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# Does MiRNA gene expression predict gastric cancer stage and localization?

**Onder Ozcan[1], Ahmet Korkut Belli[1], Selami Ilgaz Kayilioglu[1], Ozgur Ilhan Celik[2], Mehmet Kaplan[3], Murat Kara[4], Murat Polat[5]**

*[1]Mugla Sitki Kocman Universty Medical School, Department of General Surgery, Mugla, Turkey .*
*[2]Mugla Sitki Kocman Universty Medical School, Department of Pathology, Mugla, Turkey.*
*[3] NCR International Hospital, Department of General Surgery, Gaziantep, Turkey.*
*[4]Medical Genetics Specialist, Self Employment, Mersin,Turkey.*
*[5]Mugla Sitki Kocman Universty Medical School, Department of General Surgery, Mugla, Turkey*

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**Abstract**
Gastric cancer comprises 10% of all cancers in the world and is rarely seen before the age of 30. Different genetic interactions or molecular changes like e-cadherin, P16, APC, c-erb B2, c-met, ras, or c-myc have been described in the pathogenesis of the disease. MiRNAs play critical roles in various biological processes such as cell proliferation, cell differentiation, apoptosis, repairing of DNA damage, angiogenesis, stress response, and stem cell division. The aim of this study is to investigate the relationship between miRNA gene expressions and gastric cancer. Method: Sixty-four patients with gastric cancer diagnosed consecutively in our pathology laboratory and 30 consecutive participants with normal gastric tissue, as a control group, were included in our study between 2011 and 2013. Total miRNAs were obtained by using genomic miRNA extraction kit (QIAGEN Sample & Assay Technologies, Hilden, Germany) after the samples had been deparaffinized. MiR-21, 107, 141, 150, 192, 202, 218, 331 gene expressions were evaluated by using real time-PCR (RT-PCR) from the whole miRNA. Results: MiR-331 was downregulated in the stage 2 patients and the rest of the miRNAs were significantly upregulated ($p < 0.001$). All miRNAs were significantly upregulated in the stage 3a patients ($p < 0.001$). In the antrum localized tumors, miR-107, -150, -202, -218, and -331 were significantly upregulated, whereas miR-21, -192 were statistically downregulated ($p < 0.05$). In the cardia localized tumors, miR-21 ($p > 0.05$) was downregulated and miR-107, -150, -202, -218, and -331 were upregulated ($p < 0.05$) Different gene expressions of miRNAs according to the different localizations of gastric cancer and different stages suggest that it can be tumor marker to predict the stage and localization of gastric cancer.

**Keywords:** MiRNA, gastric carcinoma, gene, expression

## Introduction

Gastric cancer comprises 10% of all cancers in the world and is rarely seen before the age of 30. It develops after the age of 50 and in males 2 times more often than females (1). Diet, genetic factors, and bacterial agents such as Helicobacter pylori are some of the risk factors of the disease (2,3). Different genetic interactions or molecular changes like e-cadherin, P16, APC, c-erb B2, c-met, ras, or c-myc have been described in the pathogenesis of the disease (4,5).

MiRNAs are members of noncoding small RNA family with a length of 19-25 nucleotides (4). MiRNAs play critical roles in various biological processes such as cell proliferation, cell differentiation, apoptosis, repairing of DNA damage, angiogenesis, stress response, and stem cell division. They also work as tumor suppressor gene and/or oncogene in the diseases or specific tissues, and function in the regulation of gene expressions during transcription processes. Moreover, genetic alterations of miRNA are associated with development of various human diseases such as cancer, cardiovascular diseases, inflammation, and asthma (6-11).

The aim of this study is to investigate the relationship between miRNA gene expressions and gastric cancer.

