# A Comprehensive Study on Signal Transduction and Therapeutic Role of miR-877 in Human Cancers

Milad Rafat[1], Mahdis Kohsarian[2], Mohamad Bahiraei[3], Amin R. Nikpoor[4]

[1]Student Research Committee, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran, [2]Department of Biology, Faculty of Science, Guilan University, Rasht, Iran, [3]Department of Radiology, Besat Hospital, Hamedan University of Medical Sciences, Hamedan, Iran, [4]Department of Medical Genetics, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

## Abstract

MicroRNAs are a group of short non-coding RNAs (miRNAs), which are epigenetically involved in gene expression and other cellular biological processes and can be considered as potential biomarkers for cancer detection and support for treatment management. This review aims to amass the evidence in order to reach the molecular mechanism and clinical significance of miR-877 in different types of cancer. Dysregulation of miR-877 level in various types of malignancies as bladder cancer, cervical cancer, cholangiocarcinoma, colorectal cancer (CRC), gastric cancer, glioblastoma, head and neck squamous cell carcinoma (HNSCC), hepatocellular carcinoma, laryngeal squamous cell carcinoma, melanoma, non-small cell lung cancer (NSCLC), oral squamous cell carcinoma, ovarian cancer (OC), pancreatic ductal adenocarcinoma, and renal cell carcinoma (RCC) have reported, significantly increase or decrease in its level, which can be indicated to its function as oncogene or tumor suppressor. MiR-877 is involved in cell proliferation, migration, and invasion through cell cycle pathways in cancer. MiR-877 could be potential a candidate as a valuable biomarker for prognosis in various cancers. Through this study, we proposed that miR-877 can potentially be a candidate as a prognostic marker for early detection of tumor development, progression, as well as metastasis.

**Keywords:** Biomarker, cancer, microRNA, microRNA-877, miR-877

## INTRODUCTION

About 20000 protein-coding genes constitute 2% of human's gene. It has been proposed that at least 70% of the sequences should be transcribed into RNAs; and most transcripts have been identified as non-coding RNAs (ncRNAs).[1-5] As to the latest advancements in sequencing and genome sequencing at large scale, the long nRNAs (more than 200 nucleotides) and short ncRNAs (less than 20 nucleotides) are the principal regulators of the human genome.[6-8] MicroRNAs are non-coding, endogenous, single-stranded, and small molecules the regulate across a mammalian genome and human genome can encode around 1000 types of them. They are found in eukaryotes and are approximately 22-24 nucleotides long.[9] The main job done by them is post-transcription regulations, which is done through interaction with mRNA and silencing the target gene. MicroRNA are mostly generated in intron regions of other genes and their transcription is mostly done by RNA polymerase II.[10] It is essential to do deeper studies to detect new biological events pertinent to carcinogenesis and also new treatment targets like microRNAs. The microRNAs had different expression in different cancerous tissues so that the expression can be increased, decreased, or remained stable.[11]

In human body, MiR-877 is constituted of two homologous miRNAs on human chromosome 6p21.33, hsa-miR-877-5p and hsa-miR-877-3p.[12,13] The Rfold web server (Vienna package) was used to plot the secondary structure predictions of miR-877 with a minimum free-energy (MFE) -37.66 kcal/mol

### Access this article online

**Quick Response Code:**

**Website:**
www.advbiores.net

**DOI:**
10.4103/abr.abr_412_21

**How to cite this article:** Rafat M, Kohsarian M, Bahiraei M, Nikpoor AR. A comprehensive study on signal transduction and therapeutic role of miR-877 in human cancers. Adv Biomed Res 2023;12:118.

and dot-bracket notation (http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi) [Figure 1]. The MiR-877 evolved conservatively in humans, mice, flies and other species of similar structure and sequence. The regulation of MiR-877 is important in the biological process to ensure a physiological equilibrium among the systems of the human body. At the functional level, some studies have shown that miR-877 promotes cell proliferation and invasion and induces cell apoptosis in many cancers.[12-45] The study collected prove to support the molecular mechanism and clinical conspicuousness of miR-877 in several cancers.

## CHANGES MIR-877 IN DIFFERENT TUMORS

Several studies has shown that miR-877 has been dysregulated in a variety of human tumors such as bladder cancer,[12] cervical cancer,[13-15] cholangiocarcinoma,[16] colorectal cancer (CRC),[17-19] gastric cancer,[20-24] glioblastoma,[25-27] head and neck squamous cell carcinoma (HNSCC),[28] hepatocellular carcinoma,[29-34] laryngeal squamous cell carcinoma,[35] melanoma,[36] non-small cell lung cancer (NSCLC),[37-40] ovarian cancer (OC),[41] pancreatic ductal Adenocarcinoma,[42,43] as well as renal cell carcinoma (RCC)[44] [Table 1].

### Bladder cancer

One prevalent urological malignancy is bladder cancer, which is also becoming increasingly common. Despite several available treatments, the five-year survival rate for B.C. patients remains high.[45] Approximately 33% to 75% of cases in BC are resistant to treatment due to metastasis or relapse of the disease. Furthermore, biomarkers are considered to be substitutes that improve or decrease the risk of clinically critical events such as cancer episodes, recurrence, expansion, or patient deaths.[46] Li *et al*.,[12] (2016) verified the reason for the association of p16 activation with miR-877-3p is direct binding. Their analyzes demonstrated that anti-tumor functionality of miR-877-3p in the bladder cancer cells, which revealed another alternative pattern of miRNA responsible for gene regulation.

Zhou *et al*.,[47] (2021) illustrated that thymoquinone (TQ) seem initiate the overproduction of ROS and downregulation of MMP, as well as the impeded autophagic flux, to start the apoptosis of BC cells. They demonstrated that TQ actuates miR-877-5p/PD-L1 (Modified death-ligand 1) hub to repress the EMT method and intrusion of BC cells, thus assist restrains the progression of bladder carcinoma.

