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Clinical significance of miRNA-21, -103, -129, -150 in serous ovarian cancer

Miłosz Wilczyński[1] · Ewelina Żytko[2] · Justyna Danielska[3] · Bożena Szymańska[4] · Monika Dzieniecka[5] · Marek Nowak[2] · Jakub Malinowski[2] · Dariusz Owczarek[1] · Jacek R. Wilczyński[2]

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Abstract

Purpose We aimed to compare expression levels of miRNA-21, -103, -129, -150 in primary tumour tissues and its omental metastases from patients operated for advanced ovarian serous cancer. Expression levels of selected miRNAs were correlated with clinicopathological features, including chemosensitivity and survival.

Methods We performed total RNA extraction from archival formalin-fixed paraffin-embedded tissue samples of primary serous ovarian cancer and omental metastases. The study included 48 patients with advanced ovarian cancer. The reference group consisted of 48 normal ovarian tissue samples. We performed cDNA synthesis, real time polymerase chain reaction and assessed relative expression of selected miRNAs.

Results Samples derived from serous ovarian cancer were characterized by higher expression levels of miRNA-150 in comparison to omental metastases ($p = 0.045$). Furthermore, we observed that shorter progression free-survival was associated with lower levels of miRNA-150 in metastatic tissues. We did not find similar relationships for other miRNAs.

Conclusions MiRNA-150 may potentially serve as a prognostic factor in advanced ovarian cancer. However, further studies are required to clearly confirm such hypothesis.

Keywords miRNA · Ovarian cancer · Survival · Prognostic factor

Introduction

MiRNAs are small (approximately 22 nucleotides), single-stranded and non-coding RNA molecules that take part in RNA silencing and post-transcriptional regulation of gene expression [1]. Dysregulation of miRNAs leads to erroneous regulation of gene expression and, as a result, may be associated with multiple diseases. MiRNAs take part in such vital processes as cell proliferation, differentiation or apoptosis. Aberrant expression of miRNAs may thus contribute to carcinogenesis, tumour growth and forming of metastases [2].

MiRNAs' expression patterns have been investigated in multiple neoplasms, including ovarian cancer. However, the exact landscape of miRNAs in ovarian cancer has not been established, yet. MiRNA-21 is commonly dysregulated in a variety of human malignancies. It has been proven that miRNA-21 is upregulated in colorectal, liver, gastric, prostate, lung, cervical and breast cancers [3]. Significantly elevated miR-21 plasma level was observed in lung, colorectal and breast cancer patients compared to healthy controls [4, 5]. It seems that miRNA-21 functions as an

✉ Miłosz Wilczyński
jrwil@wp.pl

[1] Department of Operative Gynecology, Endoscopy and Gynecologic Oncology, Polish Mother's Memorial Hospital Research Institute, 281/289 Rzgowska Str., 93-338 Lodz, Poland

[2] Department of Gynecology and Oncological Gynecology, Polish Mother's Memorial Hospital Research Institute, 281/289 Rzgowska Str., 93-338 Lodz, Poland

[3] Radiotherapy Department, Medical University of Łódź, 4 Kościuszki Al., 90-419 Lodz, Poland

[4] Central Scientific Laboratory CoreLab, Medical University of Łódź, 4 Kościuszki Al., 90-419 Lodz, Poland

[5] Department of Pathology, Polish Mother's Memorial Hospital Research Institute, 281/289 Rzgowska Str., 93-338 Lodz, Poland

oncogenic miRNA, taking part in promotion of cancer cell proliferation, migration, invasion and potentially determines chemoresistance in tumours. "In vitro" studies on cultured breast cancer cell lines indicated that miRNA-21 may have an impact on cancer cell proliferation and invasion through regulation of its target genes PDCD-4, FasL, PTEN, RhoB, TIMP3, Maspin and RECK [6]. MiRNA-21 upregulation might be connected with clinical and prognostic outcomes in patients. Similarly, studies on human pancreatic cancer cells indicated that low expression of tumour suppressor genes *PDCD-4* and *PTEN,* which was triggered off by miRNA-21, may be associated with chemoresistance to 5-fluorouracil [7].