## Material and Methods

This study was conducted by the coordination of General Surgery, Pathology, and Medical Genetics in Mugla Sitki Kocman University Medical School after obtaining an approval from the clinical research ethics committee (05 August 2013, 13/109). Sixty-four patients with gastric cancer diagnosed consecutively in our pathology laboratory and 30 consecutive participants with normal gastric tissue, as a control group, were included in our study between 2011 and 2013. The samples were obtained from

***Coresponding Author:** Onder Ozcan, Mugla Sitki Kocman Universty Medical School, Department of General Surgery, Mugla, Turkey
E-mail: onderozcan@mu.edu.tr

paraffin blocks with 5-micron thickness slices. Total miRNAs were obtained by using genomic miRNA extraction kit (QIAGEN Sample & Assay Technologies, Hilden, Germany) after the samples had been deparaffinized. miR-21, miR107, miR141, miR150, miR192, miR202, miR218, miR331 gene expressions were evaluated by using real time-PCR (RT-PCR) from the whole miRNA.

Patient distribution: Of the 64 patients, 25 were female and 39 were male. Mean age of the patients were 65.15± 1 years (range 31 to 88), mean age of the female patients were 62.6 ± 1 years (range 33 to 88), and the mean age of the male patients were 66.6 ± 1 years (range 31 to 88).

Forming of the groups: Gastric cancer and control groups were compared according to the fold change values obtained by using 2 Average delta CT values (Table 1).

Gastric cancer group were divided into subgroups according to gender, tumor stage, localization, and histopathology for further analysis. Female and male patients were compared with control group separately (Table 2). Ages were divided into ≤45 and >45 (Table 3). Patients were staged according to the TNM system (Table 4) (12-13). Tumor localizations were: 1- antrum, 2- corpus-fundus, and 3- cardia (Table 5). Histopathological types of the tumor were: 1- signet ring cell carcinoma (n=11) and 2- adenocarcinoma (N=53) (Table 6). All of these groups were compared separately with the control group.

SPSS 15.0 software was used for the analyzes of the data. The results were demonstrated as mean ± standard deviation. Variance analysis was used to evaluate whether there were differences between the groups. Analyzes were performed at the page of Qiagen's data analysis expression with using the values of 2 Average delta CT. P values < 0.05 were accepted as statistical significance.

## Results

miRNA expressions, miR-21, miR-141, miR-150, miR-202, were upregulated and miR-107 was downregulated in the gastric tumor tissue. However, these differences were not statistically significant (P > 0.05) (Table 1).

miR-21 was significantly upregulated in the females comparing to the males. (P < 0.05). miR-107 was downregulated in the females. miR-331 was normal in both genders (Table 2).

All miRNA types except miR-107 and miR-331 were upregulated without a statistical significance in the patients that were ≤ 45 years old (p > 0.05). miR-21, miR-141, miR-150, and miR-202 were upregulated without a statistical significance in the patients > 45 years old, whereas miR-107 was downregulated (p > 0.05) (Table 3).

miR-331 was downregulated in the stage 2 patients and the rest of the miRNAs were significantly upregulated (p < 0.001). All miRNAs were significantly upregulated in the stage 3a patients (p < 0.001). In stage 3b, miR-21 was downregulated (p < 0.05), and miR-107, miR-141, miR-150, and miR-202 were upregulated (p < 0.001). In stage 4 patients, miR-107 was downregulated (p > 0.05) and miR-141, miR-150, miR-192, and miR-202 were upregulated (P > 0.05) (Table 4).

**Table 1.** miRNA expressions in gastric cancer group and control group

| | Control Group | Gastric Cancer Group | | |
|---|---|---|---|---|
| | 2^(Avg. (Delta(Ct)) | 2^(Avg. (Delta(Ct)) | Fold Change | p value |
| miR218 | 0.163 | 0.124 | 0.760 | 0.337 |
| miR21 | 1.673 | 4.084 | 2.440∧ | 0.460 |
| miR202 | 0.363 | 1.637 | 4.502∧ | 0.435 |
| miR192 | 4.163 | 7.989 | 1.918 | 0.446 |
| miR150 | 0.933 | 3.980 | 4.264∧ | 0.403 |
| miR107 | 0.127 | 0.052 | 0.414∨ | 0.398 |
| miR141 | 0.118 | 1.447 | 12.227∧ | 0.434 |
| miR331 | 0.249 | 0.243 | 0.974 | 0.345 |

