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**Clinical application of miRNA in gastric cancer in Eastern Asian area**

Gao M *et al.* Application of miRNA in gastric cancer

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**Abstract**

In recent years researches have showed that microRNA (miRNA), which almost involves in each step of gastric carcinogenesis, has a bright and broad application prospects in diagnosis and therapy of gastric carcinoma. Eastern Asia (South Korea, Japan and China) is the highest incidence area of gastric cancer in the world. Gastric cancer of the world accounts for 988 000 new cases and 736 000 deaths in 2008. And approximately 60% of the world gastric cancer is occupied in East Asia (mainly in China). We herein provide a brief review of miRNA about clinical applications which included the following several aspects: (1) miRNA may serve as a potential new generation of tumor markers; (2) A complete miRNA expression profile is highly specific, can reflect the evolutionary lineage and differentiation of tumors and carry out diversity analysis; (3) Detecting specific miRNA expression in peripheral blood will become a new method for diagnosis of gastric cancer; (4) miRNA can predict prognosis of gastric cancer; (5) miRNA has predictive value to Chemotherapy and Radiotherapy resistance; and (6) miRNA, as a kind of innovative drug has the application prospect in therapy. Finally, we focus on assessing the value of miRNA from laboratory to clinical application and the challenges it faced with in East Asia.

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**INTRODUCTION**

Eastern Asia (South Korea, Japan and China) is the highest incidence area of gastric cancer in the world (Figure 1). Gastric cancer, a leading cancer of East Asian area whose incidence and mortality respectively is the second and third most common cancer[1,2]. According to WHO[3] statistics, gastric cancer of the world accounts for 988 000 new cases and 736 000 deaths in 2008. And approximately 60% of the world gastric cancer is occupied in East Asia (mainly in China). In China, Approximately two thirds of patients have developed advanced or metastatic disease, and more than half of them have recurrent disease after curative surgery. The median survival time for these patients is only 6-9 mo[4-6]. Several reasons restricted the level of diagnosis and treatment of gastric cancer: (1) limited diagnostic measures for early detection; (2) weak prognostic value of outcome; (3) poor effect of surgery or cytotoxic cell treatment for the advanced disease; and (4) lack of biomarkers utilized for targeted therapy. The discovery of miRNA may change the above-mentioned difficulties, and improve the level of diagnosis and treatment of gastric cancer.

MicroRNA (miRNA) includes 20 to 24 nucleotides, which is a class of non-coding small molecular single chain RNA, and has highly conservative, temporal and tissue-specific characteristics[7-9]. Through complete or incomplete base pairing with target gene mRNA, RNA-induced silencing complex (RISC) degraded mRNA or blocked its translation, and regulated target gene expression at the posttranscriptional level[10]. It widely exists in eukaryotic organism, and regulates proliferation, differentiation and apoptosis of the cell. While the tissues of the body appeared malignant, specific miRNAs were over-expressed or low-expressed in different tumors and different stages, which implies its correlation with occurrence and development of tumor and prognosis[11-13]. Further study of miRNA mechanism related gastric cancer, it provides a new thought for applications relating to early tumor detection, monitoring, prognosis, gene therapy, solving the chemotherapy resistance.

**miRNA AND DIAGNOSIS**

Specific tumor markers are often ideal screening tools. Existing clinical tumor markers (such as CEA, CA19-9, CA72-4) for gastric cancer are lack of high specificity and sensitivity[14]. MiRNA may serve as a potential new generation of tumor markers for following reasons[15-17]: (1) good tissue specificity, Rosenfeld[18] detected unknown sources of miRNA in order to make clear its sources, its specificity is 90%; (2) expression of miRNA in tumors were significantly different with normal tissue; (3) miRNA participates in the occurrence and development of tumor; (4) the expression of miRNA has stage specificity. The same tumors in different stages have different expression profiles[19,20]; and (5) miRNA in fresh tissue, paraffin embedded tissues, and cells and peripheral blood shows good stability[21].

Detection methods of miRNA and miRNA expression in gastric cancer: miRNA as a good tumor marker must have more mature and stable detection method placed for clinical application[22,23]. At present, study method about miRNA has become mature. By deep sequencing, we can discover unknown miRNA, then miRNA chip can be a very good identification of the differences in miRNA between the study group and the control group. Finally they could be verified by real-time quantitative polymerase chain reaction detecting system (q-PCR)[24].

