20. Kalajdjiev, G. (2018). *Annual report for 2018 – Rights of refugee, migrants and asylum seekers in Reublic of Macedonia*. Skopje: The Helsinki Committee for Human Rights of the Republic of Macedonia.
21. Karlsen S. (2007). Ethnic Inequalities in Health: The Impact of Racism. Better Health Briefing 3 (a Race Equality Foundation briefing paper). *Race Equality Foundation*.
22. Kleemans M, K. J. (2009). *Understanding Attitudes Towards Migrants: A Broader Perspective*. New York: United Nations Development Programme.
23. Lages M, P. V. (2006). Immigrants and the Portuguese Population. Reciprocal Images – Analysis of Two Surveys. *Immigration Observatory/ACIME,* Lisboa.
24. *Law on foreigners*. (n.d.). Retrieved from Ministry of internal: https://mvr.gov.mk/Upload/Documents/Zakon%20za%20stranci%2097-18.pdf.
25. *Law on health insurance*. (n.d.). Retrieved from http://www.fzo.org.mk/WBStorage/Files/27.%20ZAKON%20ZA%20ZDRAVSTVENOTO%20OSIGURUVAWE%20precisten%20do%20142%20od%202016.pdf.
26. *Law on international and temporary protection,* (n.d.). Retrieved from https://www.akt.mkhttps://www.akt.mk/тип/закон.
27. Michaelsen J, K. A. (2004). Health professionals' knowledge, attitudes and experiences in relation to immigrant patients: a questionnaire study at a Danish hospital. *Scand J Public Health*, 287-295.
28. MLSP. (2017). *СТРАТЕГИЈА ЗА ИНТЕГРАЦИЈА НА БЕГАЛЦИ И СТРАНЦИ ВО РЕПУБЛИКА МАКЕДОНИЈА 2017 2027*. Retrieved from Ministry of labour and social policy: www.mtsp.gov.mk/content/pdf/strategii/Стратегија.
29. O'Donnell C. A, B. N. (2016). Reducing the health care burden for marginalised migrants: The potential role for primary care in Europe. *Health Policy, 120*(5), 495-508.
30. *Organisation for Economic Co-operation and Development: International Migration Outlook: SOPEMI – 2008 Edition. 2008, Paris*. (2008, September). Retrieved from Better policies for better lives: https://www.oecd.org/els/mig/internationalmigrationoutlook2008.htm.
31. Paksoy, H. M. (2017). Survey of Health Workers' Behaviours Towards Refugee-Patients. *Recent Developments in Sociology and Social Work*.
32. Peek ME, O.-Y. A.-B. (2010). Race and shared decision-making: perspectives of African-Americans with diabetes. *Soc Sci Med*, 1-9.
33. Phillips KA, M. M. (2000). Barriers to care among racial/ethnic groups under managed care. *Health Aff.*, 65-75.
34. Pitkänen P, K. S. (2002). Meeting foreign cultures: a survey of the attitudes of Finnish authorities towards immigrants and immigration. *J Ethn Migr Stud*, 103-118.
35. RNM, A. o. (2019, december 25). Retrieved from https://360stepeni.mk/kriznata-sostojba-na-juzhnata-i-severnata-granitsa-prodolzhena-do-juni-2020/.
36. Scheppers E, v. D. (2006). Potential barriers to the use of health services among ethnic minorities: a review. *Fam Pract.*, 325-348.
37. Schneider EC, Z. A. (2002). Racial disparities in the quality of care for enrollees in Medicare managed care. *JAMA*, 1288-1294.
38. Smedley BD, S. A. (2003). Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. *National Academy Press*.
39. *Universal Declaration of Human Rights*. (2020, 03 01). Retrieved from civil.org.mk: https://civil.org.mk/wp-content/uploads/2013/05/djeklarazia.pdf.
40. Van Ryn M, B. J. (2000). The effect of patient race and socio-economic status on physicians' perceptions of patients. *Soc Sci Med.*, 813-828.