MiRNA-129 family members have been reported to behave as a tumour suppressors in several malignancies. Glycogen synthase kinase-3β (GSK-3β) is a serine/threonine kinase involved in cancer development. MiRNA-129 has a potential of silencing GSK-3β; thus, it indirectly suppresses cell proliferation, migration, invasion and promotes cell apoptosis through downregulating NF-kB, Cyclin D1 and MMP9 expression [8]. MiRNA-129-2 may also suppress cell proliferation and migration of esophageal carcinoma cells through down-regulation of SOX4 expression [9]. On the other hand, some authors state that miRNA-129 may also act as an oncogene. Li et al. showed that miR-129-5p was upregulated in primary laryngeal squamous cell carcinoma (LSCC) [10]. Clinical significance of miRNA-129 has been proven in prostate cancer patients. Lower expression of miRNA-129 in peripheral blood mononuclear cells was significantly associated with aggressive clinical pathological features such as histological grade, high preoperative PSA level, pathological stage, high Gleason score, lymph node metastasis, and biochemical recurrence [11].

Another potentially interesting miRNA that may be involved in ovarian cancer growth is miRNA-103. Aberrant expression of miRNA-103 has been observed in many malignancies, such as endometrial, breast or bladder cancers [12, 13]. Several authors reported that miRNA-103 may act as an oncogene. Geng et al. demonstrated that miRNA-103 downregulates two tumour suppressor genes *DICER* and *PTEN*, thus, promoting colorectal cancer proliferation and migration [14]. Data presented by Yu et al. prove that miRNA-103 may post-transcriptionally downregulate the expression of *TIMP-3* and cause growth of endometrial cancer cells [12]. High levels of miRNA-103/107 in colon cancer tissues were associated with distant and lymph node metastasis and served as prognostic marker for poor survival [15].

MiRNA-150 may serve both as a tumour suppressor or oncogene in several human malignancies. In pancreatic cancer, overexpression of miRNA-150 inhibits growth and invasion of cells through down-regulation of *MUC4* gene [16]. In opposite, miRNA-150 was reported to be overexpressed in gastric cancer cell lines and tissues, targeting a pro-apoptotic tumour suppressor gene *EGR2* [17]. Zhang et al. proved that inhibition of miR-150 delays proliferation and promotes apoptosis accompanied by increased p53 expression [18].

MiRNA profiling in ovarian cancer has been performed extensively in the recent years. Multiple in vitro studies, devoted to the molecular mechanisms of miRNA's action, have been conducted. However, clinical and prognostic significance of miRNAs in ovarian cancer has been reported only by few authors. The association between expression of miRNAs in ovarian cancer and clinical characteristics remains unexplored.

Therefore, we decided to choose four miRNAs that so far have not been vastly investigated in ovarian cancer. The aim of this retrospective study was to compare expression levels of miRNA-21, -103, -129, -150 in primary tumour tissues and its omental metastases from patients operated for the advanced ovarian serous cancer. The secondary aim was to correlate its expression levels with clinicopathological features, including chemosensitivity and survival.

Materials and methods

Ethical approval was obtained from Polish Mother's Memorial Hospital Research Institute Ethics Committee and informed consent was obtained from all patients. We included in the study 48 patients with advanced, high-grade ovarian cancer of serous histology (III/IV FIGO clinical stage, Fédération Internationale de Gynécologie et d'Obstétrique). Total hysterectomy with bilateral salpingo-oophorectomy, omentectomy, appendectomy was performed in all cases. Partial resection of infiltrated intestine or bowel, peritonectomy, splenectomy, extirpation of bulky nodes was also performed to obtain optimal cytoreduction. Systemic lymphadenectomy was performed only when optimal cytoreduction was achieved. All patients were treated with adjuvant treatment that consisted of six standard courses of carboplatine 5–7.5 AUC plus paclitaxel 175 mg/m^2, modified according to the patient general status. Serum levels of CA125 (cancer antigen 125) and ROMA index [Risk of Malignancy Algorithm counted on the base of serum CA125, serum human epididymis antigen-4 (HE4) and pre- or menopausal status] were acquired before the cytoreductive surgery. Patients were divided into two clinical subgroups: chemosensitive (no relapse within at least 6 months after the completion of therapy) and chemoresistant (progression despite of the first-line chemotherapy or relapse within 6 months after the completion of therapy). Table 1 presents clinical characterization of patients.