In diagnosing of gastric cancer, the single miRNA is often dictated by poor specificity or sensitivity, but a complete miRNA expression profile is highly specific, can reflect the evolutionary lineage and differentiation of tumors and carry out diversity analysis[25,26]. Through horizontal comparison gastric carcinoma with adjacent normal tissues, we can find specific expression of miRNAs in the cancer tissue; further go on with longitudinal comparison to different periods of tumor, identify the different miRNAs in each period of the tumor and finally complete the tumor diagnosis and periodization[27,28].

We arranged gastric cancer miRNA expression profilings from numerous Chinese and international study groups for gastric cancer miRNA expression profiling from 2008 to 2012[29-36](Table 1). But we found these results were quite difference, the lack of stability and consistency, reasons for these might be: (1) differences of miRNA chip and software; (2) individual differences in race and patient; (3) difference of the collected specimens standard; (4) great difference in each experimental sample size; and (5) miRNA expression profile differences in different stages and types. According to the above expression profiling, we summed up several reliable miRNAs which confirmed in the multiple experiments and had 1.5 folk differential expressions between gastric cancer and normal gastric tissue. Next discuss about miRNAs would be based on this basis. Thus we are looking forward to having a large sampled, multi-centered or even transnational cooperation based on different pathological types, stages of the complete expression profiling of miRNAs in gastric cancer. Chinese, Japan, South Korea should carry out cooperation in the same platform and complete standard miRNA expression profiling of gastric cancer in East Asian populations.

The change of miRNA expression was an early event during the development of gastric tumor[37,38].Tracking the changes of miRNA expression profiling based on the relavent gastric tissues, we might have the tumor diagnosed early. Traditional methods for the detection of gastric cancer are endoscopy and biopsy. A minimally invasive examination method would be helpful for screening and early detection of cancer in high risk population[39]. Detection of tumor in the peripheral blood of patients with specific miRNA expression level has been a research hotspot in miRNA in recent years, which perhaps will become a new method for diagnosis of gastric cancer[40-42].

Researchers showed that 90% plasma miRNA is based on protein-miRNA complex form. As tumor markers in peripheral blood, miRNAs have following advantages: (1) miRNAs exist in great volume in peripheral blood[43,44]; (2) miRNAs can resist highly enzyme digestion[45-47]; (3) miRNAs have strong resistance to the external environment; and (4) miRNAs in tumor patients‘ serum also exist in the abnormal expression[48].

In recent 2 years, Japanese and Chinese scholars have made much beneficial exploration for miRNA expression of gastric cancer in the peripheral blood[49-55](Table 2) and obtained some positive results. For example, by comparing serum of 61 gastric cancer patients with 61 healthy persons, Liu *et al*[49] found that the expression of miR-378 in gastric cancer group was significantly higher than that in healthy group. They calculated that the value of the area under the receiver-operating characteristic (ROC) curve was 0.861 (95%CI 0.766-0.928), and sensitivity / specificity were 87.5%/70.7%, respectively. Similarly, after detecting 69 gastric cancer patients and 30 healthy volunteers in the peripheral serum by qRT-PCR, Tsujiura *et al*[55] found that the plasma concentrations of miRNAs (miR-106a, miR-106b) were significantly higher in GC patients than that in controls, whereas let-7a was lower in GC patient, in which the values of area under curve of miR-106a and let-7a were 0.879, and sensitivity / specificity were 85.5/80.0, respectively. Those miRNAs can become the ideal tumor markers for gastric cancer. In addition, Liu *et al*[49] detected that the plasma miRNA (miR-1, miR-20a, miR-27a, miR-34, miR-423-5P) of gastric cancer patients had significantly higher expression than that in control group in a larger sample (164 gastric cancer *vs* 127 healthy people). The value of area under curve was 0.879 (95%CI 0.822-0.936). It is interesting that, in the same sample, they also compared the AUC values of CEA and CA19-9 which were only 0.503 and 0.600 respectively. The results showed that miRNA as a tumor marker had great advantage. Through the current several sets of data, we found that miRNAs had a very good sensitivity and specificity for gastric cancer and were promising tumor markers. But, at the present, some factors still limit it to become clinical diagnostic applications[56]: (1) the relative difficulty of detection (in quality and quantity); (2) the lack of a unified testing platform and standardization problems; (3) plasma miRNA source and release mechanism is not clear; and (4) the differences in expression of peripheral blood miRNA and its tissue still exists[57]. Thus, searching and identifying specific miRNAs for the diagnosis of gastric cancer is the first task we must take. Establish suitable standard testing system for the clinical application including quality control and diagnosis threshold determination also continue to be the issue to work on. There is high incidence of gastric cancer in East Asian countries. High-risk populations could be screened by miRNA, which should be able to increase the detection rate of early gastric cancer and improve the effect of treatment.