### Cervical cancer

In 2018 worldwide with the estimation of 570,000 cases consisting of 311,000 mortalities, cervical cancer accounts for the 4th kind of cancer that has been usually diagnosed that is a major cause of mortality in female patients.[48] However, ~85% of the global mortalities caused by cervical cancer has been reported in developing or under-developed countries, with the rate of 18 times higher in the middle- and low-income countries in comparison to the countries with richer backgrounds.[49] In addition, a key cause of this type of cancer is human papilloma virus (HPV) infection. However, the key portion of the infections are self-evident.[50,51] Meng *et al*.,[13] (2019) demonstrated significant down-regulation of miR-877 in the tissues of cervical cancer and cell lines, so that lower level miR-877 expression has shown a considerable association to the enhanced International Federation of Gynecology and Obstetrics stage and greater lymph node metastasis in cases who suffered from cervical cancer. It is notable that we observed remarkable upregulation of MACC1 in cervical cancer tissues, with the negative correlation to the level of miR-877. Liang *et al*.[14] (2020) revealed that ATXN7L3 (Ataxin 7 Like 3) is a down-stream target gene of miR-877-5p that is undesirably regulated by miR-877-5p in cervical cancer. ATXN7L3 involved in histone deubiquitination, histone monoubiquitination, and positive regulation of transcription, DNA-templated. Their analyzes indicated the role of DSCAM-AS1 as one of the oncogenic lncRNAs via targeting miR-877-5p/ATXN7L3 axis for promoting CC development. Chen *et al*.,[15] (2020) found the function of HOXD-AS1 as one of the competing endogenous RNA (ceRNA) for sponge miR-877-3p, which upregulated FGF2 (Fibroblast Growth Factor 2) that is one of the targets of miR-877-3p. Finally, researchers have shown the MiR-877-3p as one of the suitable alternative promising therapeutic targets and new prognostic biomarkers for CC.

### Cholangiocarcinoma

Cholangiocarcinoma presents a diverse group of malignancies appearing in the biliary tree that is integrated by late diagnosis and unpleasant results.[52] Nearly 2,000 to 3,000 new cases are annually diagnosed in the U.S., which accounts for an annual occurrence of 1–2 cases per 100,000 people.[53] Moreover, researchers showed the spread of 0.01% to 0.46% of autopsy series. However, studies indicated the greater spread of cholangiocarcinoma in Asia, due to the endemic chronic parasitic
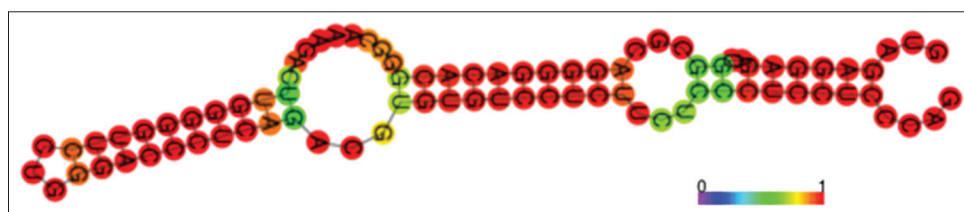


**Figure 1:** Prediction of optimal secondary structure of the has-miR-877 (EPS format) with – 36.80 kcal/mol with its dot-bracket notation using the Rfold web server. The sequence of this microRNA: GTAGAGGAGATGGCGCAGGGGACACGGGCAAAGACTTGGGGGTTCCTGGGACCCTCAGACGTGTG TCCTCTTCTCCCTCCTCCCAG

**Table 1: Functional characterization of miR-877 in cancers**

| Cancer type | Expression | Related gene | Clinical features | Role | Ref. |
|---|---|---|---|---|---|
| Bladder cancer | ↑ | p16 | Cell proliferation; colony formation; | OG | 12 |
| Cervical cancer | ↓ | MACC1, ATXN7L3, FGF2 | Cell proliferation; differentiation; migration; metastasis; inhibition of apoptosis; | TSG | 13-15 |
| Cholangiocarcinoma | ↑ | KRAS; SORBS3 | Cell proliferation; migration; invasion | OG | 16 |
| Colorectal cancer | ↓ | MTDH | Cell proliferation; colony formation; metastasis; tumor growth; inhibition of apoptosis | OG | 17-19 |
| Gastric cancer | ↓ | VEGFA, AQP3, FOXM1, PD-L1 | Cell proliferation; invasion; metastasis; Angiogenesis; inhibition of apoptosis | TSG | 20-24 |
| Glioblastoma | ↓↑ | SUZ12, TLR4 | Cell proliferation; colony formation; migration; metastasis; invasion; inhibition of apoptosis; | TSG/ OG | 25-27 |
| Head and neck squamous cell carcinoma | ↓ | - | Cell proliferation | TSG | 28 |
| Hepatocellular caarcinoma | ↓ | FOXM1, CDK14, YWHAZ, PIK3R3 | Cell proliferation; colony formation; migration; metastasis; invasion; inhibition of apoptosis; | TSG | 29-34 |
| Laryngeal Squamous Cell Carcinoma | ↓ | FOXP4 | Cell proliferation; migration; metastasis; invasion; inhibition of apoptosis | TSG | 35 |
| Melanoma | ↓ | - | Cell proliferation; metastasis | TSG | 36 |
| Non-small-cell lung cancer | ↓ | IGF-1R, ACP5, CCNA2 | Cell proliferation; epithelial-mesenchymal transition; angiogenesis; invasion; TNM stage; distant metastasis | TSG | 37-39 |
| Oral squamous cell carcinoma | ↓ | VEGFA | Cell proliferation, migration, invasion; Cell Viability; Colony Formation | TSG | 40 |
| Ovarian cancer | ↓ | FOXM1 | Cell proliferation; migration; invasion; metastasis; inhibition of apoptosis | TSG | 41 |
| Pancreatic ductal cancer | ↑ | STARD13 | Cell proliferation; migration; invasion; metastasis; inhibition of apoptosis; better survival | OG | 42, 43 |
| Renal cell carcinoma | ↓ | eEF2K | Cell proliferation; migration; invasion; inhibition of apoptosis | TSG | 44 |

↓: down-regulate; ↑: up-regulate; TSG: tumor suppressor gene; OG: oncogene

infestation.[54] Meijer *et al.*,[16] (2019) stated that miR-877 was significantly up-regulated in cases suffering from distal cholangiocarcinoma in comparison with the benign disease or pancreatic ductal adenocarcinoma (PDAC) ($P = 0.003$ & $P = 0.006$).

