Medicinski podmladak

Medical Youth

Mini review article

MICRORNAS IN HIGH-GRADE GLIOMAS: WHAT IS THEIR ROLE?

MIKRO RNK KOD VISOKOGRADUSNIH GLIOMA: KOJA JE NJIHOVA ULOGA?

Aleksandar Stepanović[1,2], Marina Nikitović[1,2], Nina Petrović[2,3]

[1] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija
[2] Institut za onkologiju i radiologiju Srbije, Beograd, Srbija
[3] Univerzitet u Beogradu, Institut za nuklearne nauke „Vinča", Beograd, Srbija

Correspondence: a.stepanovic@ncrc.ac.rs

Abstract

High-grade gliomas are malignant tumours of the central nervous system with poor overall survival. Equivalently, glioblastoma is one of the most devastating brain tumours. Treatment for most high-grade gliomas includes surgical resection, radiotherapy, and chemotherapy. Even with all treatment modalities, at a certain point, disease progression occurs. Moreover, each of the treatment modalities can lead to different toxicities. In the last ten years, many studies have aimed to find a stable and unique biomarker that can help diagnose brain tumours, overcome treatment resistance, and improve overall survival. MicroRNAs are non-coding elements of the genome that are relatively stable in serum and plasma and can be isolated from the tissue as well. It has been discovered that the alteration of many microRNAs can be seen in high-grade gliomas. The determined microRNA could potentially play a part in the diagnosis and prognosis of high-grade gliomas, have a therapeutic role in the treatment of high-grade gliomas or act as a predictive biomarker of treatment-induced toxicity. To achieve this, every high-grade glioma should have its own microRNA signature. Numerous studies have detected a big potential of certain microRNAs. The disadvantages of these studies are that they mostly included a small number of samples. Moreover, research into microRNA as potential therapeutic agents has primarily been based on cell lines, or xenografts. On the other hand, many microRNAs show significant alterations in high-grade gliomas, but still, their altered expression can be detected in other cancers and some non-oncological diseases. In this article, we made a critical mini-review of the role of microRNAs in high-grade gliomas.

Keywords:
high-grade glioma, glioblastoma, microRNA

The authors declare no conflicts of interest.

doi:10.5937/mp74-41114
Editorial board: podmladak.med.bg@gmail.com

Sažetak

Visokogradusni gliomi su maligni tumori centralnog nervnog sistema sa lošim ukupnim preživljavanjem. Glioblastom ima najagresivnije biološko ponašanje. Tretman za većinu visokogradusnih glioma uključuje hiruršku resekciju, radioterapiju i hemioterapiju. Čak i sa svim primenjenim modalitetima lečenja, u određenom trenutku dolazi do progresije bolesti. Osim toga, svaki od navedenih modaliteta lečenja može dovesti do različitih toksičnosti. U poslednjih deset godina mnoge studije su imale cilj da pronađu pouzdani i jedinstveni biomarker koji može pomoći u preciznijoj, neinvazivnoj dijagnostici tumora mozga, kao i prevazilaženju rezistencije na lečenje tih tumora, a kao potencijalni lek i poboljšati ukupno preživljavanje pacijenata. Mikro RNK su nekodirajući elementi genoma koji su relativno stabilni u serumu i plazmi, a mogu se izolovati i iz različitih tkiva. Promene ekspresije različitih mikro RNK su uočene kod mnogih visokogradusnih glioma. Samim tim, određena mikro RNK može potencijalno imati ulogu u dijagnozi i prognozi visokogradusnih glioma, terapijsku ulogu u lečenju glioma ili biti prediktivni biomarker za toksičnost izazvanu lečenjem. Da bi se to postiglo, svaki visokogradusni gliom bi trebalo da ima sopstveni i visoko specifični mikro RNK potpis. Mnogobrojne studije otkrile su veliki potencijal pojedinih mikro RNK. Nedostaci ovih studija su se odnosili na mali broj korišćenih uzoraka. Štaviše, istraživanje mikro RNK kao potencijalnih terapeutskih agenasa prvenstveno se zasnivalo na ćelijskim linijama ili ksenograftovima. S druge strane, mikro RNK koje pokazuju značajne promene ekspresije kod visokogradusnih glioma, pokazuju promenu nivoa ekspresije i kod drugih kancera i nekih nemalignih bolesti. U ovom članku smo napravili kritički, kratak pregled literature o ulozi mikro RNK kod visokogradusnih glioma.