ORIGINAL RESEARCH

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PROGNOSTIC VALUE OF MOLECULAR MARKER ON OUTCOME IN PATIENTS WITH HIGH-GRADE GLIOMA-SINGLE INSTITUTIONAL EXPERIENCE

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ABSTRACT

High-grade glioma (HGG) are among the most frequent primary brain tumors. Prognosis in HGG depends on histology, age, performance status, and other patient and tumor related factors. The 2016 revision of the WHO Classification of CNS Tumors introduced molecular characterization of HGG with possible impact on prognosis. Analysis of a total of 49 patients with HGG with known MGMT methylation status and IDH1 and IDH2 mutation has been done. All patients underwent surgery, followed by concurrent chemoradiotherapy and adjuvant chemotherapy with temozolomide. Median follow up of all patients was 21.3 months (6.2-52.1 months). The Median Disease-free survival (DFS) was 20.3 months, and the median overall survival (OS) was calculated as 21.8 months. Patients has been stratified according to MGMT methylation status and IDH1 and IDH2 mutation status. DFS and OS have been compared between groups. The assessment shows 2-years DFS and OS were 45.5% and 54% for methylated and 40.4% and 47.8% for unmethylated patients. 2-years DFS and OS were 75% and 86% for IDH1 mutated patients and 34.12% and 47.1% for IDH1 unmutated patients. Two-years DFS and OS were 56% and 83% for IDH 2 mutated patients and 28.8% and 40.9% for IDH2 unmutated patients. There were suggestions for favorable prognostic factor for both MGMT methylation and IDH1 and IDH2 mutation, but we did not show any statistically significant difference of DFS and OS between MGMT methylated and unmethylated patients and between IDH1 and IDH2 mutated and unmutated patients due to small specimen and relatively short follow up.

Key Words: *Chemoradiotherapy, Glioma, Molecular Characterization.*

Introduction

The high-grade glioma are relatively rare type of tumors with an incidence of about 1.6 on 100,000 population. It is estimated that there will be around 300,000 new cases annually, with around 250,000 diseases specific deaths worldwide (1).

Patients' treatments are usually multimodal and depend on tumor localization, tumor size, patients' age, and patients' performance status. The survival rate largely depends on the histology of the tumor and applied treatment modality (2 – 4).

The introduction of contemporary multimodality treatment that includes various modern surgical approaches, modern radiotherapy using three-dimensional conformal techniques and techniques derivates combined with temozolomide chemotherapy, extended the survival scenarios of patients on average for about 14 months for glioblastoma patients, WHO Grade IV, and around 5 years for patients with WHO Grade III glioma (5).

The revision of the WHO classification of malignant brain tumors in 2016 led to mandatory molecular classification, which could have an impact on patients' survival rate (6 – 8). Today, it is also clear that some patients who have a tumor with different molecular characterization could have more benefit from chemotherapy treatment (9).

Until recently, brain tumors diagnostics have been almost solely based on morphology and immunohistochemically staining for relatively unspecific markers. Although specific molecular markers have been known for longer than a decade, molecular biomarkers were not included in the WHO classification until the last revision (6).

Today, the classification of diffuse glioma rests on the integration of morphology and molecular results. Also, for many other CNS tumor entities, specific diagnostic, prognostic, and predictive biomarkers have been detected and continue to appear as significant in the clinical settings (10).

It is now clear that mutations of isocitrate dehydrogenase (IDH) genes, in IDH1 – R132H mutation and in IDH2 K129R mutation, have a definite effect on prognosis and may be predictive of radiation therapy and chemotherapy response (11,12).

Molecular characterization of glioma has been implemented in our institution in 2016, and this paper shows the initial results of the predictive value of MGMT methylation, IDH1, and IDH2 mutation in our series of patients.

Material and methods

Total of 49 patients with High-Grade Glioma (8 patients with WHO grade III and 41 with Who Grade IV tumors) have been referred to the University Clinic of Radiotherapy and Oncology (UCRO) in Skopje, North Macedonia in the period January 2016 – December 2018 with the intention to be treated. The institutional ethical committee approved all procedures on patients, and all patients signed informative consent before the start of the treatment. Surgical treatment had been performed before referral to UCRO, and postoperative histology has been verified by qualified neuropathologists. Only patients with verified histological findings of High-Grade Glioma (WHO Grade III and IV), which include the following histological types: glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma (6) were included in this study. In addition to morphological pathohistological findings, molecular analysis of IDH1, IHD2, and MGMT mutation has been performed on all histological specimens using Multiplex ligation-dependent probe amplification (13).