### *Colorectal cancer*

Based on the GLOBOCAN 2018 information, CRC has been introduced to be the 3rd most fatal and 4th most frequently diagnosed cancer worldwide. About two million new cases of disease and about one million mortalities have been approximated in 2018. According to the studies, we have observed the global increase of CRC occurrence, particularly, in developing countries due to their adoption of the "western" lifestyle[55] In spite of better perception as to the actual molecular mechanism and better CRC treatment in the surgical resection, radiation therapy, as well as chemotherapy, prognosis and in general survival CRC are still require major advancements.[56,57] Choi *et al.*,[17] (2016) obtained differential expression of miR-877-5p in relation to the BRAF-mutated CRCs. Their results suggested contribution of the DE-miRNAs in the BRAF-mutated CRCs compared with the KRAS-mutated CRCs to the aggressive phenotype of BRAF-mutated CRCs. Zhang *et al.*,[18] (2019) showed a considerable decline of miR-877 expression in the cell lines and CRC tissues. Lower expression of miR-877 associated to the TNM stage of patients with CRC and lymph node metastasis. Additionally, researchers found inhibition of activating the PTEN/Akt signaling pathway

using miR-877 through regulation of Metadherin (MTDH) expression in Colorectal Cancer cells. Sun *et al.*,[19] (2020) stated miR-877 systematically down-regulate expressing the metabolism-linked genes, which reprogrammed the mitochondrial metabolisms in the cancer cells.

### *Gastric cancer*

It is believed that the 2nd top cause of cancer death is gastric cancer. While the starting treatment of GC seems too efficient, the long-term survival rate of GC is not satisfactory due to lack of proper biomarker to initially determine GC. It is important to point out that CA125 and carcinoembryonic antigen are markets in clinical settings that are related to the unpleasant specificity and sensitivity even with combined utilization. Therefore, new diagnosing methods based on molecular techniques are need to diagnose such disease as soon as possible.[58] Lu *et al.*,[20] (2020) demonstrated that miR-877-3p was down-regulated in the plasma exosomes from the pre-operative GE cases. Overall, the miR-877-3p/VEGFA axis enhances the GC development. Zhu *et al.*,[21] (2020) observed lower miR-877 in the tissues of gastric cancer and cell lines than that of the related controls. Also, they demonstrated that aquaporin 3 (AQP3) is one of the coordinate down-stream targets of miR-877. Wu *et al.*,[22] (2020) referred to lower level of miR-877-5p in GC in comparison to the control group, Also their outputs indicated that the key contribution of miR-877-5p/FOXM1 (Forkhead Box M1) axis to the GC cancer development, which reflects miR-877-5p as one of the

new potent treatments for GC. FOXM1 is known to play a key role in cell cycle progression where endogenous FOXM1 expression peaks at S and G2/M phases. Guo *et al.*,[23] (2020) verified miR-877-5p capability of targeting FOXM1 and negative regulation of its expression. Another study showed the ability of miR-877-5p for negative regulation of the GC progression through suppressing the rapid growth or proliferation of the cells and elevating apoptosis that may be followed by greater cleaved caspase-3 and caspase-9, as well as level of Bax protein and lower levels of Bcl-2. Guo *et al.*,[24] (2021) stated that miR-877-5p suppressed PD-L1-3' UTR activities in gastric cancer.

### Glioblastoma

As stated in a study in the field, Glioblastoma has been introduced as the commonest and highly aggressive primary brain tumor in adult cases. Endothelial proliferation and necrosis have been considered to be typical histo-pathologic characteristics that assigns grade IV, which is the top grade in the classification of brain tumors presented by World Health Organization (WHO).[59] Researchers have estimated 12 to 15 months as the commonest length of survival after diagnosis, with ~3-7% of cases who would survive longer than five years.[60] A five-year survival in the U.S. has been reported to be 6.8% from 2012 to 2016. If it is not treated, the survival rate would be three months.[60] Xie *et al.*,[25] (2019) stated lower expression of miRNA-877-5p in glioblastoma which consists of the binding sites with SUZ12 and TRG-AS1. Additionally, researchers observed the ability of TRG-AS1 for suppressing miR-877-5p expression and of miR-877-5p for suppressing the expression of SUZ12. This zinc finger gene has been identified at the breakpoints of a recurrent chromosomal translocation reported in endometrial stromal sarcoma. Xu *et al.*,[26] (2019) stated that miR-877-3p up-regulated in the growth of the glioblastoma cells, migration, as well as invasion, and also enhancing the cell apoptosis via direct targeting of TLR4. In their data analysis from TCGA, Xu *et al.*,[27] (2021) stated cases who had higher levels of UBE2R2-AS1 or lower level expression of miR-877-3p are more likely experience satisfactory survival results. Constructing a gliomaxenograft model in the nude mice indicated suppression of the tumor growth by overexpressing UBE2R2-AS1, with the result of the same impact of inhibiting miR-877-3p expression.

### HNSCC

According to researchers, neck and head cancer progresses from the mouth, salivary glands, larynx (throat), nose, and sinus tissues or the face skin.[61] More than 500,000 novel HNSCCs have been observed each year[62] so that 40,000 new cases and 7890 mortalities have been in the U.S.[63] Moreover, longer exposure to smoking, tobacco, as well as tobacco-like products, and alcohol increased the risks of HNSCC progression.[64] Liu *et al.*,[28] (2019) indicated that hsa-mir-877 can be used as one of the very good diagnostic biomarkers for HNSCC, and potent prognostic importance for cases with HNSCC. As expressed in a consideration within the field, oral squamous cell carcinoma (OSCC) speaks to the

foremost harmful neoplasm in oral cancer with a mortality rate of more than 50%. The OSCC could be a multistep neoplasia at first created from mild oral epithelial hyperplasia to dysplasia taken after by carcinoma in situ.[65] OSCC has been rated among the 6th most frequent oral malignancy, with a yearly prevalence of more than 500,000 cases.[66] OSCC alone considered as dependable for more than 90% of oral cancers cases and have the most noteworthy rate of mortality universally.[66-69] Shao *et al.*,[40] (2020) referred to the miR-877-3p down-regulation by targeting VEGFA expression in OSCC progression.