Ključne reči:
visokogradusni gliom,
glioblastom,
mikro RNK

Introduction

High-grade gliomas (HGG) belong to a group of malignant brain tumours with poor overall survival. Among them, glioblastoma (GB) is the most aggressive HGG. In addition, patient care standards for patients with GB from 2005 to date, suggest that Stupp's regimen is applied (1). In some cases, when the stereotactic biopsy or surgery in patients with brain tumours is contraindicated, the diagnosis of brain tumours relies solely on the radiological diagnosis. Even with all medical imaging techniques, in some cases, it is extremely difficult to make a proper distinction between World Health Organization (WHO) grade 3 or grade 4 brain tumours. This problem could be overcome, to a certain degree, if there is a reliable circulating biomarker that could be identified for a specific type of brain tumour, and as such used in combination with imaging techniques for a more precise diagnosis.

Some of the patients with HGG who undergo radiotherapy and chemotherapy can experience different types and grades of toxicity (2,3). If feasible, early prediction of treatment toxicities can be potentially used in practice for dose and regimen adjustment. Biomarkers that can predict the toxicity of the treatment may lead to a more personalized treatment for each patient.

MicroRNAs (miRNAs; singular miR) are non-coding elements of the genome whose role is posttranscriptional regulation of gene expression (4). Recent studies now focus on the changes in individual miRNAs expression levels that can be used as potential biomarkers of the presence and progression of diseases, or for distinguishing the type of tumours, as well as the response to radiotherapy and chemotherapy. In other words, microRNAs could potentially be used to modulate the effect of oncological therapy, overcome oncological toxicity, or have a role as an inhibitor of cancer development and progression (**figure 1**) (4).

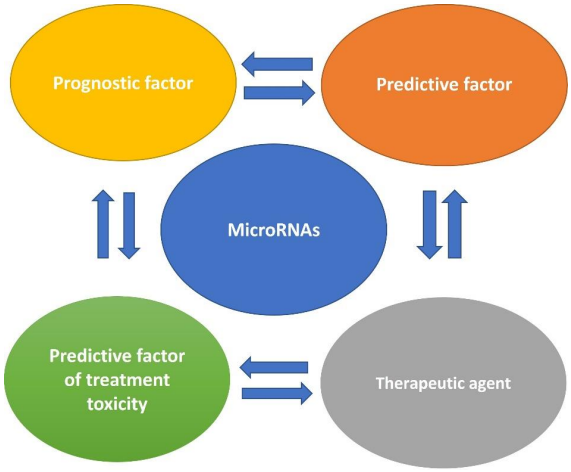

Figure 1. Schematic proposal of microRNAs signature on clinical use. The ideal signature of one or more microRNA in high-grade glioma could potentially serve as a prognostic factor, predictive factor, or toxicity predictor, have a role in therapy, or be used in the proposed directions.

The potential role of microRNAs as a biomarker of the diagnosis and prognosis of high-grade gliomas

The idea of discovering biomarkers for the diagnosis and prognosis of HGG is a logical extension of the research into circulating biomarkers in other extracranial cancers. One of the most investigated microRNAs in

cancer is miR-21.

In a systematic review and meta-analysis conducted by Dioguardi and collaborators, circulating miR-21 was presented as a promising prognostic biomarker in patients with head and neck squamous cell carcinoma (5). Indeed, in 2022, Mahmood and his collaborators observed the expression of miR-21 in the plasma of 100 patients with confirmed oral squamous cell carcinoma (6). The authors noticed a higher expression of miR-21 in patients who had tumours bigger than 4 cm, suggesting a positive correlation between higher expression of miR-21 with tumour dimensions as well as with tumour invasion and metastatic process (6). In comparison, a meta-analysis by Jiang and his team showed that in eight studies included in their research, high expression of miR-21 was correlated with poorer overall survival (OS) in patients with gliomas. However, there was no data about correlation to progression-free survival (PFS) (7). One study showed the absence of a significant association with PFS (7). Nevertheless, it should be noted that in these studies, the patients included in this research had both low-grade gliomas (LGG) and HGG. In addition, miR-21 expression was observed in glioma tissue rather than in plasma or serum. Similar to the previous study, Wu and collaborators reviewed miR-21 expression in human glioma tissue and non-tumour tissue, and they concluded that patients with high expression of miR-21 had a lower OS (8). In the particular study, they included 31 patients with WHO grade I glioma, 30 patients with WHO grade II glioma, 32 patients with WHO grade III glioma, and 59 patients with grade IV glioma, suggesting that miR-21 expression could potentially be a good diagnostic biomarker, especially for higher grade gliomas (8).