∧, up-regulation ∨, down-regulation

**Table 2.** Comparison of miRNAs in gastric cancer and control groups according to gender

| | Control Group | Female | | | Male | | |
|---|---|---|---|---|---|---|---|
| | 2^(-Avg. (Delta (Ct)) | 2^(-Avg. (Delta(Ct)) | Fold Change | p value | 2^(-Avg. (Delta(Ct)) | Fold Change | p value |
| **miR218** | 0.163 | 0.201 | 1.235 | 0.232 | 0.090 | 0.557 | 0.219 |
| **miR21** | 1.673 | 4.863 | 2.905∧ | 0.037* | 3.652 | 2.182∧ | 0.344 |
| **miR202** | 0.363 | 2.498 | 6.869∧ | 0.250 | 1.248 | 3.43∧ | 0.319 |
| **miR192** | 4.163 | 15.858 | 3.808∧ | 0.240 | 5.148 | 1.236 | 0.331 |
| **miR150** | 0.933 | 8.328 | 8.922∧ | 0.091 | 2.480 | 2.657∧ | 0.285 |
| **miR107** | 0.127 | 0.028 | 0.222∨ | 0.241 | 0.078 | 0.616 | 0.279 |
| **miR141** | 0.118 | 2.040 | 17.235∧ | 0.233 | 1.161 | 9.812∧ | 0.318 |
| **miR331** | 0.249 | 0.471 | 1.887 | 0.215 | 0.159 | 0.638 | 0.226 |

∧, up-regulation ∨, down-regulation *, significant p value

**Table 3.** Comparison of miRNAs in gastric cancer and control groups according to the age differences.

| | Control Group | Age | | | | | |
|---|---|---|---|---|---|---|---|
| | | < 45 | | | >45 | | |
| | 2^(-Avg. (Delta (Ct)) | 2^(-Avg. (Delta(Ct)) | Fold Change | p value | 2^(-Avg. (Delta(Ct)) | Fold Change | p value |
| **miR218** | 0.163 | 0.356 | 2.181∧ | 0.054 | 0.104 | 0.640 | 0.435 |
| **miR21** | 1.673 | 10.386 | 6.205∧ | 0.053 | 3.505 | 2.094∧ | 0.439 |
| **miR202** | 0.363 | 7.697 | 21.168∧ | 0.054 | 1.270 | 3.494∧ | 0.438 |
| **miR192** | 4.163 | 12.846 | 3.085∧ | 0.054 | 7.392 | 1.775 | 0.440 |
| **miR150** | 0.933 | 7.293 | 7.814∧ | 0.054 | 3.605 | 3.862∧ | 0.439 |
| **miR107** | 0.127 | 0.169 | 1.333 | 0.054 | 0.043 | 0.342∨ | 0.437 |
| **miR141** | 0.118 | 4.221 | 35.660∧ | 0.054 | 1.214 | 10.263∧ | 0.434 |
| **miR331** | 0.249 | 0.206 | 0.827 | 0.054 | 0.2501 | 1.001 | 0.428 |

