# A systematic review on the comparison of the safety and efficacy of temozolomide and radiotherapy along with another drug combination in the treatment of glioblastoma multiforme

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
Brac University
March, 2022

## Declaration

It is hereby declared that

1. The thesis submitted is my original work while completing my degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

**Student's Full Name & Signature:**

**Shamima Zerin Chowdhury**
ID: 17346018

# Approval

The thesis/project titled "A systematic review on the comparison of the safety and efficacy of temozolomide and radiotherapy along with another drug combination in the treatment of glioblastoma multiforme" submitted by Shamima Zerin Chowdhury (17346018) of Summer, 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 30 March, 2022.

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## Ethics Statement

This is to certify that this project titled "A systematic review on the comparison of the safety and efficacy of temozolomide and radiotherapy along with another drug combination in the treatment of glioblastoma multiforme" is submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.) from the Department of Pharmacy, Brac University constitutes my work under the supervision of Mohd. Raeed Jamiruddin, Assistant Professor, School of Pharmacy, Brac University and I have given appropriate credit where I have used language, ideas or writings of another. This project does not involve any human or animal trials. No animals were used or harmed in this project.

## Abstract

Glioblastoma multiforme is one of the most dangerous primary brain tumors, with a poor prognosis even after vigorous treatment. Neurosurgical enhancements, the discovery of potent chemotherapeutic medicines, developments in radiation and innovations in targeted delivery have all contributed to an increase in the extension of survival in patients. This systematic review incorporates 12 clinical trials and presents a concise evaluation of studies where temozolomide, radiotherapy along with other drugs are used in collaboration to treat glioblastoma and efficacy outcomes, rate of tolerability, and patient life expectancy are recorded, investigated, and reviewed to discover which combination treatment leads to an extended survival time or minimal side effects in patients. High dose radiation and TMZ had the longest OS and PFS with moderate toxicity. (Temozolomide+ Radiation+ 06 Benzylguanine + Carmustine + Plerixafor) also had the longest median OS and the fewest adverse effects, indicating that the study was effective. Although it considerably increased patient survival, (TMZ+ radiation + TSC) had the lowest amount of toxicity. (Temozolomide+ irinotecan+ bevacizumab) showed the highest rate of side effects, despite having a good OS and PFS.



**Keywords:** Glioblastoma multiforme; Temozolomide; Radiotherapy; Overall survival; Progression-free survival; Vascular endothelial growth factor receptor

## Dedication

Dedicated to Almighty Allah who gave me the strength and patience to finish this work.
My dedication also goes to my beloved parents.

## Acknowledgment

All honors belong to the Almighty for strengthening me with patience to complete my project work along with the courses necessary to complete the Bachelor of Pharmacy (B.Pharm) program.

I am grateful to my respected supervisor, Mohd. Raeed Jamiruddin, Assistant Professor, Department of Pharmacy, BRAC University for supporting me continuously and giving me the motivation to complete the project paper. Without his support, it was not possible to finish my project work. I am also grateful to Prof. Dr. Eva Rahman Kabir, Honorable Chairperson, Department of Pharmacy, and BRAC University for giving me the support and opportunity to complete my project work and B.Pharm program.

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## List of Acronyms

| | |
|---|---|
| GBM | Glioblastoma Multiforme |
| PFS | Progression-free survival |
| OS | Overall survival |
| EGFR | Epidermal growth factor receptor |
| TGFR | Transforming growth factor receptor |
| MGMT | O6 methylguanine DNA methyltransferase |
| TMZ | Temozolomide |
| WHO | World Health Organization |
| RTK | Receptor tyrosine kinase |
| P13K | Phosphoinositide 3-kinase |
| RB | Retinoblastoma |
| RAS | Rat sarcoma |
| RT | Radiotherapy |
| CNS | Central nervous system |
| VEGFR | Vascular endothelial growth factor receptor |

| | |
|---|---|
| mTOR | Mammalian target of rapamycin |
| PDGFR | Platelet-derived growth factor receptor |
| HR | Hazard ratio |
| EGFR | Endothelial growth factor receptor |
| PKC | Protein kinase C |
| MRI | Magnetic resonance imaging |
| RCT | Randomized controlled trials |
| BEV | Bevacizumab |
| TSC | Trans sodium crocetinate |
| SOC | Standard of Care |
| Te | Temozolomide |
| Ra | Radiation |
| Be | Bevacizumab |
| Ve | Vendatinib |
| Ev | Everolimus |
| Iri | Irinotecan |

| | |
|---|---|
| PPX | Paclitaxel Poglumex |
| O6 Be | O6 Benzylguanine |
| Ca | Carmustine |
| Ple | Plerixafor |
| CT | Computed tomography |
| HRQOL | Health-related quality of life |
| mTORC1 | Mechanistic target of rapamycin C1 |
| FDA | Food and Drug Administration |
| DD | Dose-dense |
| mLST8 | Mammalian lethal with SEC13 protein 8 |
| HIF-1α | Hypoxia inducible factor 1-alpha |
| TH-1 | Type-1 helper cell |
| FLT-PET | Fluorothymidine F 18 positron emission tomography |
| NFkB | Nuclear factor kappa B |
| IgG1 | Immunoglobulin G1 |

| | |
|---|---|
| PCV | Packed cell volume |
| CR | Complete response |
| PR | Partial response |

# Chapter 1

# Introduction

The most prevalent primary malignant brain tumors are glioblastomas and malignant gliomas, which have an annual incidence of 5.26 per 100,000 people or 17,000 new diagnoses each year. These tumors are often associated with a poor prognosis and a low quality of life. (Omuro & DeAngelis, 2013). In glioblastoma, mutations in the (RAS)/phosphoinositide 3-kinase (PI3K), receptor tyrosine kinase (RTK)/rat sarcoma, retinoblastoma protein (RB) and p53 genes are prevalent. Glioblastoma is commonly treated with surgery, radiation, and alkylating chemotherapy. (Wirsching et al., 2016). In the Who classification of primary brain tumors, gliosarcoma and giant cell glioblastoma are two rare histopathologic variations of glioblastoma (Louis et al., 2007). In freshly detected and presumably reoccurring glioblastoma, methylation of the MGMT promoter anticipates success from temozolomide chemotherapy (Wick et al., 2012; Weller et al., 2015b; Malmstrom et al., 2012; Hegi et al., 2005;). Glioblastoma is being treated with a maximum-radical surgical resection of the tumor followed by postoperative radiation. Temozolomide and radiotherapy used together may reduce active clonogenic cells more effectively than radiotherapy alone. During human glioma cell cultures, synergic action of radiotherapy and temozolomide was observed. Adjunctive temozolomide to radiotherapy may delay the recurrence and prolong the progression-free period. (Wang & Feng, 2020). Glioblastoma advances in molecular biology are being quickly converted into novel therapeutic trials, using the increased genomic, epigenetic, transcriptional, and proteomic characterization of glioblastomas as well as host variables such as the brain microenvironment and immune system interactions. TGF receptors and downstream pathways, angiogenesis, modulation of cancer stem-like cells, cell cycle regulation, oncolytic viruses, new radiotherapy techniques, and immunotherapy, including vaccines and immune checkpoint modulation (e.g., programmed cell death 1 and cytotoxic T-lymphocyte antigen 4) are all being studied (Thomas

et al., 2014). Glioblastoma is the most common type of malignant glioma, accounting for 82% of cases, and is defined histologically by high cellularity and mitotic activity, vascular growth, and necrosis. Glioblastoma and other malignant gliomas are extremely invasive, invading the surrounding brain parenchyma, although they are usually restricted to the CNS and do not spread (Omuro & DeAngelis, 2013). The appearance of a patient with a newly diagnosed GBM varies widely depending on the tumor's size and location, as well as the anatomic components of the brain involved (Lobera, 2015; Young et al., 2015). Patients frequently complain of headaches and localized or progressive neurologic impairments as a result of elevated intracranial pressure. A seizure could be the first manifestation in up to 25% of patients, and a seizure may develop over time in the disease in up to 50% of individuals (Perry et al., 2006; Schiff et al., 2015). The patient normally waits four weeks following an acceptable surgical resection for the craniotomy incision to recover before initiating therapy. Radiotherapy after the operation itself was the standard treatment for GBM until 2005 when the conclusions of a pivotal phase III trial altered the field. In this experiment, external beam radiation plus simultaneous TMZ treatment (referred to as Stupp regimen) has been shown to be more efficacious than radiation monotherapy (Stupp et al., 2005). Participants who underwent TMZ and RT lived an average of 14.6 months, opposed to 12.1 months for those who only obtained RT. Prolonged survival was observed for the cohort where temozolomide and RT were administered together (Stupp et al., 2009). Regular administration of concomitant temozolomide at a dose of 75 mg/m2 as subsidiary to radiotherapy followed by up to six cycles of temozolomide at 150–200 mg/m2 on 5 of out 28 days prolonged median OS compared to radiotherapy alone (14.6 versus 12.1 months; HR, 0.63; 95% CI, 0.52–0.75, $p<0.001$) (Stupp et al., 2005), but benefit from temozolomide was mainly restricted to patients with MGMT promoter methylation (Hegi et al., 2005). Multiple drug combinations associated with temozolomide and radiotherapy are being investigated to analyze their safety profile and

effectiveness for the treatment of patients having glioblastoma multiforme. This systematic review and meta-analysis aimed to assess the efficacy, toxicity and safety of different drug combinations incorporating radiation and temozolomide in the treatment of glioblastoma. When numerous medications are combined with the TMZ chemotherapy regimen, distinct outcomes and effects are obtained. This study assembles various clinical trials involving TMZ radiotherapy combination treatment to provide an extensive assessment of comparison to ascertain whether temozolomide and radiotherapy alone are efficacious in the treatment of glioblastoma, or whether they are more impactful when other drugs are added to TMZ and RT.

# Chapter 2

# Glioblastoma multiforme

## 2.1. Who grading and classification of glioblastoma:

Who divides gliomas into grades I through IV based on the degree of malignancy established by histological criteria. Grade I gliomas are low-proliferative potential tumors that can be cured with surgery, but grade II through IV gliomas are extremely aggressive and metastatic. Glioblastoma multiforme (GBM) is the most deadly, expansive, and homogeneous form of cancer, and it is classified as Grade IV by the World Health Organization (Louis et al., 2007; Jovčevska et al., 2013).

## 2.2. Current treatment standard of glioblastoma:

Patients with GBM are currently treated with substantially safe excision, concomitant radiation treatment (RT) to the resection cavity, and chemotherapy (with temozolomide (TMZ), supplemented with adjuvant TMZ). The median survival time after surgical resection is nearly 6 months. Surgical resection and RT together increase median survival to 12.1 months. The use of TMZ increases the median survival time to 14.6 months.

## 2.3. Epidemiology of glioblastoma:

Progressive gliomas are the third cause of cancer deaths in people aged 15 to 34 years old, accounting for 2.5 percent of all cancer-related deaths (Salcman, 1990). It can strike at any age, but it is most common between the ages of 55 and 60 (Ohgaki and Kleihues, 2005). Even though, GBM is a rare tumor with a worldwide prevalence of less than 10 per 100,000 people, its dismal prognosis, with a survival rate of 14-15 months following diagnosis, makes it a major public health hazard (Iacob & Dinca, 2009; Thakkar et al., 2014). Few research has demonstrated that blacks are less susceptible to developing GBM, while the incidence of GBM is higher in Whites, Latinos and Asians (Iacob and Dinca, 2009).

## 2.4. List of molecular targeted agents used in glioblastoma:

**Table: Molecular targeted agents used in glioblastoma**

| **Agent** | **Mechanism of action** | **Reference** |
|---|---|---|
| **EGFR inhibitors:** | | (Minniti et al., 2009) |
| Erlotinib | EGFR TKI | |
| BIBW-2992 | EGFR and HER2 inhibitor | |
| Cetuximab | EGFR blocker (monoclonal antibody) | |
| Gefitinib | EGFR TKI | |
| pelitinib | Irreversible EGFR inhibitor | |
| lapatinib | EGFR, Erb-2 TK | |
| **VEGFR inhibitors:** | | (Minniti et al., 2009) |
| Bevacizumab | VEGF Blocker (monoclonal antibody) | |
| Vendetanib | EGFR, HER2 inhibitor | |
| Sunitinib | VEGFR, PDGFR, c-Kit TKI | |
| Vatalinib | VEGFR-1, VEGFR-2, PDGFR | |
| mTOR inhibitors | | |

| | | |
|---|---|---|
| Everolimus | mTOR inhibitor | |
| Sirolimus | mTOR inhibitor | |
| Temsirolimus | mTOR inhibitor | |
| **PDGFR Inhibitors:** | | (Minniti et al., 2009) |
| Imatinib mesylate | PDGFR TKI, c-Kit, Bcr-Abl | |
| Tandutinib | PDGFR, FLT3 (FMS-like tyrosine kinase-3), c-Kit inhibitor | |
| **PKC inhibitor:** | | |
| Enzastaurin | PKC inhibitor | |
| **RAF-MEK-ERK inhibitor:** | | (Minniti et al., 2009) |
| Lonafarnib | Farnesyltransferase inhibitor | |
| Tipifarnib | Farnesyltransferase inhibitor | |
| **Integrins:** | | (Minniti et al., 2009) |
| Cilengitide | αvβ3 and αvβ5 integrin inhibitor | |

## 2.5. Advancements in surgeries:

Surgical procedures have shown substantial improvement. Preoperative diagnosis by pneumoencephalography raised suspicion of cancer, which had to be validated by histological examination in the pre-brain imaging (CT and MRI) era**.** Because it was regarded a palliative technique to alleviate intracranial pressure and extend life for a few months with surrender to the knowledge that the patient would die, neurosurgery of glioblastomas 60 years ago was rudimentary when contrasted to thorough dissection of benign brain tumors. Debridement of a tumor creates a reservoir for administration of targeted therapies for elimination of remaining tumor tissues and avoidance of resurgence, in addition to offering an acceptable sample for histological study and reduction of a mass to relieve elevated intracranial pressure. Glioblastoma can be treated with a variety of revolutionary approaches, including: anticancer medication delivery innovations, Chemotherapy delivery strategies that bypass the blood-tumor barrier, Chemotherapeutic sensitization, radiation advances, tumor growth inhibition, tumor local destruction, immune therapy, gene suppression, cell therapy, and gene therapy are some of the themes explored (Jain, 2018).

## 2.6. Radio-chemotherapy treatment for glioblastoma:

Chemoradiosensitization is a notion that has led to the use of combination radiation and chemotherapy**.** The US FDA has approved the use of TMZ in conjunction with radiation for the treatment of newly diagnosed GBM in adults on March 15, 2005. The median survival time for those who received (TMZ + radiotherapy) was 14.6 months compared to 12.1 months for those who underwent radiotherapy alone in a randomized trial of 573 individuals with GBM at various stages. In a previous Phase II clinical trial, individuals with newly diagnosed GBM who received TMZ in combination with radiation had a median survival time of 15.7 months**.**

In comparable research, patients with both initial and recurrent malignant gliomas who had postoperative TMZ radio-chemotherapy had a 4-year survival rate of 78 %. To use these multimodal treatments, the patient's health status and comorbidities must be considered. Continuous use of TMZ with concurrent radiation, on the other hand, is both medically beneficial and effective (Se, 2006). Modern RT has made great strides in its ability to administer highly conformal radiation doses that maximize therapeutic efficacy while limiting normal tissue destruction over the last few decades. Patients' overall survival has improved with the addition of concurrent and adjuvant TMZ, and the findings of trials examining hypofractionation with concomitant TMZ have allowed for intensive therapy in the elderly population without compromising the quality of life or treatment conformance. With the help of breakthroughs in neuroimaging and radiolabeled amino acids, modern treatment is going toward more target-specific demarcation consisting of smaller, more precise volumes (Mann et al., 2018).

## 2.7. Prevalence of symptoms in glioblastoma multiforme:

Glioblastoma patients experience a spectrum of disorders that have a detrimental impact on their quality of life. A total of 25 symptoms were discovered after a thorough investigation in a systematic review. Seizures (37%), cognitive deficits (36%), drowsiness (35%), dysphagia (30%), headache (27%), confusion (27%), aphasia (24%), motor deficits (21%), fatigue (20%), and dyspnea (20%) were the ten most common symptoms (IJzerman-Korevaar et al., 2018). GBM is characterized by headaches, neurologic deficits, disorientation, memory loss, behavioral issues and seizures. MRI, functional MRI, diffusion-weighted imaging, diffusion tensor imaging, perfusion imaging and positron-emission tomography can help with diagnosis and treatment response (Wen et al., 2008).

## 2.8. Chemotherapy in treating glioblastoma multiforme:

The approval of temozolomide, an alkylating drug, for newly diagnosed GBM has ushered in a new era of cytotoxic therapy for GBM. The nitrosoureas including carmustine and lomustine, platinum agents, etoposide, irinotecan, and the PCV combination are also all active agents (Alifieris & Trafalis, 2015). Sequential RT plus TMZ results in 14.6 months of median OS and 26.5% 2-year overall survival. Temozolomide is a successful treatment for recurrent GBM, and its efficacy can be improved by using a metronomic instead of a conventional schedule, and even a substantial daily average dose (>100mg/m2) (Chen et al., 2013). Lomustine and carmustine are two anticancer medicines employed for GBM treatment. These drugs are usually administered in the recommended dose and are characterized by rash, vomiting,lung fibrosis and prolonged bone marrow suppression(Green et al., 1983). For around 3 weeks, the wafers deliver BCNU topically. Even though they are quite safe, most centers avoid using them because of complaints of cerebral edema, cerebral infection, wound infection and seizures. Furthermore, changes in the blood-brain barrier make MRI interpretation questionable (Nagpal et al., 2012). As adjuvant chemotherapy, irinotecan, etoposide, and cisplatin have shown considerable efficacy in treating GBM. Anaplastic astrocytomas and oligodendrogliomas are routinely treated with the PCV regimen, which combines procarbazine, lomustine, and vincristine. In the treatment of recurrent GBM, PCV (procarbazine, lomustine, and vincristine) is not efficacious (Schmidt et al., 2006). Procarbazine is a monoamine oxidase inhibitor that has been linked to allergies and hypertension. Vincristine is a tubulin-binding vinca alkaloid that has been related to a jaw discomfort syndrome and maybe peripheral neuropathy after the first dose. (Glass et al., 1992).

# Chapter 3

# Methodology

## 3.1 Search Strategy

An extensive search was conducted through the years ranging from 2014 to 2021. Specific research dealing with temozolomide and radiation treatment techniques, efficacy outcomes, and undesirable effects associated with this regimen for glioblastoma multiforme patients were investigated and taken into account. Clinical trials (randomized controlled trials), meta-analysis, review articles and systematic review articles were included in the search, as well as papers published in English. Data and relevant information were also collected from PubMed, Google scholar and clinicaltrials.gov websites. The percentage of adverse effects of different drug combinations was taken from the "study results" portion of the trial. Keywords used in the search were: “Outcomes in the treatment of glioblastoma multiforme with temozolomide and radiotherapy”, “Temozolomide + Radiation”, “Temozolomide +radiotherapy + everolimus”, “Temozolomide + radiation + Vandetanib”, “Bevacizumab + Temozolomide + placebo + radiation”, “Bortezomib + radiation + temozolomide”, “Temozolomide + Radiotherapy + TSC”, “Temozolomide + PPX + radiation”, “High dose radiation + temozolomide”, “Temozolomide + bevacizumab + irinotecan”, “Radiation + dose-dense adjuvant temozolomide”, “Radiation + TMZ adjuvant erlotinib + bevacizumab”, “Temozolomide + Radiation+ 06 Benzylguanine + Carmustine + Plerixafor”, “Temozolomide + radiation + dose-dense TMZ+ cis retinoic acid”. Abstracts from prominent cancer conferences that appeared in PubMed search results were also taken into consideration. The reference lists of included trials and large systematic reviews were also examined for additional relevant trials. The ID number of the clinical trials that are incorporated in this study were NCT00553150,

NCT00441142, NCT00943826, NCT00998010, NCT01465347, NCT02805179, NCT00304031, NCT00200161, NCT00967330, NCT00720356, NCT00669669.

## 3.2 Inclusion Criteria

Inclusion criteria for this study included the following: (1) Glioblastoma multiforme patients, (2) Clinical trials (randomized controlled trials/single group assignment from phase I-III), meta-analysis and systematic reviews, (3) Patients who received Temozolomide and radiotherapy combination treatment for glioblastoma, (4) Patients exposed to several drug combinations associated with radiation and temozolomide, (5) Clinical trials that reported over-all survival rate (OS) and progression-free survival rate (PFS) from the beginning of therapy.

## 3.3 Exclusion Criteria

(1) Trials that did not provide outcomes for OS, PFS or time to progression were excluded from the study due to lack of sufficient information, (2) Completed studies that did not report any result were also excluded, (3) Only the most recent publication of a series published by the same institution in various years was incorporated in the analysis to eliminate the possibility of overlapping patients.

## 3.4 Selection of trials

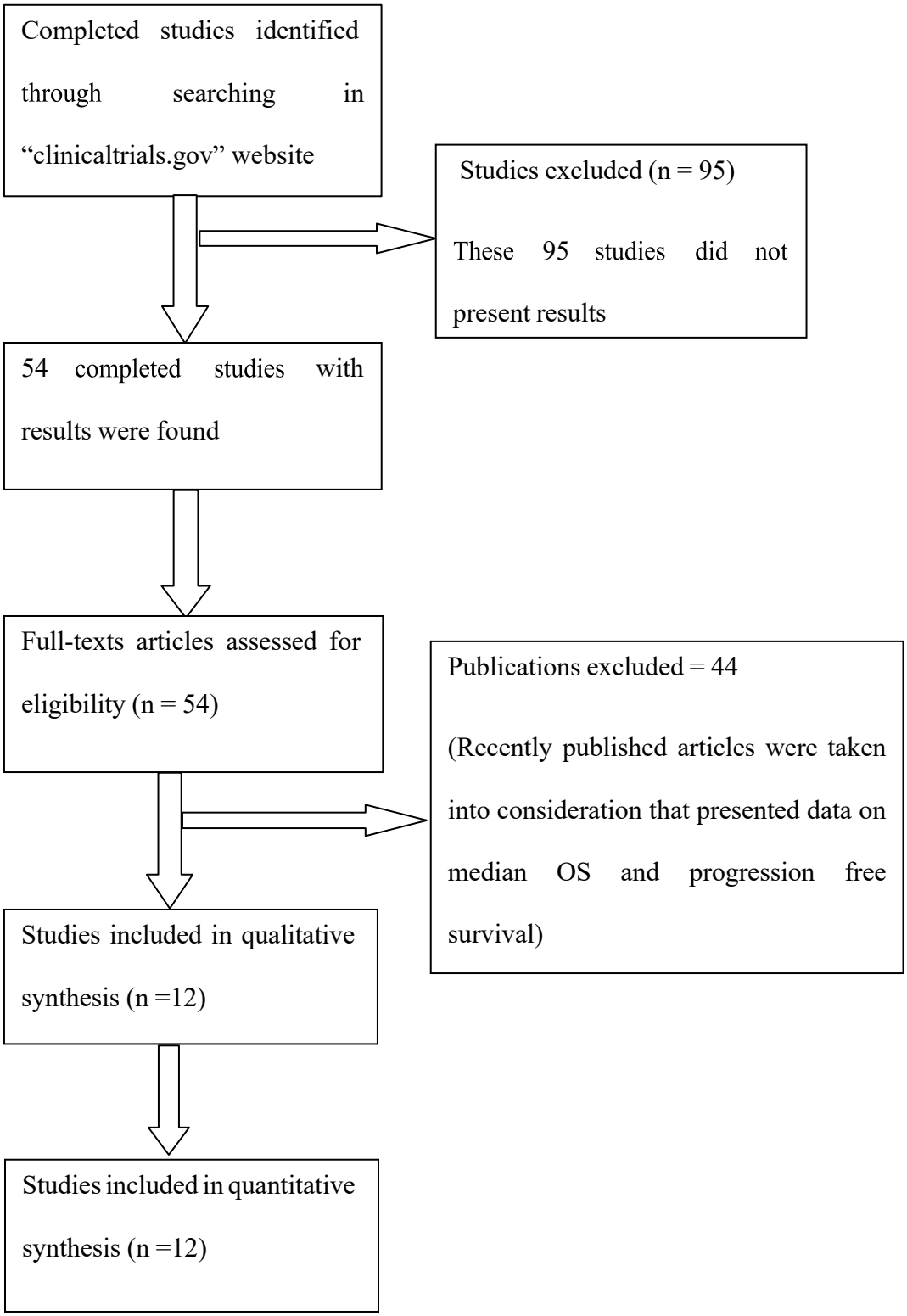
Total of 12 trials were finally selected for this study where several drug combinations are associated with temozolomide and radiation for glioblastoma management: (Temozolomide+ radiotherapy + everolimus, Bevacizumab + Temozolomide + placebo + radiation, Bortezomib + radiation + temozolomide, Temozolomide + radiation + Vandetanib, Temozolomide + Radiotherapy + TSC, Temozolomide + PPX + radiation, High dose radiation + temozolomide, Temozolomide + bevacizumab + irinotecan, Radiation + dose dense adjuvant temozolomide, Radiation + TMZ adjuvant erlotinib + bevacizumab, Temozolomide+Radiation+06

Benzylguanine + Carmustine + Plerixafor, Temozolomide + radiation + dose dense TMZ+ cis retinoic acid).

## 3.5 Endpoints

Summarization and cumulation of the over-all survival rate (OS), median progression-free survival rate (PFS) and adverse effects from different drug combinations from the published literature was the primary endpoint of this analysis. The secondary end point was to assess and contrast the efficacy of various combination treatments and analyze the reported toxicities and adverse effects associated with temozolomide and radiotherapy.

## 3.6 Flowchart for methodology:



# Chapter 4

# Result

Six of the twelve trials are randomized controlled trials (RCTs) (phase 2 or phase 3). This research includes two phase 3 randomized trials and ten phase 2 trials. Data on median OS and PFS were taken from research publications, while rates of side effects were gathered from clinical trials. The combination of (TMZ + radiation + TSC) has the lowest risk of side effects among the treatment combinations where a single medicine is delivered in conjunction with temozolomide and radiotherapy, with a rate of 17.86% adverse effects. Vandetanib, on the other hand, had the highest risk of adverse effects when used in combination with radiation and TMZ, at 63.41%. In combination with TMZ radiation, the drugs everolimus, bevacizumab, and paclitaxel resulted in 31.68%, 38.83%, and 31.71%, correspondingly. In contrast, when given with TMZ treatment, bortezomib caused only 20.83% of patients to experience significant adverse effects. There were almost no significant negative effects in the case of TMZ, dose-dense TMZ, and radiotherapy in the treatment regimens where only TMZ and radiotherapy were administered to people. While high dose radiation was used in addition to TMZ, there were 30.77% adverse events. Another radiation and TMZ trial indicated a 33.81% rate of side effects, indicating that the study with no major occurrences was more advantageous. In studies involving multiple medications with TMZ chemoradiation, the combination (TMZ + irinotecan + bevacizumab) had the highest rate of side effects, at 72.27%. The incidence of adverse events associated with radiation and TMZ adjuvant erlotinib with bevacizumab was 31.25%, which is significantly lower than the prior research. (Temozolomide+Radiation+06 Benzylguanine + Carmustin + Plerixafor) showed nearly zero significant side effects. This trial also has the longest median OS, which is 20 months. For this reason, it can be said that this study appeared to be more efficacious in comparison to other studies. The combination of (Radiation+ TMZ

adjuvant erlotinib+ bevacizumab) had the shortest median OS of 13.2 months, although the median PFS was 9.2 months for this regimen. In the case of high-dose radiation and TMZ, the longest median PFS was found to be 12 months. Although the addition of TSC to TMZ and radiation resulted in excellent results and a low percentage of adverse events, the median progression-free survival rate was not satisfactory, with a PFS of only 3.3 months, which was much shorter than other trials.

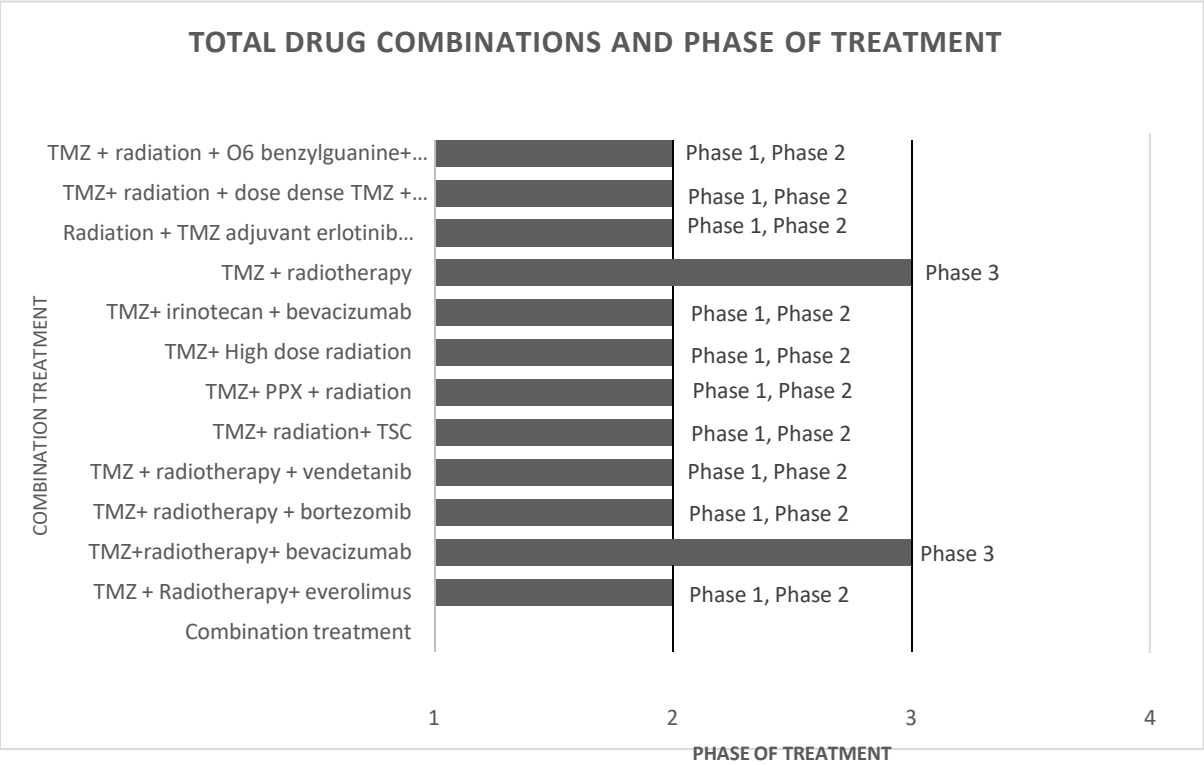



**Figure 1:** Total drug combinations and phase of treatment for glioblastoma multiforme

This graph represents the total combination of drugs that are included in this study. Here are 12 studies incorporating temozolomide & radiotherapy combination treatment. 9 studies are phase 2 studies and 2 of them are phase 3 studies.