As suggested, miR-21 has a major role in glioblastoma pathogenesis (9), which could be linked to the correlation of miR-21 expression level in glioma tissue, as well as in the plasma or serum of glioma patients. This makes an accurate interpretation difficult though. As mentioned at the very beginning of this chapter, miR-21 is one of the most known microRNAs that plays a major role in many cancers. An important question posed by all investigators is whether miR-21 is so specific that it can show which type of tumour is present if the patient exhibited 2 or 3 different types of tumours. Moreover, it has been shown that miR-21 is up-regulated in non-oncological diseases, for example, periodontitis (10).

The second microRNA that is under numerous scientific investigations is miR-221. Authors like Ozdogan and his team looked into expression levels of miR-221 in serum in patients with brain tumours (11). They included 39 patients, 21 of whom had glioblastoma, 4 patients had other HGG and 14 patients had LGG. Also, they included 40 healthy subjects as a control group. Their results showed that there is no statistically significant difference between LGG and HGG tumours (11). However, there was a statistically significant difference between patients with brain tumours and healthy subjects, suggesting that miR-221 should be further investigated as a potential serum biomarker of gliomas (11).

To identify the microRNA signature more precisely in HGG, a higher number of microRNAs may be required for investigation.

Collected preoperative serum samples were gathered by Regazzo and collaborators, from 30 patients with different brain tumours, as well as serum samples from 15 healthy subjects (12). They measured the expression level of 11 miRNAs in the serum of selected patients and found a pronounced decrease of miR-497 in GB patients in comparison to the serum expression of healthy subjects. In addition, there was a difference in the mean serum expression level of miR-497 and miR-125b in HGG compared with LGG (12). Comparing their results to the prior literature, the authors discovered the potential of these miRNAs as a tool for separating GB from LGG. But as authors listed in table 2 of their article, numerous cancers were characterized by the altered expression of miR-125b or miR-497 (up-regulated or down-regulated, respectively) compared to control groups (12). However, if a number of cancers have altered expression levels of the same miR as in brain tumours or non-oncological diseases, and if there is no specific cut-off level of that miR in each tumour, the question about the uniqueness of miRNA signature still remains.

After identifying O(6)-methylguanine-DNA methyltransferase (MGMT) status, isocitrate dehydrogenase 1 (IDH1) mutation, pathohistological subtypes, and other parameters that affect the success of treatment and its outcome, researchers make continuous efforts to classify patients into specific groups, for instance, those with better or worse prognosis and equivalent outcomes. Consequently, the research field of brain tumour molecular biology is in expansion, and the potential role of miRNAs as a biomarker of the prognosis of HGG is under investigation.

In their research, Parker et al. included 43 patients with GB in their research and they measured the level of expression of miR-132 in GB tissue and normal brain tissue (13). According to their study, high miR-132 expression is an indicator of unfavorable outcomes. The median overall survival of the patients with high expression of miR-132 was 13 months in comparison to GB patients with lower expression of the miR-132, whose median survival was 17 months (13). In their study, the level of expression was measured in GB tissue samples (13). We do not know what level of expression of this particular microRNA would be in serum, and whether it would be up-regulated as in GB samples. If the expression level of miR-132 in GB tissue correlates properly with serum expression levels, further research into miR-132 as a prognostic biomarker could be of great importance.

The potential role of microRNAs in the therapeutic approach of high-grade gliomas

The establishment of microRNA signature in HGG may be a trigger point for the next generation of therapeutic research. This refers to the potential use of miRNAs as radiosensitizers or chemosensitizers by up-regulating or

down-regulating their level expression.

Overexpression of miR-10b is recognized and often presented in HGG (14). Most of the investigations are based on glioma cell lines, xenografts, or murine allografts. Among other results, Teplyuk and his team found that inhibition of miR-10b in vivo interrupted the cell cycle progression of GB and slowed down the process of tumour advancement (15). They used specific antisense oligonucleotide inhibitors for the inhibition of miR-10b (15). Similarly, Guessous and collaborators reported that the inhibition of miR-10b remarkably reduced tumour growth in glioma stem cell lines, suggesting that miR-10b may play an important role in oncogenesis in GB (16).