**miRNA AND PROGNOSIS PREDICTION**

Predicting patient’s survival time, his or her disease progression, the prognosis outcome or response to the treatment is challenging. Because of the stability and specificity of expression in tissues and circulation, miRNA may be regarded as a forecasting tool for disease outcomes. A lot of literatures suggest that miRNA had a close relationship with survival time of gastric cancer, disease stage, tumor recurrence and metastasis of lymph node. The research of Li *et al*[58] showed that a seven-miRNA signature (miR-10b, miR-21, miR-223, miR-338, let-7a, miR-30a-5p, miR-126) was an independent predictor of overall survival (HR = 3.046; *P* = 0.015) and relapse-free survival (HR = 3.337; *P* = 0.012). And it can predict the prognosis of the patient in the stage of tumor, cytologic subtypes and Lauren classification[59,60]. In gastric cancer, many Chinese and foreign research teams discovered a number of miRNAs which played a role as predictor. For example, high expression of miRNA-20b, miRNA-150, miRNA-142-5p[61], miRNA-375, miRNA-214[62] and low expression of miRNA-451, let7g, miRNA-433, miRNA-125-5p[63] were associated with short survival time. High levels of miRNA-27a, miRNA-650[64] and low levels of miRNA-126[65], miRNA-146a[66], miRNA-148[67], miRNA-218[68], miRNA-335[69], miRNA-429[70] indicated lymph node metastasis. Overexpression of miRNA-375, miRNA-451, miRNA-199-3p, miRNA-195[71] and decreased expression of miRNA-142-5p were more likely to relapse. High levels of miRNA-221[72] and decreased levels of miRNA-126, miRNA-148a, miRNA-218 showed advanced gastric cancer. High expression of miRNA-223, miRNA-148a[73], miRNA-107[74] and reduced expression of miRNA-610[75], miRNA-200b[76], miRNA-7[77] were associated with invasion and metastasis (Table 3). Therefore many potential predictors have provided profitable helps for judging the prognosis of gastric cancer and the basis for a targeted therapy in our clinical work. However, researching miRNAs as prognostic factors involves small sample sets, high volume of work in validation and the research of independent cohorts all of which are absolutely required before assays for miRNAs can be used in the clinical application.

**miRNA AND CHEMOTHERAPY, RADIO****THERAPY**

Chemotherapy and Radiotherapy resistance is one big obstacle for improving the survival time of patients with gastric cancer[78-80]. We can predict the occurances of chemotherapy and radiotherapy resistance[81-83] (Table 4) through detecting such patients’ expression profiling of miRNA. Through investigating drug resistance to cisplatin and 5-fluorouracil in 90 patients with gastric cancer and comparing patients’ miRNA expression before and after the chemotherapy, Kim *et al*[81] found that high expression of let-7g, miR-342, miR-16, miR-181, miR-1, miR-34 prompted sensitive to chemotherapy, and high expression of miR-518f, miR-520a, miR-520d, miR-519e, miR-363, miR-517 prompted the resistance to chemotherapy. By predicting miRNA, we have a new method in choosing chemotherapy regimen and monitoring the effect of chemotherapy, even reversing the chemotherapy resistance through transfecting specific pre-miRNA. One famous example is that the miRNA-15b and miRNA-16 were down-regulated severely in multiple drug resistance in gastric carcinoma cell line SGC7901/VCR. By improving miRNA-15b and miRNA-16 expression levels, vincristine was enhanced to be sensitive to the cell line. *In vitro* experiments, someone also found a similar result. Chen *et al*[84] transfected miRNA-200c, caused it to high expression in SGC7901/DDP gastric cancer cells, and finally increased DDP, 5-FU, paclitaxel, doxorubicin to be sensitive to gastric cancer cell. The same situation also occurred in radiotherapy on gastric cancer by transfecting into AS-miRNA-221/222 which down-regulated the miRNA-221/222 expression in gastric cancer cell line SGC7901. Zhang *et al* found that the survival rate of cancer cell was significantly lower than that in control group. Radio-sensitivity was promoted through 0-6Gy irradiated. In addition, Bandres *et al*[85] transfected cancer cells with pre-miRNA-451, improved the expression level of miRNA-451 in AGS gastric cancer cells. Under 0-4Gy, the effect of treatment is significantly better than that in control group.