The initial workup of the patients consisted of biochemical blood analysis, total blood count, a collection of preoperative and postoperative imaging, and scoring of patients according to ECOG/WHO Performance Status Scoring System (14). The patients with ECOG/WHO performance scores equal to or larger than 3 have been omitted from this analysis due to different treatment intent and treatment strategies.

After the initial evaluation, the patients have been treated according to an institutional protocol for postoperative chemoradiotherapy, which consisted of radiotherapy using three-dimensional conformal radiotherapy (3D-CRT) or Intensity Modulated Radiotherapy (IMRT) together with concurrent chemotherapy with temozolomide, followed by adjuvant chemotherapy with temozolomide in the duration of a total of 6-12 cycles.

Thermoplastic immobilization mask has been molded individually for all patients, and CT simulation scans with 2.5 mm axial slices were acquired in the treatment position. Preoperative or/and postoperative MRI images were co-registered with CT simulation scans. The gross tumor volume (GTV) was contoured as the contrast-enhancing lesion on T1-weighted MRI or the post-operative cavity on CT. The clinical target volume (CTV) was a 1.5-2 cm margin around the GTV, which was expanded to include the edema and adjusted to anatomic barriers. The planning target volume (PTV) was generated with a 3-5 mm isotropic margin expansion. Planned dose of adjuvant radiotherapy (RT) was 60 Gy in 30 fractions, 2 Gy per fraction, over six weeks with 3D-CRT or IMRT technique. All patients were planned for chemotherapy with temozolomide, 75 mg/m^2 taken orally every day, throughout the radiation process followed by 150-200 mg/m^2 for 5 consecutive days every four weeks in the duration of 6-12 cycles. Treatment plans were generated with Varian Eclipse Version 10 (Varian Medical Systems) treatment planning system. Dose-volume parameters for all treatment structures (target and organs at risk) were documented, and the criteria for plan acceptance were according to QUANTEC guidelines (15).

The patients were followed up according to the institutional protocol of follow up, which comprises of physical examination and blood examination – every month, contrast-enhanced brain MRI every 3-4 months. The criteria for the progressive disease were according to revised RANO/EANO criteria (16). Diseases progression and overall survival has been quantified as a time interval in months from date of diagnosis of disease or date of conformed histological finding to date of confirmed progression for disease-free survival (DFS) or date of lethal outcome for overall survival (OS). The detailed patient characteristics have been shown in **Table 1**.

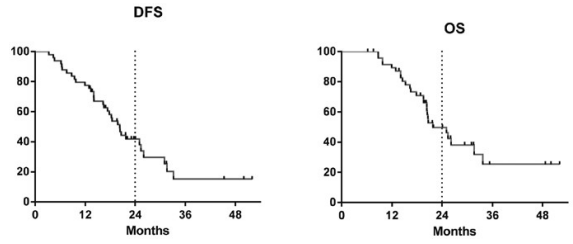
Table 1. *Patients' Characteristics*

Gender	Male	Female
	30	19
WHO Grade	III	IV
	8	41
Performance status	0,1	2,3
	26	23
Type of Surgery	Total Resection	Subtotal Resection
	37	12
IDH1	Wildtype	Mutated
	39	10
IDH2	Wildtype	Mutated
	39	10
MGMT (met)	Unmethylated	Methylated
	30	19
Age at diagnosis	≤50	>50
	13	36

Results

The Median follow-up of all 49 patients was 21.3 months (range from 6.2 to 52.1 months). The median time to progression (recurrence) was 20.3 months, and median survival was calculated as 21.8 months using the Kaplan Meir method (17).

Figure 1. *Median disease-free survival (DFS) – 20.3 months and median overall survival (OS) – 21.8 months*

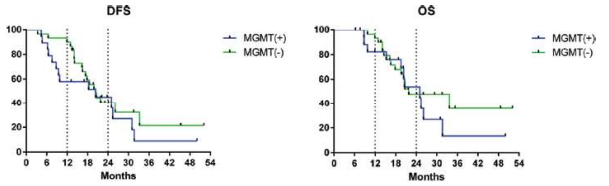


Survival analysis using the Kaplan Meir method has been done on two parameters for disease free survival (DFS) and overall survival (OS). A comparison of survival has been calculated using Mantel-Cox and Gehan-Breslow-Wilcoxon (log-rank) tests (18,19).