Table 1 Basic clinicopathological characteristics of patients

	Sensitive	Resistant	*p*
Clinical characteristics of ovarian carcinoma patients			
Number of patients	27	21	0.5915
Age (range, years)	48 (24–81)	54 (48–75)	0.7476
FIGO stage			
III	23	20	0.8413
IV	4	1	0.3946
Grading			
G1	2	2	0.6101
G2	8	8	0.7877
G3	17	11	0.4299
Recurrence rate (%)	81.5%	71.4%	–
OS (range, months)	33 (13–70)	16 (2–113)	0.0677
Cancer related deaths	3	9	0.1825

Sample collection

MiRNAs were evaluated in formalin-fixed, paraffin-embedded (FFPE) serous ovarian cancer samples. After confirmation of areas of cancerous tissue by pathologist, microdissection of samples was performed. Microdissection allowed to minimalize the risk of sample contamination by noncancerous material. Two samples were obtained in all cases: from primary ovarian tumour and from omental metastasis. The reference group consisted of 48 normal ovarian tissue samples that were retrieved from peri-menopausal women during hysterectomy with bilateral salpingo-oophorectomy due to the uterine leiomyoma.

MicroRNA expression analysis

Total RNA isolation

For the purpose of the study we used purified RNA (Roche High Pure miRNA Isolation Kit) that had been isolated for our previous study that was dedicated to the role of miRNA-146a in ovarian cancer (manuscript accepted for publication in Oncology Letters). Total RNA was stored at − 80 °C until use. In brief, FFPE samples were deparaffinized with 100% xylene, washed in 100% ethanol, dried at 55 °C for ~ 10 min and resuspended in Paraffin Tissue Lysis Buffer. Then, the samples were digested with proteinase K at 55 °C overnight. RNA purification on column was performed according to the manufacturer's recommendations. PicoDrop spectrophotometer (Picodrop Limited, UK) was used to measure the yield and quality [260/280 optical density (OD) ratios] of RNA products.

Quantification of differentially expressed microRNAs

Ten nanograms of total RNA was used for the reaction. Reverse transcription was carried out using the Universal cDNA Synthesis Kit (Exiqon, Denmark), according to the miRCURY LNA Universal RT micro RNA PCR instruction. The cDNA template was diluted 80 times in nuclease-free water and 4 µl of aliquots was subsequently used for PCR amplification using 5 µl ExiLENT SYBR Green Master Mix and 1 µl of required LNA PCR primer set for hsa-miR-21, -103, -129, -150. U6 snRNA and SNORD48 were used as the internal controls. The reactions were incubated in a 96-well plate at 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s and 60 °C for 1 min. All reactions were performed in duplicate on a 7900HT Fast Real-Time PCR System (Applied Biosystems, USA). Relative expression was calculated according to the Cq method $2^{-\Delta\Delta Ct}$.

Statistical analysis

Kaplan–Meier survival curves were used to analyse the relationship between the expression levels of miRNAs and patients' survival rate. The differences between studied groups were determined by Mann–Whitney *U* or Kruskal–Wallis test. Spearman's rank correlation coefficient was used to measure the statistical dependence between two variables and multivariate analysis for estimation of correlations between three and more variables. Statistical significance was set at $p < 0.05$.

Results

Patients

There were no statistical differences in terms of age, FIGO stage, FIGO grading and number of relapses between groups of chemosensitive and chemoresistant patients. Gross visible disease on entry into abdominal cavity was found in 35 patients. Optimal cytoreduction (defined by ≤ 1 cm residual disease) was achieved in 28 patients. Of these, 13 patients had only microscopic residual disease. Fifteen patients had residual disease measuring 0.1–1 cm in maximal diameter. Progression-free survival (PFS) was longer for platinum-sensitive patients ($p < 0.05$) as well as overall survival (OS) (insignificantly, $p = 0.07$) (Table 1).