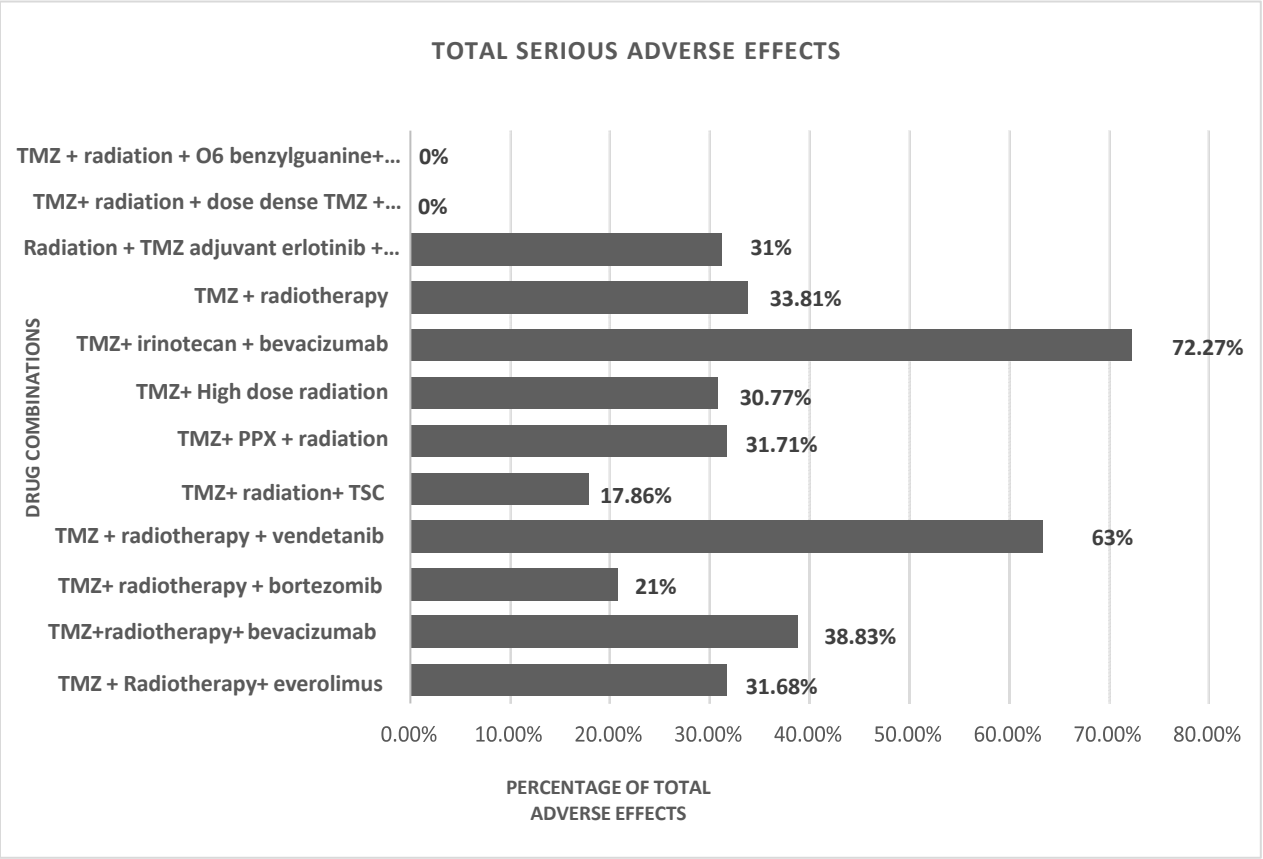



**Figure 2:** Total serious adverse events observed in patients receiving temozolomide and radiotherapy combination treatments.

The percentage of total serious adverse events in 12 studies is demonstrated in this graph. The highest serious adverse effects are observed in the study where temozolomide and radiation are combined with the drug irinotecan. Total 72.27% of adverse events are observed in the case of this treatment regimen. On the contrary, two studies have significantly no adverse events in patients. (TMZ+ radiation+ dose dense TMZ+ cis retinoic acid) and (TMZ+radiation+O6 benzylguanine+ carmustine+ Prelixafor) demonstrated 0% of adverse effects.

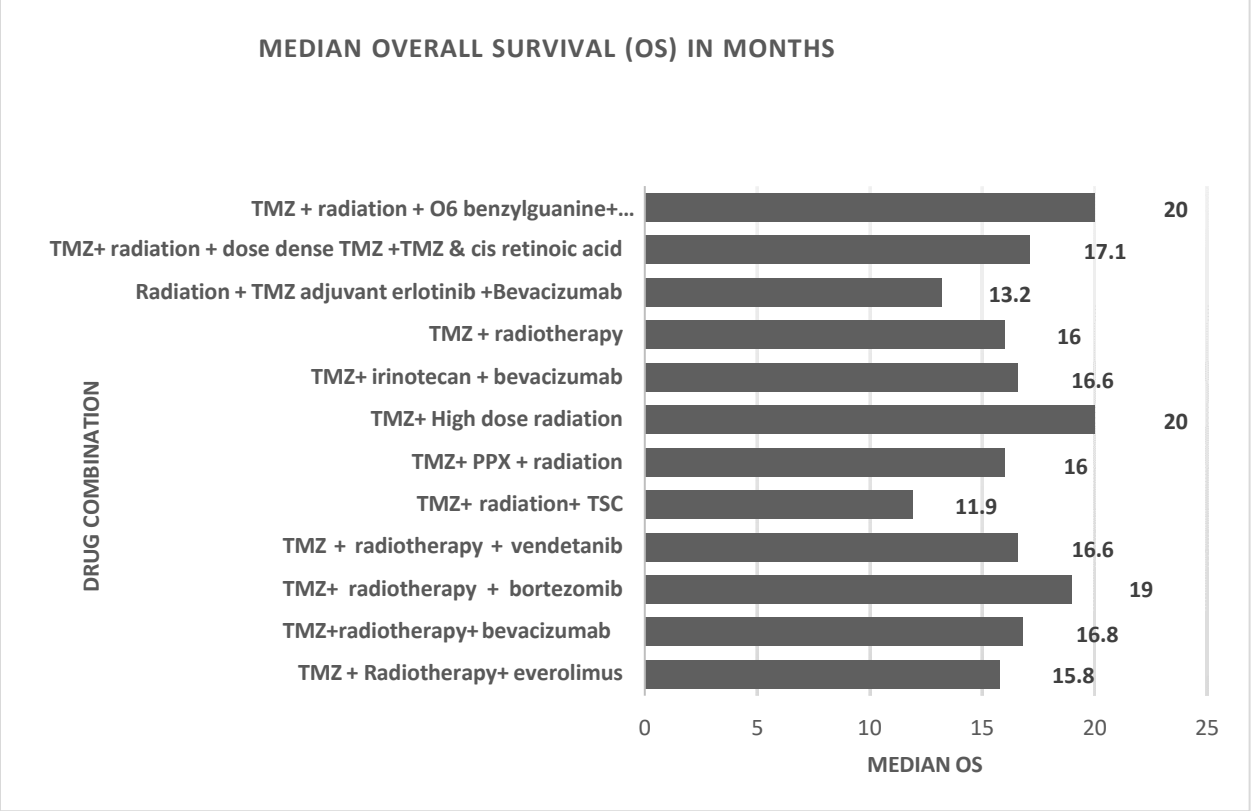



**Figure 3:** Median overall survival (OS) for drug combinations used in the treatment for glioblastoma multiforme

The median overall survival values in patients receiving temozolomide and radiotherapy treatment combinations are determined here through this graphical presentation. Two of the studies show the highest median OS (20 months) in patients. (High dose radiation +TMZ) and (TMZ+radiation+O6 benzylguanine+ carmustine + plerixafor) has the longest median OS. The shortest median OS (11.9 months) is observed in the study where Temozolomide and radiation are associated with the drug trans sodium crocetinate.

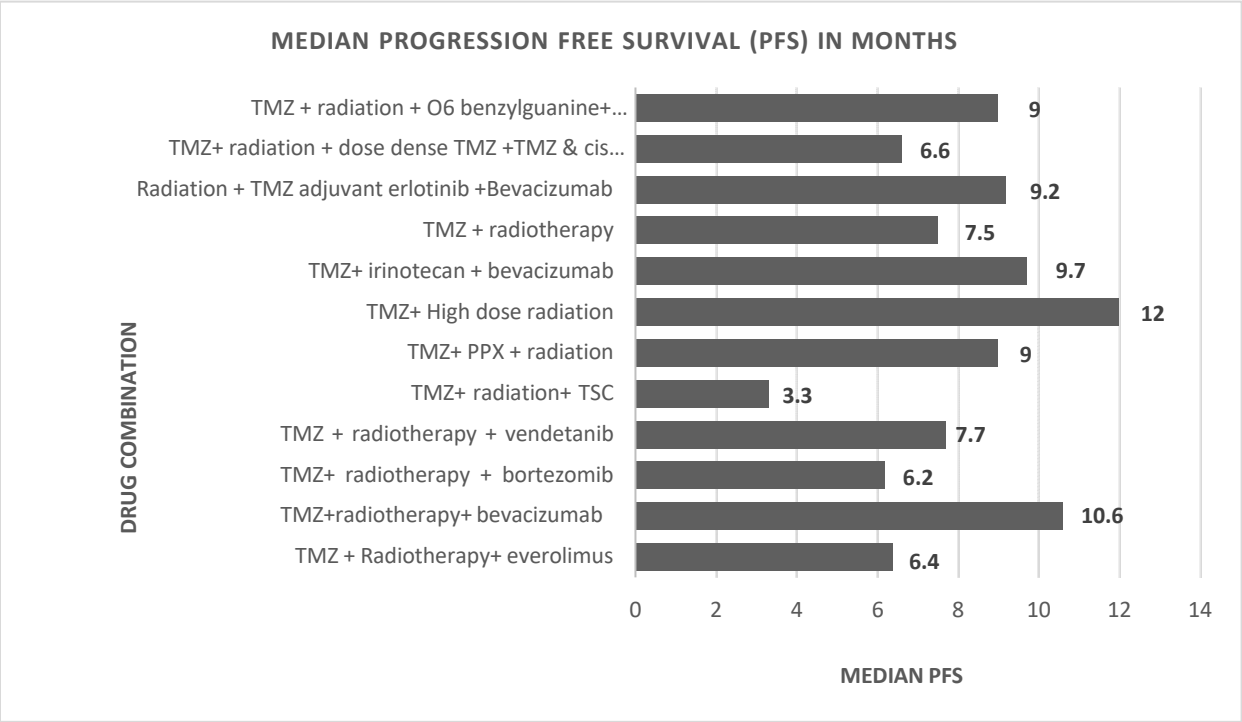
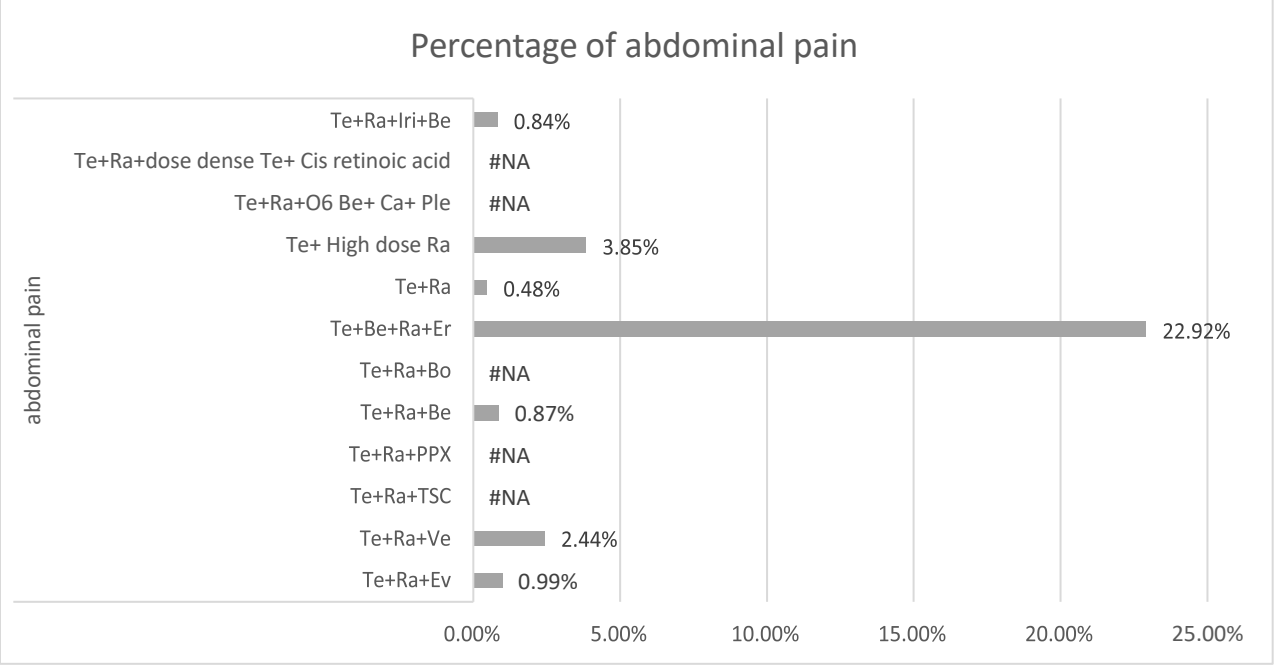



**Figure 4:** Median progression-free survival (PFS) rate for drug combinations used in the treatment for glioblastoma multiforme

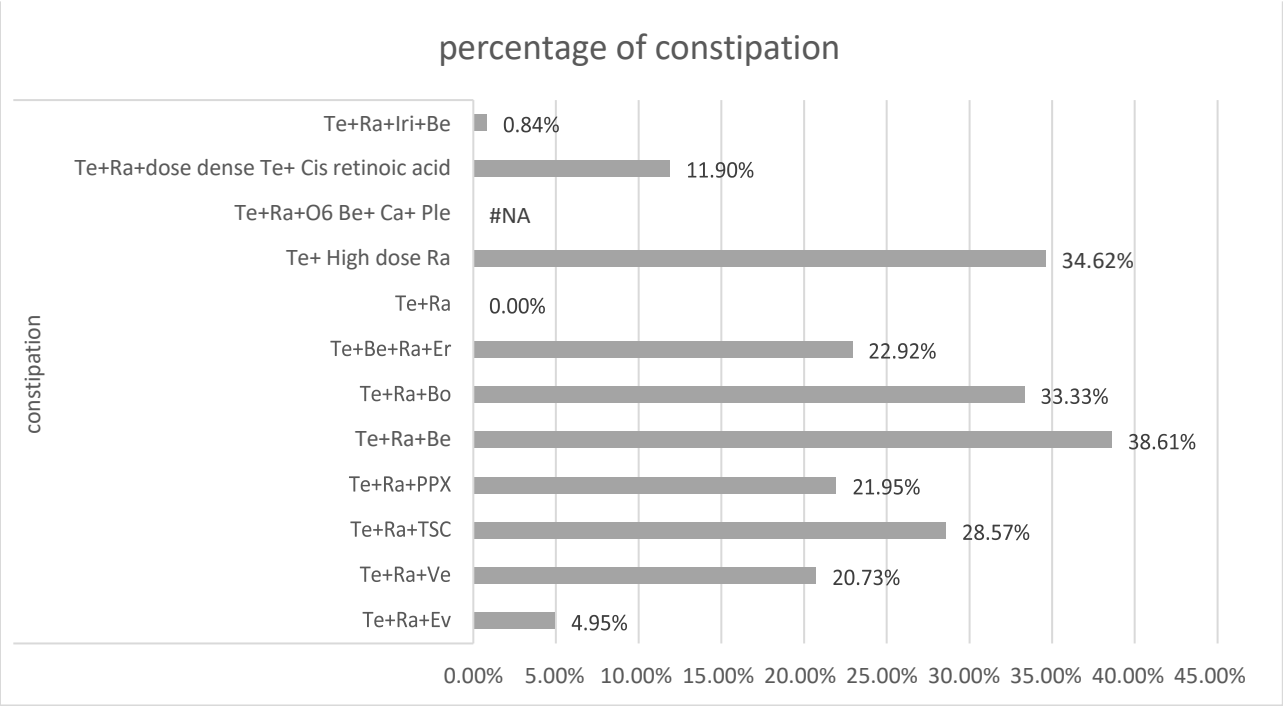
The median progression-free survival rate in patients is revealed through the presentation of this graph. (Temozolomide + high dose radiation) shows the highest median PFS which is 12 months. The shortest median PFS is observed in (Temozolomide + radiotherapy + TSC) which is 3.3 months.

The following graphs indicate the incidence of gastrointestinal issues in patients who received temozolomide and radiation as a combined treatment-

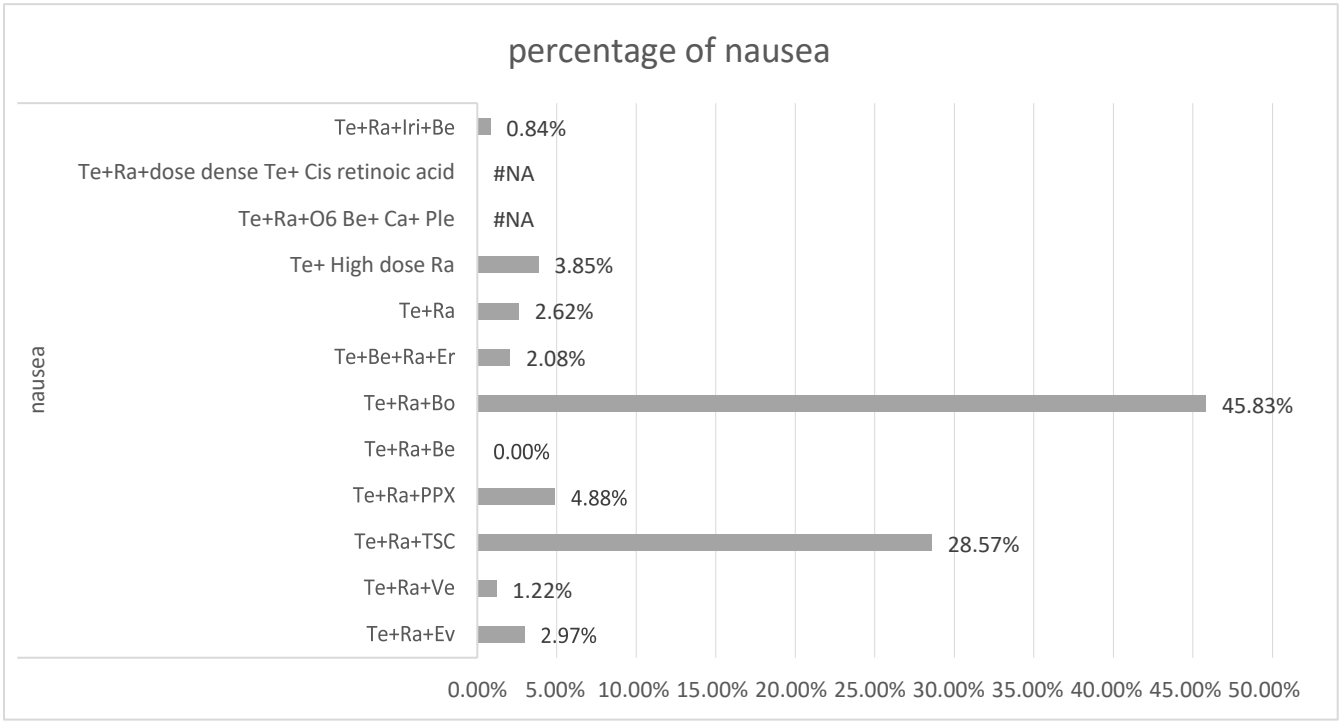
5(A)


Percentage of abdominal pain
abdominal pain
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
0.84%
#NA
#NA
3.85%
0.48%
22.92%
#NA
0.87%
#NA
#NA
2.44%
0.99%
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%

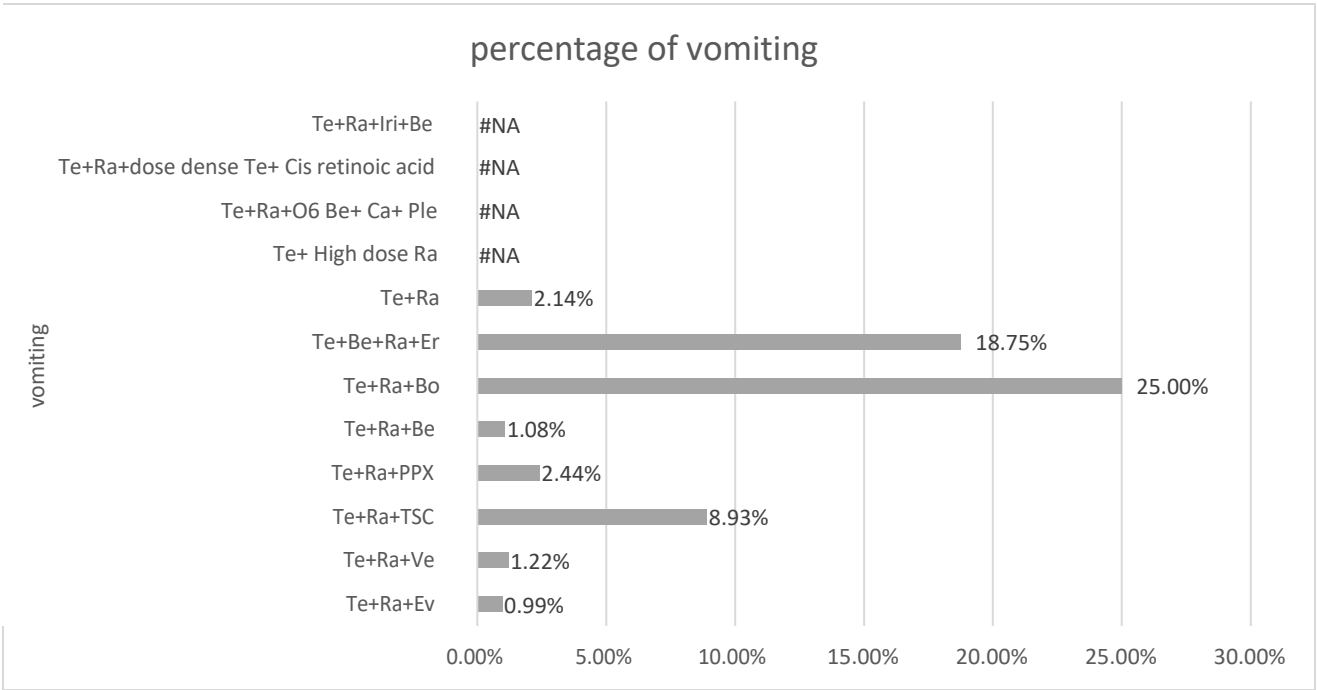
5(B)


percentage of constipation
constipation
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
0.84%
11.90%
#NA
34.62%
0.00%
22.92%
33.33%
38.61%
21.95%
28.57%
20.73%
4.95%
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%
35.00%
40.00%
45.00%

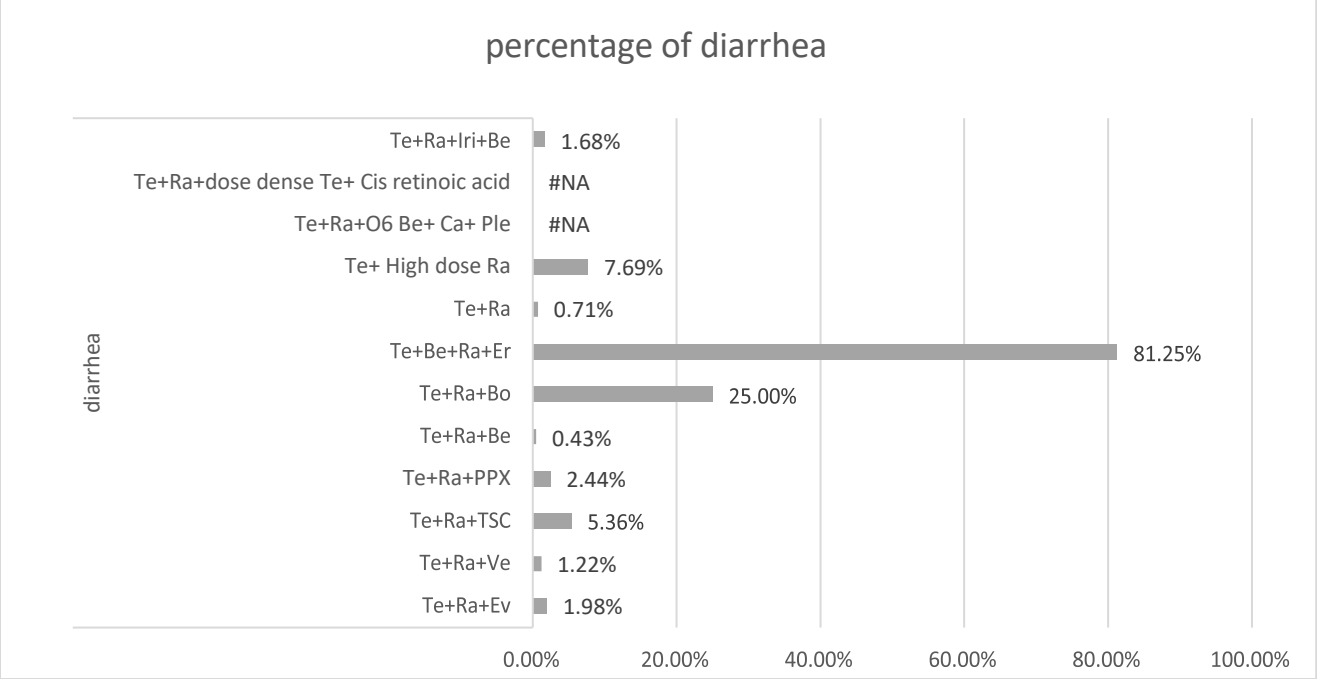
5(C)


percentage of nausea
nausea
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
0.84%
#NA
#NA
3.85%
2.62%
2.08%
45.83%
0.00%
4.88%
28.57%
1.22%
2.97%
0.00% 5.00% 10.00% 15.00% 20.00% 25.00% 30.00% 35.00% 40.00% 45.00% 50.00%

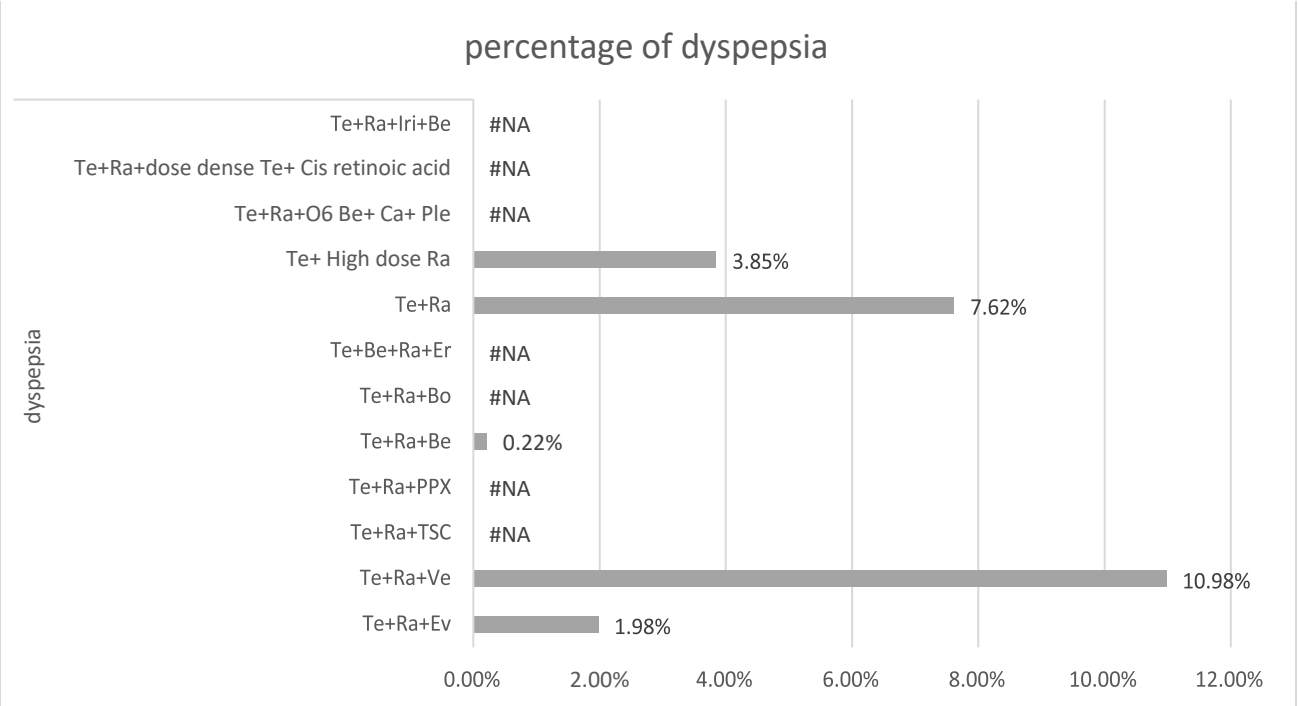
5(D)


percentage of vomiting
vomiting
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
#NA
2.14%
18.75%
25.00%
1.08%
2.44%
8.93%
1.22%
0.99%
0.00% 5.00% 10.00% 15.00% 20.00% 25.00% 30.00%