### Hepatocellular carcinoma

Every year, 600,000 patients die because of HCC so that the disease is the 3rd major cause of death due to cancer in the world. In addition, hepatitis B and C virus infections are important parameters in the development of HCC. Moreover, inefficient prognosis and higher rate of recurrence are mostly due to intracerebral and bone metastasis in the early HCC.[70] In show disdain toward of the extraordinary progresses within the restorative procedures of HCC, such as hepatectomy, removal, and chemotherapy, the prognosis results of the patients are still unfavorable owing to its boundless expansion and distant metastasis.[71] It is common information that the start and progression of HCC is related with a few hereditary changes as well as the enactment of oncogenes or the inactivation of tumor silencer qualities.[72] As such, distinguishing promising restorative targets can give understanding into the early discovery and treatment of HCC. Huang *et al.*,[29] (2015) affirmed that miR-877 particularly links to the location within the untranslated mRNA FOXM1. When miR-877 was overexpressed in HCC cells, the protein levels of FOXM1 were deregulated. Their findings indicate that miR-877 could affect the sensitivity of paclitaxel therapy in hepatocellular carcinoma cell lines by targeting FOXM1. Yan *et al.*[30] (2018) found miR-877-5p expression was regulated downward in tissues or cell lines of HCC. In addition, cycline-dependent kinase 14 (CDK14) is a direct target for miR-877-5p in HCC cells. Clinical pathological analysis revealed a correlation between low miR-877-5p expression and histological grade (p = 0.008) and TNM stage (p = 0.018) and shorter overall survival (p = 0.0041) and disease-free survival (p = 0.0005). Shi *et al.*,[31] (2018) stated that ENSG00000232855-miR-877-RCAN1 interaction were found in the in hepatocellular carcinoma. Liu *et al.*,[32] (2020) stated that miR-877-5p was down-regulated in HCC tissues and cells. YWHAZ was identified as miR-877-5p direct target. Wang *et al.*[33] (2020) demonstrated an important correlation between the risk of rs1264440 and the risk of HCC. Individuals with the rs1264440 TT genotype and T allele presented an increased risk of HCC of 2.20 and 1.44 times. Furthermore, the TT rs1264440 carriers showed lower levels of miR-877. As well, Yu *et al.*,[34] (2021) demonstrated that miR-877-5p was down-regulated by targeting PIK3R3 in HCC.

### Laryngeal squamous cell carcinoma

According to the studies, laryngeal cancers are mostly squamous-cell carcinomas (SCCs), which reflects their source

from the epithelium of the larynx.[73] The new therapeutic outcomes of laryngeal SCCs are moderate with the universal five-year overall rate of occurrence of 154 977 male patients and 22 445 female patients in 2018[74] also, 81 806 mortalities in the men and 12 965 mortalities in the women have been globally reported from larynx cancer.[75] In another study, a five-year relative rate of survival for each stage of larynx cancer is broadly different based on the stage and site of tumor.[76] Wang *et al.*,[35] (2020) showed decreased miR-877-5p expression in LSCC cells and tissues by interacting with FOXP4 (Forkhead Box P4). Wu *et al.*,[77] (2021) illustrated that hsa_circ_0042823 quickens cancer movement by controlling miR-877-5p/FOXM1 pivot in LSCC.

### *Melanoma*

Melanoma is an aggressive skin cancer, which accounted for nearly 73% of skin cancer-related death and usually caused by direct exposure to the Sun's ultraviolet radiation.[78,79] The incidence of melanoma is gradually increasing worldwide in the past years.[80] Current therapies of melanoma are surgery, chemotherapy, and target therapy.[81] However, the prognosis of melanoma is still poor with only 10–15% of the 10-year survival rate in metastatic melanoma.[82] Therefore, a better understanding of melanoma pathogenesis needs to be investigated to improve the prognosis. In a study, Qi *et al.*,[36] (2014) aimed at specifying differential expression of microRNAs in the metastatic melanoma with the use of the next-generation sequencing technology stated that hsa-miR-877 were differentially expressed between the primary cutaneous melanoma specimens and metastatic melanoma.

### *Non-small cell lung cancer*

Non-small cell lung cancer (NSCLC) is the number one lung cancer and the most lethal malignant tumor in the world. As research shows, lung cancer is one of the leading causes of death worldwide, accounting for approximately 1.5 million deaths in 2012.[83] In Europe, 353,000 die annually because of the disease, which means about 20% total cancer death.[84] NSCLC is the reason for about 80% of the lung cancer cases, which has been a major type of lung cancer with low prognosis following chemotherapy. Therefore, it is important to pay attention to prognostic biomarkers and molecular targets for lung cancer.[85] Zhou *et al.*,[37] (2019) reported that miR-877 expression was downregulated in NSCLC tissues and cell lines. A low miR-877 expression was significantly associated with TNM and long-range metastases in NSCLC patients. Furthermore, they demonstrated that restoring miR-877 limits the proliferation and invasion of NSCLC cells. Additionally, their bioinformatics analysis predicted that the insulin-like growth factor-1 receptor (IGF-1R) would be a potential miR-877 target in the NSCLC. Bai *et al.*[38] (2020) indicated that miR-877 decreased the growth of NSCLC cells via PI3K/AKT by targeting tartrate-resistant acid phosphatase 5 (ACP5). Moreover, the overexpression of miR-877 inhibited viability, migration, invasion and EMT of NSCLC cells, but promoted cell apoptosis. Du *et al.*,[39] (2020) indicated that the expression

miR-877-5p was considerably impaired by the regulation of the CCNA2 pathway in tumorigenesis and metastasis of NSCLC.

### *Ovarian cancer*

According to the studies, OC has been considered as one of the harmful tumors of the women's reproductive system so that the death rate of epithelial OC allocated the 1st rank to it amongst the gynecological cancers.[86] Treating OC principally involves platinum-based chemotherapy and surgery.[87] As the population gradually ages, OC occurrence is enhancing annually.[88] As a result of the absence of particular initial clinical symptoms, OC is highly diagnosed at the developed stages.[89] Hence, it is essential to investigate the molecular mechanism of OC development for discovering efficient tumor markers in order to diagnose and treat OC. Fang *et al.*,[41] (2021) illustrated that miR-877 played a part of tumor silencer in OC by contrarily directing FOXM1 which may bring a novel understanding into modern molecular therapeutic targets and biomarkers for OC.

### *Pancreatic ductal adenocarcinoma*

PDAC is the foremost broad neoplastic illness of the pancreas and accounts for more than 90% of all dangerous tumors of the pancreas.[90,91] To date, PDAC has been the fourth leading cause of cancer death in the world, with an overall survival of less than 8% over five years.[92] Despite much complication research, treatment regimens, chemotherapy and radiation therapy have been largely ineffective.[93] Hence, the only effective treatment is surgery; whereas only 15-20% of these patients may undergo surgery.[94] Su *et al.*,[42] (2018) identified that mir-877 could as potential diagnostic and prognostic biomarkers for PDAC. Xu *et al.*[43] (2020) detailed that miR-887-3p could be a negative controller of STARD13 expression. STARD13 serves as a Rho GTPase-activating protein (Gap), a sort of protein that controls individuals of the Rho family of GTPases. Expanded miR-887-3p levels diminished STARD13 expression, which driven to multiplication, cell cycle handle, cell migration and invasion, and hindered apoptosis of pancreatic cancer cells.

