparing BC patients to healthy subjects, researchers discovered increased miR-21 expression in their serum. It was found to be more abundant in primary breast cancer tissues and breast cancer cell lines [42, 43].

MicroRNA-375 (on chromosome 2q35) was discovered as a -cell regulator for function and development and insulin secretion in pancreatic islets by targeting the PDK-1 and MTPN genes [44]. According to additional research, miRNA-375 is involved in multiple types of cancer by targeting several important genes such as AEG-1, YAP1, and IGF1R [45]. miR-375 has been proposed to function as an oncogene or a tumor suppressor, depending on the specific gene targets in various cancer types. However, its role in BC remains a topic of debate [46].

miR-155 expression levels are consistently upregulated in breast tumor samples, acting as an anchor-miRNA. miR-155 has been linked to clinical markers, aggressive tumors, and decreased survival in BC patients. Some contradictory findings have been reported, such as the variable association of miR-155 with hormone receptor status [47]. It is also unclear whether miRNA-155 causes cancer or promotes its progression. miR-155 has been shown in a mouse model to transform B-cells, but only in breast cells has it been shown to enhance cancerous properties. More research is needed to fully comprehend the significance of elevated miR-155 levels in BC [48].

In BC xenograft models and cell lines, miRNA-155 promotes tumor growth and cell proliferation, inhibits apoptosis, and mediates TGF-driven EMT. Since miRNA-155 levels are elevated in invasive tumors and BC metastases, the role of miRNA-155 in EMT holds promising therapeutic potential [49]. Also, many miRNAs play regulatory roles in BC, which can be summarized by the following:

- **Control of cell proliferation**: miRNAs regulate genes involved in cell cycle progression and replication. Deregulation contributes to the uncontrolled growth of cancer cells [50].
- **Regulation of apoptosis**: Both pro- and anti-apoptotic genes are targeted by miRNAs, affecting susceptibility to programmed cell death. Misregulation promotes the survival of damaged cells [51].
- **Modulation of invasion and metastasis**: miRNAs influence EMT, extracellular matrix degradation, angiogenesis, and other processes involved in cancer cell invasion and spread to other organs [52].
- **Metabolic reprogramming**: Emerging role in regulating cancer cell metabolism at the post-transcriptional level to support bioenergetic and biosynthetic demands of rapid proliferation [53].
- **Stem cell regulation**: miRNAs are implicated in the self-renewal and differentiation of normal and cancer stem cells, believed to drive tumor initiation and recurrence [54].
- **Treatment response**: Aberrant miRNA levels modulate sensitivity to chemotherapy, radiotherapy, hormonal, and targeted agents. May influence the acquisition of resistant phenotypes [55].
- **Epigenetic and genetic regulation**: Reciprocal regulatory interactions between miRNAs and other epigenetic/genetic factors form complex networks governing breast cancer pathogenesis [56].
- **Immune modulation**: Impact anti-tumor immunity through local and systemic effects on immune cell populations, cytokine production, and immune checkpoints [57].
- **Tumor microenvironment**: Crosstalk with stromal cells influences multiple processes like angiogenesis and tumor-promoting inflammation [58].

So, in summary, miRNAs control numerous facets of breast cancer biology at the post-transcriptional level. Their deregulation has wide-ranging impacts on disease behavior and outcomes.

4. The Dual Role of miRNAs in BC

MicroRNAs can act as oncogenes and tumor suppressors (Table 1) in BC development and progression. Their role depends on the specific miRNA and target genes affected. Oncogenic miRNAs, also known as oncomiRs, are frequently upregulated in BC. They promote tumor growth and metastasis by repressing tumor suppressor genes. Examples include the miR-17-92 cluster and miR-

21, which target apoptosis, proliferation, and metastasis genes. Other miRNAs can function as oncogenes by negatively regulating the expression of tumor suppressor genes, and upregulation of these miRNAs inhibits anti-cancer genes, again promoting tumor growth and progression for examples, miR-21, miR-155, miR-10b, miR-373, and miR-520c [59-61].