It can be found in the literature that two or more miRNAs have a synergistic role in the oncogenesis of cancer. Thus, two or more miRNAs can be recognized as miRNAs signature of specific HGG. Authors like Sun et al. proposed a pair of two miRNAs that could have a meaningful impact on oncogenesis in GB, and therefore a possible role in the therapeutic approach (17). According to their research, which consisted of in vitro (GB cells) and in vivo (mouse) investigation, the inhibition of miR-10b and miR-222 firmly affects GB cell growth and invasion (17).

MicroRNA inhibitors (anti-miRNAs; singular antimiR) may potentially act as therapeutic agents in the future, administered alone or in combination with other therapeutic modalities such as radiotherapy, chemotherapy, immunotherapy, etc. Some authors investigated the effects of the usage of a specific chemical agent in combination with an antimiR substance in the glioma cell line and observed its possible influence on anticancer treatment.

Zurlo and his team of researchers observed the influence of 2-(3'-chloro-4'-ethoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)-1H-imidazole named as 4o and antimiR-10b-5p, alone and in combination with each other, on glioma cell line U251 (18). After observing the effects on cell cycle and apoptosis, the investigators suggested that the combination of these two components in suboptimal doses induced a higher rate of apoptosis in comparison to the effects of each compound separately (18).

Earlier, in 2013, Chao and his team reported that higher expression of miR-21 is correlated with radioresistance (19). After using antimiR-21, they noticed that GB cells were more sensitive to radiation (19). Moreover, they suggested a correlation between miR-21 and its effect on radioresistance on GB cells through its target genes such as PDCD4 and hMSH2 (19). Authors like Xiao et al. announced that miR-135b is upregulated in radioresistance GB cell line U87R and that Glycogen synthase kinase 3 beta (GSK3β) may be a potential target for miR-135b, as they perceived that higher expression of GSK3β can enhance radiosensitivity (20).

Temozolomide has been a part of the standard treatment of GB since 2005 (1). Still, chemoresistance of glioblastoma is often observed. As glioblastoma stand out as one of the most aggressive tumours in humans, there is a need for overcoming TMZ resistance as well. MicroRNAs may also play an important part in the resistance of GB cells to TMZ. As found by Yin et al., miR-1238 is overexpressed in TMZ-resistant GB cells but their exosomes are in chemosensitive cells, suggesting a possible role of miR-1238 as a potential target for overcoming TMZ resistance (21).

Understanding the underlying mechanism of radioresistance or chemoresistance mediated by specific miRNAs is as important as the question of which miRNAs are up-or down-regulated in HGG. Moreover, there is a spectrum of miRNAs that are altered in HGG, and there is a need to find out which miRNAs are the most specific and the most sensitive for every histological type of HGG. In addition, research into anti-miRNA usage is mostly based on glioma cell lines, and should be interpreted with caution.

The potential role of microRNAs as a predictive biomarker of treatment toxicity of high-grade gliomas

In general, every treatment carries a risk of some toxicity. To date, there are no exact biomarkers that can predict toxicity in these patients. However, there are literature data on the correlation between microRNAs and toxicity induced by certain medications. For example, Starkey Lewis and his team found elevated levels of miR-122/192 in the serum of patients diagnosed with acetaminophen-induced liver injury when compared to healthy controls (22).

Radiotoxicity and chemotoxicity are often observed in HGG, both during or after the treatment. Even low-grade toxicities may influence the treatment of patients to some extent or infringe on the quality of life of these patients. Predicting radio- or chemotoxicities can help us reach a more personalized approach to every single patient.

The correlation between the expression of miR-21b/146/155 and acute radiotoxicity was investigated by Kopcalic et al., in patients with prostate cancer (23). They measured the expression of miR-21b/146/155 before radiotherapy, after radiotherapy, and at the first follow-up control. The authors noticed the highest level of miR-21 expression in patients with acute genitourinary toxicity after the completion of radiation therapy (23). In addition, expression levels of miR-146/15 significantly changed during the period of irradiation in patients without toxicity (23).

A meta-analysis performed by Stafford et al., highlighted that the elevated level of miR-21 expression correlates with a bad outcome in patients with prostate cancer (24). As mentioned before, miR-21 is also overexpressed in GB as well as in other tumours. Following this path, it is safe to conclude that miR-21 plays an important role in tumour biology. Furthermore, according to research by Kopcalic et al., miR-21 could have a possible role in predicting acute radiotoxicity as well. Theoretically, miR could serve as a prognostic factor, as well as a predictor

of treatment toxicity of numerous tumours. However, this could also pose a unique problem. The higher expression of any particular miR can be the result of various factors and processes, so the understanding of mechanisms of toxicities (radiotoxicity, chemotoxicity) may help identify potential biomarkers for toxicity prediction. For example, there is data on an elevated level of interleukin-6 in prostate cancer patients with more severe acute genitourinary radiotoxicity (25). A possible correlation between certain miRNAs and cytokine levels could be crucial to the understanding of the underlying mechanism of toxicity.