Expression levels of miRNAs

We found that there were no differences in expression levels of miRNA-21, -103, -129, -150 between primary ovarian cancer samples and control tissues (miRNA-21—$p = 0.87$; miRNA-103—$p = 0.65$; miRNA-129—$p = 0.4$;

miRNA-150—$p = 0.67$). Such results are unexpected, especially if to consider that we did find differences in expression levels between primary tumour and metastatic tissues. Samples derived from serous ovarian cancer were characterized by higher expression levels of miRNA-150 in comparison to omental metastases ($p = 0.045$, Fig. 1). However, we did not find similar relationship for other miRNAs that were evaluated in the study (miRNA-21—$p = 0.85$; miRNA-103—$p = 0.114$; miRNA-129—$p = 0.66$).

Clinical significance of miRNAs

Expression levels of selected miRNAs did not correlate with neither FIGO stage nor histological grading. Kaplan–Meier survival curves were analysed to evaluate prognostic significance of the miRNAs. The Kaplan–Meier analysis revealed that the probability of survival was insignificantly decreased for patients with lower levels of miRNA-129 (HR 0.65, $p = 0.06$) in the primary tumour

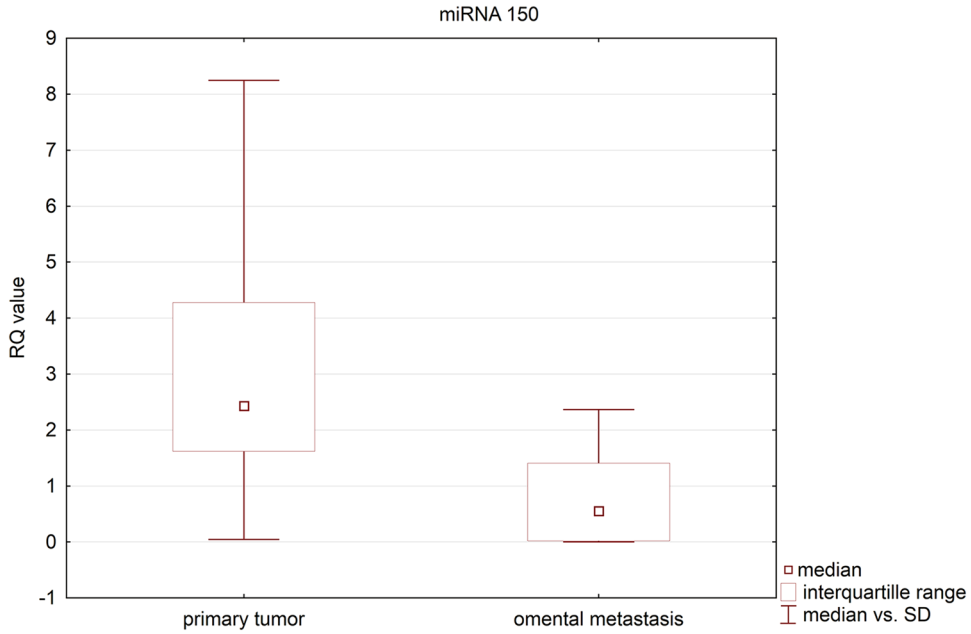

Fig. 1 Expression levels of miRNA-150: primary serous ovarian cancer tissue *vs* omental metastases ($p = 0.045$)