5(E)


percentage of diarrhea
diarrhea
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
1.68%
#NA
#NA
7.69%
0.71%
81.25%
25.00%
0.43%
2.44%
5.36%
1.22%
1.98%
0.00%
20.00%
40.00%
60.00%
80.00%
100.00%

5(F)


percentage of dyspepsia
dyspepsia
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
3.85%
7.62%
#NA
#NA
0.22%
#NA
#NA
10.98%
1.98%
0.00%
2.00%
4.00%
6.00%
8.00%
10.00%
12.00%

5(G)

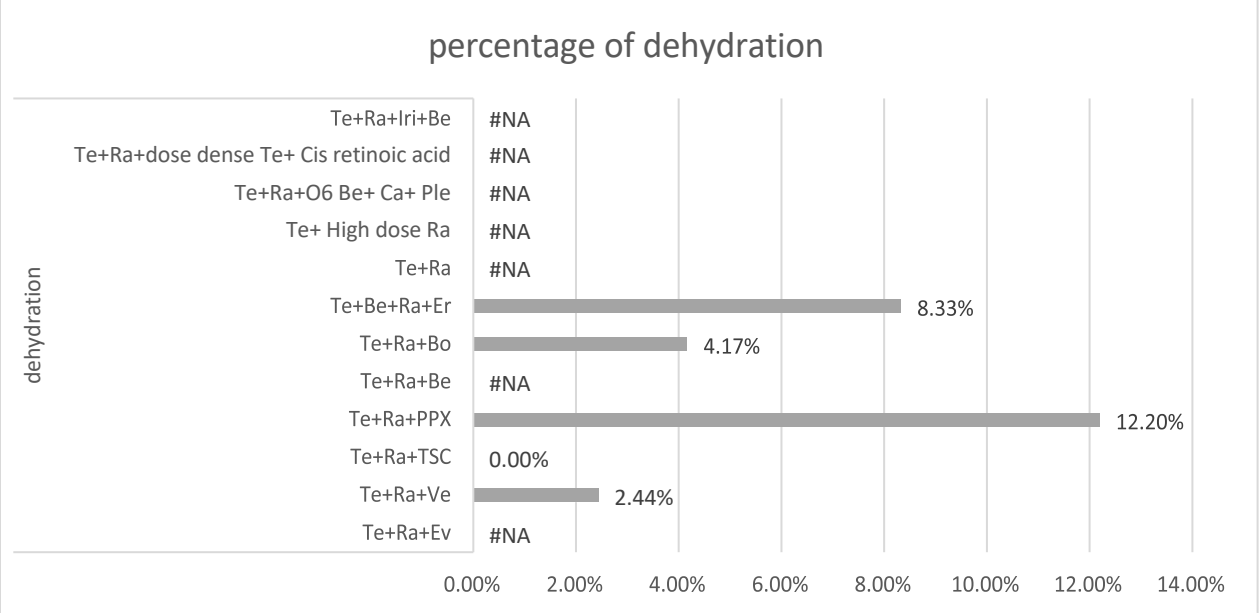


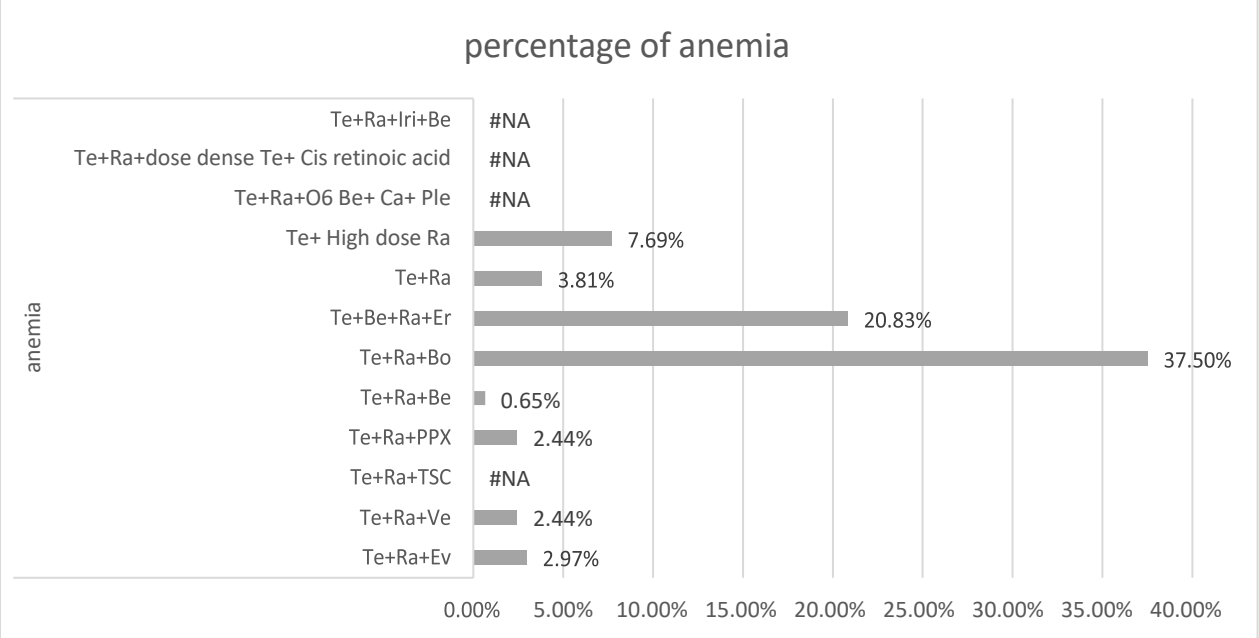

**Figure 5:** Occurrence of gastrointestinal disorders in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib ( Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Abdominal pain; (B) Constipation; (C) Nausea; (D) Vomiting; (E) Diarrhea; (F) Dyspepsia; (G) Dehydration. All the percentages of adverse effects are shown in the graphs.

The abdominal pain that patients experienced while undergoing temozolomide and radiation treatment regimens is depicted in Figure 5(A). The regimen (TMZ+ radiotherapy + bevacizumab + erlotinib) has the highest rate of stomach pain, at 22.92%. (TMZ+ high dose radiation) and (TMZ + radiation + vandetanib) cause stomach pain in 3.85% and 2.44% of patients, respectively. The combination of (TMZ+ radiation) and (TMZ+ radiation + everolimus) causes relatively little abdominal pain in individuals. #NA signifies that data for abdominal pain as a specific parameter is not available. Figure 5(B) signifies the percentage of constipation among patients who received multiple TMZ and radiation treatment regimens. The regimen (TMZ+ bevacizumab + radiotherapy) has the highest rate of constipation, at 38.61%. Constipation is also a common side effect of (TMZ+ radiotherapy + bortezomib), with a prevalence of 33.33%. (TMZ + high dose radiation) has a constipation rate of 34.625, which is comparable to other drug combinations in terms of number. The (TMZ+ radiation) regimen, on the other hand, has a 0% constipation rate in patients. Another gastrointestinal condition seen in patients is nausea, which is portrayed in figure 5(C) as a proportion of the total. The combination of (TMZ + radiation + bortezomib) has the highest incidence of nausea in patients, at 45.83%. Another drug combination (TMZ+ radiotherapy + TSC) reduces nausea by 28.57% throughout the treatment. The remaining drug combinations induce only a minimal amount of nausea in individuals. The frequency of vomiting in individuals receiving radiation and TMZ treatment is depicted in this figure 5(D). The largest incidence of vomiting is seen in the (TMZ+ radiotherapy + bortezomib) regimen, as seen by the bars in the graph. In comparison to other treatment combinations, the (TMZ+ radiotherapy + bevacizumab + erlotinib) combination causes 18.75 % vomiting in patients. Diarrhea is a major gastrointestinal disorder and figure 5(E) outlines the prevalence of diarrhea among patients during various TMZ & radiotherapy combination treatments. (TMZ+ radiation + bevacizumab + erlotinib) regimen shows the highest rate of diarrhea compared to other regimens which are 81.25%. 25% incidence of

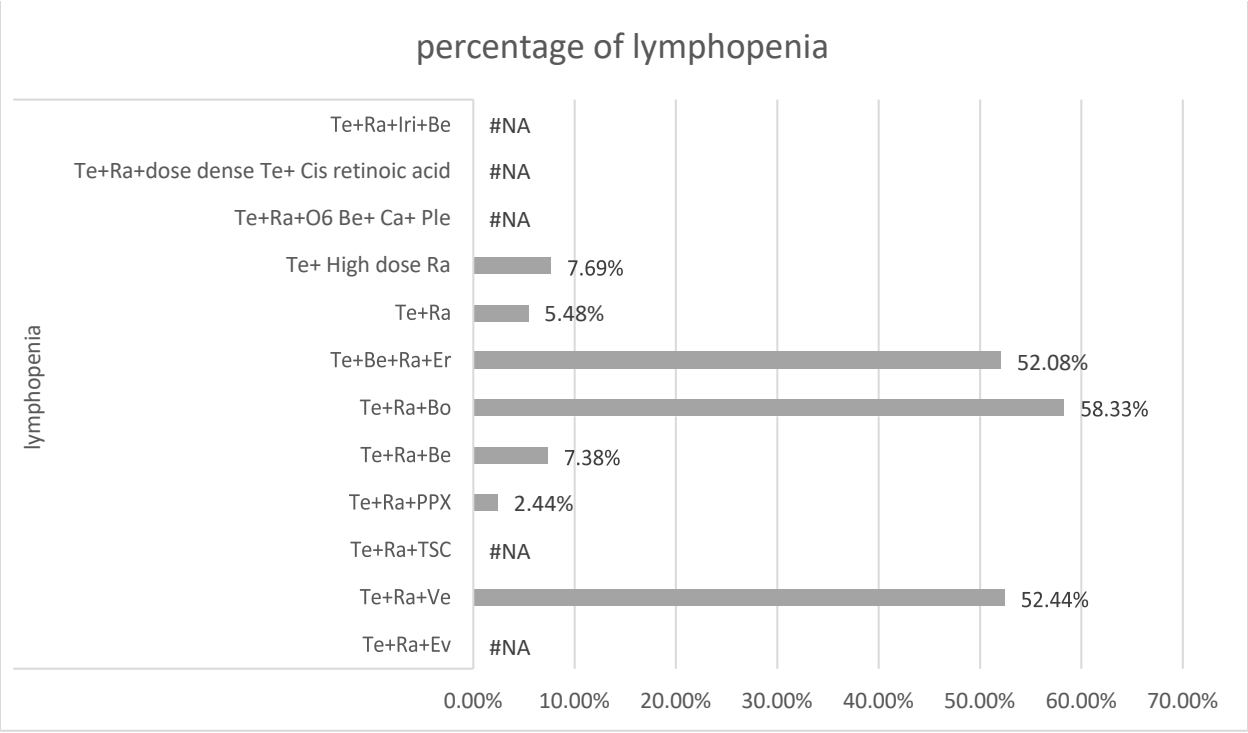
diarrhea is shown in the case of (TMZ+ Radiation+ bortezomib) treatment combination. Figure 5(F) represents the percentage of patients with dyspepsia who are receiving TMZ and radiation treatment. It is seen that, the drug combination (TMZ+ radiation + vandetanib) has the highest risk (10.98%) of dyspepsia when compared to other TMZ and radiation regimens. (Radiation + TMZ) regimen causes 7.62% dyspepsia. The predominance of dehydration among patients can be seen in Figure 5(G), with (TMZ+ radiation +PPX) combination treatment having the highest rate of 12.20 percent. When TMZ and radiation are coupled with bevacizumab and erlotinib, the rate of dehydration is 8.33%. The dehydration rate is 0% when TMZ & radiation is incorporated with the drug trans sodium crocetinate. The percentage of dehydration in patients is shown in figure 5(G) where we can observe that (TMZ + radiation + PPX) combination has a 12.20% incidence which indicates the highest rate of dehydration occurring among patients undergoing these multiple drug combinations therapies.

Figures for blood & lymphatic system disorders appearing in patients undergoing temozolomide & radiotherapy are demonstrated below-

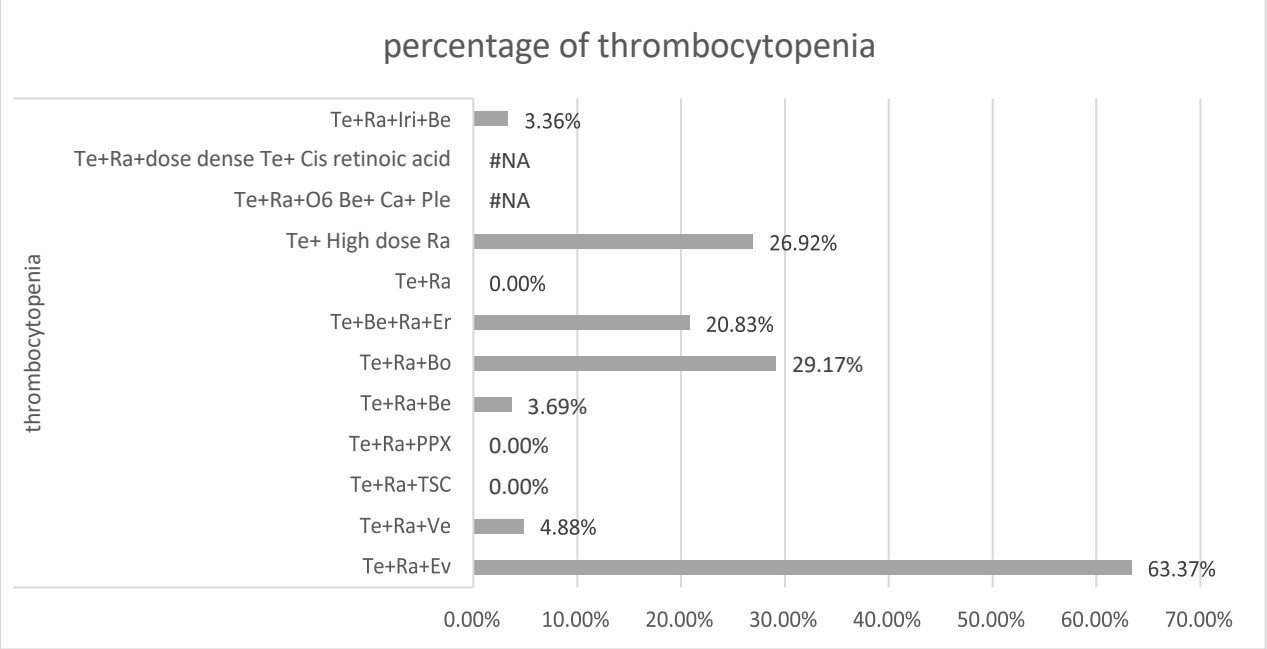
6(A)


percentage of anemia
anemia
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
7.69%
3.81%
20.83%
37.50%
0.65%
2.44%
#NA
2.44%
2.97%
0.00% 5.00% 10.00% 15.00% 20.00% 25.00% 30.00% 35.00% 40.00%

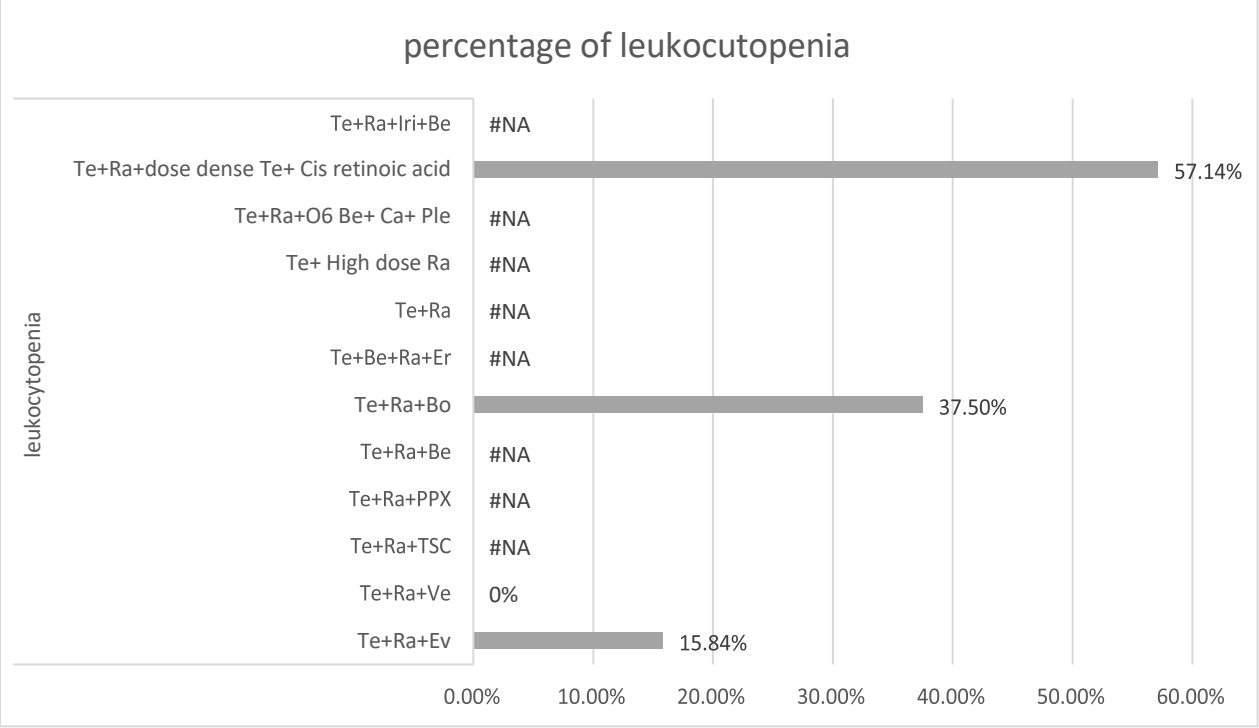
6(B)


percentage of lymphopenia
lymphopenia
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
7.69%
5.48%
52.08%
58.33%
7.38%
2.44%
#NA
52.44%
#NA
0.00% 10.00% 20.00% 30.00% 40.00% 50.00% 60.00% 70.00%

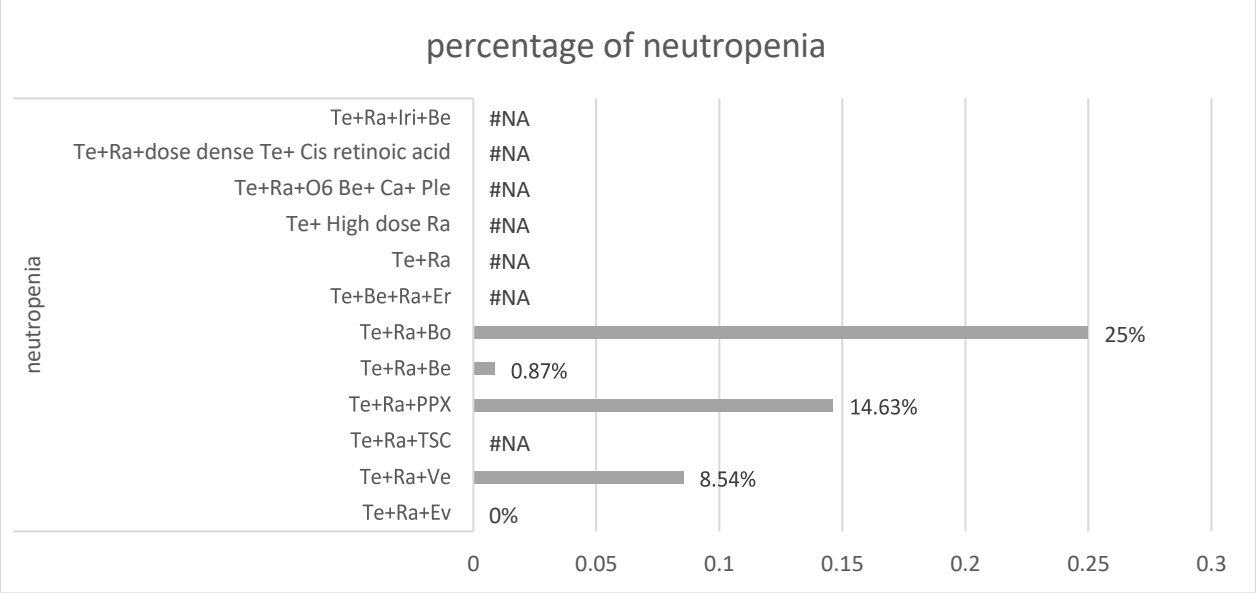
6(C)


percentage of thrombocytopenia
thrombocytopenia
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
3.36%
#NA
#NA
26.92%
0.00%
20.83%
29.17%
3.69%
0.00%
0.00%
4.88%
63.37%
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%
70.00%

6(D)


percentage of leukocutopenia
leukocytopenia
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
57.14%
#NA
#NA
#NA
#NA
37.50%
#NA
#NA
#NA
0%
15.84%
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%

6(E)




6(F)

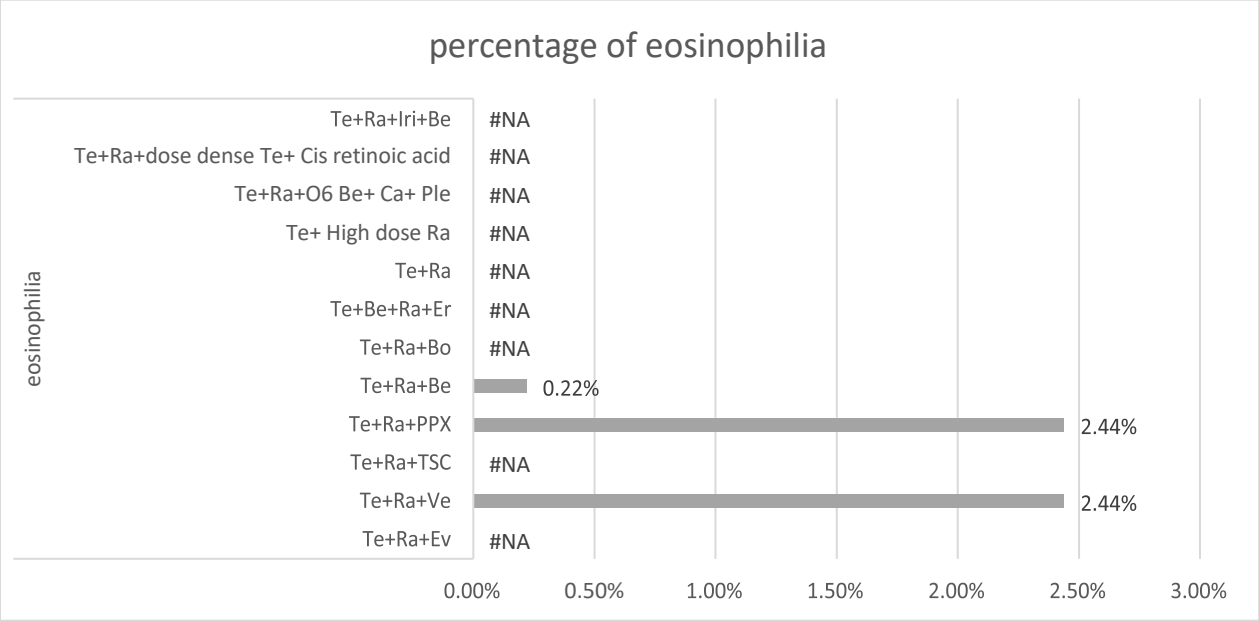



**Figure 6:** Occurrence of Blood and lymphatic system disorders in patients receiving temozolomide and radiotherapy combination treatment. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri +

Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib ( Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Anemia; (B) Lymphopenia; (C) Thrombocytopenia; (D) Leukocytopenia; (E) Neutropenia; (F) Eosinophilia. All the percentages of blood disorders are shown in the graphs.

Figure 6(A) indicates the prevalence of anemia in patients undergoing TMZ combined with irradiation, with the highest rate (37.50%) of anemia for (TMZ+ radiation + bortezomib) therapy. Another combination (TMZ+ radiotherapy + bevacizumab + erlotinib) results in a rate of anemia of 20.83%, which is very close to it. When TMZ is administered to individuals with a high dosage of radiation, there is a 7.69% anemia rate. The incidence of lymphopenia among patients is demonstrated in Figure 6(B), with (TMZ+ radiation+ bortezomib) having the highest prevalence of lymphopenia at 58.33%. Another therapeutic combination, in which TMZ radiation is paired with bevacizumab and erlotinib, results in a 52.08% rate of lymphopenia in patients. Thrombocytopenia, which is one of the most common blood problems in patients, is

depicted in Figure 6(C). The (TMZ+ radiation+ everolimus) regimen has the highest incidence of thrombocytopenia, with a rate of 63.37%. When bortezomib is administered with TMZ and radiotherapy, it causes 29.17% thrombocytopenia. Another blood disease is leukocytopenia, which is displayed in figure 6(D) as a percentage of patients for numerous drug combinations related to TMZ and radiotherapy. In the context of (TMZ+ radiation+ dosage dense TMZ+ cis

retinoic acid), the greatest rate is 51.14%. Bortezomib plus TMZ plus radiation results in 37.50% leukocytopenia. The (TMZ+ radiation+ everolimus) regimen has a 15.84% rate of leukocytopenia. However, when vandetanib was paired with traditional chemoradiation, there was no evidence of leukocytopenia. Figure 6(E) demonstrates that the (TMZ+ radiation+ bortezomib) regimen has the greatest rate of neutropenia at 25%. (TMZ+ radiation+ PPX) causes 14.64% neutropenia. The rate of eosinophilia in patients is extremely low, as shown in figure 6(F), with just 2.44% of cases for (PPX+ TMZ+ radiation) and (TMZ+ radiation+ vendatibin) therapy. (Bevacizumab+ TMZ+ radiation), on the other hand, only displays 0.22% eosinophilia.

Figure demonstrating endocrine disorder in patients-

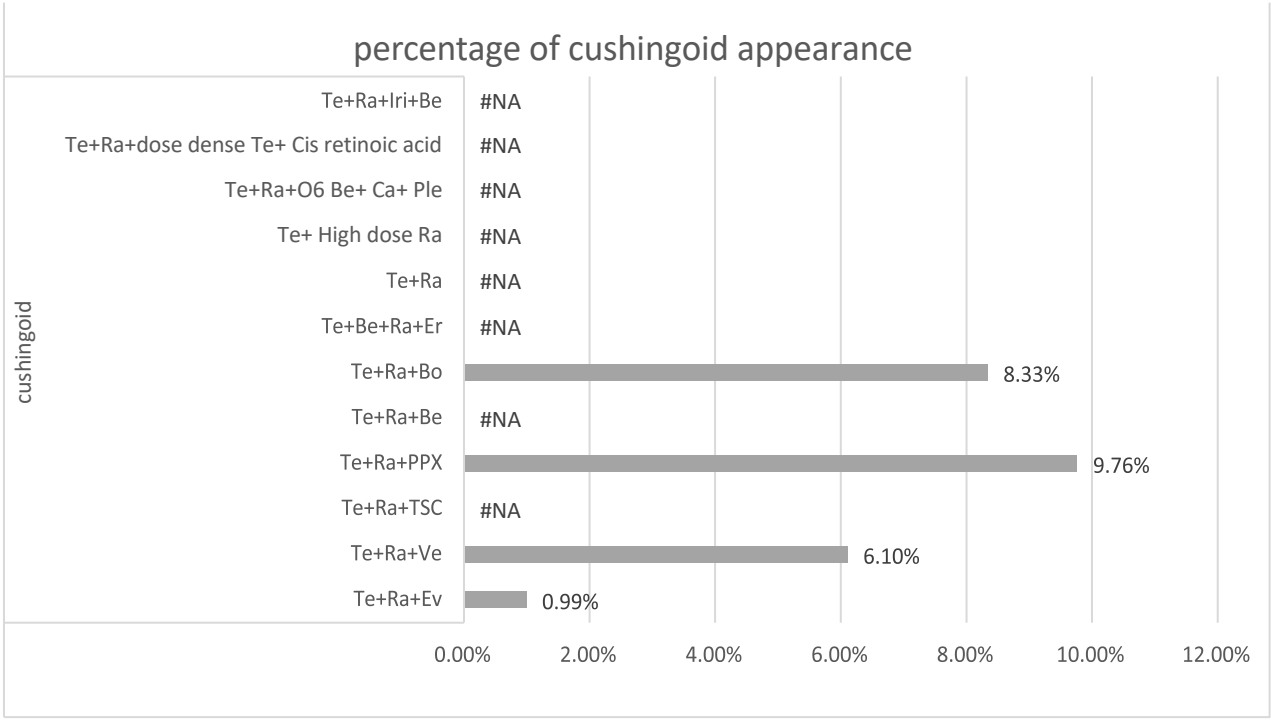
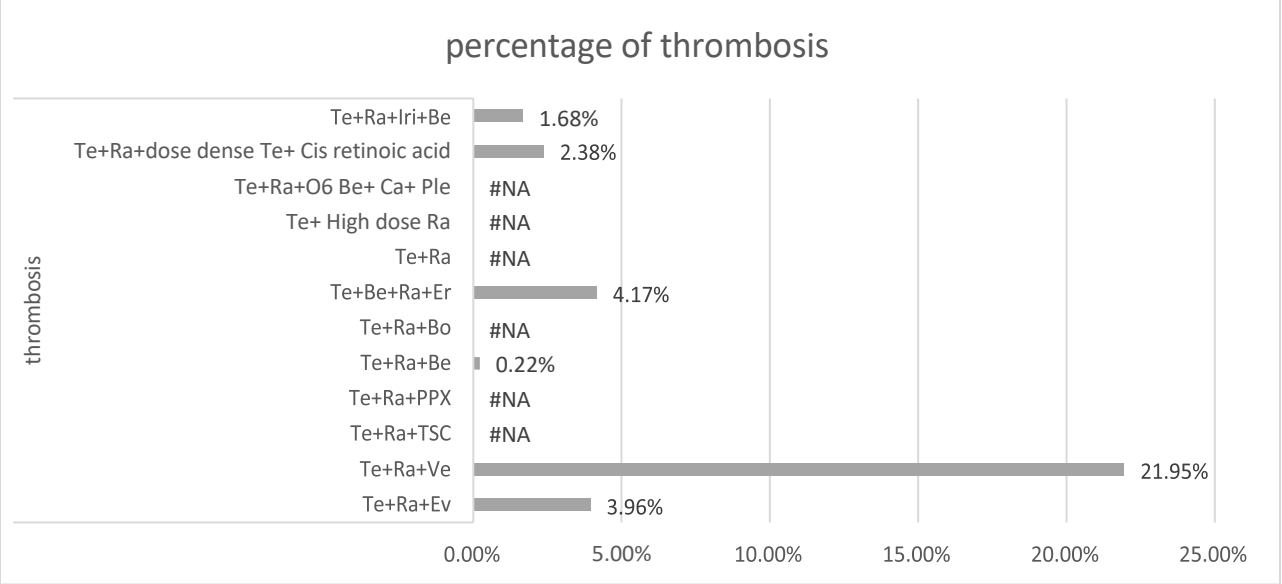



**Figure 7:** Occurrence of endocrine disorder in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib ( Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Cushingoid Appearance. The above figure demonstrates the percentage of endocrine disorders that appeared among participants.