Survival analysis for both DFS and OS has been done for patients with MGMT promoter methylated and unmethylated patients. All 49 patients were with MGMT methylation determined status. Nineteen patients were with methylated MGMT and 30 with unmethylated MGMT.

Disease-free survival (DFS) was 20.32 months for MGMT methylated and 20.29 months for unmethylated MGMT patients, and Overall Survival (OS) was 25 months for MGMT methylated and 21.75 months for MGMT unmethylated patients **(Figure 2)**.

Figure 2. *Two-years Disease-Free Survival (DFS) and Overall Survival (OS) in MGMT methylated and unmethylated patients: 45.5% and 54% for methylated and 40.4% and 47.8% for unmethylated patients.*

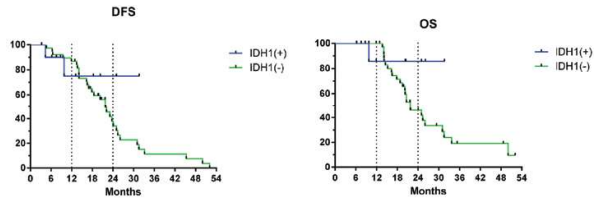


Two-year DFS was 45.5% for methylated and 40.4% for unmethylated patients and 2-year OS was 54% for methylated and 47.8% for unmethylated patients. Log-rank (Mantel-Cox) test of comparison of survival was non-significant (p=0.3513).

Also, IDH status was known for all patients. R132H mutation of the IDH 1 gene was detected in 10 patients, and 39 were IDH1 wild-type gene. R172K mutation of the IDH2 gene was detected in 11 patients, and 38 were IDH2 unmutated (wildtype gene).

Disease-free survival (DFS) was unreached for IDH 1 mutated patients and 21.75 months for IDH1 unmutated patients. Overall Survival (OS) was unreached for IDH 1 mutated patients and 21.75 months for IDH1 unmutated patients. Two-year DFS was 75% for IDH 1 mutated patients, and 34.12% for IDH1 unmutated patients, and 2-years OS was 86% for IDH 1 mutated and 47.1% for IDH1 unmutated patients. The Log-rank (Mantel-Cox) test of comparison of survival was non-significant (p=0.1205) **(Figure 3)**.

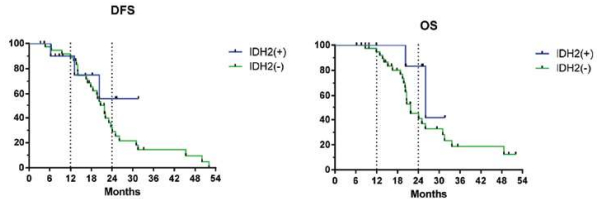
Figure 3. *Two-years Disease-Free Survival (DFS) and Overall Survival (OS) in IDH1 mutated and nonmutated patients: 75% and 86% for IDH 1 mutated patients and 34.12% and 47.1% for IDH1 unmutated patients.*



Disease-free survival (DFS) was unreached for IDH 2 mutated patients and 20.7 months for IDH2 unmutated patients. Overall Survival (OS) was 26.1 months for IDH 2 mutated patients

and 21.75 months for IDH 2 unmutated patients. Two-year DFS was 56% for IDH 2 mutated patients, and 28.8% for IDH2 unmutated patients, and 2-years OS was 83% for IDH 2 mutated and 40.9% for IDH2 unmutated patients. Log-rank (Mantel-Cox) test of comparison of survival was non-significant (p=0.1574) **(Figure4)**.

Figure 4. *Two-years Disease-Free Survival (DFS) and Overall Survival (OS) in IDH2 mutated and nonmutated patients: 56% and 83% for IDH 2 mutated patients and 28.8% and 40.9% for IDH2 unmutated patients.*



Discussion

Malignant gliomas are tumors with one of the worst scenarios, and standard treatment hardly changed overall survival in the past three decades (20).

