Neuro-Oncology

A Systematic Review and Meta-analysis of the Impact of Radiation-Related Lymphopenia on Outcomes in High-Grade Gliomas

Supriya Mallick[1]   Anjali V.R.[2]   Prashanth Giridhar[2]   Rituraj Upadhyay[3]   Byung-Kyu Kim[4]
Amrish Sharma[5]   Hagar Elghazawy[6]   Thiraviyam Elumalai[7]   Vinod Solipuram[8]   Cheng En Hsieh[9,10]
Courtney Hentz[11]   Abhishek A. Solanki[11]   Jing Li[3]   Dennis Pai Chan[11]   Emily Ness[11]
Bhanu Prasad Venkatesulu[11]   David R. Grosshans[3]

[1] Department of Radiation Oncology, National Cancer Institute, New Delhi, India
[2] Department of Radiation Oncology, AIIMS, New Delhi, India
[3] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States
[4] Department of Experimental Radiation Oncology, Graduate School of Biomedical Sciences, The University of Texas Health Science Center at Houston and The University of Texas MD Anderson Cancer Center, Houston, Texas, United States
[5] Department of Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States
[6] Department of Clinical Oncology, Faculty of Medicine, Ain Shams University, Abbaseya, Cairo, Egypt
[7] Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom

Address for correspondence Bhanu Prasad Venkatesulu, MD, Department of Radiation Oncology, Loyola University and Edward Hines Veteran Affairs Hospital, Chicago, Illinois 60153, United States (e-mail: bpmmc24@gmail.com).

[8] Department of Internal Medicine, Saint Agnes Hospital, Baltimore, Maryland, United States
[9] Department of Radiation Oncology, Institute for Radiological Research, Chang Gung Memorial Hospital at Linkou and Chang Gung University, Taoyuan City, Taiwan
[10] Department of Experimental Radiation Oncology, Graduate School of Biomedical Sciences, The University of Texas Health Science Center at Houston and The University of Texas MD Anderson Cancer Center, Houston, Texas, United States
[11] Department of Radiation Oncology, Loyola University and Edward Hines Veteran Affairs Hospital, Chicago, Illinois, United States

Abstract

Supriya Mallick

Keywords

► radiation
► lymphopenia
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► systematic review

Introduction   Malignant gliomas are the most common primary malignant brain tumors and are typically treated with maximal safe surgical resection followed by chemoradiation. One of the unintended effects of radiation is depletion of circulating lymphocyte pool, which has been correlated with inferior overall survival outcomes.

Methods   A comprehensive and systematic searches of the PubMed, Cochrane Central, and Embase databases were done to assess the studies that have reported radiation-related lymphopenia in high-grade gliomas. Hazard ratios (HRs), odds ratios (OR), and mean differences were represented with Forest plots comparing patients with severe lymphopenia and no severe lymphopenia. Review Manager Version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for the analysis.

Results   Nineteen studies were included in the final systematic review and 12 studies were included in the meta-analysis. The odds of developing severe lymphopenia were 0.39 (95% CI:0.19, 0.81, $I^2 = 94\%$, $p = 0.01$). Patients with severe lymphopenia were at increased risk of death with a pooled HR = 2.19 (95% CI: 1.70, 2.83, $I^2 = 0\%$, $p < 0.00001$) compared to patients with no severe lymphopenia. The mean difference in survival between patients with severe lymphopenia and no severe lymphopenia was -6.72

months (95% CI: -8.95, -4.49, $I^2 = 99\%$, $p <0.00001$), with a better mean survival in the no severe lymphopenia group.

Conclusion Radiation-induced severe lymphopenia was associated with poor overall survival and increased risk of death. Photon therapy, larger planning target volume, higher brain dose, higher hypothalamus dose, and female gender were associated with increased risk of severe lymphopenia.