Figure 7 represents the cushingoid expression in patients treated with a combination of TMZ and radiation therapy. The highest rate of cushingoid is recorded at a rate of 9.76% in the case of (TMZ+ radiation+ PPX), as shown in the graph. The (TMZ+ radiation+ bortezomib) regimen had an 8.33% cushingoid appearance. 6.10% appearance of cushingoid in patients is observed for the drug combination (TMZ + radiotherapy + Vendatinib).

Vascular disorders in patients receiving TMZ & radiation combination treatments are shown in the following graphs-

8(A)




8(B)

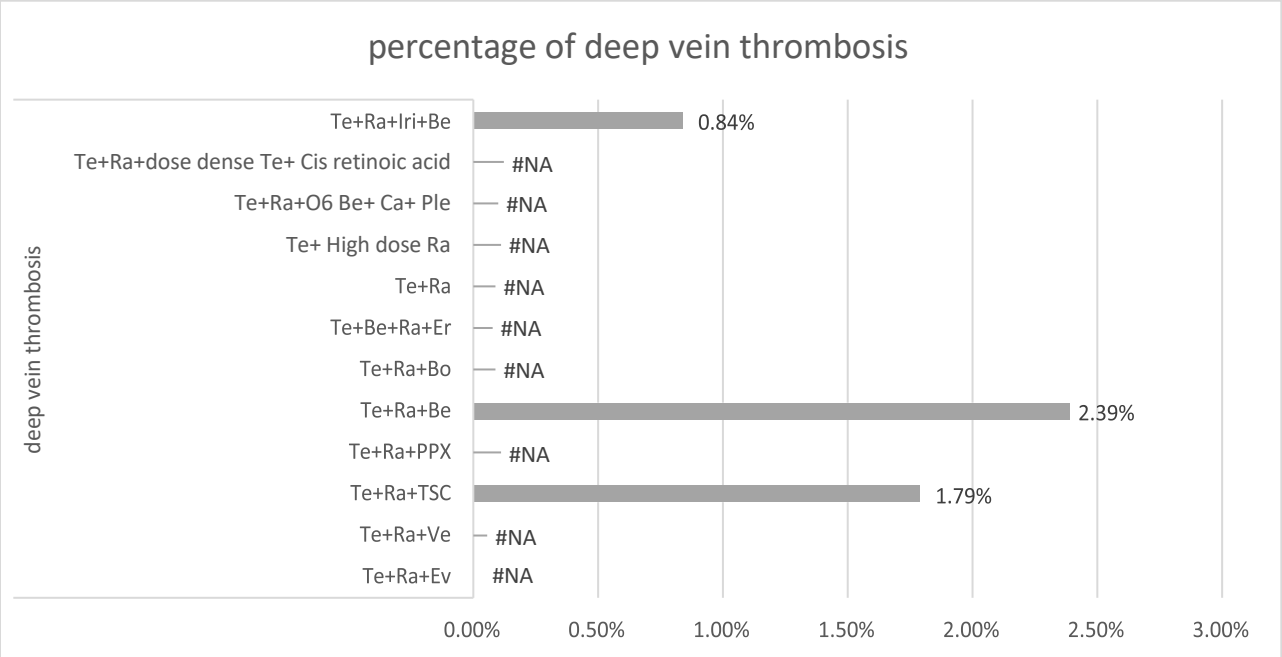



**Figure 8:** Occurrence of vascular disorders in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide

+ Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib ( Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Thrombosis; (B) Deep vein thrombosis. The appearance of vascular disorders in patients are shown as percentages in the above graphs.

Thrombosis is quite prevalent among patients, and figure 8(A) indicates the rate of thrombosis, with the biggest amount arising from the combination (TMZ+ radiation+ vandetanib). Thrombosis occurs at a rate of 21.95% in this case. Figure 8(B) depicts the occurrence of a little quantity of deep vein thrombosis. 2.39% with (Bevacizumab + radiation + TMZ) develop deep vein thrombosis. (TMZ+ radiation+ bevacizumab + irinotecan) has a 0.84% rate of deep vein thrombosis, while (TMZ+ TSC + radiation) has 1.79% rate.

The figure for Injury, poisoning & procedural complications-

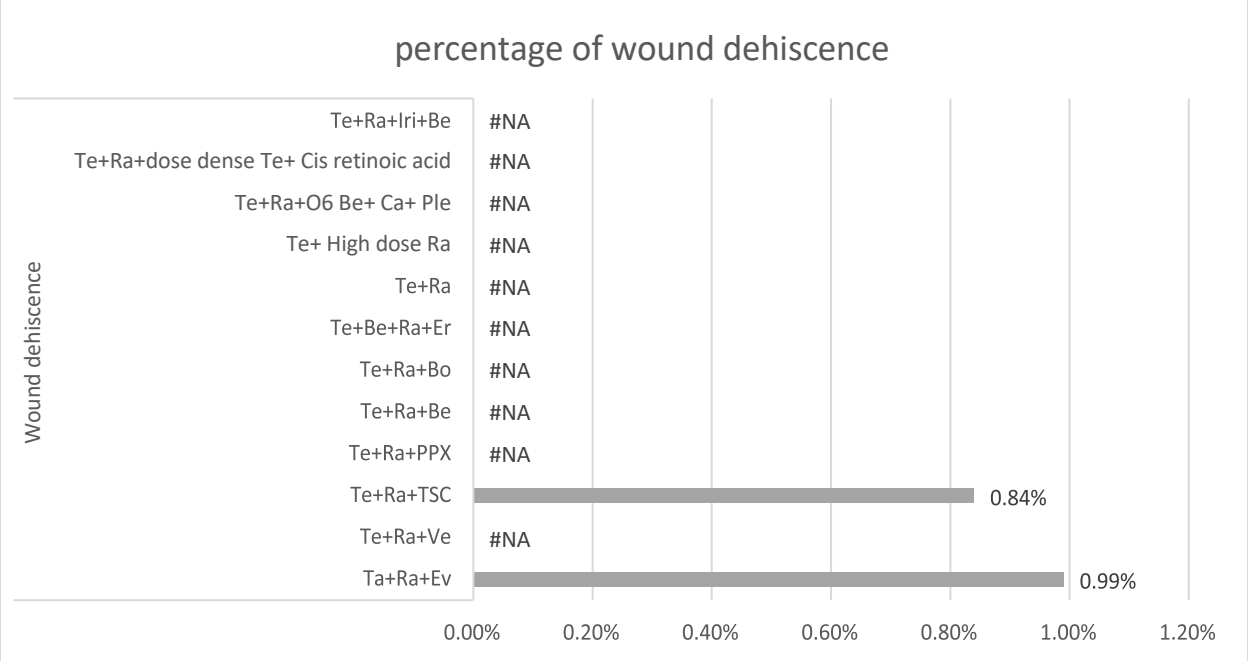



**Figure 9:** Occurrence of injury, poisoning & procedural complications in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib ( Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Wound dehiscence. The values are shown in percentages in the graph.

Figure 9 demonstrates that, the (TMZ + radiation + everolimus) combination has only 0.99% of wound dehiscence in patients. 0.84% wound dehiscence was found in the case of (TMZ + TSC + radiation) therapy indicating that there was no significant amount of injury, poisoning and procedural complications in all the drug combinations.

Renal failure in patients can be described by the following figure-

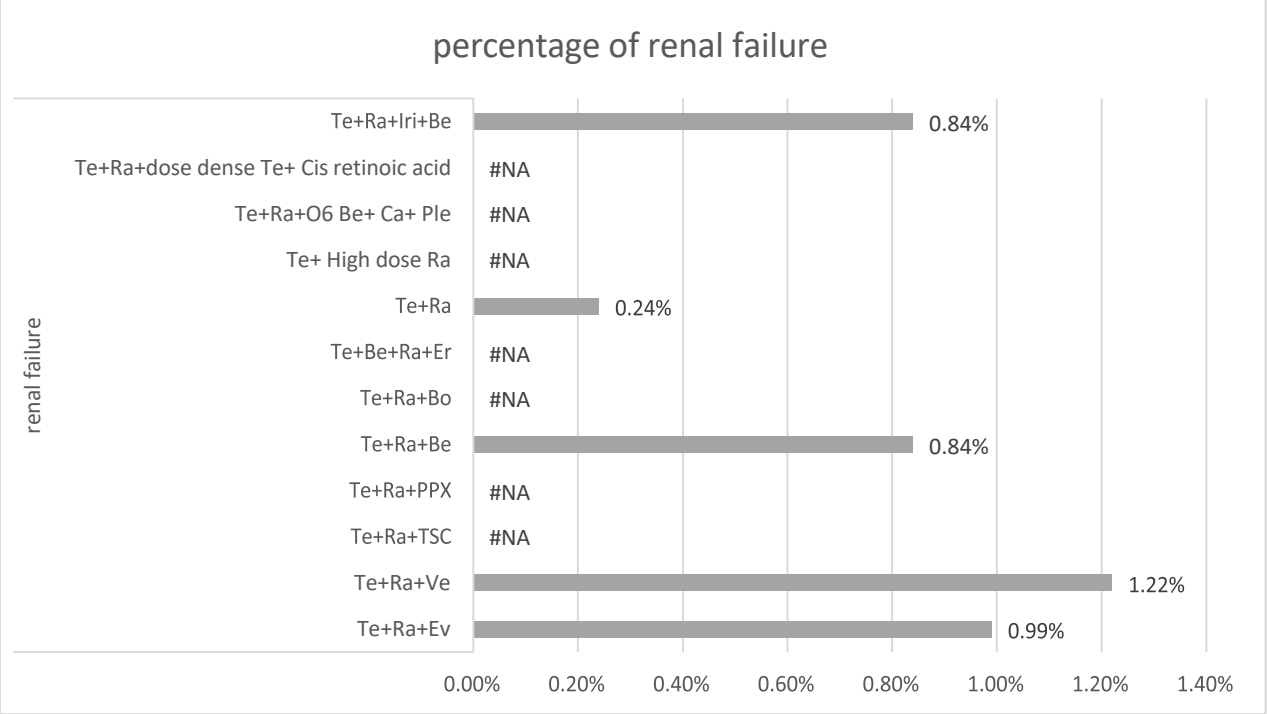



**Figure 10:** Occurrence of renal failure in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib ( Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Renal failure. The values are expressed as percentages in the figure.

The frequency of renal failure in individuals receiving TMZ and radiation in combination is shown in Figure 10. Renal failure is depicted in the graph at a very low rate. In the case of the (TMZ+ vandetanib + radiotherapy) regimen, only 1.22% developed renal failure. Both combinations (TMZ+ radiation+ bevacizumab + irinotecan) and (TMZ + bevacizumab + radiation) have a 0.84% chance of causing renal failure.

Eye disorder in various drug combinations can be observed by this graph-

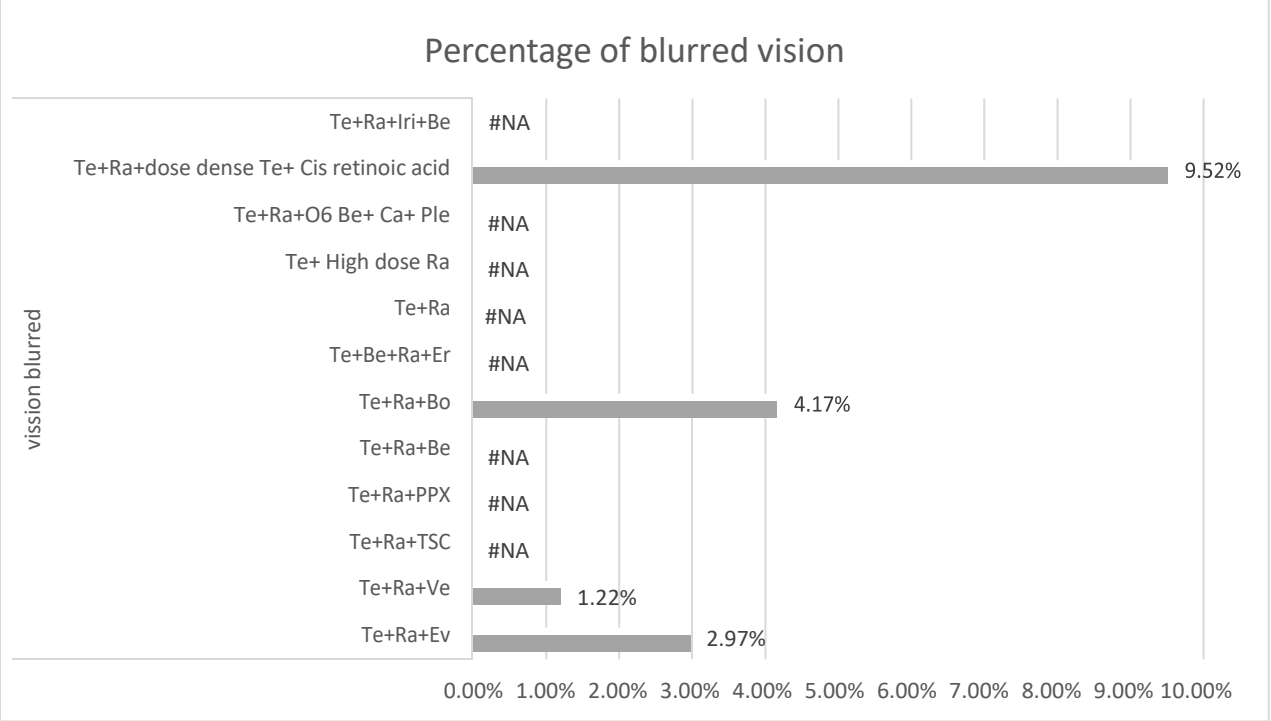
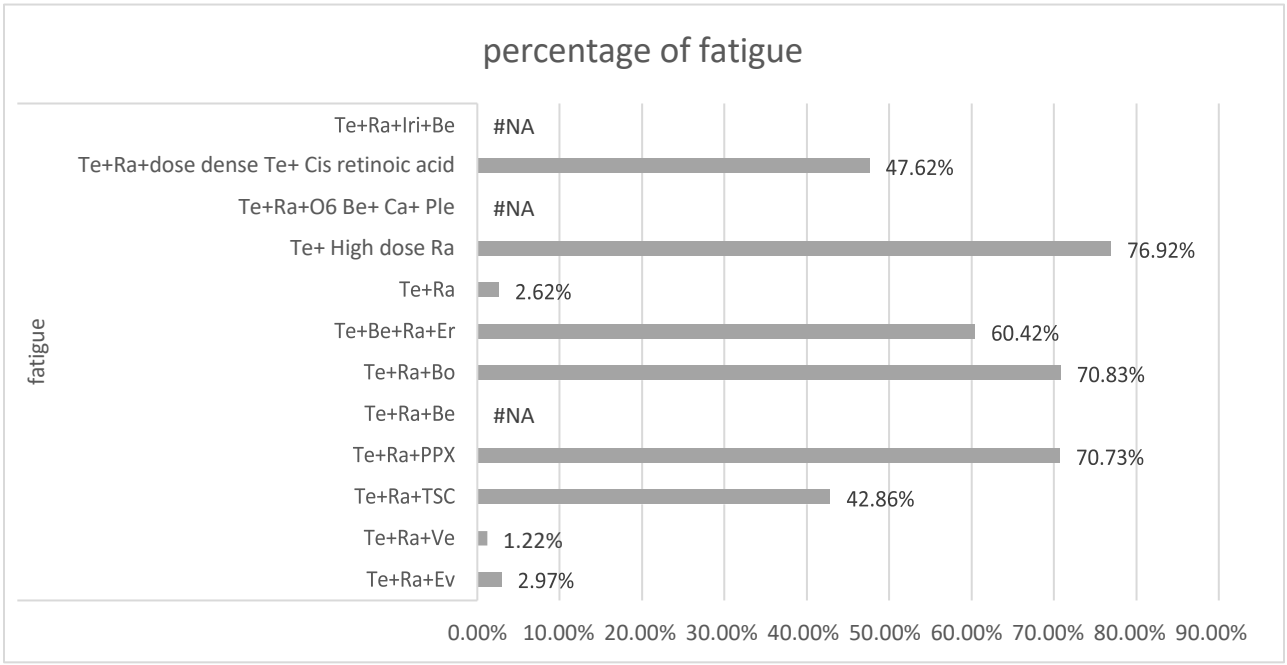



**Figure 11:** Occurrence of eye disorder in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib ( Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Blurred vision. The values are shown as percentages here.

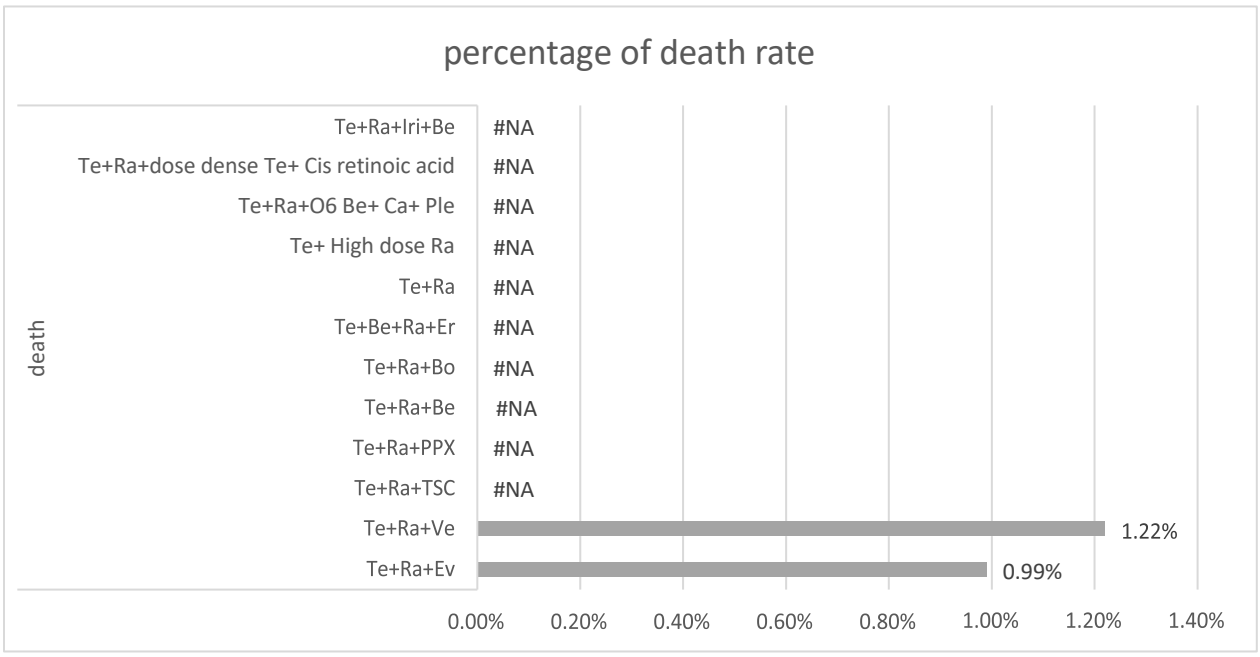
Figure 11 shows the percentage of eye disorders in patients receiving temozolomide and radiotherapy combination treatments. 9.52% blurred vision is seen for (TMZ + radiation + O6 benzyl guanine + carmustine + plerixafor) combination treatment which is the greatest of them all. (TMZ + radiation + bortezomib) the regimen has a 4.17% incidence of blurred vision among patients. Other combination therapies such as (TMZ+ radiation + vandetanib) and (TMZ + everolimus + radiotherapy) has a very minimal amount of blurred vision appearance in patients.

General disorders appearing in patients during TMZ & radiotherapy treatment can be analyzed through the following graphs-

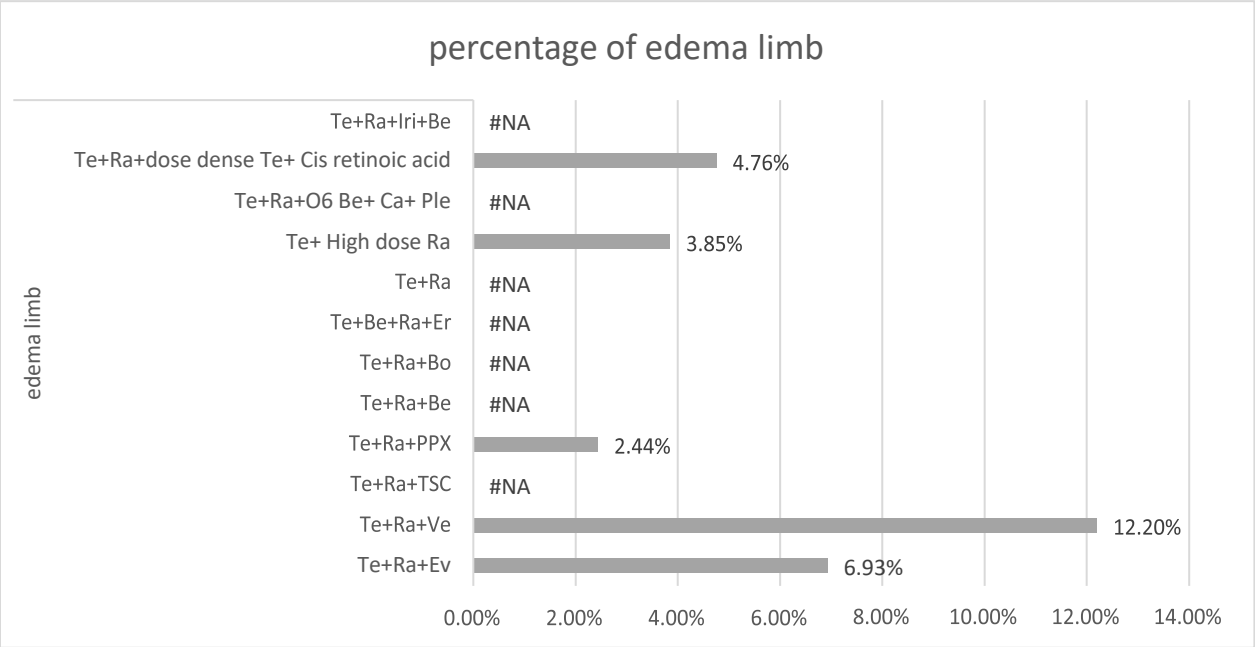
12(A)



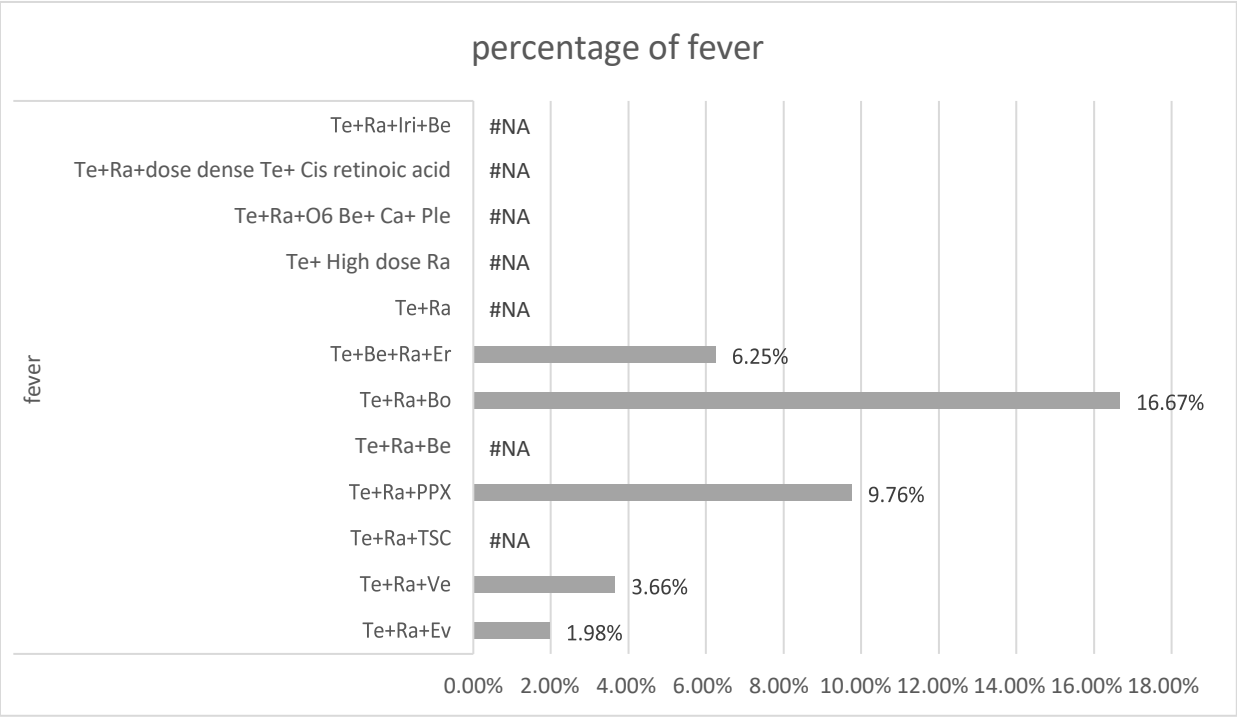

12(B)



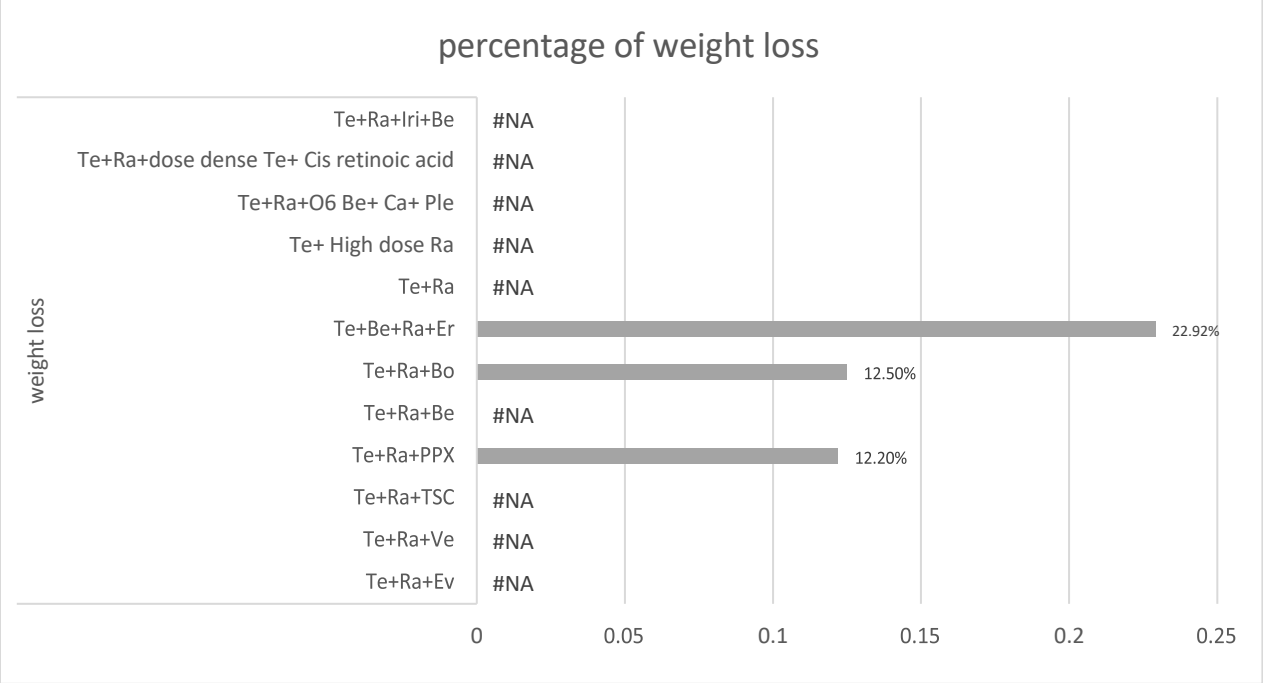
12(C)


percentage of edema limb
edema limb
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
4.76%
#NA
3.85%
#NA
#NA
#NA
#NA
2.44%
#NA
12.20%
6.93%
0.00% 2.00% 4.00% 6.00% 8.00% 10.00% 12.00% 14.00%