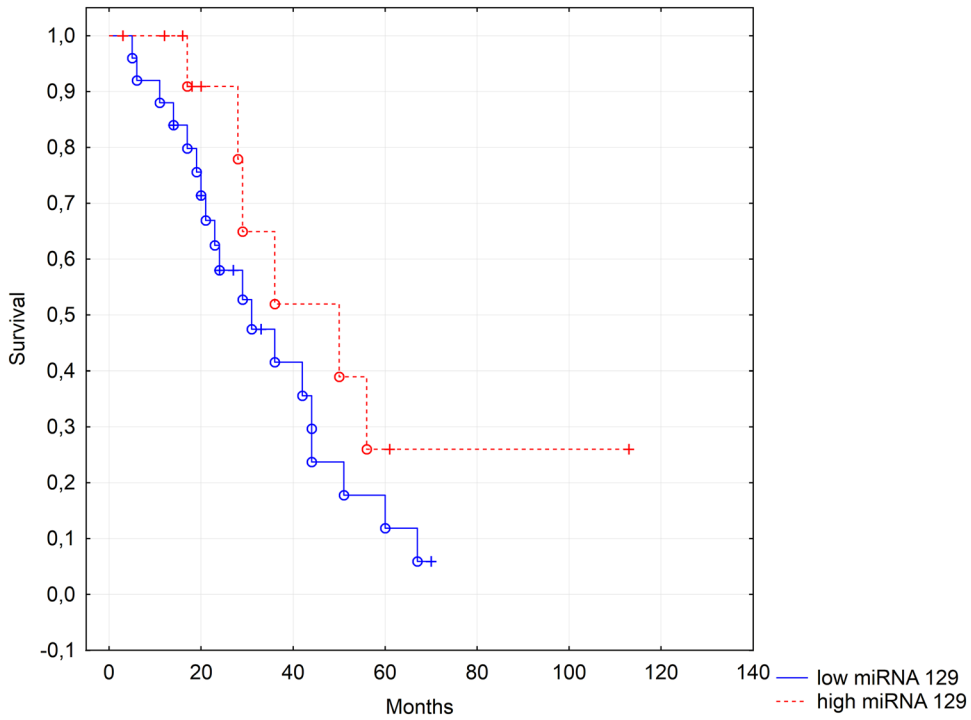

Fig. 2 Kaplan–Meier analysis of survival of ovarian cancer patients based on miRNA-129 expression levels in primary tumour tissues ($p = 0.06$)

(Fig. 2). There was no similar tendency in cases of other miRNAs (Figs. 3, 4, 5). Furthermore, statistical analysis revealed that shorter PFS (progression free survival) correlated with lower levels of miRNA-129 in primary tumour (ANOVA, $p < 0.05$). Similarly, shorter PFS was associated with lower levels of miRNA-150 in metastatic tissues (ANOVA, $p < 0.05$). We also additionally performed analysis of variance in which we aimed to evaluate expression levels of selected miRNAs in regard to chemosensitivity/chemoresistance, but no correlation was found.

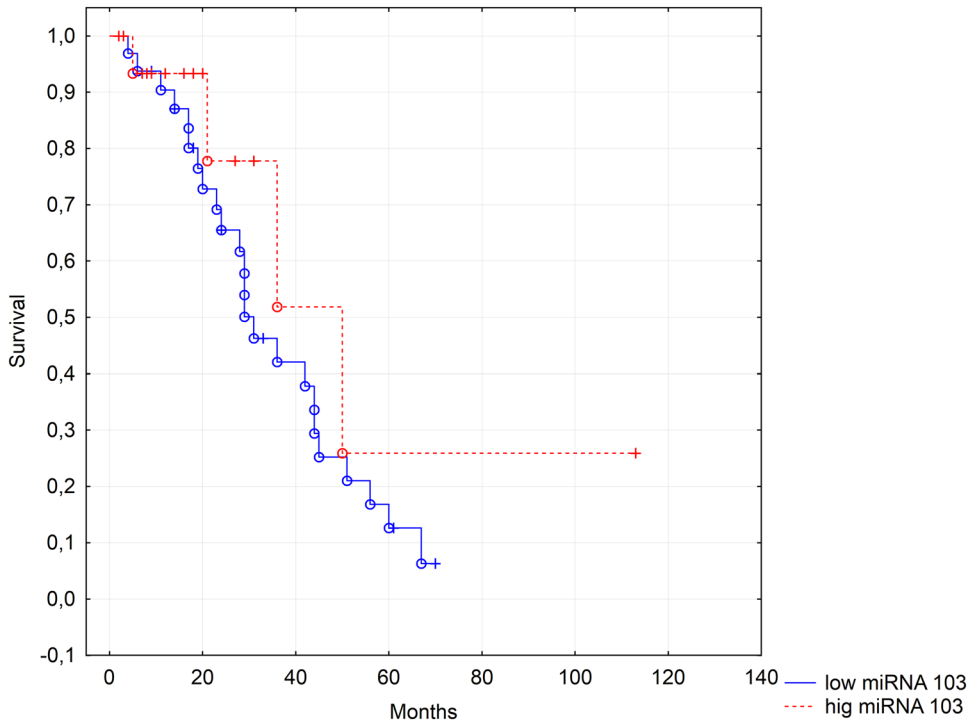

Fig. 3 Kaplan–Meier analysis of survival of ovarian cancer patients based on miRNA-103 expression levels in primary tumour tissues ($p = 0.81$)