Introduction

Malignant gliomas are the most common primary malignant brain tumors, which account for more than 80% of central nervous system (CNS) tumors.[1,2] Among these, high-grade gliomas (HGG) are the most resistant and challenging solid tumors with dismal long-term outcomes. Despite standard of care multimodality treatment consisting of maximal safe surgical resection and adjuvant concurrent chemoradiation, the median survival is 12 to 24 months.[3–5] Adjuvant radiation and chemotherapy are both associated with treatment-induced lymphopenia. Lymphocytes play a crucial role in regulating immune response against cancer cells.[6–8] It is estimated that in patients with high-grade glioma, after a single fraction, 0.5 Gy is delivered to 5% of the circulating blood cell pool, and after 30 fractions of conventional treatment 99% of blood cells have received $\geq$0.5 Gy.[9] Lymphocytes are a highly radiosensitive with a D_{10} of approximately 3 Gy and D_{50} of approximately 2 Gy.[10] The radiosensitivity among lymphocytes is heterogenous, with B lymphocytes slightly more radiosensitive than T lymphocytes. Irradiation of the circulating pool of blood cells results in lymphopenia and is associated with poor outcomes, including worse survival, in high-grade gliomas and other solid malignancies. Various studies have been attempted and the results have shown a relationship between radiation-induced lymphopenia and poor survival outcomes in high-grade glioma. Here we performed a systematic review and meta-analysis of radiation-induced lymphopenia in high-grade gliomas assessing the impact of lymphopenia on tumor control and survival outcomes.

Methods

Data Search

The PubMed (National Institutes of Health), Cochrane Central (Cochrane collaboration), and Embase (Elsevier) databases were queried with the following search terms – radiation; Gliomas; lymphopenia, and survival. The search strategy with keywords is provided in **Supplementary Material S1** (available online only). The duration of the search was from the inception of each database up to September 6, 2020. The search was performed on September 6, 2020.

Non-Database Search Methods

Conference proceedings from the American Society of Radiation Oncology, European Society of Therapeutic Radiation Oncology, European Society of Medical Oncology, and American Society of Clinical Oncology conferences for the timeframe 2000 to 2020 was reviewed to identify additional articles. The search did not have a language filter. B.P.V. and R.U. did the search independently and any disagreements were resolved by mutual discussion.

Eligibility Criteria for Articles

Inclusion criteria were: (1) any prospective clinical trial, retrospective study, cohort study of gliomas in humans, (2) radiation should have been part of treatment and intent had to be in the neoadjuvant, definitive, or adjuvant settings and (3) the study should have data on cancer-specific outcomes and treatment-related lymphopenia.

Exclusion criteria: (1) preclinical models; (2) studies on lymphopenia in patients undergoing immunotherapy or chemotherapy or surgery alone; (3) Any radioactive nucleotides; (4) studies reporting outcomes in HIV positive patients or immunodeficiency states.

Study Review

The search process was done in a systematic manner consistent with the PRISMA flow diagram as shown in ►**Fig. 1**. The articles were reviewed by B.P.V. and R.U. The duplicates were excluded, and the titles of articles were evaluated. The articles found to be relevant to the topic of interest were shortlisted and the full-length paper was assessed for the eligibility criteria. The included study references were cross searched for additional studies.