∧, up-regulation ∨, down-regulation

**Table 4.** Comparison of miRNAs in gastric cancer and control groups according to the stages of tumors

| | Control Group | Tumor Stage | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Stage II | | | Stage IIIa | | | Stage IIIb | | | Stage IV | | |
| | 2^(Avg. (Delta (Ct)) | 2^(Avg. (Delta (Ct)) | Fold Change | p value | 2^(Avg. (Del-ta(Ct)) | Fold Change | p Value | 2^(Avg. (Del-ta(Ct)) | Fold Change | p value | 2^(Avg. (Del-ta(Ct)) | Fold Change | p value |
| miR218 | 0,163 | 0.239 | 1.467 | 0.008* | 3.415 | 20.924 | 0.008* | 0.102 | 0.626 | 0.488 | 0.160 | 0.985 | 0.213 |
| miR21 | 1.673 | 5.897 | 3.523∧ | 0.008* | 269.100 | 160.782 | 0.008* | 0.062 | 0.037 | 0.047* | 2.652 | 1.585 | 0.213 |
| miR202 | 0.363 | 19.400 | 53.349∧ | 0.008* | 87.790 | 241.418 | 0.008* | 1.426 | 3.922 | 0.053 | 3.374 | 9.280 | 0.212 |
| miR192 | 4.163 | 14.340 | 3.444∧ | 0.008* | 288.0149 | 69.172 | 0.008* | 3.182 | 0.764 | 0.004* | 8.754 | 2.102 | 0.213 |
| miR150 | 0.933 | 2.179 | 2.332∧ | 0.008* | 122.445 | 131.179 | 0.008* | 2.236 | 2.396 | 0.023* | 2.818 | 3.019 | 0.213 |
| miR107 | 0.127 | 0.797 | 6.274∧ | 0.008* | 2.496 | 19.636 | 0.008* | 0.375 | 2.957 | 0.048* | 0.015 | 0.121 | 0.213 |
| miR141 | 0.118 | 2.751 | 23.239∧ | 0.008* | 46.205 | 390.312 | 0.008* | 1.271 | 10.738 | 0.082 | 1.179 | 9.959 | 0.213 |
| miR331 | 0.249 | 0.171 | 0.686 | 0.008* | 4.9519 | 19.816 | 0.008* | 0.261 | 1.044 | 0.792 | 0.156 | 0.626 | 0.213 |

∧, up-regulation ∨, down-regulation *, significant p value

In the antrum localized tumors, miR-107, miR-150, miR-202, miR-218, and miR-331 were significantly upregulated, whereas miR-21, -192 were statistically downregulated ($p < 0.05$). In the corpus localized tumors, miR-21 was downregulated and miR-107, miR-141, miR-150, miR-202, miR-218, and miR-331 were upregulated ($p > 0.05$). In the cardia localized tumors, miR-21 ($p > 0.05$) was downregulated and miR-107, miR-150, miR-202, miR-218, and miR-331 were upregulated ($p < 0.05$) (Table 5).

**Table 5.** Comparison of miRNAs in gastric cancer and control groups according to the tumor localization

| | Control Group | Tumor Localization | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Stage II | | | Stage IIIa | | | Stage IIIb | | | Stage IV | | |
| | 2^(Avg. (Delta (Ct)) | 2^(Avg. (Delta (Ct)) | Fold Change | p value | 2^(Avg. (Del-ta(Ct)) | Fold Change | p Value | 2^(Avg. (Del-ta(Ct)) | Fold Change | p value | 2^(Avg. (Del-ta(Ct)) | Fold Change | p value |
| miR218 | 0,163 | 3,723 | 22,815∧ | <0,001* | 3,711 | 22,737∧ | 0,272 | 1,431 | 8,770∧ | <0,001* | 0.160 | 0.985 | 0.213 |
| miR21 | 1,673 | 0,466 | 0,278∨ | 0,007* | 0,661 | 0,395∨ | 0,272 | 0,341 | 0,203∨ | 0,075 | 2.652 | 1.585 | 0.213 |
| miR202 | 0,363 | 33,423 | 91,912∧ | 0,002* | 28,166 | 77,456∧ | 0,272 | 1,241 | 3,413∧ | <0,001* | 3.374 | 9.280 | 0.212 |
| miR192 | 4,163 | 8,307 | 1,995 | 0,010* | 8,124 | 1,951 | 0,272 | 2,823 | 0,678 | 0,667 | 8.754 | 2.102 | 0.213 |
| miR150 | 0,933 | 25,428 | 27,242∧ | <0,001* | 42,660 | 45,702∧ | 0,272 | 30,874 | 33,076∧ | <0,001* | 2.818 | 3.019 | 0.213 |
| miR107 | 0,127 | 13,328 | 104,826∧ | 0,006* | 23,293 | 183,203∧ | 0,272 | 12,958 | 101,919∧ | <0,001* | 0.015 | 0.121 | 0.213 |
| miR141 | 0,118 | 0,061 | 0,516 | 0,567 | 0,850 | 7,184∧ | 0,272 | 0,138 | 1,168 | 0,758 | 1.179 | 9.959 | 0.213 |
| miR331 | 0,249 | 4,924 | 19,706∧ | <0,001* | 10,149 | 40,615∧ | 0,272 | 2,637 | 10,554∧ | 0,085 | 0.156 | 0.626 | 0.213 |