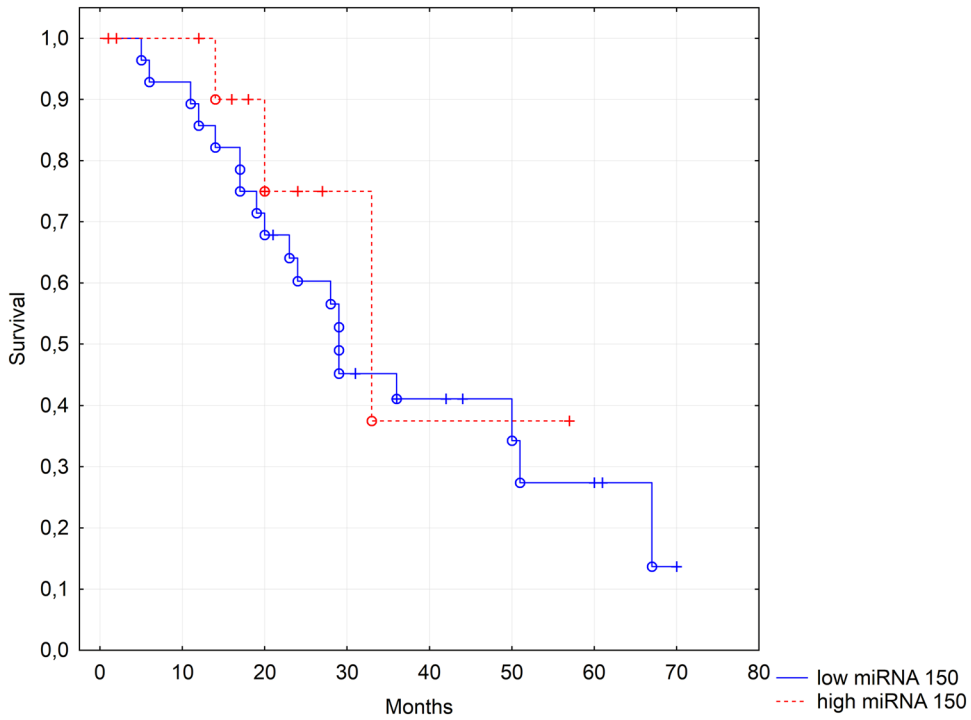

Fig. 4 Kaplan–Meier analysis of survival of ovarian cancer patients based on miRNA-150 expression levels in primary tumour tissues ($p = 0.18$)