Statistical Analysis

Categorical variables were presented as percentages and continuous variables were presented as medians with interquartile range. Hazard ratios (HR), odds ratios (OR), and mean differences were represented with corresponding Forest plots comparing patients with severe lymphopenia and no severe lymphopenia which were reported with 95% CI and p-value <0.05 was considered statistically significant. The Forest plot for HR and mean difference was plotted by Generic inverse variance method, OR by Mantel-Haenszel method and p-value from the Z-test to examine whether the pooled estimate of effect is statistically significant. The random-effects model described by Der Simonian and Laird was used for analysis. Study heterogeneity was assessed using the inconsistency index (I^2-statistic) with values of 0 to 30%, 31 to 60%, 61 to 75%, and 76 to 100% indicating low, moderate, substantial, and considerable heterogeneity, respectively. Review Manager Version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for the analysis.
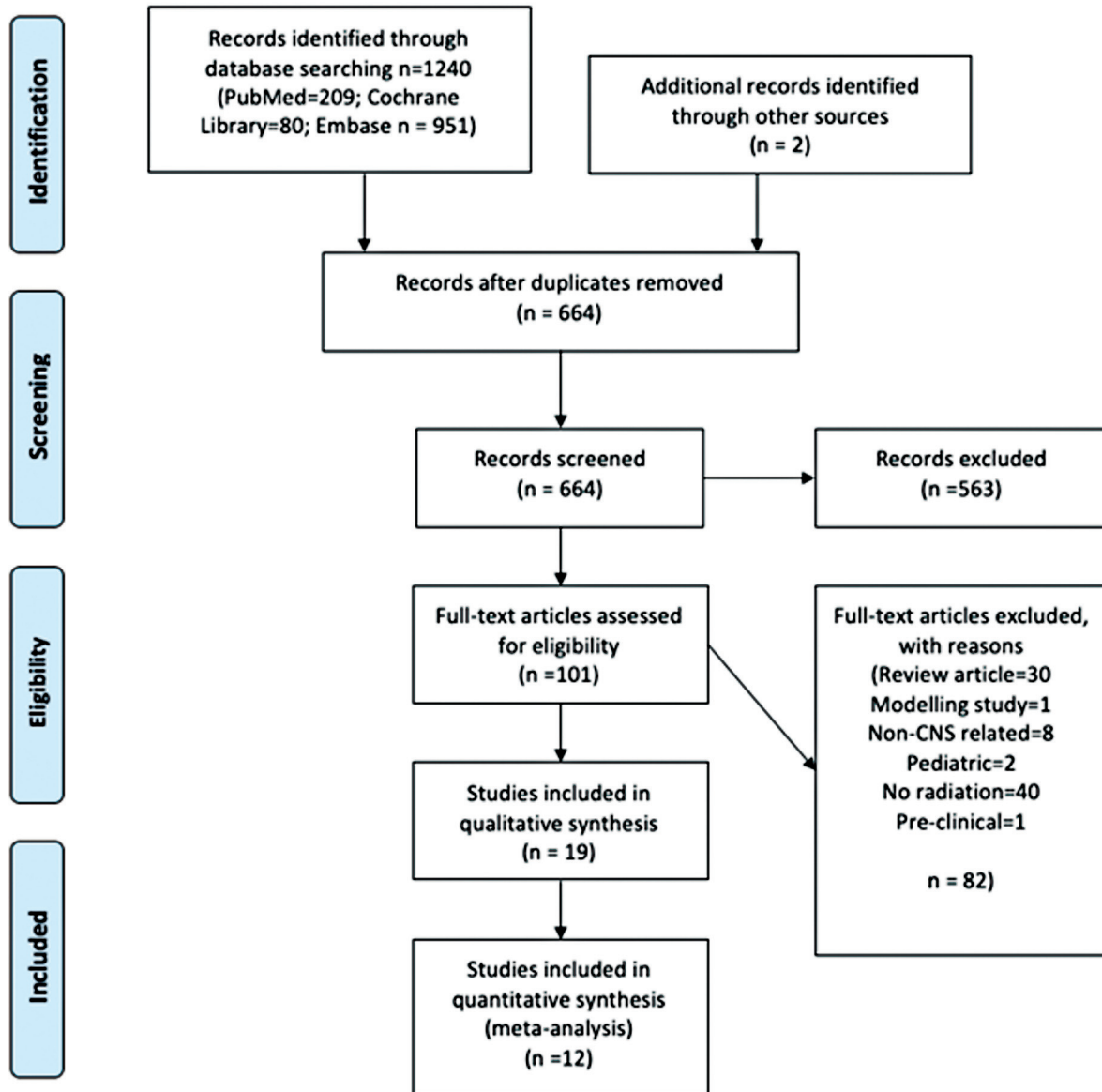
PRISMA 2009 Flow Diagram

Fig. 1 PRISMA flow diagram depicting the search strategy in the systematic review literature search.

Search Results

The systematic search of literature resulted in 1,240 articles of which 101 articles underwent complete review. Nineteen studies were included in the final systematic review and 12 studies were included in the meta-analysis. ►Table 1 summarizes the details of studies reporting on radiation-related lymphopenia outcomes in HGG.

Results

Pooled Analysis of Outcomes of Radiation-Related Lymphopenia

Twelve studies reported the rates of severe lymphopenia. The odds of developing severe lymphopenia are 0.39 (95%

CI: 0.19, 0.81, $I^2 = 94\%$, $p = 0.01$). Four studies reported on the survival outcomes in patients with severe lymphopenia. The patients with severe lymphopenia were at increased risk of death with a pooled HR = 2.19 (95% CI: 1.70, 2.83, $I^2 = 0\%$, $p < 0.00001$) compared to patients with no severe lymphopenia. The mean difference in survival between patients with severe lymphopenia and no severe lymphopenia is −6.72 months (95% CI: −8.95, −4.49, $I^2 = 99\%$, $p < 0.00001$), with a 6.72 month better mean survival in the no severe lymphopenia group. The Forest plots of the above reported outcomes are shown in ►Fig. 2A–C with corresponding funnel plots shown in **Supplementary Material S1** (available online only).