**miRNA AND TREATMENT**

MiRNA is a regulatory factor of gene expression and acts as a control center in the process of tumor development[86,87]. A miRNA can modulate a variety of protein expression and affect multiple informational pathways[88]. MiRNA as a biological treatment of tumor target molecules will be more effective than coding gene. The basic strategy of current treatment based on miRNA is to adopt gene knockout to inhibit or down-regulate the expression level of miRNA for oncogene; on the contrary, for anti-oncogene, to use the method of gene knock-in to introduce foreign miRNAs, increase the expression level and achieve the purpose of treatment of tumor. For example, small molecule drugs of inhibition of miRNA: anti-miRNA oligonucleotide (AMOs) followed by base pairing rules, competitively blocked the miRNA with target gene interaction[89],such as locked nucleic acid (LNA)[90-91]; MiRNA sponge: the adsorption with miRNA which could not combine with the natural target[92]; besides miR-Mask[93], miRNA inhibitor and so on. The method of increasing miRNA expression is often by virus as a carrier to introduce a specific miRNA or miRNA mimics and finally up-regulate miRNA and inhibit the tumor[94].

 A number of Eastern Asian scholars followed the above-mentioned principle by miRNA mediated treatment method and achieved good results in vitro experiments and animal experiments. For example, miRNA-221/222 were up-regulated in gastric cancer cell line SGC7901. By transfecting AS-miR-221 /222 2000 into cancer cell with liposome, miRNA-221/222 were knocked off. That inhibited gastric cancer cell growth and invasion. Their targeted molecule is PTEN[95]. MiR-516-3p was transfected into a gastric scirrhous carcinoma cell line 44AS3 with liposome, significantly over-expressed in cell line, and finally inhibited cancer cells growth, invasion and metastasis[96]. Similar results were obtained in nude mice transplantation model of the human stomach cancer. Zhang *et al*[97] through AMOS, knocked down the originally high expression of miRNA-21 and caused the proliferation of gastric cancer cell to slow down and apoptosis to increase visibly. In additions, Ji *et al*[98] added miRNA-34 analogue in p53 mutated gastric cancer cell lines, to restore its function and up-regulated the expression, which harmed cells’ growth and kept them staying in phase G1.

 Many test results based on treatment of gastric cancer by miRNA showed us the good application prospect. In particular, Chinese, Japanese, South Korean scholars undertook active attempt in this respect. But we still have several major obstacles to overcome. Firstly, the multi-targeting nature of miRNAs brings the risk of unconscious off-target effect. Secondly, the expression of target gene may often be regulated by multiple miRNAs which would greatly reduce the effect of treatment based on a specific miRNA. Finally, we still lack a good specificity and an efficient miRNA delivery system for the treatment[99,100].

**CONCLUSION**

MiRNA, which almost involved in each step of gastric carcinogenesis, has a bright and broad application prospects in the early diagnosis of gastric carcinoma, prognosis, detection effect of radiotherapy and chemotherapy, and a new target for the treatment. But study based on clinical application of miRNA for gastric cancer, still lacks the reliable and exact data from the large sample and multi-centers. In recent years, miRNA has been a biomedical research focus. New miRNAs were discovered, research technique was constantly updated. It will be a great challenge to integrate new data and set a standard platform and the procedure. For diagnosis, we need a unified standards and testing platform. For treatment, we need better designed small molecule drugs based on the well detailed and more accurate medication carrier without toxic side effect. We look forward to further more profound study of miRNA in bringing much more value in clinical application for the diagnosis and treatment of gastric cancer. East Asia as a frequent incidence area of gastric cancer, should develop more explorations and researches for the application of miRNA in gastric cancer.