12(D)


percentage of fever
fever
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
#NA
#NA
6.25%
16.67%
#NA
9.76%
#NA
3.66%
1.98%
0.00% 2.00% 4.00% 6.00% 8.00% 10.00% 12.00% 14.00% 16.00% 18.00%

12(E)


percentage of weight loss
weight loss
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
#NA
#NA
22.92%
12.50%
#NA
12.20%
#NA
#NA
#NA
0
0.05
0.1
0.15
0.2
0.25

12(F)

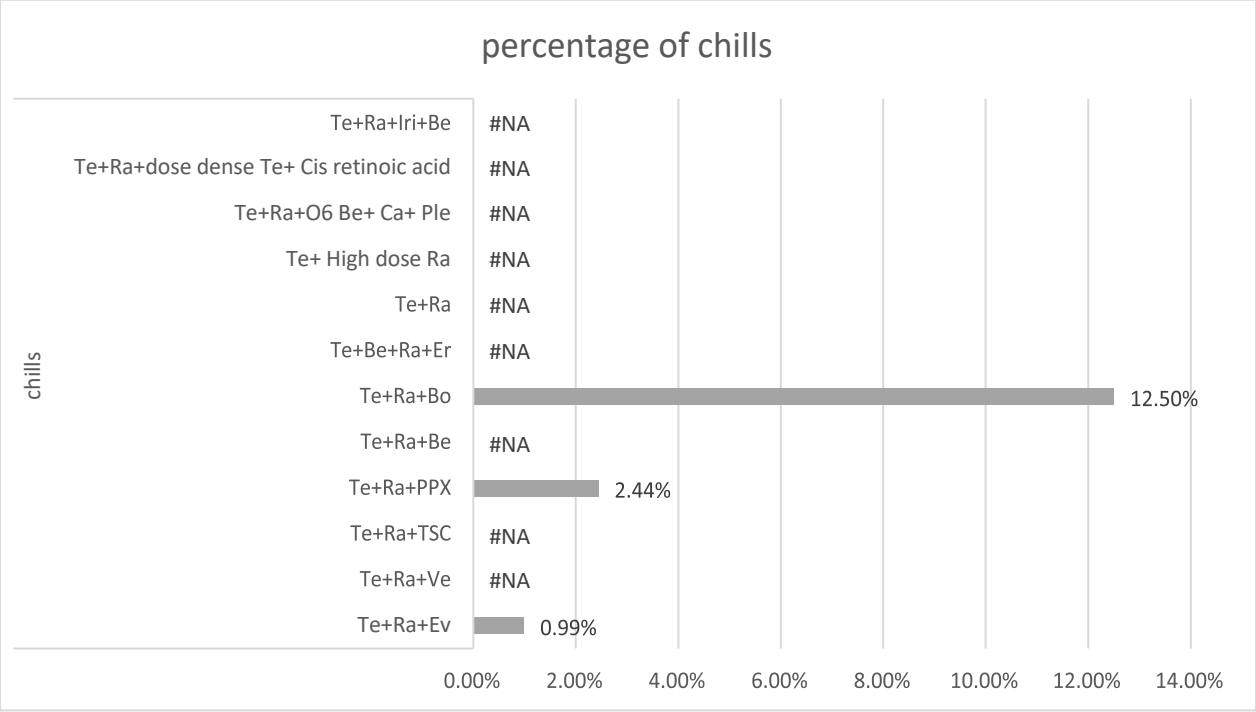

percentage of chills
chills
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
#NA
#NA
#NA
12.50%
#NA
2.44%
#NA
#NA
0.99%
0.00%
2.00%
4.00%
6.00%
8.00%
10.00%
12.00%
14.00%

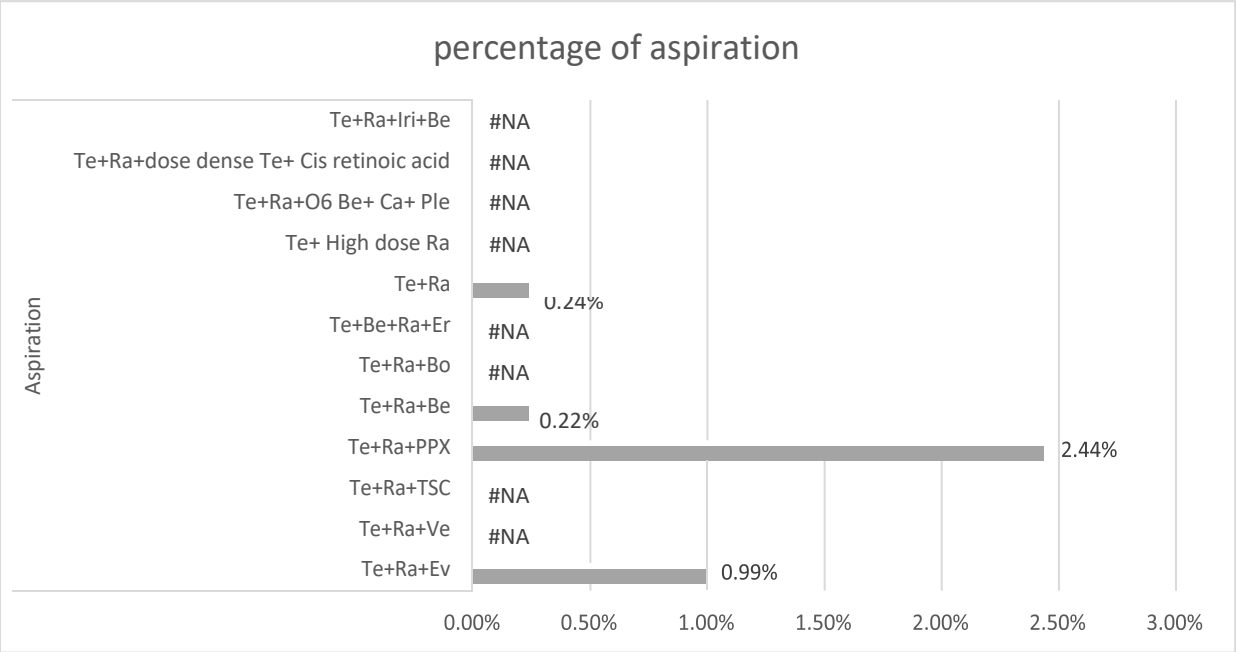
**Figure 12:** Occurrence of general disorders in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib ( Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Fatigue; (B) Death rate; (C) Edema limb; (D) Fever; (E) Weight loss; (G) Chills. The values are shown as percentages in the graphs.

Fatigue is an extremely common general disorder in patients. Figure 12(A) demonstrates fatigue levels in patients who underwent multiple TMZ & radiotherapy combination therapies. From the graph, it can be observed that the highest rate of fatigue is 76.92% which is caused by (TMZ + high dose radiation) regimen. (TMZ + radiation + bortezomib) and (TMZ + radiation + PPX) results in 70.83% and 70.73% of fatigue rates respectively. Figure 12(B) shows death rates in patients receiving temozolomide and radiotherapy combination treatments. The incidence of death is quite low. Only 1.22% and 0.99% death rates are found for (TMZ + radiation + vandetanib) and (TMZ + radiation + everolimus) regimen. The percentage of edema limbs is shown in figure12(C) where (TMZ + radiation + vandetanib) offers the highest rate of 12.20%. 6.93% incidence of edema limb is found when everolimus is associated with TMZ and radiotherapy. From figure 12(D), the appearance of fever in patients can be determined. Highest rate is 16.67% which is observed for (TMZ + radiation +

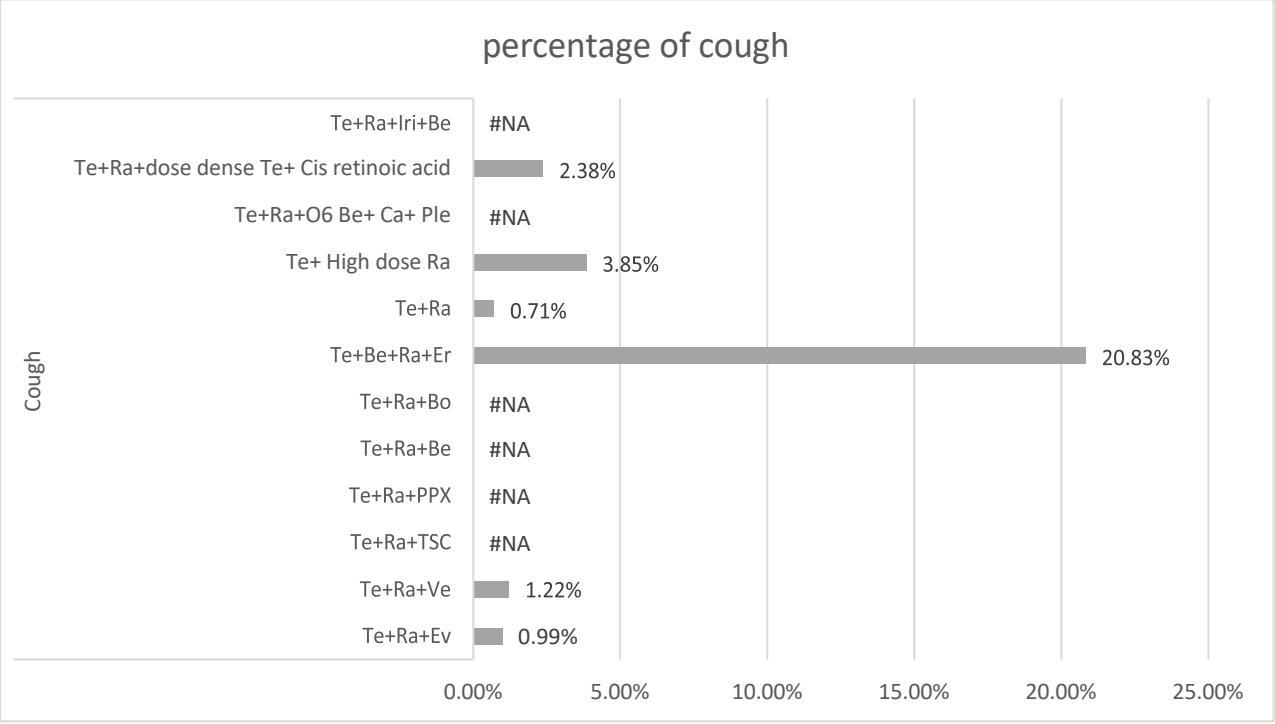
bortezomib) regimen. 9.76% fever rates are found for (TMZ + PPX + radiation). Figure 12(E) reveals the rate of weight loss in patients receiving temozolomide and radiotherapy combination treatments. A significant amount of weight loss is seen in the case of (TMZ + radiation + bevacizumab + erlotinib) regimen where 22.92% is considered as the highest rate compared to other regimens. Chills in patients are significantly more noticeable as a result of the presence of the medicine bortezomib to radiotherapy and TMZ, as seen in the figure. 12(F).

Respiratory disorders in patients during TMZ & radiation treatment regimen are described below with appropriate figures-

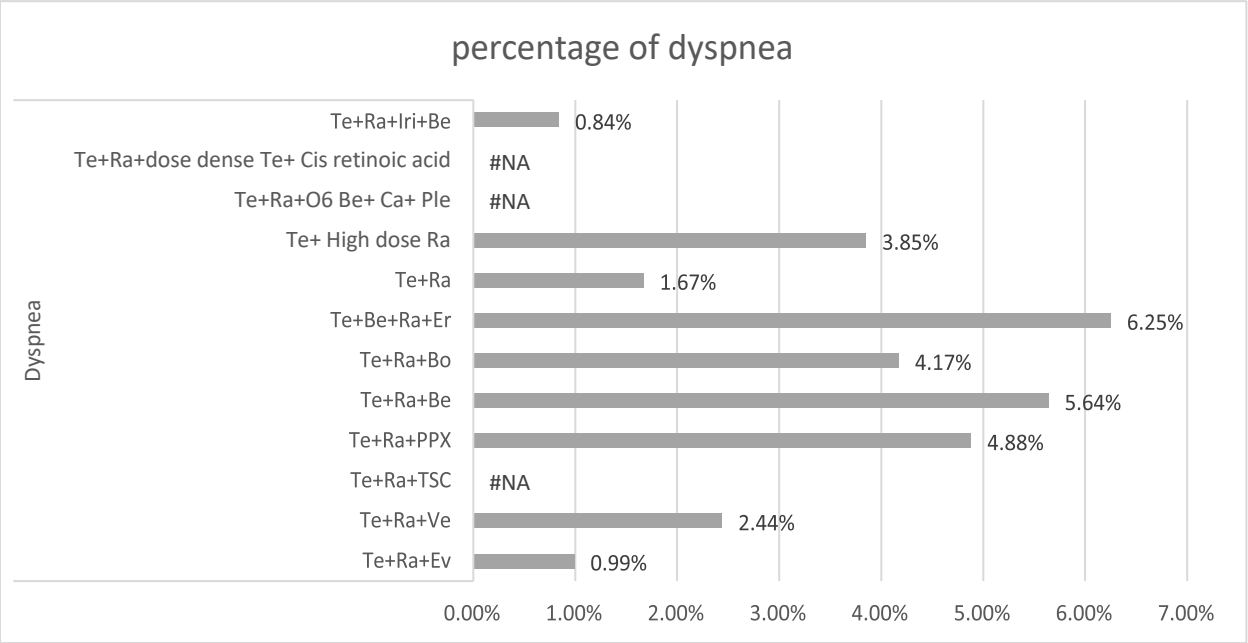
13(A)


percentage of aspiration
Aspiration
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
#NA
0.24%
#NA
#NA
0.22%
2.44%
#NA
#NA
0.99%
0.00%
0.50%
1.00%
1.50%
2.00%
2.50%
3.00%

13(B)


percentage of cough
Cough
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
2.38%
#NA
3.85%
0.71%
20.83%
#NA
#NA
#NA
#NA
1.22%
0.99%
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%

13(C)


percentage of dyspnea
Dyspnea
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
0.84%
#NA
#NA
3.85%
1.67%
6.25%
4.17%
5.64%
4.88%
#NA
2.44%
0.99%
0.00%
1.00%
2.00%
3.00%
4.00%
5.00%
6.00%
7.00%

13(D)

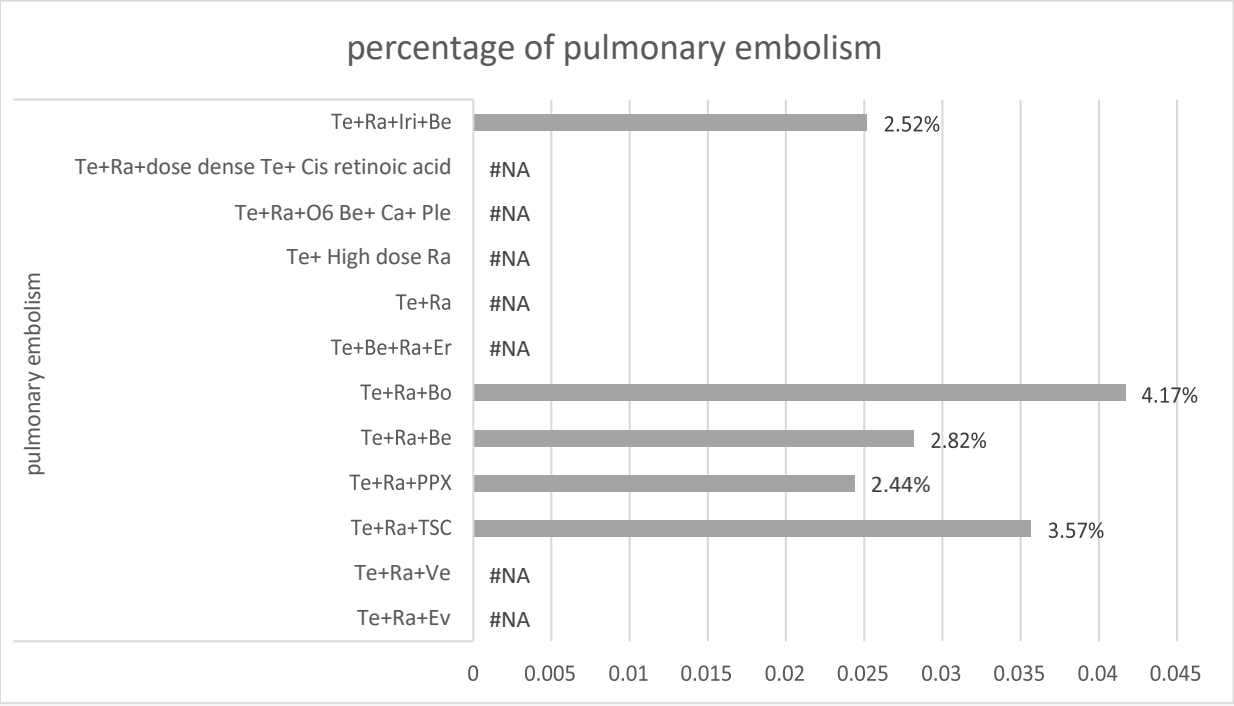
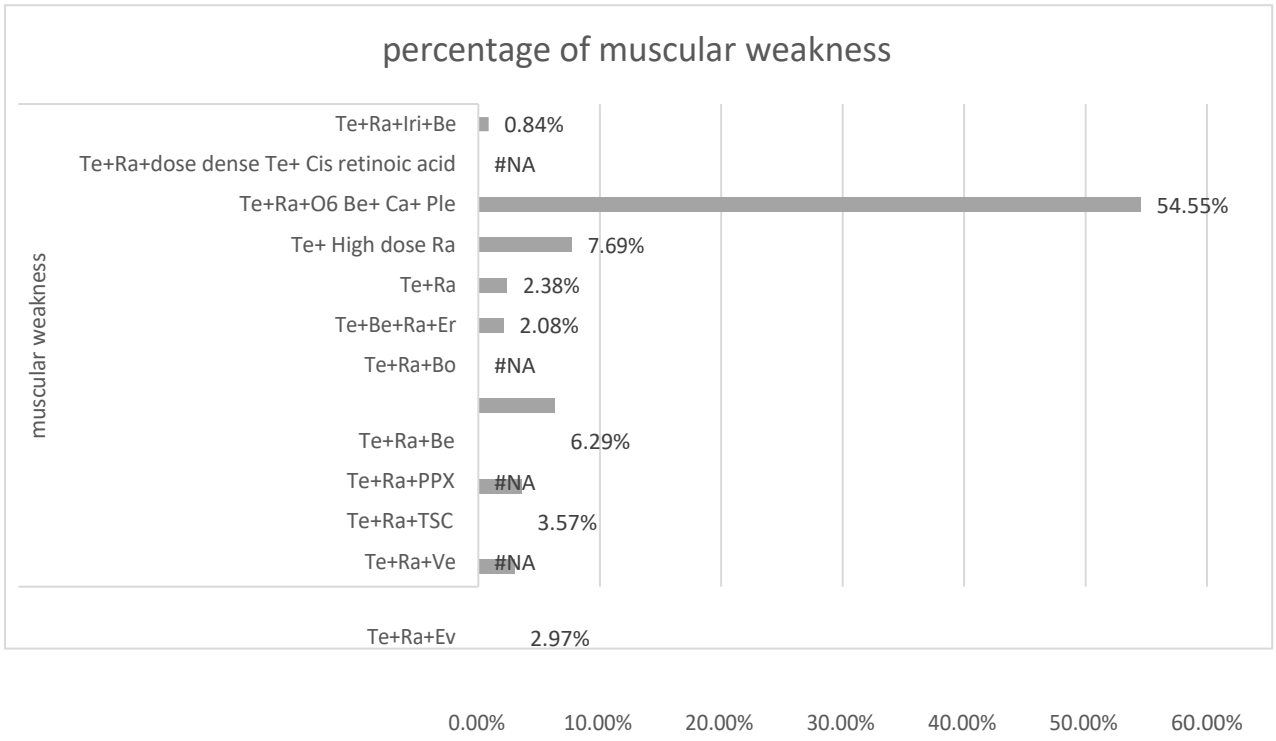

percentage of pulmonary embolism
pulmonary embolism
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
2.52%
#NA
#NA
#NA
#NA
#NA
4.17%
2.82%
2.44%
3.57%
#NA
#NA
0
0.005
0.01
0.015
0.02
0.025
0.03
0.035
0.04
0.045

**Figure 13:** Occurrence of respiratory disorders in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib ( Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Aspiration; (B) Cough; (C) Dyspnea; (E) Pulmonary embolism. All these adverse events are shown as percentages in graphs.

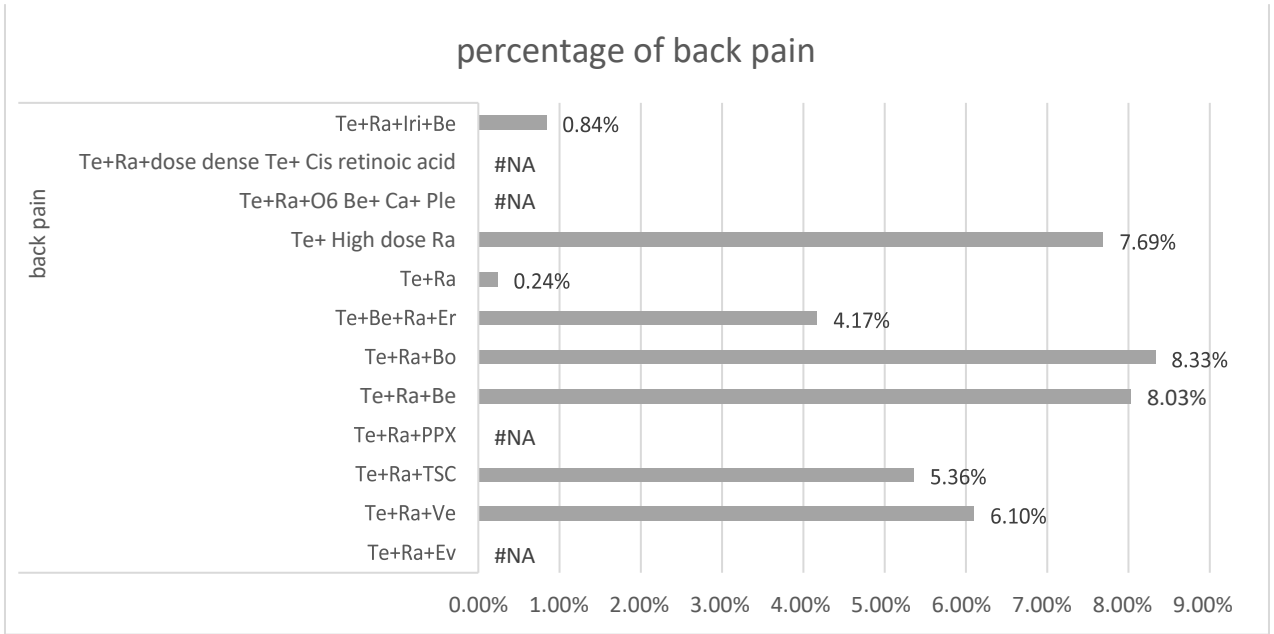
Aspiration rates are quite mild which can be figured from the above figure 13(A). 2.44% aspiration rate is found for (TMZ + radiation + PPX) combination. Figure 13(B) depicts that 20.83% cough appears in patients who received (TMZ + bevacizumab + radiation + erlotinib) combination treatment and it is the highest in comparison to other treatment regimens. From figure 13(C), it is well observed that 6.25% dyspnea occurs for (TMZ + bevacizumab + radiation + erlotinib) regimen. (Bevacizumab + radiation + TMZ) offers 5.64% rates of dyspnea in patients. Rates of pulmonary embolism are quite low. A 4.17% rate of pulmonary embolism is found for (TMZ + bortezomib + radiation) regimen, which is shown in figure 13(D).

Graphical presentation of musculoskeletal disorders in patients receiving different TMZ and radiotherapy regimens are shown below-

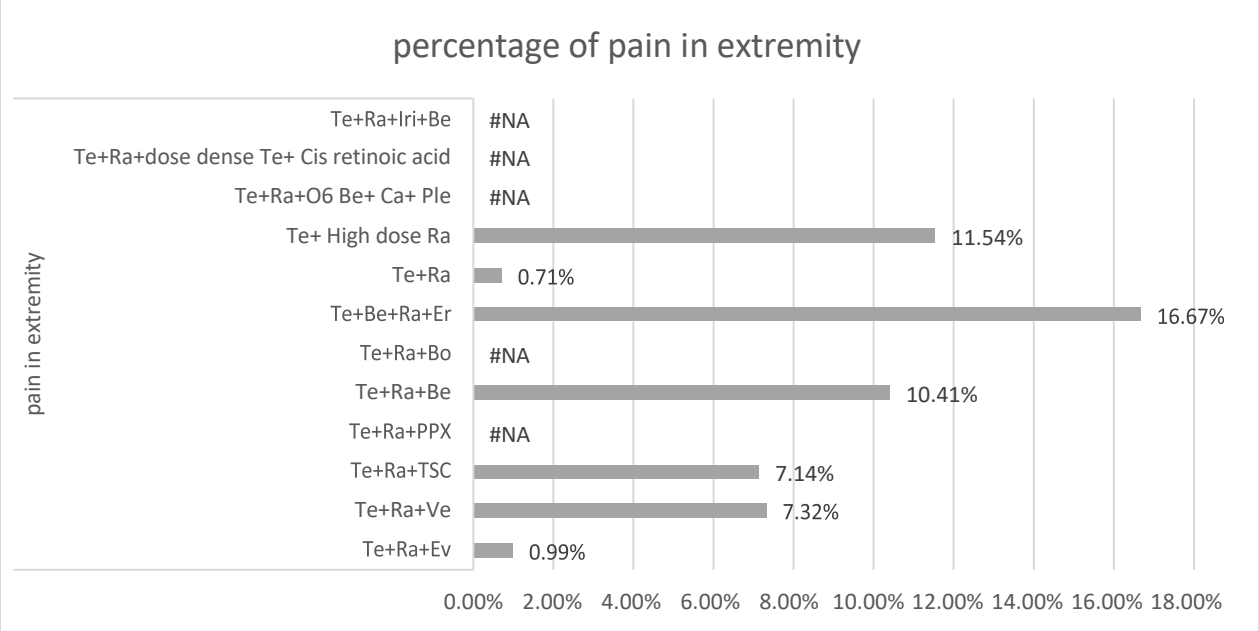
14(A)




14(B)



14(C)




14(D)

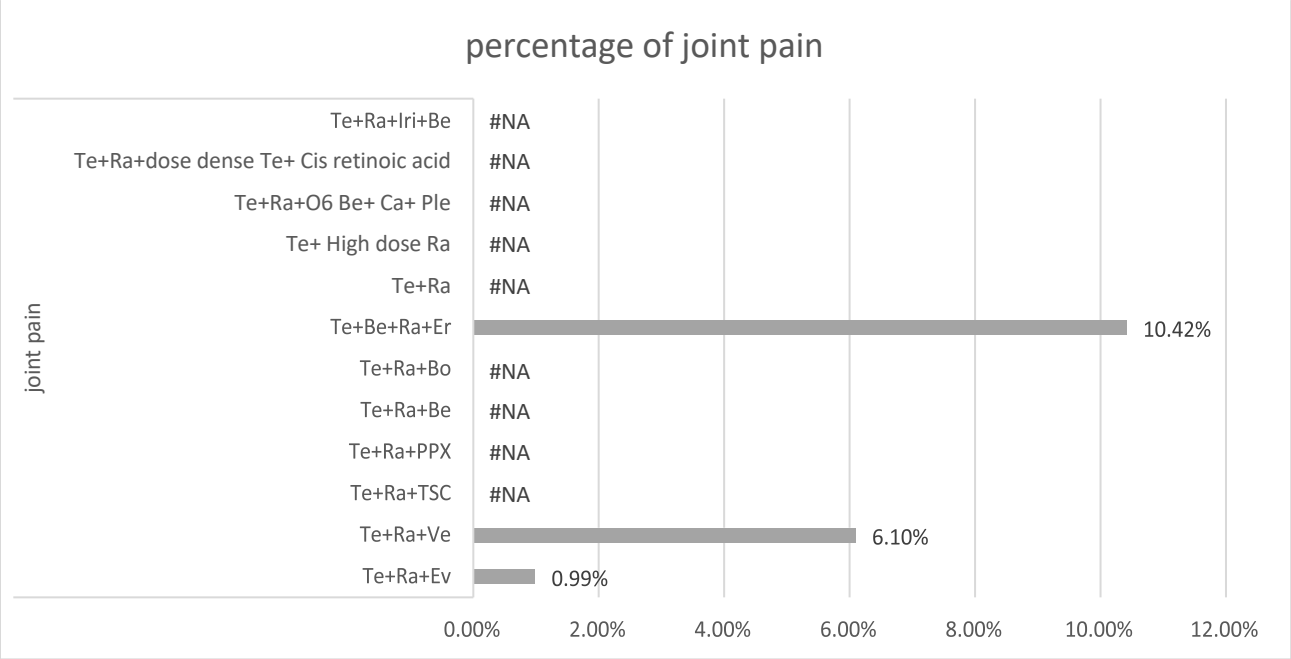


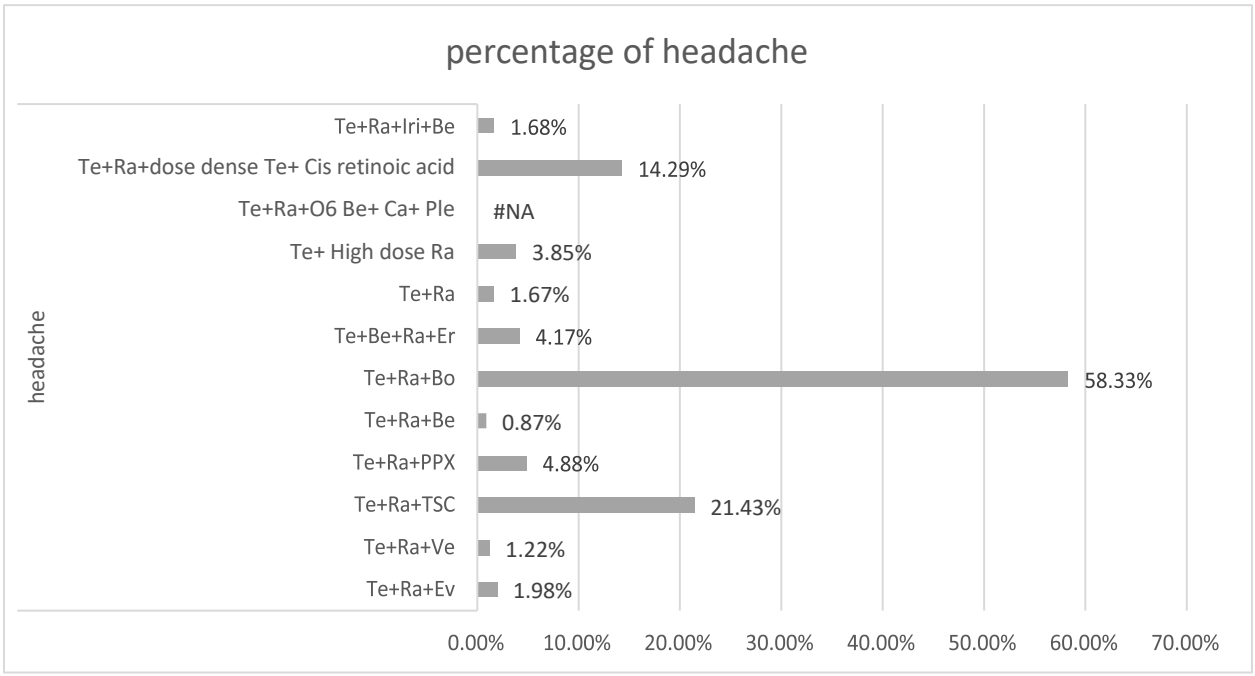

**Figure 14:** Occurrence of musculoskeletal disorders in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide

+ Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib ( Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Muscular weakness; (B) Back pain; (C) Pain in extremity; (D) Joint pain. All the values are expressed as percentages in the figures.