The median survival of patients with glioma is around 12-15 months for glioblastoma and up to 5 years for grade 3 tumors. However, reclassification within the novel WHO classification will not increase survival, but will be more important for predicting outcome and prognosis. In our small series of patient treatments, we noticed that IDH mutation and MGMT methylation are shown as favorable prognostic factors. Also, there is a trend of separation of survival curves, both for DFS and OS. Unfortunately, our series of patients was small, so we did not show a statistically significant difference. The prognostic difference has been shown between methylated/ mutated patients and nonmethylated/ unmutated in various patients and multicentric studies (8,10,20 – 23).

Conclusion

We are planning to further enlarge our series of patients with a continuously increasing number of included patients. Still, it is challenging to confirm this difference in a real-world setting. With longer follow up we think that we will be able to reproduce the result from large data series and maybe in the future to re-shape treatment with the introduction of new agents and procedures in the treatment of patients with high-grade glioma.

Authors' Contribution

All authors contributed equally to this manuscript.

List of abbreviations used in the manuscript

IDH – Isocitrate dehydrogenase
MGMT – O6-methylguanine DNA methyltransferase
3D-CRT – Three-dimensional conformal radiotherapy
IMRT – Intensity Modulated Radiotherapy
RT – Radiotherapy
DFS – Disease-Free Survival
OS – Overall Survival
WHO – World Health Organization
CNS – Central Nervous System
ECOG – Eastern Cooperative Oncology Group
CT – Computed Tomography
MRI – Magnetic Resonance Imaging
QUANTEC – Quantitative Analyses of Normal Tissue Effects in the Clinic
RANO – Response assessment in neuro-oncology criteria
EANO – European Association of Neuro-Oncology
GTV – Gross tumor volume
CTV – Clinical target volume
PTV – Planning target volume

References

1. Bray F, Ferlay J, Soerjomataram I, et al. A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6):394 – 424.
2. Rusthoven CG, Carlson JA, Waxweiler T V., et al. The Impact of Adjuvant Radiation Therapy for High-Grade Gliomas by Histology in the United States Population. Int J Radiat Oncol [Internet]. 2014 Nov 15 [cited 2018 Jan 27];90(4):894 – 902. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25585784.
3. Ostrom QT, Gittleman H, Kruchko C, et al. Completeness of required site-specific factors for brain and CNS tumors in the Surveillance, Epidemiology and End Results (SEER) 18 database (2004 – 2012, varying). J Neurooncol [Internet]. 2016 Oct 14 [cited 2018 Jan 28];130(1):31 – 42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27418206.
4. Nuño M, Birch K, Mukherjee D, et al. Survival and Prognostic Factors of Anaplastic Gliomas. Neurosurgery [Internet]. 2013 Sep [cited 2018 Jan 27];73(3):458 – 65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23719055.
5. Seliger C, Luber C, Gerken M, et al. Use of metformin and survival of patients with high-grade glioma. Int J Cancer. 2019;144(2):273 – 80.
6. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016 Jun 9;131(6):803 – 20.
7. Idbaih A, Omuro A, Ducray F, etal. Molecular genetic markers as predictors of response to chemotherapy in gliomas [Internet]. Vol. 19, Current Opinion in Oncology. Lippincott