Table 1 Summarizes the details of studies reporting on radiation related lymphopenia outcomes in high-grade glioma

First author, Year	Study design	No. of patients	Definition of lymphopenia	Dosimetric correlation	Results
Ishikawa et al 2010 Japan	Retrospective	28	CTC version 3.0		Pre RT/CT lymphocyte count <1,200/mm^3 predictive of severe lymphopenia during RT/CT
Grossman et al 2011 United States	Prospective-	96	CD4 count <200 cells/m^3		CD4 count at 2 mo< 200 cells/mm^3 had shorter median survival (13.1 m vs. 19.7) ($p = 0.002$)
Huang et al 2015 United States	Retrospective	183	TLC of <500/mL	Higher Brain V25Gy> 56% increased risk of severe lymphopenia	Worse overall survival in severe lymphopenia (median: 12.5 vs. 20.2 mo, $p< 0.001$). Female sex, older age, lower baseline TLC significant predictors of ASL
Mendez[45] 2017 United States	Retrospective	72	CTCAE V 4.03		TLC <500 cells/mm^3 at 2 mo had a shorter survival
Campian et al[46] 2017 United States	Prospective	20	CTCAE, CD4< 200		
Rudra et al 2018 United States	Retrospective	217	<500 cells/µL	Brain V25Gy was an independent predictor of ASL	
Byun et al 2019 Korea	Retrospective	336	TLC of <500/µL	IMRT and smaller PTV are associated with decreased severe lymphopenia	
Hui et al 2019 United States	Retrospective	319	TLC of <500/µL		High dose dexamethasone (>2 mg/d) was associated with higher rates of ASL and worse OS
Ye et al 2019 China	Retrospective	148	PCL < 500/µL	WBD$_{max}$ ≥34 Gy WBD$_{min}$ ≥2 Gy Hypothalamus D$_{max}$ ≥56 Gy associated with increased risk of severe lymphopenia	Older age, high-grade glioma, HT D$_{max}$, WBD$_{min}$, WBD$_{max}$ associated inferior survival
Lee et al[47] 2020 Korea	Retrospective	186	TLC< 1,000/µL		Female sex, dexamethasone > 2 mg/d is associated with acute lymphopenia
Mohan et al 2021 United States	Prospective	84	ALC< 500/µL	Higher WBV20 strongest predictor of G3 lymphopenia	Female, photon therapy, baseline ALC associated with severe lymphopenia

Abbreviations: ALC, absolute lymphocyte count; PCL, plasma cell leukemia; PTV, planning target volume; TLC, thin-layer chromatography; WBD, whole brain dose.

Impact of Baseline ALC Value on the Incidence of Lymphopenia

Mohan et al[11] found that baseline ALC was the strongest predictor of G3 + lymphopenia (OR 0.18, 95% CI 0.05⎼0.51, $p = 0.003$). The baseline ALC values in the G3 + L arm was $1.3 \pm 0.6 \times 103/µL$ and $1.7 \pm 0.5 \times 103/µL$ in the no lympho-penia arm ($p < 0.001$). Huang et al[12] also revealed lower baseline thin-layer chromatography (TLC) is a predictor of acute severe lymphopenia (ASL) (OR: 0.92; 95% CI: 0.87–0.98, $p = 0.009$), however, the optimal threshold was not established. Ishikawa et al[13] showed similar results with a lower peripheral lymphocyte count before radiotherapy and temozolomide of <1,200/µL was associated with severe lymphopenia ($p < 0.032$).

A

Study or Subgroup	Severe lymphopenia Events	Total	No severe lymphopenia Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Byun 2019	118	336	218	336	9.4%	0.29 [0.21, 0.40]
Campian 2017	4	20	16	20	6.6%	0.06 [0.01, 0.29]
Ellsworth 2014	9	11	2	11	5.1%	20.25 [2.32, 176.79]
Grossman 2011	38	96	58	96	9.0%	0.43 [0.24, 0.77]
Huang 2015	53	183	130	183	9.2%	0.17 [0.11, 0.26]
Hummel 2015	14	27	13	27	7.9%	1.16 [0.40, 3.37]
Ishiwaka 2010	14	28	14	28	8.0%	1.00 [0.35, 2.85]
Maraka 2019	44	85	41	85	9.0%	1.15 [0.63, 2.10]
Mendez 2016	15	72	57	72	8.6%	0.07 [0.03, 0.15]
Mohan 2020	26	84	58	84	8.9%	0.20 [0.10, 0.39]
Rudra 2018	41	217	176	217	9.2%	0.05 [0.03, 0.09]
Wakabayashi 2018	71	121	50	121	9.1%	2.02 [1.21, 3.36]
Total (95% CI)		**1280**		**1280**	**100.0%**	**0.39 [0.19, 0.81]**
Total events	447		833			

Heterogeneity: Tau² = 1.41; Chi² = 173.02, df = 11 (P < 0.00001); I² = 94%
Test for overall effect: Z = 2.55 (P = 0.01)