### *Renal cell carcinoma*

This disease has been considered as the commonest malignant solid tumor in the adult population. Totally, 13,860 mortalities and 63,920 novel cancer cases due to renal pelvis and kidney cancers have been reported in the U.S in 2014.[95] Even though surgical resection is still the optimal curative technique for RCC, about 20% to 30% of the cases have experienced distant and local disease recurrence.[96] In addition, nearly 30% of the cases experienced metastasis when the disease has been initially diagnosed.[74] Shi *et al.*[44] (2016) demonstrated the miR-877 function as one of the tumor suppressors via modulating the eEF2K/eEF2 signaling cascade in the RCC.

## MIR-877 REGULATORY MECHANISMS

It is generally mentioned in the above articles, miR-877 mostly correlated with carcinogenesis and related with cancer progression through known pathways included PI3K, JAK/STAT, MAPK Signaling, apoptosis pathways,

Chromatin organization, and Signaling by GPCR, which all these pathways have correlation with each other also and has a main function in growth, proliferation or rapid growth, cell differentiation, as well as in invading and migrating the cancer cells in a variety of tumors.

MiR-877 participates in different pathways, which are mentioned in Table 2. The results of our bioinformatics work using DIANA-miRPath, Tarbase, and KEGG pathway show that miR-877 is associated with various other pathway, including ECM-receptor interaction, Proteoglycans in cancer, Adherens junction, Gap junction, Focal adhesion, Endometrial cancer, Renal cell carcinoma, Ras signaling pathway, ErbB signaling pathway, Lysine degradation, Prostate cancer, Colorectal cancer, Estrogen signaling pathway, NSCLC which targeted by miR-877-3p and -5p and also involved in carcinogenesis.

## CONCLUSION

MicroRNAs play a major role in gene regulation, so the dysregulation of MicroRNA is a distinguishing characteristic of cancer. As studies have pointed out, miR-877 is a non-coding RNA that plays a major role in migration and invasion, as well as in the rapid growth and proliferation of cancer cells. Studies have mainly shown that miR-877 is a tumor suppressor while in some cancers, it has played an oncogene role. The mechanism by which miR-877 with ascending or descending regulation plays a role in tumor growth and carcinogenesis. Studies have shown that changes in miR-877 expression are strongly linked to the severity of tumor growth. Consequently, it may be a marker for determining the extent of cancer, prognosis,

response to treatment, and also as a potential therapeutic target for solid tumors. Additionally, serum miR-877 concentrations and decreased survival and disease development are directly related. Given the functional mechanisms of miR-877 in the cellular pathways, some believe that miR-877 can be one of the markers to determine the development, stage and prognosis of the disease and determine the efficacy of treatment. Furthermore, it can be a therapeutic target where effective antitumor drugs improve miR-877 expression and work as an effective treatment. MiR-877 may be an applicant as a prognostic marker for early detection of tumor development, progression, and metastases.

## FUTURE PROSPECT

The precise working mechanisms at the upstream and downstream miR-877 are still required to be systematically studied and reviewed. The miR-877 may clinically propose as a versatile biomarker of the prognosis and diagnosis for survival rates, cancer progression, and even determining the efficacy of treatment. Targeting miR-877 may be a way to promising treatment of cancer, and it may become an essential clinical treatment approach in the future.

## METHOD

As noted above, researchers have chosen two strategies. The first approach was searching all research articles and reports published after the year of 2000 in Scopus, PubMed, Embase, Google Scholar, and Cochrane databases using keywords of MIRN877, MiRNA877, Hsa-Mir-877, MicroRNA 877, and Hsa-miR-877. Inclusion criteria included the expression and

## Table 2: DIANA-miRPath v3. 0 and Tarbase v8. experimentally supported interactions for hsa-miR-877-5p and -3p

| KEGG pathway | Related genes | |
| --- | --- | --- |
| | miR-877-5p | miR-877-3p |
| ECM-receptor interaction | ITGB1, ITGB8, COL6A2, LAMC1, TNC, COL4A1 | LAMB1 |
| Proteoglycans in cancer | ERBB2, ITGB1, KRAS, VAV2, AKT2, IGF2, TIMP3, RAC1, FGF2, FAS, GAB1, PDPK1, ITPR2, RPS6KB1 | ERBB2, SMAD2, RPS6, PPP1R12A, CTNNB1, FLNA, SOS1, RAC1, MAPK1, MDM2 |
| Adherens junction | ERBB2, WASL, RAC2, NLK, RAC1 | ERBB2, SMAD2, MLLT4, CTNNB1, RAC1, EP300, MAPK1, CREBBP |
| Gap junction | TUBA1B, KRAS, ITPR2 | GUCY1B3, GUCY1A3, TUBA1B, TUBB, CSNK1D, SOS1, GNAI2, GJA1, MAPK1 |
| Focal adhesion | ERBB2, ITGB1, ITGB8, RAC2, CRKL, CCND2, VAV2, AKT2, COL6A2, RAC1, LAMC1, TNC, PDPK1, COL4A1 | GSK3B, CAPN2, ERBB2, LAMB1, RAPGEF1, PAK2, ARHGAP35, PPP1R12A, CTNNB1, FLNA, SOS1, RAC1, VAV3, MAPK1 |
| Endometrial cancer | ERBB2, KRAS, AKT2, PDPK1 | GSK3B, ERBB2, CTNNB1, SOS1, MAPK1 |
| Renal cell carcinoma | CRKL, ETS1, KRAS, AKT2, RAC1, GAB1 | RAPGEF1, PAK2, SOS1, RAC1, EP300, MAPK1, CREBBP |
| Ras signaling pathway | RAC2, CALM1, ETS2, ETS1, KRAS, AKT2, RAC1, FGF2, GAB1, RALGDS, ABL1, RASSF5 | STK4, PAK2, MLLT4, SOS1, RAC1, NF1, MAPK1, RAPGEF5 |
| ErbB signaling pathway | ERBB2, CRKL, KRAS, AKT2, GAB1, ABL1, RPS6KB1 | GSK3B, ERBB2, PAK2, SOS1, MAPK1 |
| Lysine degradation | SETD1B, KMT2E, SUV39H1 | SETD1B, SETD2, KMT2D |
| Prostate cancer | ERBB2, KRAS, AKT2, PDPK1 | GSK3B, ERBB2, CREB3L4, CTNNB1, CCNE2, HSP90AB1, SOS1, EP300, MAPK1, CREBBP, MDM2 |
| Colorectal cancer | RAC2, KRAS, AKT2, RAC1, RALGDS | GSK3B, SMAD2, APPL1, CTNNB1, RAC1, MAPK1 |
| Estrogen signaling pathway | ATF2, CALM1, KRAS, AKT2, ITPR2 | FKBP4, CREB3L4, HSP90AB1, SOS1, GNAI2, MAPK1 |
| Non-small-cell lung cancer | ERBB2, KRAS, AKT2, PDPK1, RASSF5 | ERBB2, STK4, SOS1, MAPK1 |