Tumor suppressor miRNAs are commonly downregulated in BC, and their decrease contributes to uncontrolled cell growth. For instance, the miR-205/200 families typically suppress oncogenes such as RAS, HER2/neu, and ZEB1/2. Low levels of these miRNAs deactivate tumor suppressive pathways [62, 63].

Depending on tumor stage and subtype, the same miRNA can function as both an oncogene and tumor suppressor. For example, high miR-10b promotes metastasis, but low levels also contribute to invasion and progression in some subtypes. The targets of a given miRNA and the cellular context determine whether it drives tumor initiation or suppresses cancer cells [64, 65]. Overall, the precise regulatory roles of miRNAs are complex and context-dependent in BC development. Understanding their dual functions is important for developing new prognostic biomarkers and miRNA-based therapies Table 1.

Table 1 Changes in miRNA expression in BC. (According to previously reported data by other research groups).

miRNA	Detection site	Change in miRNA expression
miRNA-10b	Whole blood	It is more prevalent in ER-negative subjects than ER+-positive subjects but cannot distinguish BC from healthy subjects [66].
	Serum	↑ When comparing metastatic BC (M1 stage) to normal subjects [67].
	BC cell lines	BC-M_1 and BC-S_1 micrometastatic breast cell lines had higher levels than MDA-MB231 and G_I-101 [67].
	Metastatic BC cells	↑ It is used as a prognostic marker in metastatic BC cells, and if it is elevated in non-metastatic tumors, it indicates poor prognosis, metastasis, and invasion [52].
miRNA-21	Serum	↑ Especially stage IV cancer [68].
	BC tissues	↑ In BC (grade III) than ER-/PR- BC or benign BC [69].
	BC tissues	↑ In BC than normal, especially in cases of lymph node metastasis [70].
	BC tissue	↑ In primary BC tissue with advanced tumor stage and lymph node metastasis. It has been proposed as a prognostic marker [71].
	Serum	↑ In BC and benign BC compared to healthy subjects [72].
miRNA-155	Serum	↑ Can distinguish M0- and M1-patients from normal women [73].
	plasma	PR^{+ve} tumors have higher expression than PR^{-ve} tumors [74].
miRNA-195	Whole blood	↑ From stage I to IV [75].

	Whole blood	↑ then ↓ in BC patients post-operatively, levels comparable with healthy women following curative tumor removal [76].
	BC tissue and cell lines	↓ works as important inhibitory roles in BC malignancy [76].
Let-7a	BC tissue	↑ then ↓ in BC patients post-operatively, levels comparable with healthy women following curative tumor resection [77].
Let-7c	plasma	↓ In BC in its early stages [78].
Let-7d	plasma	↓ In the early stages of BC [79].
miRNA-589	plasma	↑ In BC at an early stage [80].
miRNA-425	plasma	↑ In BC's early stage [81].
miRNA-34a	Serum	↑ Can distinguish M1 patients from normal subjects [82].
miRNA-106a	Serum	↑ [83].
miRNA-126	Serum	↓ [84].
miRNA-199a	Serum	↓ [85].
miRNA-335	Serum	↓ [86].
miRNA-202	Whole blood	↑ Early stage in BC [87].
miRNA-148b	Plasma	↑ In BC in its early stages [88].
miRNA-801	Plasma	↑ Early stage in BC [89].
miRNA-9	Plasma	↑ Linked with ER^+ and local recurrence [90].
miRNA-375	Serum	↑ Linked with ER^+ [91].
miRNA-16	Serum	↑ It has been proposed as a marker for prediction [92].
miRNA-222	Serum	↑ It has been suggested as a predictive biomarker [93].
Let-7b	Plasma	↑ Then, significantly reduced after-surgery removed BC [94].
Let-7g	Plasma	↑ Then ↓, after- surgically removing BC [94].
miRNA-20a	Serum	↑ In BC or benign BC patients [95].
miRNA-125b	Serum	↑ Linked to resistance to chemotherapeutics [96].
miRNA-195-5p	Plasma	↓ When comparing pretreated BC patients to normal women [97].
miRNA-96-5p	Plasma	↑ Pretreated BC patients were compared with normal women [97].
miRNA-505-5p	Plasma	↑ When comparing pretreated BC patients to normal women [98].
miRNA-125-5p	Plasma	↑ When pretreated, BC patients were compared to healthy subjects [99].
miRNA-21-5p	Plasma	↑ When pretreated, BC patients were compared to normal women [100].
miRNA-27a	Plasma	↑ In BC patients before chemotherapy [101].
miRNA-132	Plasma	↑ In BC, patients who have already been treated are compared with normal women [102, 103].