B

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Byun 2019	0.892	0.2762	22.2%	2.44 [1.42, 4.19]
Grossman 2011	0.6881	0.2291	32.2%	1.99 [1.27, 3.12]
Lee 2020	0.7324	0.2226	34.1%	2.08 [1.34, 3.22]
Mendez 2016	1.0152	0.3841	11.5%	2.76 [1.30, 5.86]
Total (95% CI)			**100.0%**	**2.19 [1.70, 2.83]**

Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 6.04 (P < 0.00001)

C

Study or Subgroup	Severe lymphopenia Mean	SD	Total	No severe lymphopenia Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Byun 2019	18.2	1	118	22	1	218	20.3%	-3.80 [-4.02, -3.58]
Grossman 2011	13.1	1	38	21.7	1	58	20.2%	-8.60 [-9.01, -8.19]
Huang 2015	12.5	1	53	20.2	1	130	20.2%	-7.70 [-8.02, -7.38]
Hui 2019	13	1	3	19.5	1	89	19.3%	-6.50 [-7.65, -5.35]
Mendez 2016	4.6	1	15	11.6	1	57	20.0%	-7.00 [-7.57, -6.43]
Total (95% CI)			**227**			**552**	**100.0%**	**-6.72 [-8.95, -4.49]**

Heterogeneity: Tau² = 6.39; Chi² = 640.66, df = 4 (P < 0.00001); I² = 99%
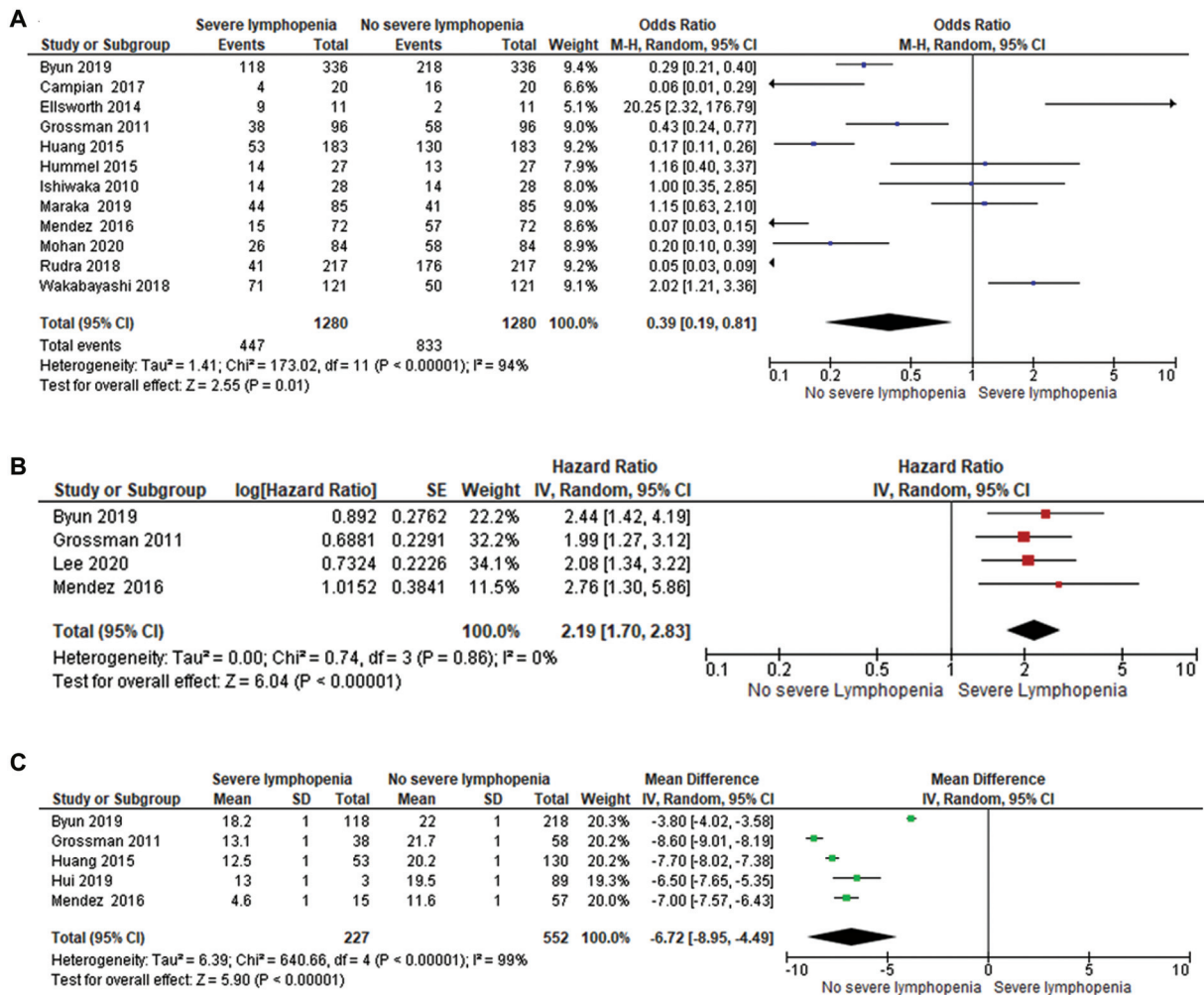Test for overall effect: Z = 5.90 (P < 0.00001)