Our study published in 2022, included 43 patients with GB treated with radiotherapy and TMZ (26). Twenty-two of those patients exhibited toxicity and twenty-one patient did not show any toxicity (26). We measured and observed the expression levels of microRNA-10b/21/34a before radiotherapy and TMZ, at the 15th fraction of the concurrent treatment, and at the last fraction of radiation plus TMZ. Our results revealed higher expression levels of microRNA-10b/21 in patients with higher grades of toxicity (26). The level of expression of miR-34 significantly changed during concurrent treatment, as well (26). In comparison, in our study (26), the patients received concurrent radiation with chemotherapy, while in a study conducted by Kopcalic et al., (23), patients received only radiotherapy. However, in both studies, levels of expression of miR-21 were correlated with acute toxicity.

Conclusion

To date, numerous microRNAs have been investigated both in cancer and in high-grade gliomas. MicroRNAs are relatively stable in the blood and therefore, in the future, could be used as a potential target for treatment or as a prognostic and predictive factor. In order to achieve this goal, a microRNA signature needs to be accurately defined and highly specific for each high-grade glioma. In addition, the cut-off value for every microRNA should be established. Understanding the mechanism of radiotherapy and chemotherapy induced toxicities could help us to identify specific involvement of microRNAs in toxicity process. Therefore, one microRNA or set of microRNAs could have potential to be recognized as biomarker(s) for radio- or chemotoxicity prediction. The prediction of toxicity could have clinical significance and may lead to a more personalized treatment for each patient. One of the potential approaches is decreasing chemotherapy or radiotherapy dose in patients with high grade toxicity. More comprehensive studies are needed to obtain further data on the possible role of microRNAs in high-grade glioma in the future.

Acknowledgment

Special thanks to Ms. Marija Jovičić for her help with the linguistic aspect of this paper.