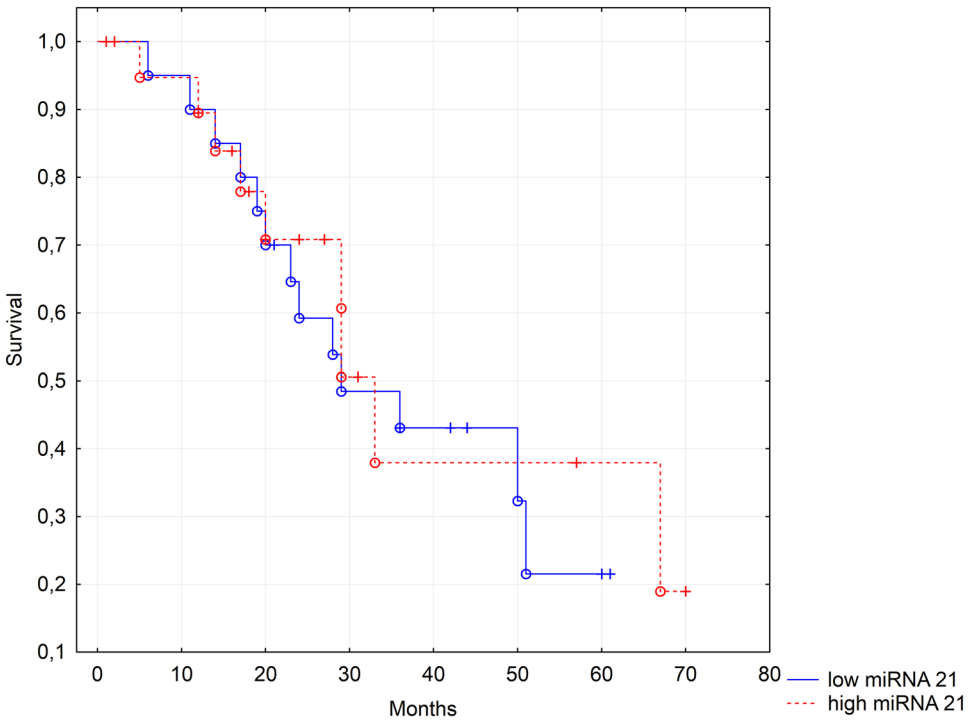

Fig. 5 Kaplan–Meier analysis of survival of ovarian cancer patients based on miRNA-21 expression levels in primary tumour tissues ($p = 0.17$)

Discussion

MiRNA-21 is an oncogenic miRNA, that is dysregulated in multiple neoplasms, taking part in cancer growth or survival. Molecular evidence suggests that miRNA-21 may be up-regulated in hypoxic conditions [19]. Polytarchou et al. showed that miRNA-21 expression is altered in Akt-2-expressing cells (Akt—family of PH domain-containing serine threonine kinases). It was also demonstrated that Akt2 is overexpressed in ovarian tumours [20]. According to Polytarchou et al., hypoxic signals dependent on Akt2 induce miRNA-21, which targets PTEN (tumour suppressor), PDCD4 (proapoptotic inhibitor of protein translation) and Spry1 (inhibitor of extracellular signal-regulated kinases activation). Downregulation of PTEN, PDCD4 and Spry1 may lead to inhibition of hypoxia induced cell death [19]. Furthermore, it was shown by Echevarria-Vargas et al. that miRNA-21 overexpression might be characteristic for cisplatin resistant compared to cisplatin sensitive cells [21]. Xie et al. performed in vitro experiments which indicated that miRNA-21 may be involved in paclitaxel chemoresistance of ovarian cancer A2780 cell line through up-regulation of MDR1/Pg-p and HIF-1α activity [22]. Inhibition of miRNA-21, which results in PDCD-4 augmentation and attenuation of apoptosis inhibitor c-IAP2, exerts an effect on cells making them sensitive to chemotherapeutics [23]. Considering the facts stated above, miRNA-21 expression levels in ovarian cancer tissues should be altered. Furthermore, it can be hypothesized that up-regulation of miRNA-21 may be associated with decreased survival and shorter PFS. However, we did not find any evidence supporting such assumptions. It is worth mentioning that correlation between HE4 and miR-21 was found by Chen et al. MiRNA-21 was also elevated in tissue samples derived from patients who relapsed [24].

Study by Iorio et al. demonstrated that miRNA-21 may be upregulated in endometrioid, but not in serous or clear cell ovarian cancer [25]. These findings are concordant to our results, as we did not find any differences in miRNA-21 expression levels between normal ovarian tissue and serous ovarian cancer samples. On contrary, Nam et al. found that miRNA-21 was up-regulated in 17/20 (85%) serous cystadenocarcinoma samples [26]. Dahiya et al. concluded that miRNA-21 is down-regulated in both cell line cultures and ovarian tumour tissues [27]. The above-mentioned studies show that there is no consensus on miRNA-21 expression levels in ovarian cancer tissues. Such discrepancies are observed not only in case of miRNA-21, but also in other types of miRNAs. Inconsistent results among authors may depend on methodology (i.e. diverse endogenous controls implemented in the studies) or different clinical tumour stages included in the studies. Furthermore, inclusion of patients diagnosed with ovarian cancer of heterogeneous histology may lead to erroneous conclusions. The mutational landscape of ovarian tumours shows that different histological cancer subtypes are characterised by distinct genomic aberrations. The TGCA showed that mutations in TP53 dominated in high grade serous ovarian cancers. Clear-cell ovarian cancers were characterised by few TP53 mutations and recurrent ARID1A and PIK3CA mutations [28–30]. CTTNB1, ARID1A, and PIK3CA mutations were observed

in case of endometrioid ovarian cancer [28–30]. Similarly, some miRNAs seem also to be histotype specific. Taking into consideration the fact that miRNA-21 may be associated with PTEN/PI3K pathway in cancer, it is not surprising that in case of serous ovarian cancer (characterised mainly by TP53 mutations) we did not find aberrant miRNA-21 expression in our samples' set.