Fig. 2 (A) Forest plot of odds ratio of developing severe lymphopenia. (B) Forest plot of pooled hazard ratios of overall survival between patients with severe lymphopenia and no severe lymphopenia. (C) Forest plot of mean difference between patients with severe lymphopenia and no severe lymphopenia. The Forest plot for HR and mean difference was plotted by generic inverse variance method; OR by Mantel-Haenszel method and p-value from the Z-test to examine whether the pooled estimate of effect is statistically significant. CI, confidence interval.

Impact of Steroid on the Incidence of Lymphopenia

The commonly used steroid during the treatment course of brain tumors is dexamethasone. Dexamethasone has an innate property to reduce lymphocyte count. Hui et al[14] performed retrospective study on 319 patients to analyze the impact of dexamethasone on lymphopenia. It was found that high dose dexamethasone (>2 mg/d) was independently associated with significantly higher ASL. Similar results were seen in the study by Lee et al, which also showed dexamethasone >2 mg/d during chemoradiation and till 4 weeks after completion was associated with lymphopenia (HR: 2.85, $p = 0.032$). On the contrary, the study by Mohan et al, Huang et al, and Rudra et al[15] did not find any association between lymphopenia and steroid use.

Impact of Sex on Incidence of Lymphopenia

In a study by Huang et al, female sex was a significant predictor of ASL, with a higher risk of G3 + L. The ASL at 3 months, for females with brain V25 ≥56Gy, is 56 versus 25% for males and for females with V25 <56% was 39 versus 10% for males, respectively. Similar results were seen in the study by Mohan et al where women had higher rates of G3 + L, 51 versus 15% ($p < 0.001$), and multivariate analysis revealed female gender as a significant predictor of G3 + L. Lee et al also found female sex was independently associated with lymphopenia ($p = 0.003$). Rudra et al showed women to be an independent predictor of ASL. Byun et al[16] also had similar results with female sex being an independent factor associated with increased ASL.

Impact of Dosimetric Parameters and Incidence of Lymphopenia

Impact of Target Volumes on Lymphopenia

Byun et al showed a direct correlation with planning target volume (PTV) size and ASL. Larger PTV volume was independently associated with increased risk of ASL ($p = 0.042$) and use of IMRT was independently associated with decreased

Table 2 Prognostic factors associated with increased risk of severe lymphopenia

Photon (39%) treatment as compared to proton (14%) therapy
Larger PTV
3 DCRT (37%) as compared to IMRT (20%)
Higher brain V 25 >40 Gy
High whole brain mean dose (WBMD) >34 Gy
Higher whole brain minimum dose
Higher hypothalamus D_{max} ≥56 Gy
Female gender
Lower baseline TLC

Abbreviations: PTV, planning target volume; TLC, thin-layer chromatography.

risk of ASL ($p = 0.015$). The rate of ASL with PTV of <200 and >600 mL was 14 and 33% in IMRT as compared to 25% arm 53% in the 3DCRT arm, respectively. After propensity score matching the ASL in IMRT was 20.4 and 37.2% in the 3DCRT arm ($p = 0.005$).