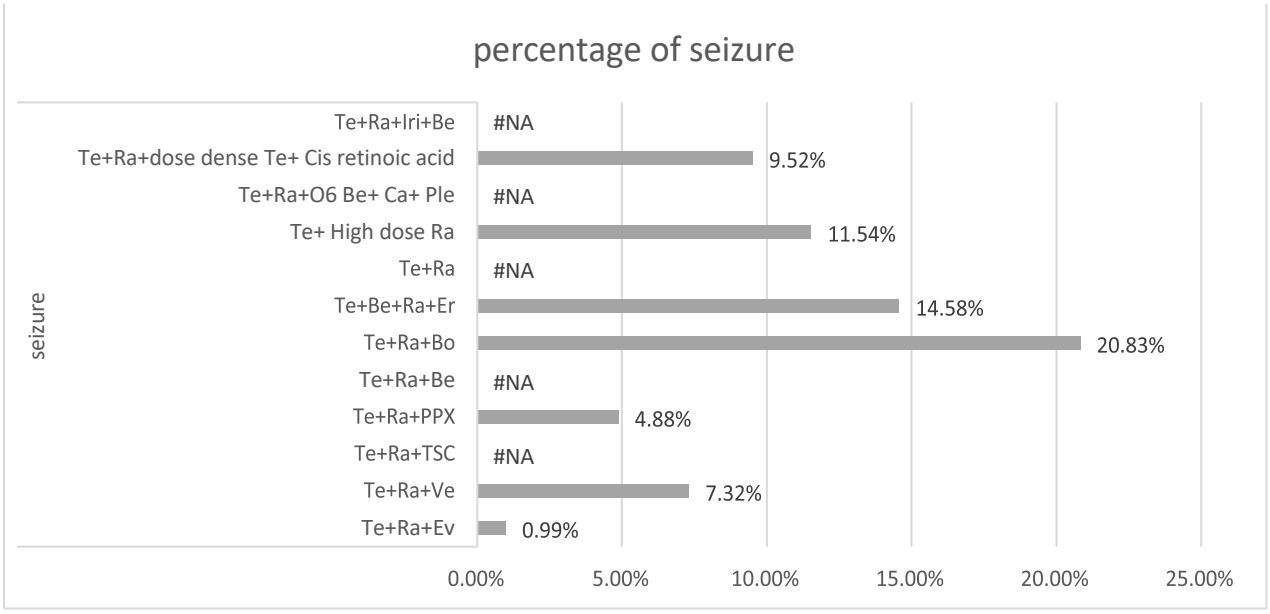
From figure 14(A), the highest rate of muscular weakness can be determined which is 54.55%. (TMZ + radiation +O6 benzylguanie + carmustine + plerixafor) the regimen is responsible for this high rate of muscular weakness in comparison to other treatment regimens. Figure14(B), depicts the rate of back pain prevalence in patients. 8.33% is the highest rate for (TMZ + radiation + bortezomib) regimen. Figure 14(C) presents the percentage of pain in extremities in patients receiving temozolomide and radiotherapy combination treatments. 16.67% is the highest rate for this parameter which appeared due to (TMZ + radiation + bevacizumab + erlotinib) regimen. Joint pain is a common muscular disorder in patients. Figure 14(D) demonstrates that 10.42% rates of joint pain are observed among patients when erlotinib is given in conjunction with TMZ, radiation, and bevacizumab.

Different nervous disorders occurring in patients receiving TMZ & radiation treatment can be observed through the following graphs-

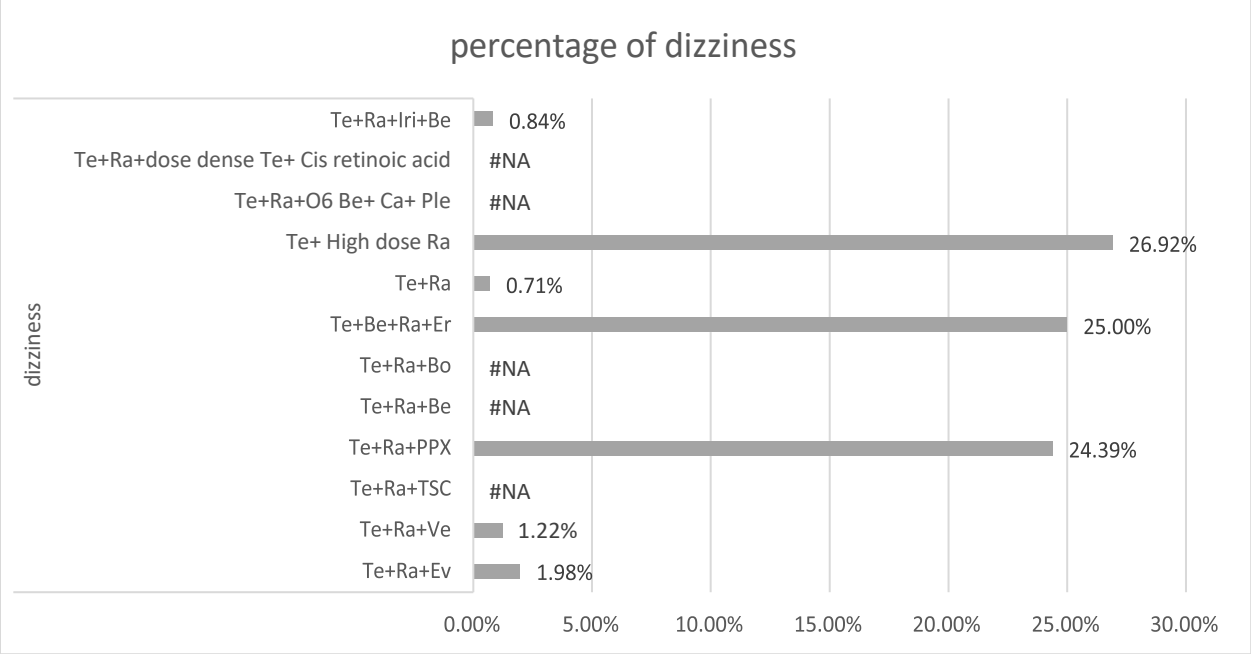
15(A)



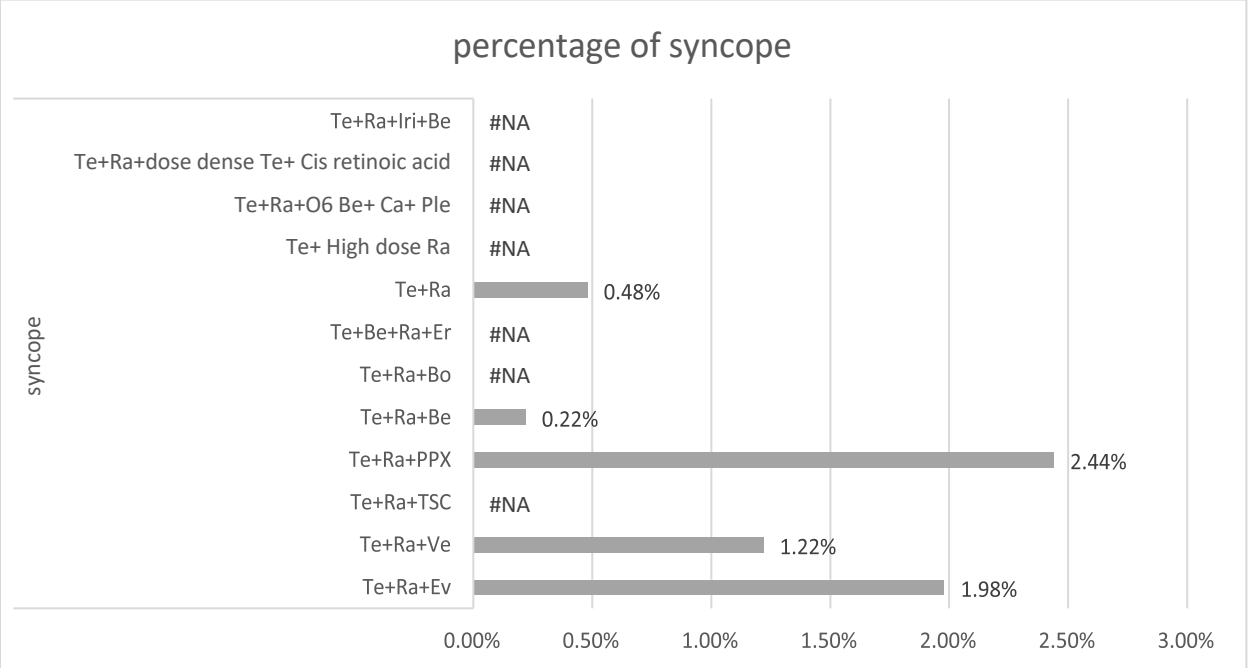

15(B)



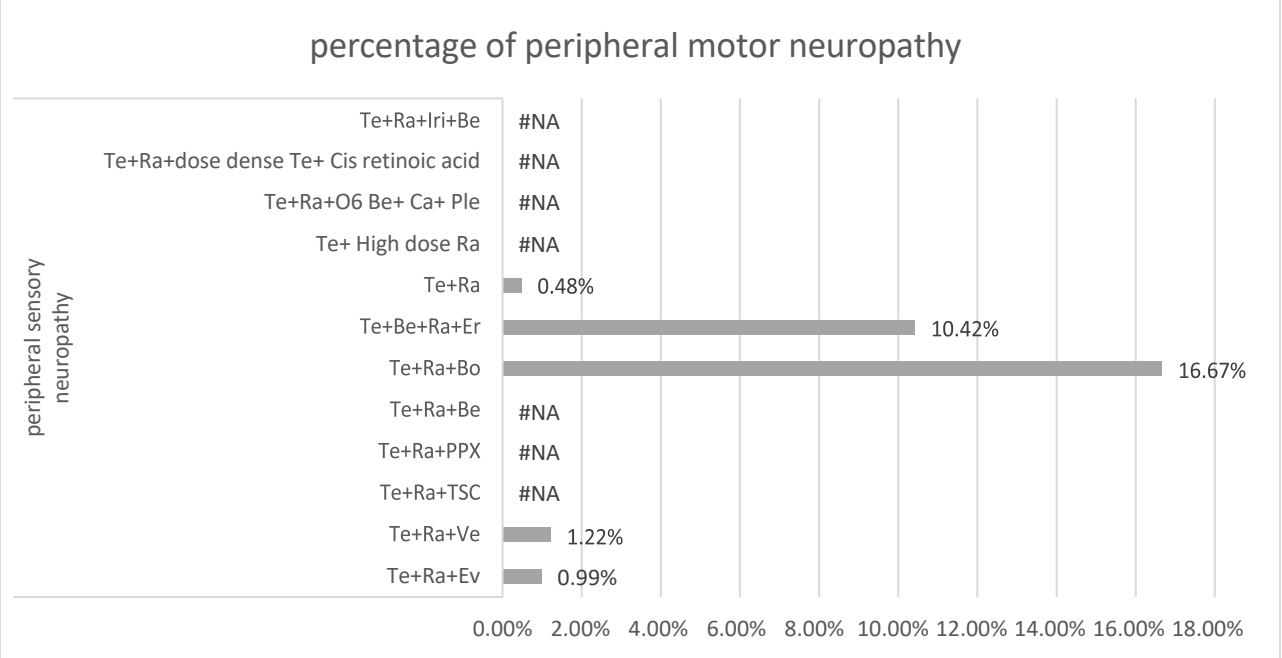
15(C)


percentage of dizziness
dizziness
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
0.84%
#NA
#NA
26.92%
0.71%
25.00%
#NA
#NA
24.39%
#NA
1.22%
1.98%
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%

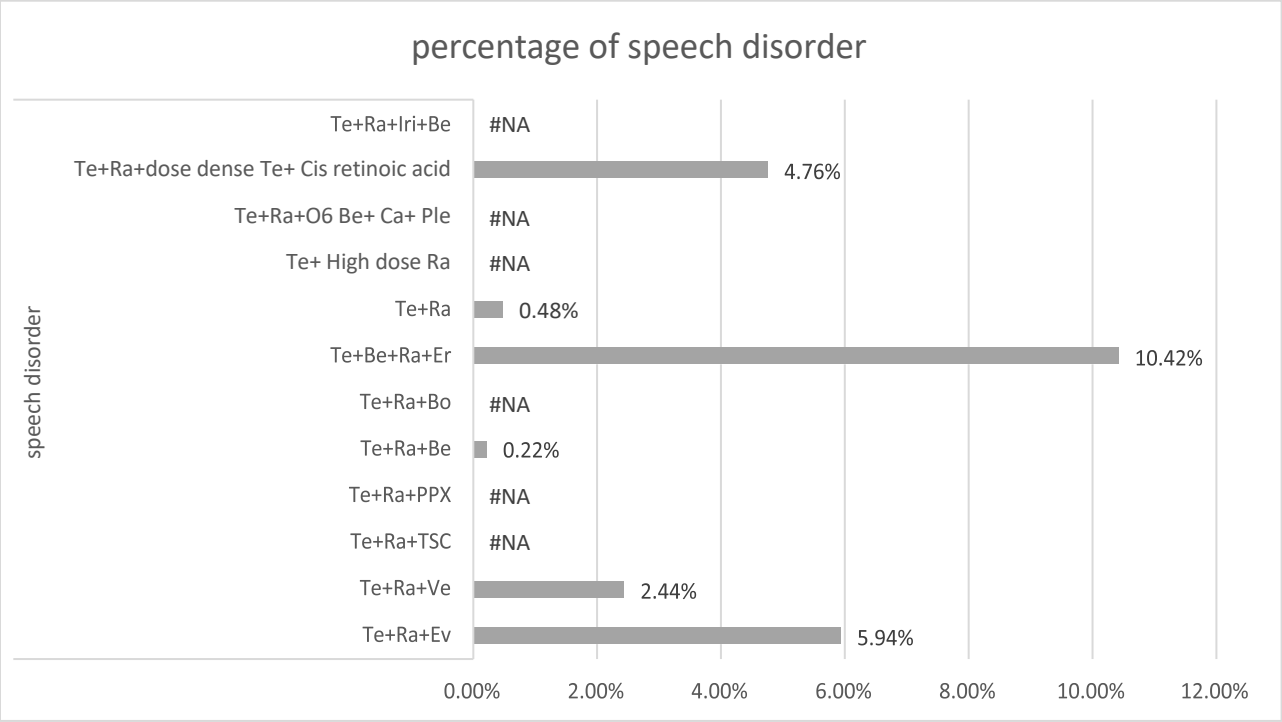
15(D)


percentage of syncope
syncope
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
#NA
0.48%
#NA
#NA
0.22%
2.44%
#NA
1.22%
1.98%
0.00%
0.50%
1.00%
1.50%
2.00%
2.50%
3.00%

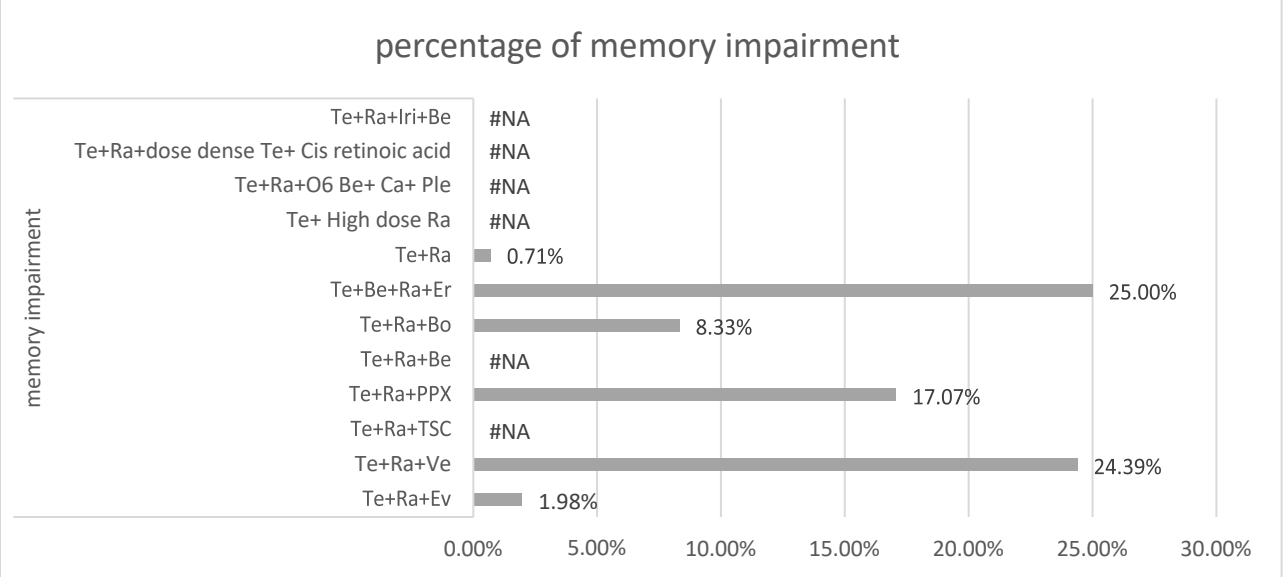
15(E)


percentage of peripheral motor neuropathy
peripheral sensory neuropathy
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
#NA
0.48%
10.42%
16.67%
#NA
#NA
#NA
1.22%
0.99%
0.00% 2.00% 4.00% 6.00% 8.00% 10.00% 12.00% 14.00% 16.00% 18.00%

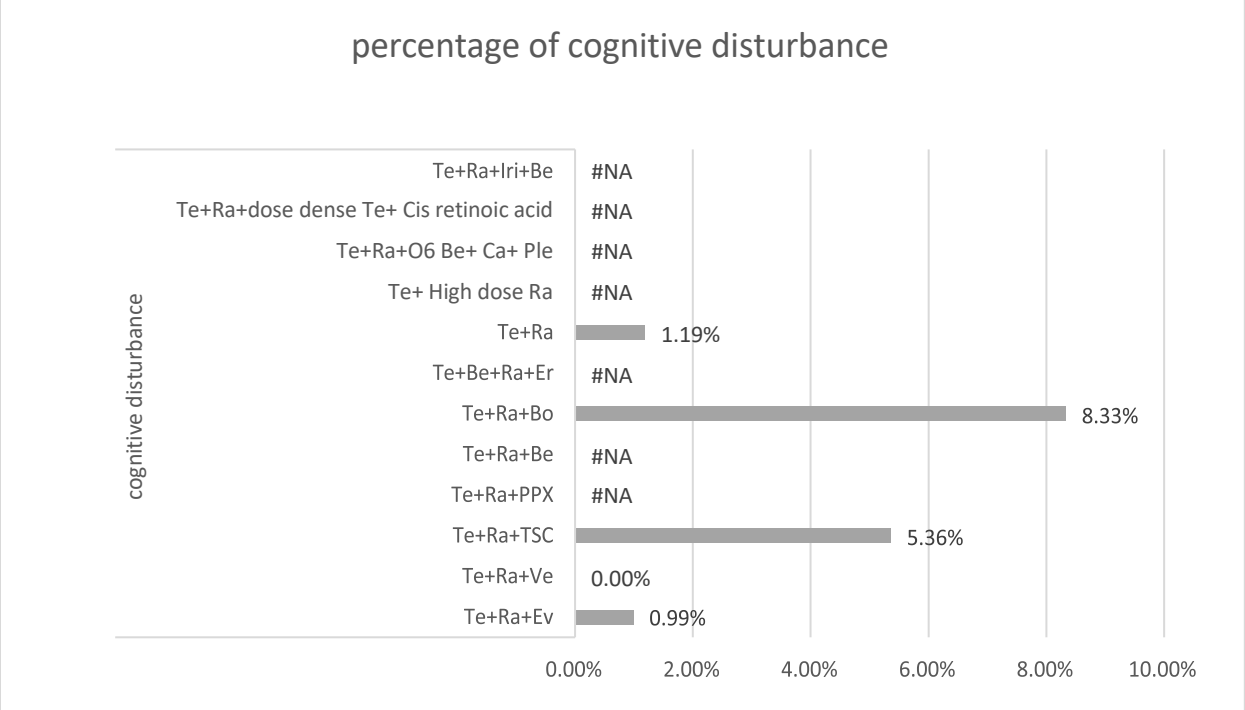
15(F)


percentage of speech disorder
speech disorder
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
4.76%
#NA
#NA
0.48%
10.42%
#NA
0.22%
#NA
#NA
2.44%
5.94%
0.00% 2.00% 4.00% 6.00% 8.00% 10.00% 12.00%

15(G)


percentage of memory impairment
memory impairment
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
#NA
0.71%
25.00%
8.33%
#NA
17.07%
#NA
24.39%
1.98%
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%

15(H)


percentage of cognitive disturbance
cognitive disturbance
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
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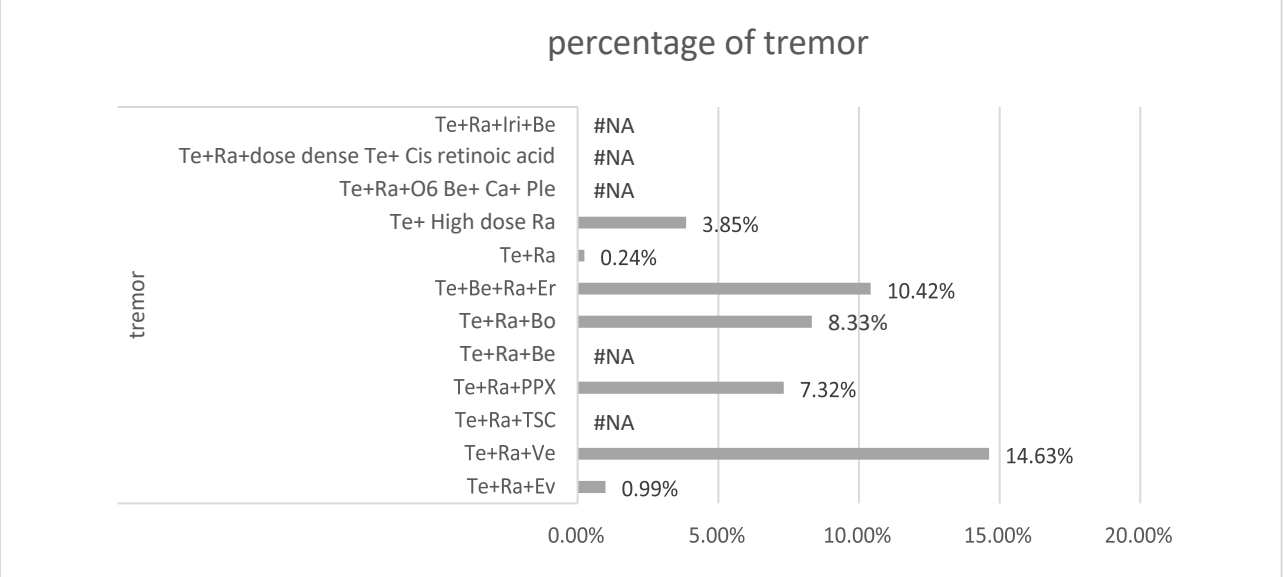
#NA
#NA
#NA
1.19%
#NA
8.33%
#NA
#NA
5.36%
0.00%
0.99%
0.00%
2.00%
4.00%
6.00%
8.00%
10.00%

15(I)


percentage of tremor
tremor
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
3.85%
0.24%
10.42%
8.33%
#NA
7.32%
#NA
14.63%
0.99%
0.00%
5.00%
10.00%
15.00%
20.00%

15(J)

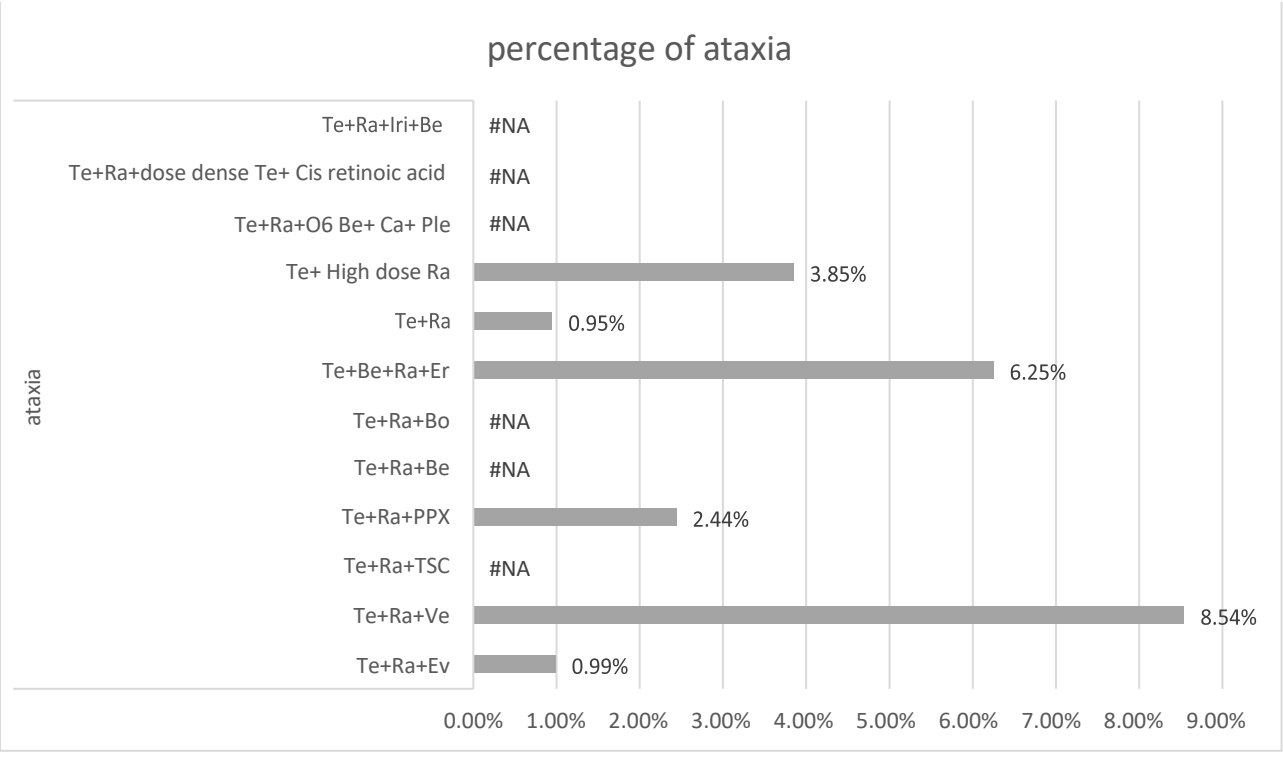

percentage of ataxia
ataxia
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
3.85%
0.95%
6.25%
#NA
#NA
2.44%
#NA
8.54%
0.99%
0.00%
1.00%
2.00%
3.00%
4.00%
5.00%
6.00%
7.00%
8.00%
9.00%

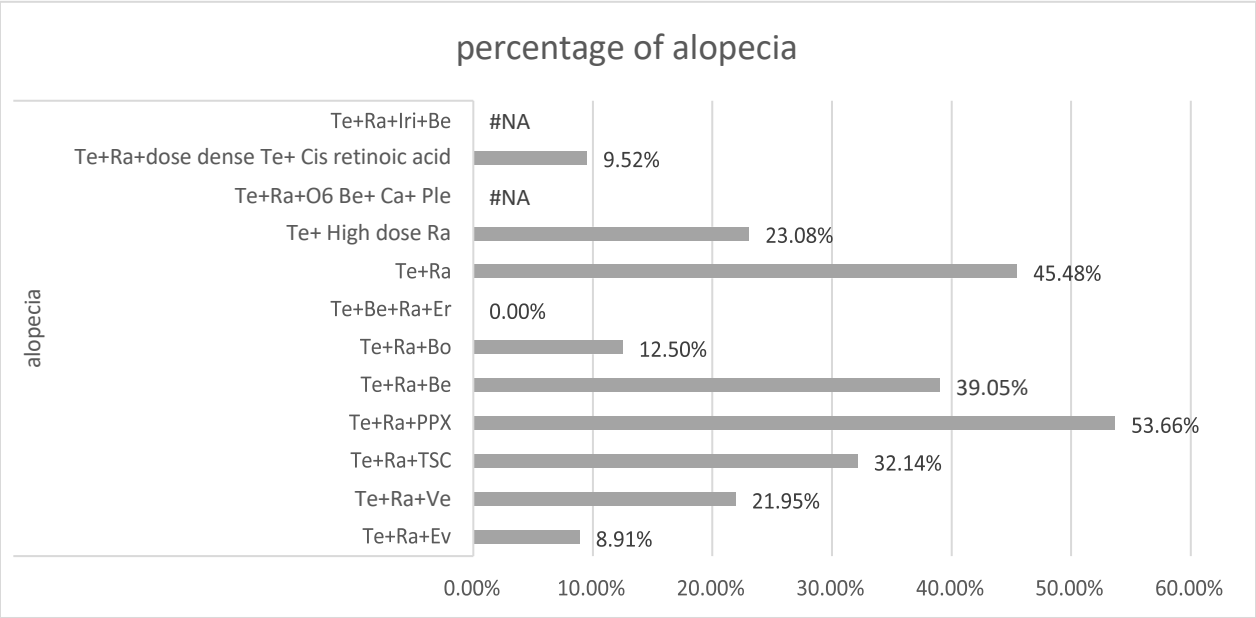
**Figure 15:** Occurrence of nervous disorders in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib (Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Headache; (B) Seizure; (C) Dizziness; (D) Syncope; (E) Peripheral motor neuropathy; (F) Speech disorder; (G) Memory impairment; (H) Cognitive disturbance; (I) Tremor; (J) Ataxia. Occurrence of all the nervous disorders in participants are shown in the above graphs.