Clinical significance of miRNA-129, -103 and -150 have been assessed by only few authors. Tan et al. evaluated prognostic utility of miRNA-129-5p in ovarian cancer cells and concluded that its downregulation correlated with tumour progression and might be associated with the poor survival [31]. Transcriptional co-activator Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) are oncogenes connected with the Hippo pathway. When Hippo pathway is inactive, YAP/TAZ are unphosphorylated and shifted into the nucleus inducing transcriptional activity of TEA domain (TEAD). MiRNA-129-5p functions as a repressor of YAP/TAZ proteins, which results in inhibition of ovarian cancer cells' proliferation and survival. In our study, we identified a tendency for poor survival among patients in case of lower levels of miRNA-129 expression in primary ovarian cancer tissues. Furthermore, we found that low levels of miRNA-129 were associated with significantly shorter PFS. Such results stay in concordance with the conclusions reached by Tan et al. Lower levels of miRNA-129 may be a negative prognostic factor in ovarian cancer patients.

Data on miRNA-103 in ovarian cancer is scarce. We did not identify any clinical correlations nor altered expression of miRNA-103 in ovarian cancer. However, Kan et al. investigated whether levels of serum miRNAs could discriminate women with high-grade serous epithelial ovarian cancer from healthy individuals. Their results indicate that miRNA-103 along with miR-200a, miR-200b and miR-200c might serve as a serum marker of serous ovarian cancer [32].

Vang et al. performed miRNA profiling in 18 matched samples of primary serous ovarian cancer and its omental metastases. The authors proved that metastases are characterized by different pattern of miRNAs. Their results showed that miRNA-150 and miRNA-146 had lower expression in primary tumours compared to omental metastases. Both miRNAs promote spheroid formation and enhances the survival of cells subjected to lethal cisplatin concentrations [33]. Such results suggest that higher expression levels of miRNA-150 in omental metastases may lead to clinically more aggressive and resistant disease. Jin et al. reported that miRNA-150 was down-regulated in ovarian cancer tissues in comparison to normal ovarian samples. The authors found that low expression of miRNA-150 in ovarian cancer tissues was associated with high clinical stage, shorter overall and progression-free survival. Ectopic expression of miRNA-150 caused inhibition of ovarian cancer cells proliferation by suppressing ZEB1 (regulator of epithelial-mesenchymal transition), which emphasizes the role of miRNA-150 as a tumour suppressor [34]. On the other hand, Wang et al. suggested that miRNA-150 may promote lung cancer tumorigenesis by targeting p53 [35]. Such results indicate that miRNA-150 may also act as an oncogene. The TGCA study proved that high grade serous ovarian cancers are characterised by TP53 mutations. Therefore, it seems that miRNA-150 interacts with the p53 pathway. However, its significance and molecular way of action in different tissues need further clarification. Our study proved that samples derived from serous ovarian cancer were characterized by higher expression levels of miRNA-150 in comparison to metastases. We did not find any differences in miRNA-150 expression levels between primary ovarian cancer tissues and control tissues of normal ovarian epithelium. Analysis of survival showed that shorter PFS was associated with lower levels of miRNA-150 in metastatic tissues. Lower levels of miRNA-150 in omental metastases may be a characteristic of cells with enhanced migratory and invasive capabilities.

Author contributions All authors read and approved the final manuscript. MW—corresponding author who designed the study, wrote the paper and analysed data. EZ—selection of patients and tissue samples, data analysis. JD—clinical data collection, analysis of data. MD—histopathological assessment of samples. BS—PCR quantification. MN—data collection and interpretation. JM—data collection. DO—data collection. JRW—designed the study, supervised and edited the manuscript, final approval of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval was obtained from Polish Mother's Memorial Hospital Research Institute Ethics Committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

Human/animal rights statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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