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**Figure 1 Gastric cancer incidence, mortality and prevalence South Korea, Japan, China, Eastern Asia and world in 2008.**

**Table 1 In 2008-2012 year 8 groups obtained miNRA expressions in gastric cancer**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Group | Method | Sample | Upregulated | Downregulated |
| Katada *et al*[29] | TaqManmiRNA assays+qRT-PCR | 42u ndifferentiated gastric cancer and controls | miR-34b miR-34c miR-128a | miR-128b miR-129 miR-148 |
| Guo *et al*[30] | Microarray | 3 gastric cancers and adjacent normal tissues | miR-20b, miR-20a, miR-17, miR-106a, miR-18a, miR-21,miR-106b, miR-18b, miR-421,miR-340,miR-19a , miR-658 | miR- 768-3p, miR- 378, miR-31, miR- 139-5p, miR- 195, miR-497, miR- 133b |
| Yao *et al*[31] | Microarray+ qRT-PCR | 10 Gastric cancers and adjacent normal tissue | miR-223,miR-106b,miR-147,miR-34a,miR-130b,miR-106a, miR-18a, miR-17, miR-98, miR-616,miR-181a-2, miR-185, miR-1259, miR-601, miR-196a, miR-221, miR-302f, miR-340, miR-337-3p, miR-520c-3p, miR-575 and miR-138 | miR-638 miR-378 |
| Luo *et al*[32] | Microarray+ qRT-PCR | 24 gastric cancers | MiR-26b miR-30a-5p miR-212 miR-320 miR-379 miR-518b miR-409-3b | MiR-9 miR-19b miR-155 miR-188 miR-197 miR-338 miR-370 miR-383 miR-433 miR-490 miR-503 miR-545 miR-551a miR-567 miR-575 miR-611 miR-630 miR-649 miR-652 |
| Ueda *et al*[33] | Microarray+ qRT-PCR | 353（184 gastric cancers 169controls） | miR-181d miR-181a-1, miR-181a-2 miR-181c miR-181b-1, miR-181b-2 miR-21 miR-25 miR-92-1, miR-92-2 miR-93 miR-17-5p miR-106a miR-20b miR-135a-1, miR-135a-2 miR-425-5p miR-106b miR-20a miR-19b-1, miR-19b-2  | miR-148a miR-148b miR-375 miR-29b-1, miR-29b-2 miR-29c miR-152 miR-218-2miR-451 miR-30d |
| Tsukamoto *et al*[34] | Microarray(470)+ qRT-PCR | 22gastric cancers | miR-18a miR-106a miR-17 miR-146a miR-93 miR-19a miR-20a miR-20b miR-25 miR-15b miR-425 miR-92a miR-194 miR-10a miR-222 miR-7 miR-106b miR-320a miR-21 miR-34a miR-19b miR-103 miR-215 miR-192 miR-429 miR-27a miR-223miR-23a miR-107 miR-200b miR-24 miR-15a miR-16 | miR-375 miR-29c miR-148a miR-30a-5p miR-30e-5p miR-638  |
| Li *et al*[35] | TaqManmiRNA assays+qRT-PCR | 30gastric cancer and controls | miR-223, miR-21, miR-23b, miR-222, miR-25, miR-23a, miR-221, miR-107, miR-103, miR-99a, miR-100, miR-125b, miR-92, miR-146a, miR-214 and miR-191,  | let-7a, miR-126, miR-210, miR-181b, miR-197, miR-30aa-5p. |
| Carvalho *et al*[36] | Microarray+ qRT-PCR | 76 gastric cancers | miR-582-5p miR-151-5p miR-296-5p miR-30b miR-513-5p miR-335 miR-576-5p miR-219-2-3p miR-331-5p miR-889 miR-152 miR-992 miR-93 miR-519c miR-599 miR-520a-5p miR-631 miR-550 miR-136 miR-22 miR-515-5p miR-127-3p miR-374a miR-181a miR-192 miR-532-3p miR-30d miR-640 miR-425 miR-92b miR-501-5p miR-514 miR-576-3p miR-519e miR-149 miR-219-1-3p miR-424 miR-220 miR-96 miR-218-2 miR-649 miR-215 miR-182 miR-122 miR-524-3p miR-187 miR-526b miR-770-5p miR-545 miR-200b miR-9 miR-141 miR-579 miR-493 miR-137 miR-216a miR-503 miR-126 miR-23b miR-99b miR-101 miR-323-3p miR-25 miR-92a-1 miR-429 | miR-451 miR-502-3p miR-101 miR-33a miR-516a-3p/miR-516b |

qRT-PCR: Quantitative reverse transcriptase polymerase chain reaction.