Figure 15(A) analyzes that headache is the greatest at a rate of 58.33% in the case of (TMZ + radiation + bortezomib) regimen. Figure 15(B) shows the percentage of seizures in patients. 20.83% of seizure occurrence is recorded for (TMZ + radiation + bortezomib) combination. From figure 15(C), it is revealed that higher rates of dizziness are obtained from (TMZ + high dose radiation). 26.92% of dizziness occurs due to this treatment regimen. (TMZ +Radiation + bevacizumab + erlotinib) is responsible for 25% occurrence of dizziness in patients. Mild rates of syncope occurrence are analyzed from figure 15(D). 2.44% syncope appears for (TMZ + radiation + PPX) combination. Figure 15(E) shows that the rates of peripheral motor neuropathy are quite low in patients as only 4.17% rates are found in the case of (Bortezomib +TMZ + radiation). Other drug combinations provide lesser rates for peripheral motor

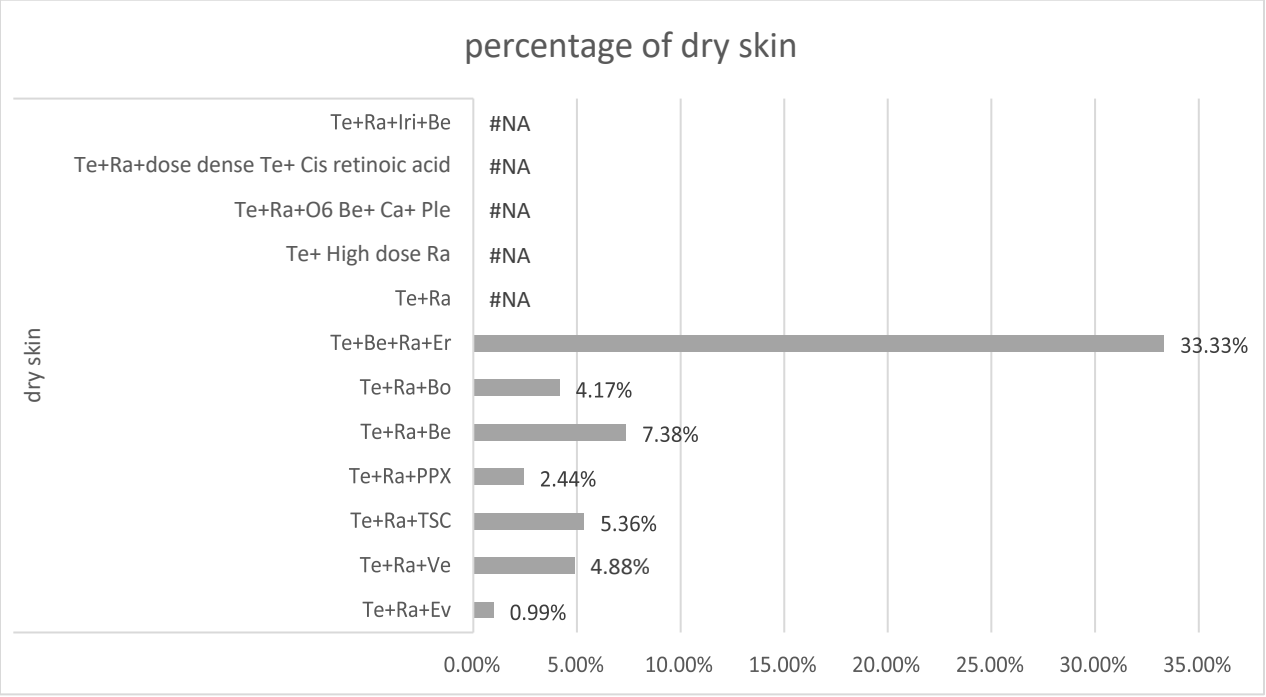
neuropathy. Speech disorder rates are determined for patients in figure 15(F) who underwent temozolomide and radiotherapy combination treatments. 10.42% rate of speech difficulties are found when erlotinib is incorporated with TMZ, radiation and bevacizumab. Figure 15(G) identifies the levels of memory impairments in patients where 25% is the highest rate due to (TMZ + radiation + bevacizumab + erlotinib) regimen. 24.39% rate of memory impairment occurs when vandetanib is included with TMZ and radiation therapy. A moderate level of cognitive disturbance (8.33%) is observed for (TMZ + bortezomib + radiation) therapy from figure 15(H). 5.36% rate of cognitive disorder is found for (TSC + TMZ + radiation). On the contrary, a 0% rate of cognitive disturbance is achieved due to the association of vandetanib with TMZ & radiation. Rates of tremor in patients are identified through figure 15(I), where 14.63% is the highest amount due to (TMZ + radiation + vandetanib) regimen. The occurrence of ataxia in patients who received temozolomide and radiotherapy treatment can be analyzed from figure 15(J). The highest level of ataxia (8.54%) is seen when vandetanib is incorporated with TMZ and radiation.

Skin disorders in patients receiving temozolomide and radiotherapy combination treatments-

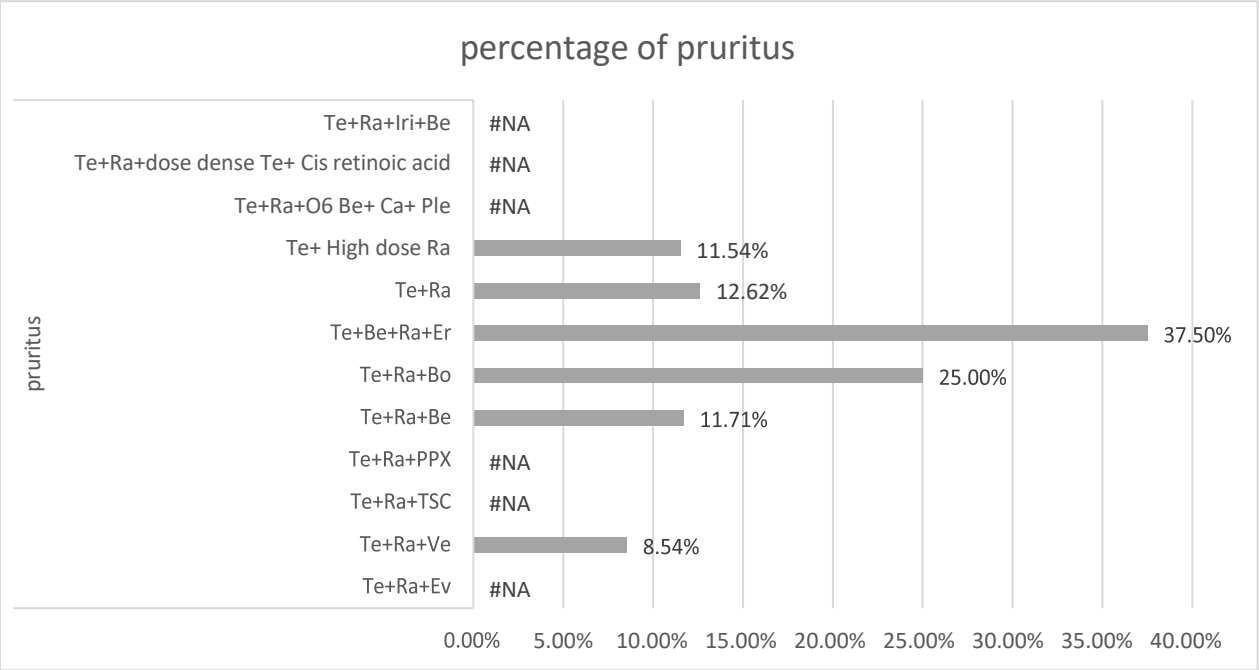
16(A)




16(B)



16(C)


percentage of pruritus
pruritus
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
11.54%
12.62%
37.50%
25.00%
11.71%
#NA
#NA
8.54%
#NA
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%
35.00%
40.00%

16(D)

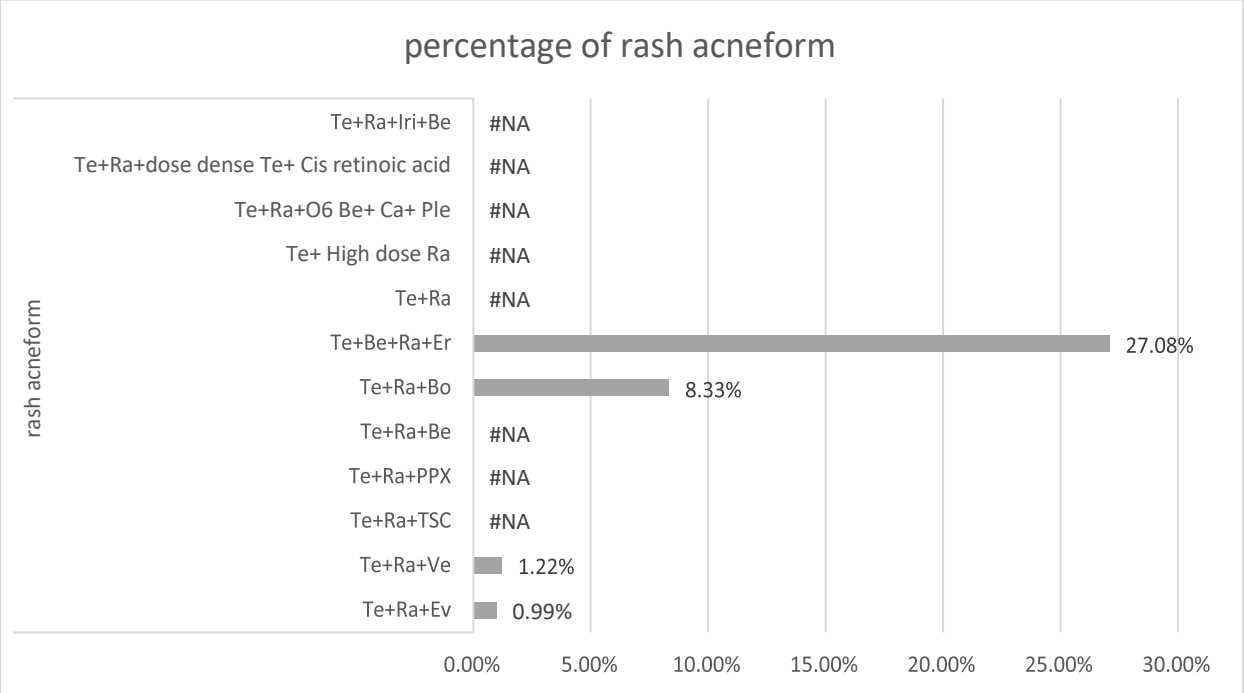
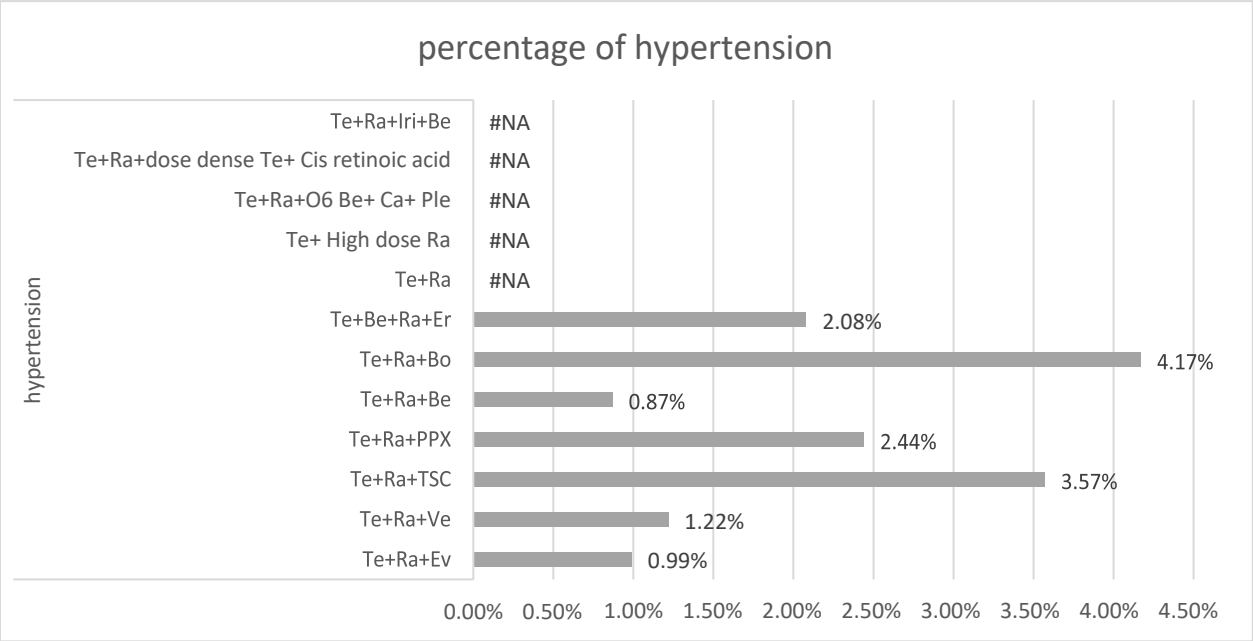

percentage of rash acneform
rash acneform
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
#NA
#NA
27.08%
8.33%
#NA
#NA
#NA
1.22%
0.99%
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%

**Figure 16:** Occurrence of skin disorders in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib (Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Alopecia; (B) Dry skin; (C) Pruritus; (D) Rash acneform. The values are shown as percentages in the figures.

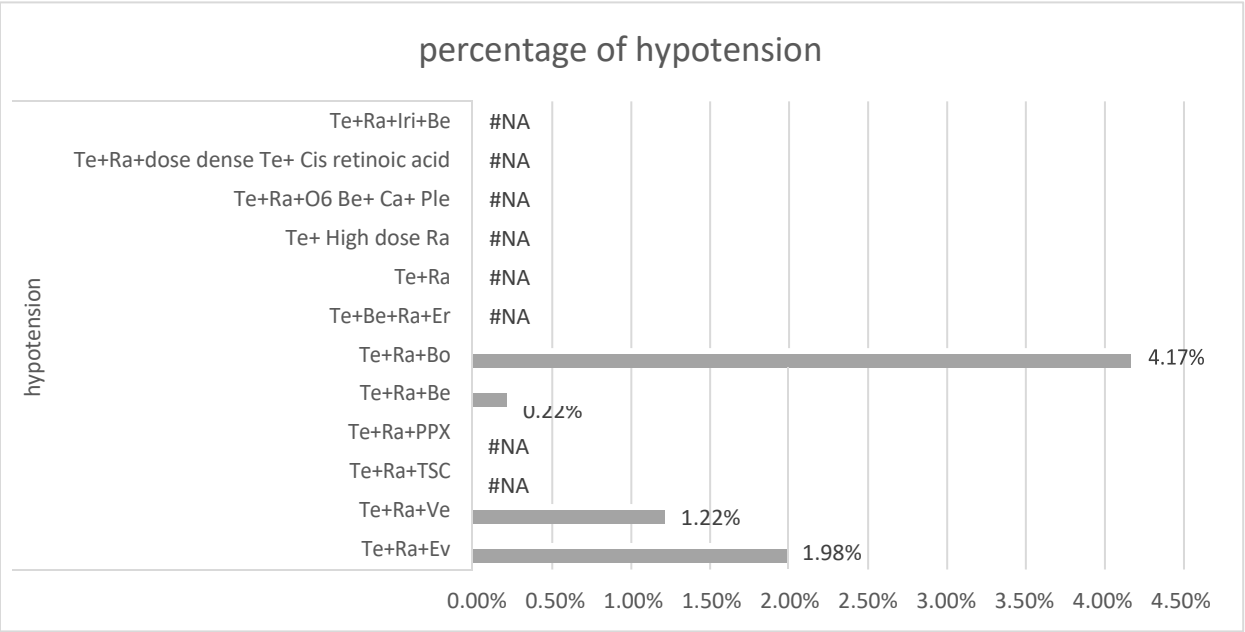
Alopecia is a very common skin disorder prevalent in patients and from figure 16(A), the rates of alopecia occurrence can be well observed. Total 53.66% alopecia occurs in patients while undergoing (TMZ+ PPX + radiation) therapy. Conventional TMZ and radiation treatment results in 45.48% alopecia among patients. The appearance of dry skin in patients during combination treatment is well observed from figure 16(B), where the highest percentage of dry skin is shown for (TMZ + bevacizumab + radiation + erlotinib) regimen at a rate of 33.33%. Figure 16(C) displays the percentage of pruritus among patients receiving temozolomide and radiotherapy combination treatments. Highest rate is observed for (TMZ + radiation + bevacizumab + erlotinib) regimen. 25% prevalence is determined for (TMZ + radiation + bortezomib). From figure 16(D), it is evident that the prevalence of rash acneform is much higher in (TMZ + bevacizumab + radiation + erlotinib) compared to other drug combinations. Only 8.33% incidence is seen for (Bortezomib + TMZ + radiation) regimen.

Cardiac disorders in patients undergoing TMZ & radiation treatment are demonstrated by the following figures-

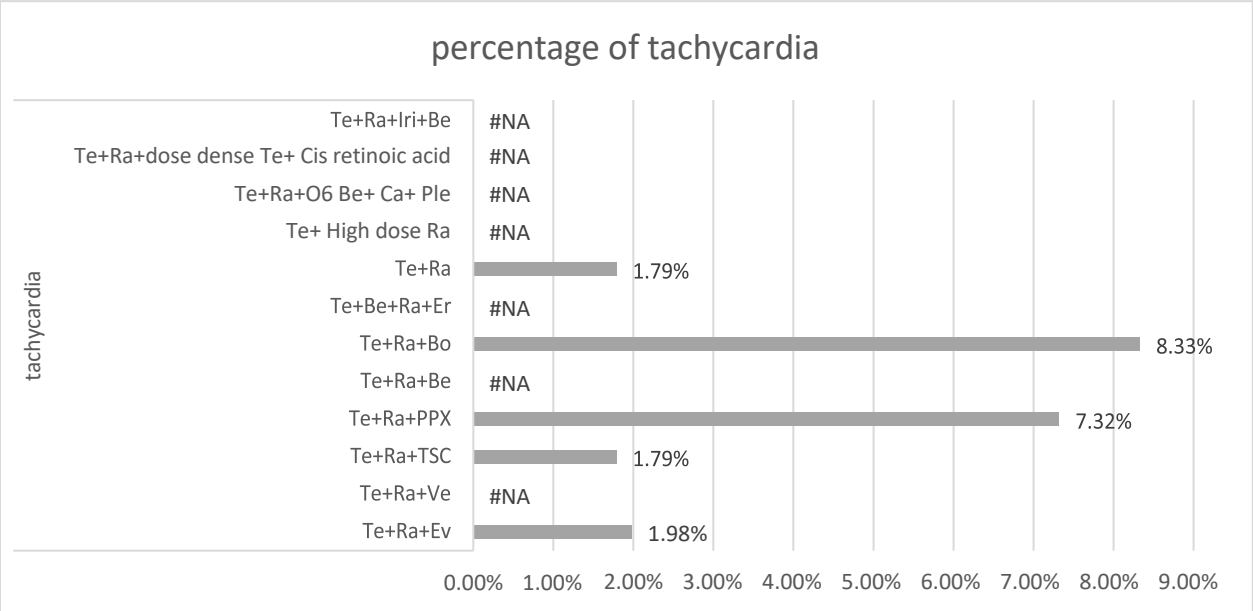
17(A)




17(B)



17(C)


percentage of tachycardia
tachycardia
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
#NA
1.79%
#NA
8.33%
#NA
7.32%
1.79%
#NA
1.98%
0.00% 1.00% 2.00% 3.00% 4.00% 5.00% 6.00% 7.00% 8.00% 9.00%

17(D)

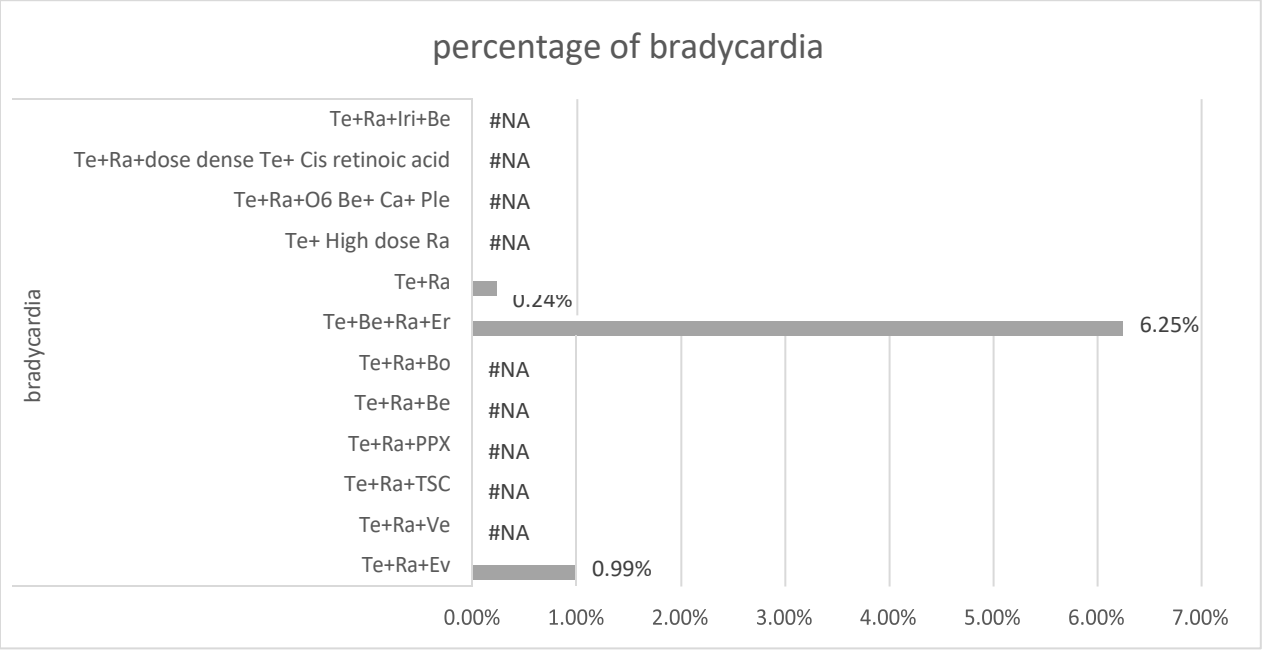
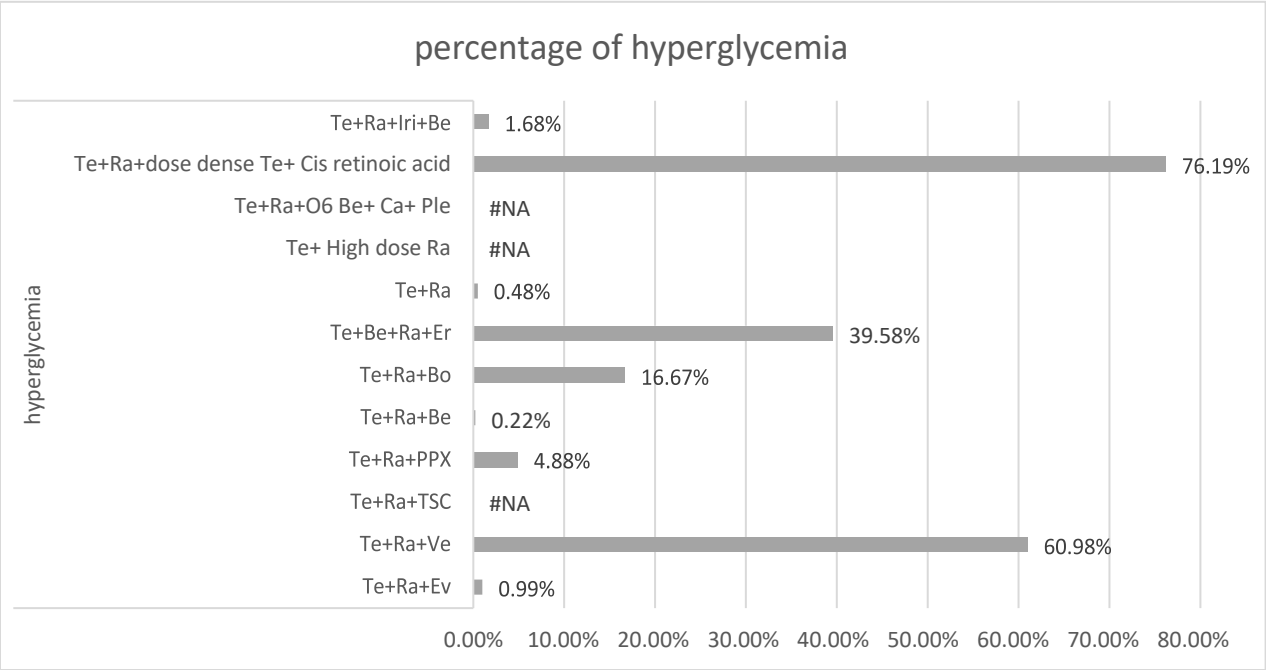

percentage of bradycardia
bradycardia
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
#NA
0.24%
6.25%
#NA
#NA
#NA
#NA
#NA
0.99%
0.00% 1.00% 2.00% 3.00% 4.00% 5.00% 6.00% 7.00%

**Figure 17:** Occurrence of cardiac disorders in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib (Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Hypertension; (B) Hypotension; (C) Tachycardia; (D) Bradycardia. The values are shown in graphs as percentages.

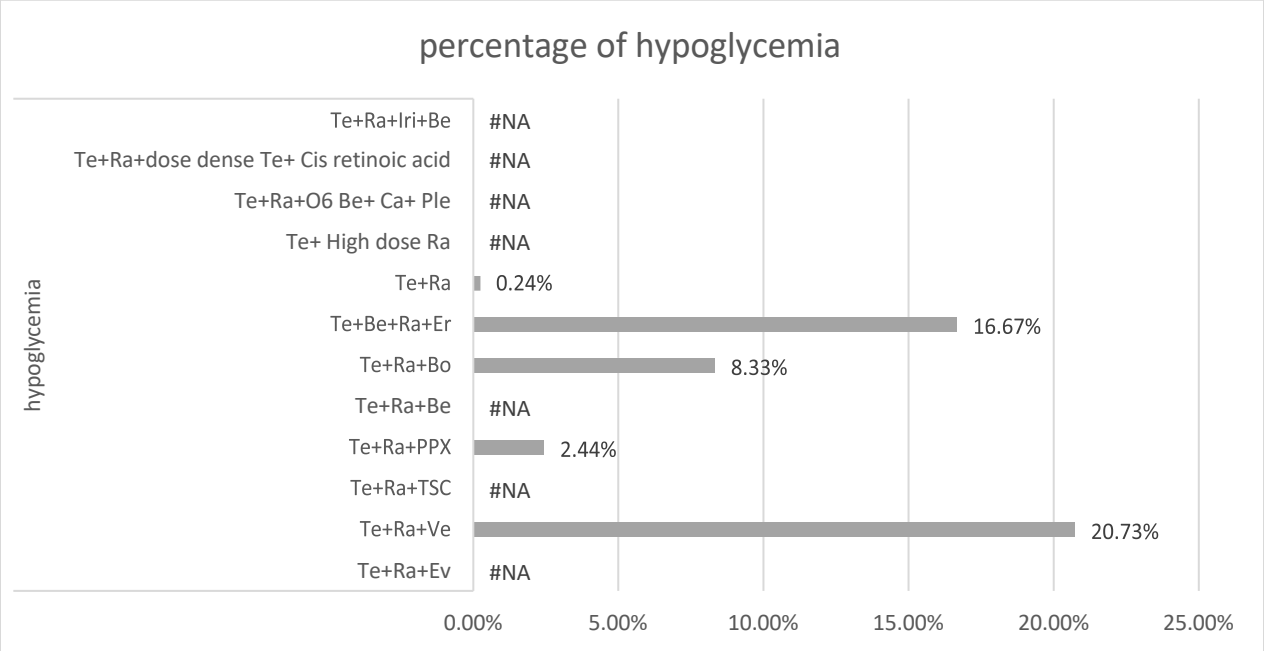
Hypertension is one of the major cardiac disorders and figure 17(A) is representative of hypertension prevalence in patients. (TMZ + radiation + bortezomib) resulted in 4.17% of hypertension. On the other hand, 3.57%, 2.44% and 1.22% rates of incidence were found for (TMZ + radiation + TSC), (TMZ + radiation + PPX) and (TMZ + vandetanib + radiation) respectively. Figure 17(B) determines the level of hypotension among patients undergoing multiple chemoradiation treatments. Only 4.17% hypotension occurrence is observed in case of (bortezomib + TMZ + radiation). Percentages of incidence of hypotension are much low for other combinations. Figure 17(C) demonstrates the incidence of tachycardia in patients where 8.33% rate of tachycardia is determined for (TMZ + radiation + bortezomib) regimen. (TMZ + radiation + PPX) shows 7.32% rate of tachycardia. Minimal level of bradycardia rate in patients is seen from figure 17(D). 6.25% occurrence rate is found for (TMZ+ erlotinib + bevacizumab + radiation) regimen.