miRNA-106-5p	Plasma	↑ Compared to normal women, BC patients have already been treated [83, 104].
miRNA-376c	Plasma	↑ In the BC preliminary stage [105, 106].
miRNA-495	Plasma	↓ When comparing BC patients already treated to normal women [107].
miRNA-27a	Plasma	↑ In BC patients before chemotherapy [108, 109].

5. MicroRNAs and BC Drug Resistance

MiRNAs play a critical role in medication resistance. Several miRNAs, including miR-451, miR-200c, miR-298, and miR-27a, have been found to affect doxorubicin in BC cell lines. Few studies, however, have found a link between drug resistance in patients and miRNAs. A recent study, for example, discovered that miR-200c was upregulated in chemoresistant patients' BC tissues compared to responders [110]. In contrast, other studies using breast cancer tissues found a link between low miR-200c expression and poor response to neoadjuvant chemotherapeutics [111]. In these cases, the exact mechanism underlying the drug resistance is unknown; however, some clues can be identified through cell line studies. Other pathways can influence drug resistance and, as a result, be miRNA targets. For example, down-regulation of miR-15a/16 causes an increase in the anti-apoptotic protein BCL2 and, as a result, tamoxifen resistance. This occurs due to oncogenic HER216's alternative regulation of the miR-15a/16 cluster, found in more than 30% of ER+ tumors [112, 113]. As a result, this could explain some patients' poor treatment outcomes. MiR221/222 cluster, on the other hand, targets the cell cycle inhibitor p27Kip1 to act as an oncogenic miRNA. Tamoxifen resistance was linked to low levels of p27Kip1 [114]. Interestingly, The presence of the miR-221/222 cluster influences fulvestrant resistance, most likely by targeting the previously mentioned protein. MiR221/222 can act as a tumor suppressor and an oncogenic miRNA in this case [115, 116].

MiR-221/222 levels rise in response to fulvestrant treatment, and it suppresses the growth of tumors by targeting the ER. On the other hand, long periods of estradiol deprivation can result in constitutively increased expression of miR-221/222, which becomes oncogenic by targeting cell cycle inhibitors like p27Kip1 [117, 118].

MiR-128a is another hormone-responsive miRNA that is overexpressed in letrozole-resistant cell lines and can enhance cell growth and resistance to letrozole by targeting TGF. Inhibition of miR-128a restores TGF inhibition, leading to increased sensitivity of cells to letrozole. Because miR-128a is highly expressed in cells with high hormone levels [119]. In a drug-resistant cell line, MiR-125b is indeed upregulated. MiR-125b, in particular, is overexpressed in taxol-resistant cell lines, inhibiting taxol's apoptotic effect. Most likely, miR-125b causes this resistance by targeting BAK1, a pro-apoptotic protein [120, 121]. Concurrent administration of a miR-21 inhibitor and taxol improved chemotherapeutic agent toxicity and, as a result, apoptosis in the MCF-7 cell line. This study shows that using miRNA inhibitors in some tumors is feasible. However, caution is advised, as is additional research into the potential side effects of using miRNAs/anti-miRNAs as a therapy [122, 123]. Trastuzumab appears to be influenced by miR-21 in HER2/3 targeted therapy, whereas lapatinib and gefitinib appear to be influenced by miR-205 [124, 125].