biological mechanism(s) of miR-877 in tumor development in each cancer type.

Moreover, the second strategy tried to find the targeted genes by miR-877 and relative pathways involved in carcinogenesis in the base of prediction in relative of databases specific for microRNAs such as Software available in DIANA-miRPath v3. 0 (http://snf-515788.vm.okeanos.grnet.gr/), Tarbase V.8 (http://carolina.imis.athena-innovation.gr/diana_tools/web/index.php?r = tarbasev8/index) and finally KEGG database (available at www.genome.jp/kegg/pathway.html).

### Ethical approval

This study was performed without any human or animal model experiments by the authors.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

# REFERENCES

1. Djebali S, Davis C. merkel A, Dobin A, Lassmann T, mortazavi A, *et al*. Landscape of transcription in human cells nature. 2012;489:101-8.
2. Lee JT. Epigenetic regulation by long noncoding RNAs. Science 2012;338:1435-9.
3. Zhu S, Li W, Liu J, Chen C-H, Liao Q, Xu P, *et al*. Genome-scale deletion screening of human long non-coding RNAs using a paired-guide RNA CRISPR–Cas9 library. Nat Biotechnol 2016;34:1279.
4. Kambara H, Niazi F, Kostadinova L, Moonka DK, Siegel CT, Post AB, *et al*. Negative regulation of the interferon response by an interferon-induced long non-coding RNA. Nucleic Acids Res 2014;42:10668-80.
5. Li Z, Shen J, Chan MT, Wu WK. TUG 1: A pivotal oncogenic long non-coding RNA of human cancers. Cell Prolif 2016;49:471-5.
6. Jiang X, Ma N, Wang D, Li F, He R, Li D, *et al*. Metformin inhibits tumor growth by regulating multiple miRNAs in human cholangiocarcinoma. Oncotarget 2015;6:3178-94.
7. Vance KW, Sansom SN, Lee S, Chalei V, Kong L, Cooper SE, *et al*. The long non-coding RNA Paupar regulates the expression of both local and distal genes. The EMBO J 2014;33:296-311.
8. Huang B, Song JH, Cheng Y, Abraham JM, Ibrahim S, Sun Z, *et al*. Long non-coding antisense RNA KRT7-AS is activated in gastric cancers and supports cancer cell progression by increasing KRT7 expression. Oncogene 2016;35:4927-36.
9. Ambros V. microRNAs: Tiny regulators with great potential. Cell 2001;107:823-6.
10. Zhao Y, Srivastava D. A developmental view of microRNA function. Trends Biochem Sci 2007;32:189-97.
11. Lin S, Gregory RI. MicroRNA biogenesis pathways in cancer. Nat Rev Cancer 2015;15:321-33.
12. Li S, Zhu Y, Liang Z, Wang X, Meng S, Xu X, *et al*. Up-regulation of p16 by miR-877-3p inhibits proliferation of bladder cancer. Oncotarget 2016;7:51773-83.
13. Meng F, Ou J, Liu J, Li X, Meng Y, Yan L, Deng P, Sun B. MicroRNA877 is downregulated in cervical cancer and directly targets MACC1 to inhibit cell proliferation and invasion. Exp Ther Med 2019;18:3650-8.
14. Liang J, Zhang S, Wang W, Xu Y, Kawuli A, Lu J, Xiu X. Long non-coding RNA DSCAM-AS1 contributes to the tumorigenesis of cervical cancer by targeting miR-877-5p/ATXN7L3 axis. Biosci Rep 2020;40:BSR20192061.
15. Chen S, Li K. HOXD-AS1 facilitates cell migration and invasion as an oncogenic lncRNA by competitively binding to miR-877-3p and upregulating FGF2 in human cervical cancer. BMC Cancer 2020;20:1-9.
16. Meijer LL, Puik JR, Le Large T, Heger M, Dijk F, Funel N, *et al*. Unravelling the diagnostic dilemma: A microRNA panel of circulating miR-16 and miR-877 as a diagnostic classifier for distal bile duct tumors. Cancers 2019;11:1181
17. Choi YW, Song YS, Lee H, Yi K, Kim YB, Suh KW, Lee D. MicroRNA expression signatures associated with BRAF-mutated versus KRAS-mutated colorectal cancers. Medicine 2016;95:e3321.
18. Zhang L, Li C, Cao L, Li H, Zou H, Li H, Pei H. microRNA-877 inhibits malignant progression of colorectal cancer by directly targeting MTDH and regulating the PTEN/Akt pathway. Cancer Manag Res 2019;11:2769-81.
19. Sun L, Wan A, Zhou Z, Chen D, Liang H, Liu C, *et al*. RNA-binding protein RALY reprogrammes mitochondrial metabolism via mediating miRNA processing in colorectal cancer. Gut 2021;70:1698-712.
20. Lu J, Wang YH, Yoon C, Huang XY, Xu Y, Xie JW, *et al*. Circular RNA circ-RanGAP1 regulates VEGFA expression by targeting miR-877–3p to facilitate gastric cancer invasion and metastasis. Cancer Lett 2020;471:38-48.
21. Zhu H, Wu Y, Kang M, Zhang B. MiR-877 suppresses gastric cancer progression by downregulating AQP3. J Int Med Res 2020;48:0300060520903661.
22. Wu K, Yu Z, Tang Z, Wei W, Xie D, Xie Y, Xiao Q. miR-877-5p suppresses gastric cancer cell proliferation through targeting FOXM1. OncoTargets Ther 2020;13:4731-42.
23. Guo XD, Zhang N, Sha L. miR-877-5p antagonizes the promoting effect of SP on the gastric cancer progression. Neoplasma 2020;67:1293-302.
24. Guo T, Wang W, Ji Y, Zhang M, Xu G, Lin S. LncRNA PROX1-AS1 facilitates gastric cancer progression via miR-877-5p/PD-L1 axis. Cancer Manag Res 2021;13:2669-80.
25. Xie H, Shi S, Chen Q, Chen Z. LncRNA TRG-AS1 promotes glioblastoma cell proliferation by competitively binding with miR-877-5p to regulate SUZ12 expression. Pathol Res Pract 2019;215:152476.
26. Xu W, Hu GQ, Da Costa C, Tang JH, Li QR, Du L, *et al*. Long noncoding RNA UBE2R2-AS1 promotes glioma cell apoptosis via targeting the miR-877-3p/TLR4 axis. OncoTargets Ther 2019;12:3467-80.
27. Xu W, Che DD, Chen L, Lv SQ, Su J, Tan J, Liu Q, Pan YW. UBE2R2-AS1 inhibits xenograft growth in nude mice and correlates with a positive prognosis in glioma. J Mol Neurosci 2021;71:1605-13.
28. Liu C, Yu Z, Huang S, Zhao Q, Sun Z, Fletcher C, *et al*. Combined identification of three miRNAs in serum as effective diagnostic biomarkers for HNSCC. EBioMedicine 2019;50:135-43.
29. Huang X, Qin J, Lu S. Up-regulation of miR-877 induced by paclitaxel inhibits hepatocellular carcinoma cell proliferation though targeting FOXM1. Int J Clin Exp Pathol 2015;8:1515.
30. Yan TH, Qiu C, Sun J, Li WH. MiR-877-5p suppresses cell growth, migration and invasion by targeting cyclin dependent kinase 14 and predicts prognosis in hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2018;22:3038-46.
31. Shi B, Zhang X, Chao L, Zheng Y, Tan Y, Wang L, Zhang W. Comprehensive analysis of key genes, microRNAs and long non-coding RNAs in hepatocellular carcinoma. FEBS Open Bio 2018;8:1424-36.
32. Liu Y, Guo J, Shen K, Wang R, Chen C, Liao Z, Zhou J. Paclitaxel suppresses hepatocellular carcinoma tumorigenesis through regulating Circ-BIRC6/miR-877-5p/YWHAZ axis. OncoTargets Ther 2020;13:9377-88.
33. Wang H, Wang B, Wang T, Fan R. A genetic variant in the promoter region of miR-877 is associated with an increased risk of hepatocellular carcinoma. Clin Res Hepatol Gastroenterol 2020;44:692-8.
34. Yu Y, Bian L, Liu R, Wang Y, Xiao X. Circular RNA hsa_circ_0061395 accelerates hepatocellular carcinoma progression via regulation of the miR-877-5p/PIK3R3 axis. Cancer Cell Int 2021;21:1-2.
35. Wang X, Liu L, Zhao W, Li Q, Wang G, Li H. LncRNA SNHG16 promotes the progression of laryngeal squamous cell carcinoma by mediating miR-877-5p/FOXP4 axis. OncoTargets Ther 2020;13:4569-79.
36. Qi M, Huang X, Zhou L, Zhang J. Identification of differentially expressed microRNAs in metastatic melanoma using next-generation sequencing technology. Int J Mol Med 2014;33:1117-21.
37. Zhou G, Xie J, Gao Z, Yao W. MicroRNA877 inhibits cell proliferation and invasion in nonsmall cell lung cancer by directly targeting IGF1R. Exp Ther Med 2019;18:1449-57.