Impact of Brain Dose on Incidence of Lymphopenia

In a phase II randomized study by Mohan et al with 84 patients, the Pearson correlation matrix showed whole brain mean dose (WBMD) and brain volumes V5-V30 were associated with risk of ASL. Multivariate logistic regression analysis showed brain V20 as a significant predictor for ASL ($p = 0.002$). The investigators developed a model for plan optimization which showed the risk of G3+ L could be restricted to 20% by limiting V20 to 32% for women and 58% for men. Rudra et al also showed a similar association, with higher brain V25 having a higher risk of ASL. Rate of ASL with V25< 40% was 12.6% compared with 35.7% for V25 >40% ($p = 0.01$). The study by Ye et al,[17] showed a positive correlation with high WBMD mean ($p = 0.006$), high WBMD mean >34 Gy ($p = 0.022$), and high hypothalamus maximum point dose ≥56 Gy ($p = 0.022$) with significantly increased risk of ASL. Retrospective analysis of 183 patients by Huang et al also showed higher brain V25 as the most significant predictor for ASL. Multivariable logistic regression analysis showed brainV25 <56% to be associated with lesser ASL ($p = 0.03$). V25 <56% has an ASL rates of 20 versus 38% if above 56% ($p = 0.006$).

Impact of Proton Therapy on the Incidence of Lymphopenia

Proton beam therapy has the unique nature to minimize the low dose bath to non-target tissue and thus reduces the integral dose. This may help to spare the circulating peripheral blood pool containing lymphocytes from radiation dose. In a study by Mohan et al, it was shown that G3+ lymphopenia was strongly associated with WBMD and brain V5-40. The proton therapy was able to reduce the WBMD ($p <0.001$) and brain V5-V30 significantly as compared to the photon group and was associated with a lower G3+ lymphopenia. The G3+ lymphopenia was lower in proton therapy (14%) as

compared to photon (39%) ($p = 0.024$). The decline in mean ALC from baseline over time was greater for photons, but recovery after treatment was at the same rate for both proton and photon. ►Table 2 provides a summary of the prognostic factors associated with increased risk of lymphopenia in Brain tumors.

Discussion

For high-grade glioma, surgical resection and adjuvant chemoradiation followed by chemotherapy for 6 to 12 cycles remains the standard of care. Despite recent advances in treatment modality, there was no significant improvement in outcomes for high-grade glioma. Recent studies have shown that radiation-induced lymphopenia is correlated with poor prognosis and inferior survival outcomes in patients with HGG. Similar results have been seen in other solid tumors such as cancers of the esophagus,[18] lung,[19] breast,[20] pancreas,[21,22] head and neck[23] and pelvis.[24,25] Multiple rationales have been proposed for radiation-induced lymphopenia or depletion of T cells. Some of these are irradiation of bone marrow, thymic irradiation, and irradiation of a circulating pool of lymphocytes. For brain tumors with limited radiation fields, the bone marrow and thymus are not in the irradiated area, and thus both these reasons do not hold responsible for any lymphopenia seen in high-grade gliomas. Given the fact that in gliomas we have historically moved away from whole brain or hemi brain irradiation to small margins as well as evolution of IMRT for radiation fields, the degree of radiation dose spill off to the skull bone marrow may be minimal to cause significant lymphocyte depletion. However, irradiation of circulating pool of lymphocytes can be proposed for severe lymphopenia,[26] thereby influencing the tumor infiltrating lymphocytes (TILs).

Tumor cells can be attached by the host immune system in a process called immunological surveillance. The brain was considered immune privileged because of blood–brain barrier,[27] and tumor cells can proliferate without any resistance from the immune system. With newer studies the brain is no longer considered as immune-privileged. It is considered that immune cells can traverse through epithelial layer of choroid plexus, through endothelial fenestration in meninges or directly through the meningeal blood vessels. The glioma tumor microenvironment consists of tumor cells, immune cells/lymphocytes, endothelial cells, and cytokines. The TIL is mainly composed of CD8+ cytotoxic T lymphocytes (CTLs), CD4 + T helper cells, regulatory T cells (Tregs), and other immune cells including glioma infiltrating microglia and macrophage (GAMs), natural killer) cells, myeloid-derived suppressor cells (MDSCs), and dendritic cells.[6,28] In the initial phase of tumor development immune system is capable of identifying and eliminating the cancer cells. But in later phase by immunoediting and release of immunosuppressive agents by tumor cells the cancer cells escape the immune surveillance mechanism.