6. The Future Aspects Concerning Developing Therapeutic Targets of BC

The role of microRNAs (miRNAs) in developing therapeutic targets for breast cancer is expected to evolve, as these small non-coding RNAs play a crucial role in regulating gene expression at the post-transcriptional level. miRNAs are involved in the main biological behaviors of tumors, making them attractive targets for anticancer drug development [126-128]. Some key aspects of the future vision for miRNA-based therapeutics in breast cancer include:

6.1 Nanotechnology-Mediated Delivery

Nanoparticles (NPs) loaded with miRNAs have shown promise in precisely targeting and silencing oncogenic miRNAs, which could help improve the efficacy of cancer chemotherapy and mitigate its associated unwanted side effects [129, 130].

6.2 Clinical Trials

Clinical trials examining the clinical potential of miRNAs as biomarkers for cancer therapy diagnosis and prognostication are underway, with some trials focusing on diagnostic miRNAs in blood or tissue samples from cancer patients [131].

6.3 Improved Drug Strategies

Ongoing clinical trials are exploring advanced delivery technologies and synthetic RNA molecules to enhance the efficacy of miRNA-based therapies [132, 133].

6.4 Combination Therapies

miRNAs could be combined with other therapeutic agents, such as chemotherapy drugs, to enhance their effectiveness in treating BC [134, 135].

Despite the progress made in miRNA-based therapeutics, there are still challenges to overcome, such as the limitations of current detection methods and the need for more efficient and cost-effective approaches. Overcoming these challenges could pave the way for miRNA detection and treatment to enter the clinic smoothly and become a new target for BC treatment [136, 137].

7. Conclusion

MicroRNAs demonstrate a dual role in BC development and progression depending on the specific miRNA and context. Both increases and decreases in miRNA expression can promote breast tumorigenesis, so targeting specific oncogenic or tumor-suppressive miRNAs holds promise as a therapeutic strategy, either by inhibiting oncogenic miRNAs or restoring loss of tumor-suppressive miRNA function through supplementation.

List of Abbreviations

ATM	Ataxia-Telangiesctasia Mutated
AJCC	American Joint Committee on Cancer
AUC	Area under the curve

BC	Breast cancer
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
CA 15-3	Cancer antigen 15-3
CA 27.29	Cancer antigen 27.29
CD-36	Cluster of Differentiation 36
CHEK2	Checkpoint Kinase 2
CT	Computed Tomography
DNA	Deoxyribonucleic Acid
EDTA	Ethylenediamine tetraacetic acid
ELISA	Enzyme-linked Immunosorbent Assay
EMT	Epithelial-to-mesenchymal transition
ER	Estrogen receptor
HER-2	Human Epidermal Growth factor Receptor- 2
HWE	Hardy-Weinberg equilibrium
IQR	Interquartile Range
MAF	Minor allele frequency
miRNA	Micro RNA
MRI	Magnetic Resonance Imaging
ncRNA	Non-Coding RNA
NK	Natural killer cells
ORs	odds ratios
PALB2	Partner and Localizer of BRCA2
PET	positron emission tomography
PR	Progesterone Receptor
QPCR	Quantitative Polymerase Chain Reaction
RNA	Ribonucleic acid
ROC	Receiver-operating-characteristic
rs	Reference SNP
RT	Reverse transcription
SNP	Single Nucleotide Polymorphism
SOCS6	Suppressor of cytokine signalling 6
TAMs	Tumor Associated Macrophages
TNM	Tumor/Nodes/Metastases staging
VEGF	Vascular endothelial growth factor

Author Contributions

Asmaa R. Abdel-Hamed participated in the design of the study, data curation and investigation and manuscript writing. Morkoss M. Fakhry was responsible for the laboratory work and writing the original draft and resources of the manuscript. Noha M. Mesbah and Dina M. Abo-Elmatty participated in the design of the study, drafting, and revising the work, and final approval of the submitted version. Mohamed M. Sayed-Ahmed, Abdel-Moneim M. Osman and Ola S. Ahmed participated in data analysis, drafting, and revising the work.

Competing Interests

The authors have declared that no competing interests exist.

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