38. Bai X, He C, Fu B, Kong X, Bu J, Zhu K, Zheng W, Zhou F, Ni B. microRNA-877 contributes to decreased non-small cell lung cancer cell growth via the PI3K/AKT pathway by targeting tartrate resistant acid phosphatase 5 activity. Cell Cycle 2020;19:3260-76.

39. Du LJ, Mao LJ, Jing RJ. Long noncoding RNA DNAH17-AS1 promotes tumorigenesis and metastasis of non-small cell lung cancer via regulating miR-877–5p/CCNA2 pathway. Biochem Biophys Res Commun 2020;533:565-72.

40. Shao Y, Song Y, Xu S, Li S, Zhou H. Expression profile of circular RNAs in oral squamous cell carcinoma. Front Oncol 2020;10:533616.

41. Fang L, Zhang B, Zhu N. MiR-877 suppresses tumor metastasis via regulating FOXM1 in ovarian cancer. J BUON 2021;26:229-34.

42. Su Q, Zhu EC, Qu YL, Wang DY, Qu WW, Zhang CG, *et al*. Serum level of co-expressed hub miRNAs as diagnostic and prognostic biomarkers for pancreatic ductal adenocarcinoma. J Cancer 2018;9:3991-9.

43. Xu X, Zheng S. MiR-887-3p negatively regulates STARD13 and promotes pancreatic cancer progression. Cancer Manag Res 2020;12:6137-47.

44. Shi Q, Xu X, Liu Q, Luo F, Shi J, He X. MicroRNA877 acts as a tumor suppressor by directly targeting eEF2K in renal cell carcinoma. Oncol Lett 2016;11:1474-80.

45. Wu J, Wang J. HMGN5 expression in bladder cancer tissue and its role on prognosis. Eur Rev Med Pharmacol Sci 2018;22:970-5.

46. Chamie K, Litwin MS, Bassett JC, Daskivich TJ, Lai J, Hanley JM, *et al*. Recurrence of high-risk bladder cancer: A population-based analysis. Cancer 2013;119:3219-27.

47. Zhou X, Wang F, Wu H, Chen X, Zhang Y, Lin J, Cai Y, Xiang J, He N, Hu Z, Jin X. Thymoquinone suppresses the proliferation, migration and invasiveness through regulating ROS, autophagic flux and miR-877-5p in human bladder carcinoma cells. Int J Biol Sci 2021;17:3456-75.

48. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.

49. Prabhu M, Eckert LO. Development of World Health Organization (WHO) recommendations for appropriate clinical trial endpoints for next-generation Human Papillomavirus (HPV) vaccines. Papillomavirus Res 2016;2:185-9.