∧, up-regulation ∨, down-regulation *, significant p value

According to histopathological type of the tumor, although miRNAs other than miR-21 and miR-107 were upregulated without statistical significance (p > 0.05) in the signet ring cell group. In the adenocarcinoma group, miR-107 was downregulated and miR-21, miR-141, miR-150, and miR-202 were upregulated (p > 0.05) (Table 6).

**Table 6.** Comparison of miRNAs in gastric cancer and control groups according to the histopathologic type of tumors

| | Control Group | Histopathologic Type | | | | | |
|---|---|---|---|---|---|---|---|
| | | Signet Ring Cell | | | Adenocarcinoma | | |
| | 2^(-Avg. (Delta (Ct)) | 2^(-Avg. (Delta(Ct)) | Fold Change | p value | 2^(-Avg. (Delta(Ct)) | Fold Change | p value |
| **miR218** | 0,163 | 0,654 | 4,011^ | 0,068 | 0,091 | 0,559 | 0,430 |
| **miR21** | 1,673 | 2,318 | 1,385 | 0,060 | 4,536 | 2,710^ | 0,435 |
| **miR202** | 0,363 | 15,358 | 42,235^ | 0,068 | 1,081 | 2,974^ | 0,434 |
| **miR192** | 4,163 | 24,134 | 5,796^ | 0,068 | 6,510 | 1,563 | 0,436 |
| **miR150** | 0,933 | 13,104 | 14,039^ | 0,068 | 3,192 | 3,420^ | 0,435 |
| **miR107** | 0,127 | 0,101 | 0,798 | 0,068 | 0,046 | 0,366v | 0,433 |
| **miR141** | 0,118 | 7,808 | 65,958^ | 0,068 | 1,059 | 8,949^ | 0,429 |
| **miR331** | 0,249 | 0,503 | 2,013^ | 0,068 | 0,212 | 0,852 | 0,424 |

^, up-regulation v, down-regulation

## Discussion

miRNAs have been shown to act as an oncogenic or a tumor suppressor during cancer progress, metastasis, or invasion phases (14). After noticing the role of miRNAs, alterations of its expressions in variable cancer types have been investigated and differences in pathological tissues have been demonstrated (15).

Several studies investigated the relationship between gastric cancer and miRNA mediated gene regulation. Genes encoding miRNAs act as a proto-oncogene (miR-516a-3p, miR-192, miR-199a, and miR-107) or tumor suppressor (such as miR-43c and miR-126) in the malign cells of the stomach. Several studies showed that modification of miRNA expressions enhance cell proliferation, apoptosis resistance, and ability of invasion and metastasis (16-18).