Literature

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005; 352(10):987-96.
2. Stepanović A, Nikitović M, Bogdanović A, Grujičić D. Long-lasting Thrombocytopenia after Transient Pancytopenia Induced by Short-Term Concomitant Radiotherapy and Temozolomide. Eur J Case Rep Intern Med. 2020; 7(10):001785.
3. Stepanovic A, Nikitovic M. Severe hematologic temozolomide-related toxicity and lifethreatening infections. J BUON. 2018; 23(1):7–13.
4. Petrovic N, Ergun S. miRNAs as Potential Treatment Targets and Treatment Options in Cancer. Mol Diagn Ther. 2018; 22(2):157–68.
5. Dioguardi M, Caloro GA, Laino L, Alovisi M, Sovereto D, Crincoli V, et al. Circulating miR-21 as a Potential Biomarker for the Diagnosis of Oral Cancer: A Systematic Review with Meta-Analysis. Cancers. 2020; 12(4):936.
6. Mahmood N, Hanif M, Ahmed A, Jamal Q, Mushtaq S, Khan A, et al. Circulating miR-21 as a prognostic and predictive biomarker in oral squamous cell carcinoma. Pak J Med Sci. 2019; 35(5):1408-12.
7. Jiang G, Mu J, Liu X, Peng X, Zhong F, Yuan W, et al. Prognostic value of miR-21 in gliomas: comprehensive study based on meta-analysis and TCGA dataset validation. Sci Rep. 2020; 10(1):4220.
8. Wu L, Li G, Feng D, Qin H, Gong L, Zhang J, et al. MicroRNA-21 expression is associated with overall survival in patients with glioma. Diagn Pathol. 2013; 8(1):200.
9. Masoudi MS, Mehrabian E, Mirzaei H. MiR-21: A key player in glioblastoma pathogenesis. J Cell Biochem. 2018; 119(2):1285–90.
10. Zhou W, Su L, Duan X, Chen X, Hays A, Upadhyayula S, et al. MicroRNA-21 down-regulates inflammation and inhibits periodontitis. Mol Immunol. 2018; 101:608–14.
11. Ozdogan S, Yaltirik CK, Yilmaz SG, Akdeniz FT, Sumerkent K, Duzkalir AH, et al. Investigation of the Effects of MicroRNA-221 Expression Levels in Glioblastoma Multiforme Tumors. Anticancer Res. 2020; 40(6):3265–70.
12. Regazzo G, Terrenato I, Spagnuolo M, Carosi M, Cognetti G, Cicchillitti L, et al. A restricted signature of serum miRNAs distinguishes glioblastoma from lower grade gliomas. J Exp Clin Cancer Res. 2016; 35(1):124.
13. Parker NR, Correia N, Crossley B, Buckland ME, Howell VM, Wheeler HR. Correlation of MicroRNA 132 Up-regulation with an Unfavorable Clinical Outcome in Patients with Primary Glioblastoma Multiforme Treated with Radiotherapy Plus Concomitant and Adjuvant Temozolomide Chemotherapy. Transl Oncol. 2013; 6(6):742-8.
14. Sasayama T, Nishihara M, Kondoh T, Hosoda K, Kohmura E. MicroRNA-10b is overexpressed in malignant glioma and associated with tumor invasive factors, uPAR and RhoC. Int J Cancer. 2009; 125(6):1407–13.
15. Teplyuk NM, Uhlmann EJ, Gabriely G, Volfovsky N, Wang Y, Teng J, et al. Therapeutic potential of targeting micro RNA-10b in established intracranial glioblastoma: first steps toward the clinic. EMBO Mol Med. 2016; 8(3):268–87.
16. Guessous F, Alvarado-Velez M, Marcinkiewicz L, Zhang Y, Kim J, Heister S, et al. Oncogenic effects of miR-10b in glioblastoma stem cells. J Neurooncol. 2013; 112(2):153–63.
17. Sun B, Zhao X, Ming J, Liu X, Liu D, Jiang C. Stepwise detection and evaluation reveal miR-10b and miR-222 as a remarkable prognostic pair for glioblastoma. Oncogene. 2019; 38(33):6142–57.
18. Zurlo M, Romagnoli R, Oliva P, Gasparello J, Finotti A, Gambari R. Synergistic Effects of A Combined Treatment of Glioblastoma U251 Cells with An Anti-miR-10b-5p Molecule and An AntiCancer Agent Based on 1-(3',4',5'-Trimethoxyphenyl)-2-Aryl-1H-Imidazole Scaffold. IJMS. 2022; 23(11):5991.

19. Chao TF, Xiong HH, Liu W, Chen Y, Zhang JX. MiR-21 mediates the radiation resistance of glioblastoma cells by regulating PDCD4 and hMSH2. J Huazhong Univ Sci Technolog Med Sci. 2013; 33(4):525-9.
20. Xiao S, Yang Z, Lv R, Zhao J, Wu M, Liao Y, et al. miR-135b Contributes to the Radioresistance by Targeting GSK3β in Human Glioblastoma Multiforme Cells. PLoS One. 2014; 9(9):e108810.
21. Yin J, Zeng A, Zhang Z, Shi Z, Yan W, You Y. Exosomal transfer of miR-1238 contributes to temozolomide-resistance in glioblastoma. EBioMedicine. 2019; 42:238–51.
22. Starkey Lewis PJ, Dear J, Platt V, Simpson KJ, Craig DGN, Antoine DJ, et al. Circulating microRNAs as potential markers of human drug-induced liver injury. Hepatology. 2011; 54(5):1767–76.
23. Kopcalic K, Petrovic N, Stanojkovic TP, Stankovic V, Bukumiric Z, Roganovic J, et al. Association between miR-21/146a/155 level changes and acute genitourinary radiotoxicity in prostate cancer patients: A pilot study. Pathol Res Pract. 2019; 215(4):626–31.
24. Stafford MYC, Willoughby CE, Walsh CP, McKenna DJ. Prognostic value of miR-21 for prostate cancer: a systematic review and meta-analysis. Biosci Rep. 2022; 42(1):BSR20211972.
25. Stanojković TP, Matić IZ, Petrović N, Stanković V, Kopčalić K, Besu I, et al. Evaluation of cytokine expression and circulating immune cell subsets as potential parameters of acute radiation toxicity in prostate cancer patients. Sci Rep. 2020; 10(1):19002.
26. Stepanović A, Nikitović M, Stanojković TP, Grujičić D, Bukumirić Z, Srbljak I, et al. Association between microRNAs 10b/21/34a and acute toxicity in glioblastoma patients treated with radiotherapy and temozolomide. Sci Rep. 2022; 12(1):7505.