50. Rodríguez AC, Schiffman M, Herrero R, Wacholder S, Hildesheim A, Castle PE, *et al*. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. J Natl Cancer Inst 2008;100:513-7.

51. Vo N, Klein ME, Varlamova O, Keller DM, Yamamoto T, Goodman RH, *et al*. A cAMP-response element binding protein-induced microRNA regulates neuronal morphogenesis. Proc Natl Acad Sci 2005;102:16426-31.

52. Banales JM, Cardinale V, Carpino G, Marzioni M, Andersen JB, Invernizzi P, *et al*. Expert consensus document: Cholangiocarcinoma: Current knowledge and future perspectives consensus statement from the European Network for the study of cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol 2016;13:261-80.

53. Landis SH, Murray T, Bolden S. Wingo PA. Cancerstatistics. CA Cancer J Clin 1998;48:6-29.

54. Vauthey JN, Blumgart LH. Recent advances in the management of cholangiocarcinomas. Semin Liver Dis 1994;14:109-14.

55. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors. Prz Gastroenterol 2019;14:89-103.

56. Sostres C, Gargallo CJ, Lanas A. Aspirin, cyclooxygenase inhibition and colorectal cancer. World J Gastrointest Pharmacol Ther 2014;5:40-9.

57. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.

58. Sitarz R, Skierucha M, Mielko J, Offerhaus GJ, Maciejewski R, Polkowski WP. Gastric cancer: Epidemiology, prevention, classification, and treatment. Cancer Manag Res 2018;10:239-48.

59. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. Clin Cancer Res 2013;19:764-72.

60. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, *et al*. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2012–2016. Neuro Oncol 2019;21(Suppl 5):v1-100.

61. Marur S, Forastiere AA. Head and neck squamous cell carcinoma: Update on epidemiology, diagnosis, and treatment. Mayo Clin Proc 2016;91:386-96.

62. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA A Cancer J Clin 2015;65:87-108.

63. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA A Cancer J Clin 2015;65:5-29.

64. Marur S, Forastiere AA. Head and neck cancer: Changing epidemiology, diagnosis, and treatment. Mayo Clin Proc 2008;83:489-501.

65. Yu JS, Chen YT, Chiang WF, Hsiao YC, Chu LJ, See LC, *et al*. Saliva protein biomarkers to detect oral squamous cell carcinoma in a high-risk population in Taiwan. Proc Natl Acad Sci 2016;113:11549-54.

66. Giovannacci I, Vescovi P, Manfredi M, Meleti M. Non-invasive visual tools for diagnosis of oral cancer and dysplasia: A systematic review. Med Oral Patol Oral Cir Bucal 2016;21:e305-15.

67. Maleki D, Ghojazadeh M, Mahmoudi SS, Mahmoudi SM, Pournaghi-Azar F, Torab A, *et al*. Epidemiology of oral cancer in Iran: A systematic review. Asian Pac J Cancer Prev 2015;16:5427-32.

68. Liu D, Zhao X, Zeng X, Dan H, Chen Q. Non-invasive techniques for detection and diagnosis of oral potentially malignant disorders. Tohoku J Exp Med 2016;238:165-77.

69. Rivera C. Essentials of oral cancer. Int J Clin Exp Pathol 2015;8:11884-94.

70. Blum HE. Hepatocellular carcinoma: Therapy and prevention. World J Gastroenterol 2005;11:7391-400.

71. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-14.

72. Lee JS. The mutational landscape of hepatocellular carcinoma. Clin Mol Hepatol 2015;21:220-9.

73. Mortal GB. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117-71.

74. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Erratum: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2020;70:313.

75. Misono S, Marmor S, Yueh B, Virnig BA. Treatment and survival in 10,429 patients with localized laryngeal cancer: A population-based analysis. Cancer 2014;120:1810-7.

76. Brandstorp-Boesen J, Sørum Falk R, Folkvard Evensen J, Boysen M, Brøndbo K. Risk of recurrence in laryngeal cancer. PLoS One 2016;11:e0164068.

77. Wu T, Sun Y, Sun Z, Li S, Wang W, Yu B, Wang G. Hsa_circ_0042823 accelerates cancer progression via miR-877-5p/FOXM1 axis in laryngeal squamous cell carcinoma. Ann Med 2021;53:961-71.

78. Carr S, Smith C, Wernberg J. Epidemiology and risk factors of melanoma. Surg Clin 2020;100:1-2.

79. Owens B. Melanoma. Nature 2014;515:S109.

80. Rastrelli M, Tropea S, Rossi CR, Alaibac M. Melanoma: Epidemiology, risk factors, pathogenesis, diagnosis and classification. *In vivo* 2014;28:1005-11.

81. Varrone F, Caputo E. The miRNAs role in melanoma and in its resistance to therapy. Int J Mol Sci 2020;21:878.

82. O'Neill CH, Scoggins CR. Melanoma. J Surg Oncol 2019;120:873-81.

83. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al*. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.

84. van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. Lancet (London, England) 2011;378:1741-55.

85. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, *et al*. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374-403.

86. Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. Lancet 2014;384:1376-88.

87. Matulonis UA, Sood AK, Fallowfield L, Howitt BE, Sehouli J, Karlan BY. Ovarian cancer. Nat Rev Dis Primers 2016;2:1-22.

88. Tew WP, Muss HB, Kimmick GG, Von Gruenigen VE, Lichtman SM.

Breast and ovarian cancer in the older woman. J Clin Oncol 2014;32:2553-61.

89. Longuespée R, Boyon C, Desmons A, Vinatier D, Leblanc E, Farré I, *et al*. Ovarian cancer molecular pathology. Cancer Metastasis Rev 2012;31:713-32.

90. Kleeff J, Costello E, Jackson R, Halloran C, Greenhalf W, Ghaneh P, *et al*. The impact of diabetes mellitus on survival following resection and adjuvant chemotherapy for pancreatic cancer. Br J Cancer 2016;115:887-94.

91. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.

92. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, *et al*. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200-10.

93. Simianu VV, Zyromski NJ, Nakeeb A, Lillemoe KD. Pancreatic cancer: Progress made. Acta oncologica 2010;49:407-17.

94. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.

95. Rathmell WK, Godley PA. Recent updates in renal cell carcinoma. Curr Opin Oncol 2010;22:250-6.

96. Janzen NK, Kim HL, Figlin RA, Belldegrun AS. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin North Am 2003;30:843-52.