**Table 2 The expression of miRNA patients and area under curve value,** **sensitivity and specificity in the serum samples of gastric cancer**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Group | Sample | MicroRNA | AUC | Method | Sensitivity/specificity (%) |
| Liu *et al*[49] | 61GC/61C | miR-378↑ | 0.861 | qRT-PCR | 87.5/70.7 |
| Liu *et al*[50] | 164GC/127C | (miR-1, miR-20a, miR-27a, miR-34,miR-423-5P)↑ | 0.8790.831 | Microarray+ qRT-PCR | 79.3/86.5 |
| Konish *et al*[51] | 56GC/30C | miR-451↑miR-486↑ | 0.960.92 | Microarray+ qRT-PCR | 96.0/10086.0/97.0 |
| Song *et al*[52] | 82GC/82C | miR-221, miR-744 and miR-376c↑ | N/A | qRT-PCR | 82.4/58.8 |
| Zhou *et al*[53] | 90GC/27C | miR-106a↑miR-17↑ | 0.6840.743 | Microarray+ qRT-PCR | 48.2/90.251.9/92.7 |
| Wang *et al*[54] | 174GC/39C | miR-21↑ | 0.81 | Microarray+ qRT-PCR | 56.7/94.9 |
| Tsujiura  *et al*[55] | 69GC/30C | miR-106b↑miR-106a↑, let-7a↓ | 0.720.879 | Microarray+ qRT-PCR | N/A 85.5/80.0 |

qRT-PCR: Quantitative reverse transcriptase polymerase chain reaction; GC: Gastric cancer, C: Control; AUC: Area under curve; ↑: Upregulated; ↓: Downregulated.

**Table 3 Gastric cancer with** **potential predictive role of miRNA**

|  |  |
| --- | --- |
|  | Potential predictive role of miRNA |
| MiRNAs of high expression MiRNAs of low expression |
| Short survival time | miRNA-20b, miRNA-150[29], miRNA-142-5p[61], miRNA-375, miRNA-214[62] | miRNA-451, let7g1, miRNA-4331[33], miRNA-125-5p3[63] |
| Lymph node metastasis | miRNA-27a[29], miRNA-650[64] | miRNA-126[65], miRNA-146a[66], miRNA-148[67], miRNA-218[68], miRNA-335[69], miRNA-429[70] |
| relapse | miRNA-375[61], miRNA-4512, miRNA-199-3p2, miRNA-1952[71]  | miRNA-142-5p[61] |
| Advanced gastric cancer | miRNA-2214[72] | miRNA-126[65], miRNA-148a[67], miRNA-218[68] |
| Invasion, metastasis | miRNA-223[35], miRNA-148a[73],miRNA-107[74] | miRNA-610[75], miRNA-200b5[76], miRNA-7[77] |

1The 2 miRNA also indicate the short survival and lymph node metastasis, deeper invasion; 2The 3 miRNA also indicate the short survival and recurrence, especially miRNA-451; 3The miRNA also indicates the short survival and hepatic metastases, deeper invasion, the tumor enlarged; 4The miRNA also indicates lymph node metastasis and deeper invasion, advanced gastric cancer; 5The miRNA also indicates lymph node metastasis and deeper invasion, the tumor enlarged.

**Table 4 The expression of miRNA and the prediction of the effect of chemotherapy and radiotherapy**

|  |
| --- |
|   Upregulated Downregulated |
| Chemosensitivity | (let-7g, miR-342, miR-16, miR-181, miR-1, miR-34)1[81] |  |
| Chemoresistance | (miR-518f, miR-520a, miR-520d, miR-519e, miR-363, miR-517)1[81] | (miR-196a, miR-200family, miR-338, miR-126, miR-31, miR-98, let-7g, miR-7)2 [82]miR-15b, miR-16[83] |
| Radiosensitivity | miR-451[85] |  |
| Radioresistance | miR-221/222[97] |  |

1Drugs were cisplatin and 5-fluorouraci; 2Drug was hydroxy camptothecin.