High levels of MiR-21 expression has been shown in acute or chronic myeloid leukemia, glioblastoma, and solid organ malignancies like pancreas, prostate, gastric, colon, lung, breast and liver cancers with its oncogenic potential. MiR-21 also has a role in invasion and metastasis process with altering mRNA of a tumor suppressor protein, called PTEN. Studies that showed miR-21 upregulation in gastric cancer tissues and cell cultures suggest that it enhances proliferation and invasion of gastric cancer cells. When miR-21expression was blocked by inhibitors, proliferation process was significantly decreased, apoptosis was increased, and gastric cancer cell invasion or migration was markedly declined (19-21). Since upregulation of miR-21 has been demonstrated in various cancers, it is called oncomir (22). In our study, miR-21 was also upregulated in tumor tissues.

According to the stages of the tumors, miR-21 was upregulated in the stage 2 and stage 3a (P < 0.05), downregulated in the stage 3b (P < 0.05), and nonregulated in the stage 4 patients. In addition, miR-21 was significantly upregulated in the women with gastric cancer (P < 0.05). According to the histopathological type of tumor, miR-21 was upregulated in adenocarcinoma (P < 0.05). When it was evaluated according to the localization of the tumor, it was surprisingly downregulated (Table 5). These results suggested that miR-21 can be a good candidate to be a bio-marker during the assessment of gastric cancer.

Many studies carried on miR-107 showed different results. Li et al (23) reported that miR-107 expression was increased in gastric cancer tissues, which was correlated with tumor metastasis and poor prognosis. However, another study reported that expression of miR-107 was decreased (24). The discrepancy between these studies may be due to the ethnic differences and the different number of subjects studied. Hence, further studies are needed to determine in vivo and in vitro biologic effects of miR-107 expression in gastric cancer cells. In our study, we found mir-107 expression downregulated in the gastric cancer tissues. According to the stages, miR-107 was upregulated in stage 2, 3a, and 3b, on the other hand downregulated in stage 4 (Table 2). Moreover, we observed that miR-107 was downregulated with advancing age. (Table 3).

Expressions of miR-192 and miR-215 decreased in colorectal cancer, thus, it was suggested to be a tumor suppressor marker (25). Xu et al. stated that increase in miR-192 and miR-215 expressions is associated with lymph node metastasis in gastric cancer (26). In our study, expression was normal but was upregulated in the tumor tissues without statistical significance (p > 0.05). According to the stages miR-192 expressions was significantly upregulated (P < 0.05).

In this study, miRNA 141, 150, 192, and 202 were upregulated in all stages, however, there was no statistically significant difference except the patients in stage 2 and 3a. When the gene expressions were evaluated according to the tumor stages, it is noticed that upregulation was significant in the early stages. Regarding gene expression in the tumor localizations, only antrum located tumors had significant downregulation. Furthermore, miR-192 was downregulated and miR-331 was upregulated in the antrum and miR-107, miR-50, miR-202, and miR-218 were upregulated significantly in the cardia and antrum localizations. These results suggest that miRNA expressions changes in different localizations of the tumor in addition to different histopathologic types of the tumor.

In the recent years, with the advances in molecular biology, the role of the miRNAs in cancer development is better understood. Hence, may give rise to promising studies in targeted treatments in gastric cancer.

## Conclusion

In conclusion, different gene expressions of miRNAs according to the different localizations of gastric cancer and different stages suggest that it can be tumor marker to predict the stage and localization of gastric cancer.

**Competing interests**
*The author confirms that this article content has no conflict of interest.*

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**Ethical approval**
*Mugla Sitki Kocman University Medical School after obtaining an approval from the clinical research ethics committee (05 August 2013, 13/109)*

*Onder Ozcan ORCID: 0000-0001-8252-3339*
*Ahmet Korkut Belli ORCID: 0000-0003-1552-5697*
*Selami Ilgaz Kayilioglu ORCID: 0000-0002-2933-8983*
*Ozgur Ilhan Celik ORCID: 0000-0002-3549-822X*
*Mehmet Kaplan ORCID: 0000-0002-8758-543X*
*Murat Kara ORCID: 0000-0002-0230-4214*
*Murat Polat ORCID: 0000-0002-8492-6411*

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