Williams and Wilkins; 2007 [cited 2020 Mar 29]. p. 606 – 11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17906460.
8. Hegi ME, Liu L, Herman JG, et al. Correlation of O6-methylguanine methyltransferase (MGMT) promoter methylation with clinical outcomes in glioblastoma and clinical strategies to modulate MGMT activity [Internet]. Vol. 26, Journal of Clinical Oncology. 2008 [cited 2020 Mar 29]. p. 4189 – 99. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18757334
9. Weller M, Le Rhun E, Preusser M, et al. How we treat glioblastoma. ESMO Open. 2019; 4:1 – 4.
10. Scheie D, Kufaishi HHA, Broholm H, et al. Biomarkers in tumors of the central nervous system – a review. Apis. 2019; 1(6):1 – 23.
11. Turkalp Z, Karamchandani J, Das S. IDH mutation in glioma: New insights and promises for the future. JAMA Neurol. 2014; 71(10):1319 – 25.
12. Yan H, Williams D, Jin G, et al. IDH1 and IDH2 Mutations in Gliomas. N Engl J Med. 2009; 360:765 – 73.
13. Schouten JP, McElgunn CJ, Waaijer R, et al. Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. Nucleic Acids Res. 2002; 30(12):e57.
14. Oken MM, Creech RH, Tormey DC, et al. Toxicology and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol [Internet]. 1982 Dec [cited 2016 Aug 4]; 5(6):649 – 55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7165009.
15. Lawrence YR, Li XA, el Naqa I, et al. QUANTEC: Radiation Dose – Volume Effects in the Brain. Int J Radiat Oncol. 2010;76(3): S77 – 85.
16. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response assessment in the neuro-oncology working group. J Clin Oncol. 2010 Apr 10; 28(11):1963 – 72.
17. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. J Am Stat Assoc. 1958 Jun; 53(282):457 – 81.
18. Cox DR (David R, Oakes D (Statistician). Analysis of survival data. New York: Chapman and Hall; 1984.201 p.
19. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother reports [Internet]. 1966 Mar [cited 2016 Aug 22]; 50(3):163 – 70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/5910392.
20. Liang J, Lv X, Lu C, et al. Prognostic factors of patients with Gliomas-An analysis on 335 patients with Glioblastoma and other forms of Gliomas. BMC Cancer. 2020; 20(1):1 – 7.
21. Yu W, Zhang L, Wei Q, Shao A. O6-Methylguanine-DNA Methyltransferase (MGMT): Challenges and New Opportunities in Glioma Chemotherapy. Front Oncol. 2020;9(January):1 – 11.
22. Herrlinger U, Tzaridis T, Mack F, et al. Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA – 09): a randomized, open-label, phase 3 trial. Lancet. 2019; 393 (10172):678 – 88.
23. Collins VP, Ichimura K, Di Y, Pearson D, et al. Prognostic and predictive markers in recurrent high-grade glioma; results from the BR12 randomized trial. Acta Neuropathol Commun. 2014; 2(1):1 – 15.

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NEONATAL MORTALITY RATE AT GYNECOLOGY AND OBSTETRICS CLINIC IN SKOPJE IN THE PERIOD OF FIVE YEARS IN NEWBORNS TREATED AT NEONATAL INTENSIVE CARE UNIT

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ABSTRACT

Introduction: Neonatal mortality is a number of neonatal deaths per 1,000 live births in a given year or period. Neonatal mortality is defined as a death in the first 28 days of life or a neonatal period after delivery. It includes all life born neonates after 22 gestational week of pregnancy and with birth weight over 500 g. Neonatal mortality is divided into early neonatal mortality which count deaths in 0-7 days after delivery, and late neonatal mortality 8-28 days after delivery.

AIM: The aim of the study is to present hospital neonatal mortality rate at the GOC-Skopje, among newborns treated at NICU in the neonatal period of 0-28 days after births, in the period of five years 2013-2017 and to determinate the leading causes of neonatal deaths at NICU.

Material and Methods: Retrospective study counts neonatal mortality rate in the early and late neonatal period, as well as the leading causes for neonatal deaths in neonatal period of 0-28 days after delivery at the GOC-Skopje, in the period of 5 years. The data is collected from the Data basis of NICU at GOC-Skopje.

Results: Hospital neonatal mortality rate in the 5 years period was 25.6‰, or 25.6 neonatal deaths in the neonatal period. There were 688 neonatal deaths on 26,891 live-born neonates. Neonatal mortality rate in early neonatal period (0-7 days) is – 547 or 20.34‰ of all neonatal deaths in the five years period. Late neonatal mortality (8-28 days) after delivery was in 141 casesor 5.24‰. The leading causes for neonatal death in newborns treated at NICU were complications due to prematurity, respiratory distress syndrome and neonatal sepsis.

Conclusion: The hospital neonatal mortality rate at GOC-Skopje in five years period is high, and requires more prospective studies and strategies to reduce neonatal mortality in the future.

***Keywords**: early neonatal mortality, late neonatal mortality, neonatal mortality, NICU, GOC – Skopje.*