In high-grade glioma an immuno-suppressive tumor microenvironment is created by high levels of Treg cells,[29,30]

inhibitory cytokines,[31] checkpoint molecules,[32] and lack of T-cell activation. GAMs and MDSCs are reported in higher density in HGGs and have the ability to attract Treg lymphocytes and correlate inversely with survival. CD4+ cells are associated with tumor grade with 39% in WHO grade II tumors to 73% in grade III and 98% in grade IV tumors.[33] In glioblastoma tumor infiltration with T cells (CD3+, CD8+) is associated with increased survival ($p = 0.027$) and is independent of age, postoperative status, and MGMT promoter methylation status.[34] On the other hand, Tregs are immunosuppressive cells which have an important role in tumor recurrence and poor survival.[29,35] Treg is not seen in normal brain but seen in increased number in the tumor microenvironment of gliomas.[36] Tregs act through various direct and indirect mechanisms in the downregulation of T lymphocytes (CD4+, CD8+). There is higher expression of Tregs in GBM with a mean of 24.7% Treg among the glioma-infiltrating lymphocytes and these were absent in control brain specimen ($p < 0.01$).[37] The fraction of Tregs in peripheral blood was 2.63 times higher than control group ($p = 0.004$) and patients with elevated Treg fraction had significant CD4+ T cell proliferative dysfunction ($p < 0.0001$).[29] The immune checkpoint programmed cell death ligand 1 (PD-L1) causes direct inhibition of TIL and thereby increased expression of PD-L1 correlates with poor outcome.[38,39] In glioblastoma PD-L1 expression is seen in 2.8 to 32.2% of tumors.[40,41] Studies are ongoing with nivolumab and pembrolizumab (checkpoint inhibitors) in primary and recurrent GBM. Similarly, dendritic cell vaccines have been tried in GBM treatment, which showed an increase in survival from 15.7 to 35.9 months. Recent analysis showed a positive objective response of 15.6% with DC vaccine in patients with high-grade glioma.[42]

Systemic T-cell number and function is depleted in GBM. 24.7% of treatment naïve GBM patients had lymphopenia compared to the control group (lymphocyte count< 1,000 cells/μL). There was a significant reduction approximately 15% in both CD4+ and CD8+ T cell counts (CD4 <200 cells/μL) in peripheral blood pool.[43] In study by Grossman et al,[44] about 40% of patients had CD4+ count less than 200 cells/mm^3 and patients with CD4+ count <200 cells/mm^3 at 2 months after chemoradiation had shorter survival ($p = 0.002$) and early death from tumor progression. The adjusted HR for death was 1.66 for the patient with ASL.

Pooled analysis of the impact of severe lymphopenia on overall survival in our study showed that patients with severe lymphopenia were at increased risk of death with HR of 2.19 when compared to patients with no severe lymphopenia. The mean survival was increased in no severe lymphopenia group by 6.72 months. By identifying the factors influencing severe lymphopenia and modifying them to reduce the incidence of ASL can result in improved survival outcomes. We found various clinical and treatment-related factors influencing ASL. Understanding dosimetric parameters that can predict the incidence of severe lymphopenia can assist during plan optimization to reduce the impact on lymphopenia and thereby the outcomes.

A larger PTV and photon beam therapy was significantly associated with higher rates of severe lymphopenia. IMRT showed significantly lesser lymphopenia compared to 3DCRT. Higher brain V25Gy dose and higher WBMD were correlated with ASL. Low dose brain volumes V5-V30 were associated with severe lymphopenia. Apart from the whole brain dose, a higher hypothalamus dose was significantly associated with lymphopenia and had an impact on inferior overall survival in a single study. Use of high dose steroids also correlated with significantly higher severe lymphopenia, but studies were conflicting. IMRT has the ability to sculpt the radiation to the given target of interest and hence may reduce the high dose regions but the low dose spill off may be more compared to 3DCRT. Given the fact that higher dose regions V25Gy and WBMD are the factors predictive of lymphopenia, IMRT can lessen the propensity for lymphocyte depletion.

This study is not without limitations. The analysis included retrospective studies, which can bring bias and heterogeneity among the studies present. There was no clear data on the impact of chemotherapy on lymphopenia which might be a potential confounding variable as well as there was not enough data on the impact of hypofractionated radiotherapy on lymphopenia outcomes. The impact of chemotherapy such as TMZ on lymphopenia and survival outcomes would not be assessed from the data available. The studies also have significant heterogeneity which is again a limitation of the study. But this present study forms the first meta-analysis conducted on the effect of lymphopenia in high-grade gliomas. Future randomized prospective studies can be conducted, taking into consideration various predictive factors mentioned in the study.

Conclusion

Radiation-induced severe lymphopenia was associated with poor overall survival and increased risk of death in patients with HGGs. Photon therapy, IMRT compared to proton therapy, larger PTV, higher brain dose, higher hypothalamus dose, and female gender were associated with increased risk of severe lymphopenia. Severe lymphopenia and reduced immune cells (CD4+, CD8+) following chemoradiation correlated with worse outcomes. These findings, if validated, may offer an avenue to explore to improve outcomes in this patient population.

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