Metabolism & nutritional disorders are depicted by the following graphs-

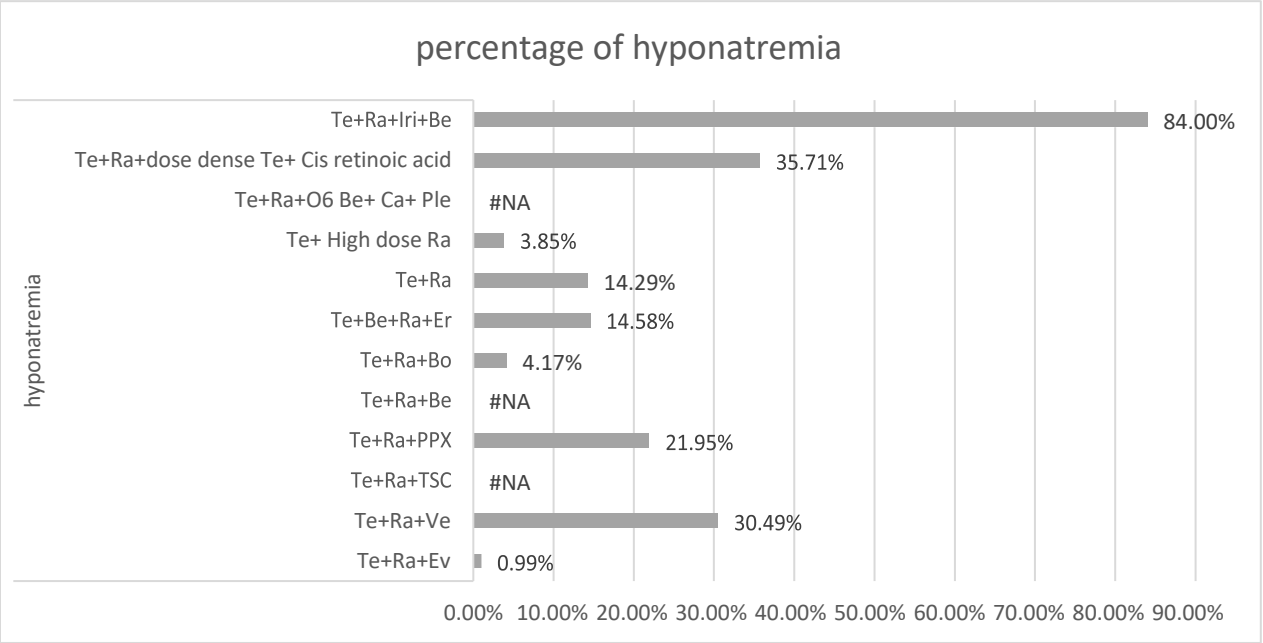
18(A)




18(B)



18(C)


percentage of hyponatremia
hyponatremia
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
84.00%
35.71%
#NA
3.85%
14.29%
14.58%
4.17%
#NA
21.95%
#NA
30.49%
0.99%
0.00% 10.00% 20.00% 30.00% 40.00% 50.00% 60.00% 70.00% 80.00% 90.00%

18(D)

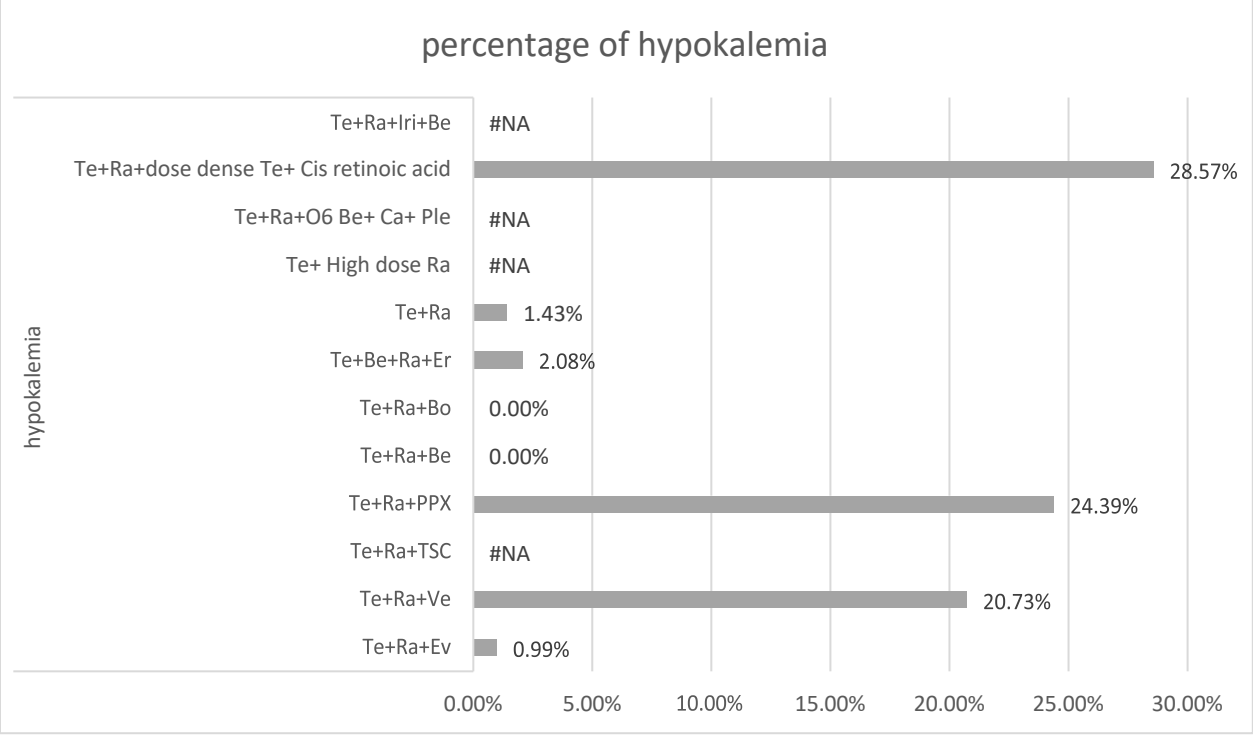

percentage of hypokalemia
hypokalemia
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
28.57%
#NA
#NA
1.43%
2.08%
0.00%
0.00%
24.39%
#NA
20.73%
0.99%
0.00% 5.00% 10.00% 15.00% 20.00% 25.00% 30.00%

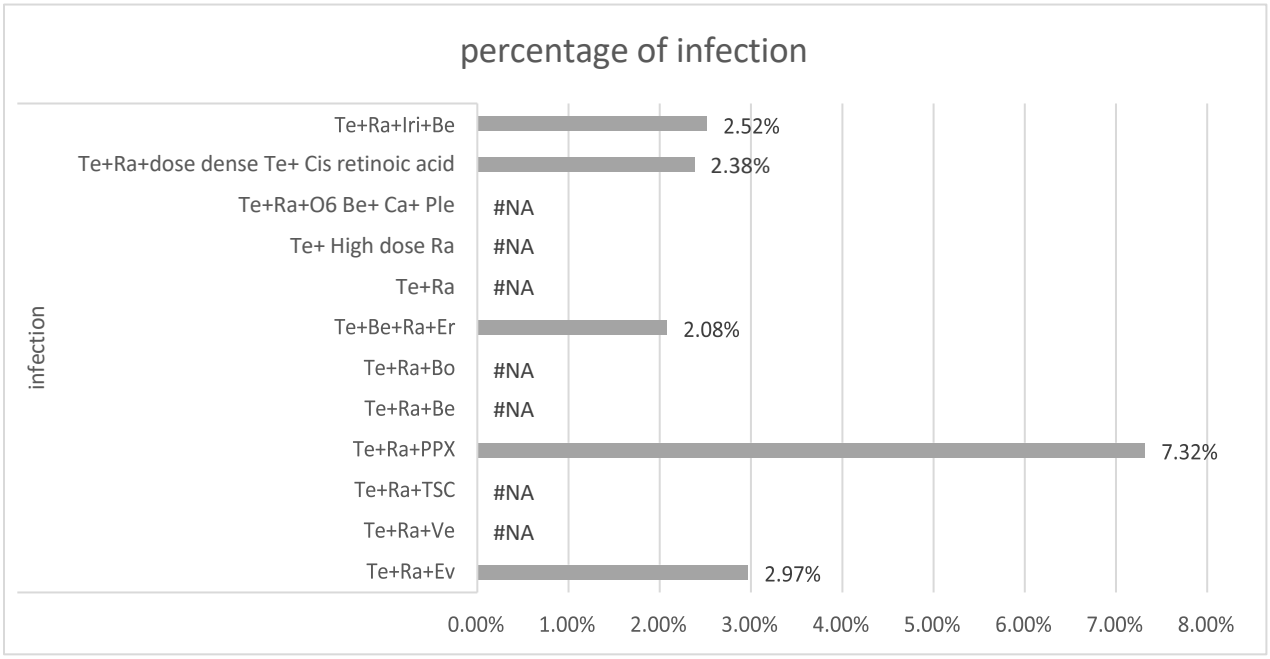
**Figure 18:** Occurrence of metabolism & nutritional disorders in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib (Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Hyperglycemia; (B) Hypoglycemia; (C) Hyponatremia; (D) Hypokalemia. The values are presented as percentages in graphs.

Hyperglycemia is a common nutritional disorder and from figure 18(A), a clear representation of hyperglycemia rates in patients can be obtained. (TMZ + radiation + dose dense TMZ + cis retinoic acid) offers the highest rate of hyperglycemia in patients at 76.19%. 60.98% rate of hyperglycemia is seen for (TMZ+ radiation + everolimus) regimen. Hypoglycemia rates in patients receiving temozolomide and radiotherapy combination treatments are demonstrated in figure 18(B) which reveals a 20.73% rate of hypoglycemia prevalence for (TMZ + radiation + vandetanib) regimen. 16.67% rate of hypoglycemia is seen for (Erlotinib + TMZ + radiation + bevacizumab) therapy. The prevalence of hyponatremia is quite major in the case of one drug combination which is shown in figure 18(C). 84% occurrence of hyponatremia is observed when TMZ & radiotherapy is combined with irinotecan and bevacizumab. Figure 18(D) represents the percentage of hypokalemia in patients and the highest rate is observed for (TMZ

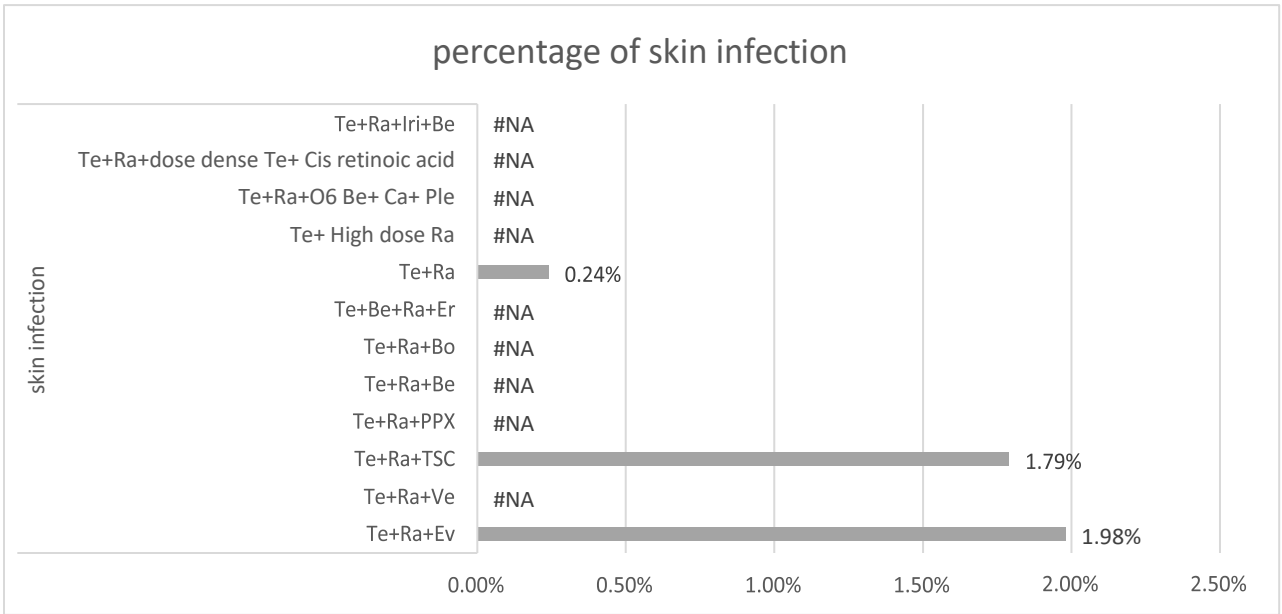
+ radiation + dose-dense TMZ + cis retinoic acid) regimen. (TMZ + radiation + PPX) shows 24.39% of hypokalemia in patients.

Prevalence of infectious disorders in patients receiving TMZ & radiotherapy combination treatments is demonstrated by the following figures-

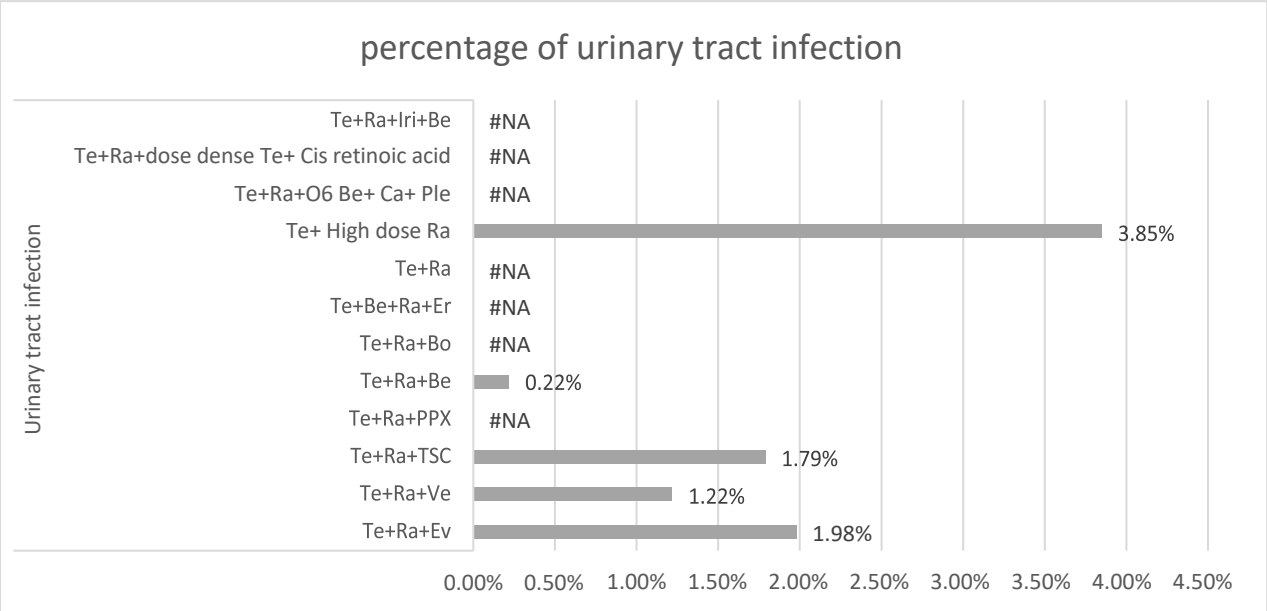
19(A)




19(B)



19(C)


percentage of urinary tract infection
Urinary tract infection
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
#NA
#NA
#NA
3.85%
#NA
#NA
#NA
0.22%
#NA
1.79%
1.22%
1.98%
0.00% 0.50% 1.00% 1.50% 2.00% 2.50% 3.00% 3.50% 4.00% 4.50%

19(D)

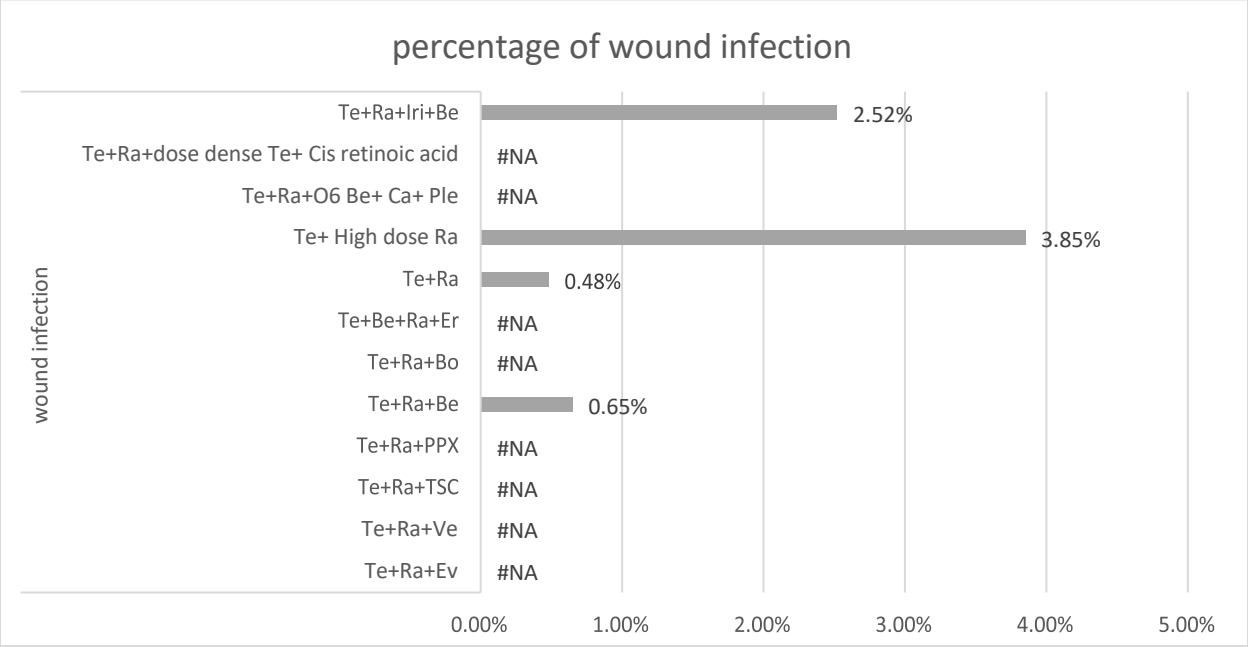

percentage of wound infection
wound infection
Te+Ra+Iri+Be
Te+Ra+dose dense Te+ Cis retinoic acid
Te+Ra+O6 Be+ Ca+ Ple
Te+ High dose Ra
Te+Ra
Te+Be+Ra+Er
Te+Ra+Bo
Te+Ra+Be
Te+Ra+PPX
Te+Ra+TSC
Te+Ra+Ve
Te+Ra+Ev
2.52%
#NA
#NA
3.85%
0.48%
#NA
#NA
0.65%
#NA
#NA
#NA
#NA
0.00% 1.00% 2.00% 3.00% 4.00% 5.00%

**Figure 19:** Occurrence of infectious disease in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib (Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Infection; (B) Skin infection; (C) Urinary tract infection; (D) Wound infection. The values are presented as percentages here.

From figure 19(A), it is evident that infection is higher for (TMZ+ radiation +PPX) regimen at a rate of 7.32%. Other treatments demonstrate that patients have a low level of infection. Figure 19(B) shows that only 1.98% of skin infection occurs for the (TMZ+ radiation+ everolimus) regimen and 1.79% of skin infection occurs for the (TMZ+ TSC+ radiation) regimen, whereas conventional chemoradiation only resulted in 24% of skin infection in patients. Urinary tract infection is a common infectious disease, and figure 19(C) shows that when high dose radiation is combined with TMZ, only 3.85 % get urinary tract infections. Other combinations, such as (TMZ+ radiation+ TSC), (TMZ + radiation + vandetanib), and (TMZ+ radiation+ everolimus), had a reduced rate of side effects. In the case of drug combinations comprising TMZ and radiotherapy, minor wound infection is found, and figure 19(D) reveals that 3.85 % of wound infection occurs in patients getting high doses of radiation combined with TMZ. The (TMZ+ radiation+ bevacizumab + irinotecan) regimen results in just 2.52% wound infection. The

wound infection levels in (TMZ+ radiation) and (TMZ+ radiation+ bevacizumab) are exceedingly low.

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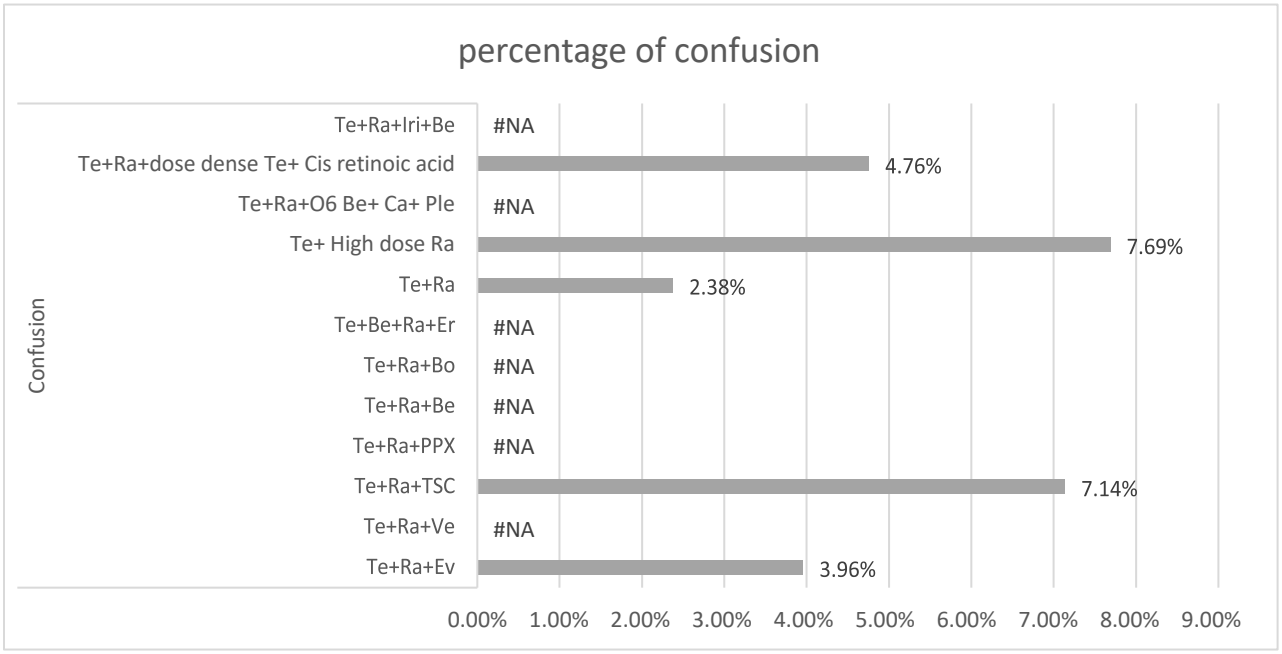
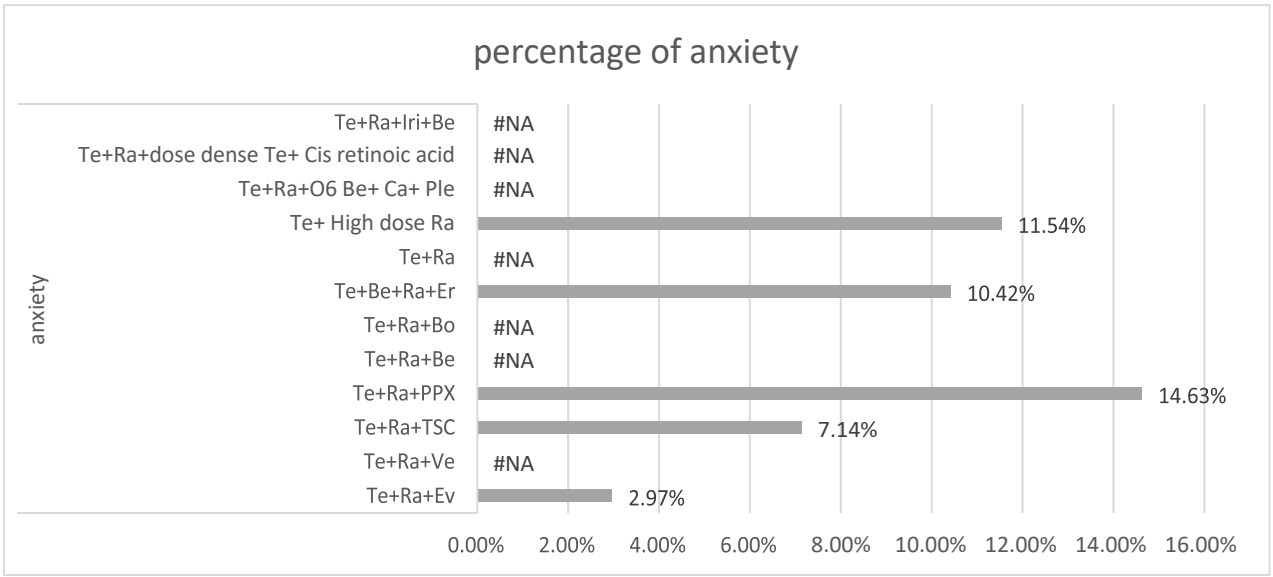
Psychiatric disorders appearing in patients while receiving TMZ & radiotherapy combination treatment is shown below-

20(A)




20(B)



20(C)

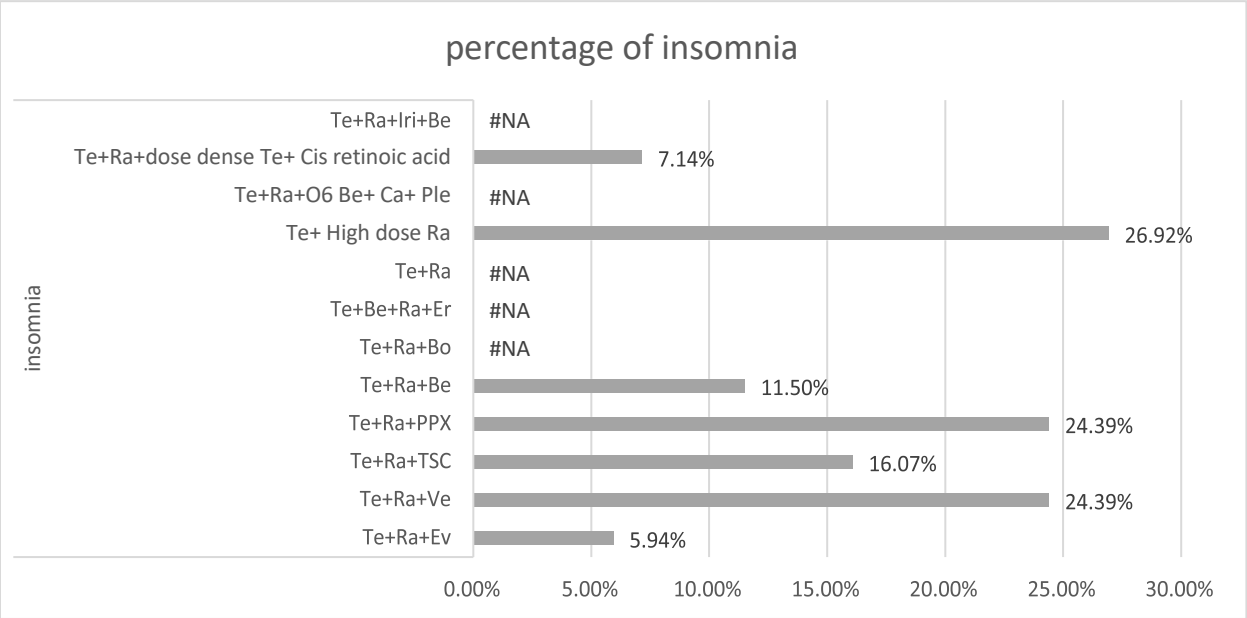



**Figure 20:** Occurrence of psychiatric disorders in patients receiving temozolomide and radiotherapy combination treatments. The various drug combinations that were observed are: Temozolomide + Radiation + Irinotecan + Bevacizumab (Te + Ra + Iri + Be), Temozolomide + Radiation + Dose dense temozolomide + Cis retinoic acid (Te + Ra + dose dense Te + Cis retinoic acid), Temozolomide + Radiation + O6 benzylguanine + Carmustine + Plerixafor (Te + Ra + O6 Be + Ca + Ple), Temozolomide + High dose radiation (Te + High dose Ra), Temozolomide + Radiation (Te + Ra), Temozolomide + Bevacizumab + Radiation + Erlotinib (Te + Be + Ra + Er), Temozolomide + Radiation + Bortezomib (Te + Ra + Bo), Temozolomide + Radiation + Bevacizumab (Te + Ra + Be), Temozolomide + Radiation + Paclitaxel Poglumex (Te + Ra + PPX), Temozolomide + Radiation + Trans Sodium Crocetinate (Te + Ra + TSC), Temozolomide + Radiation + Vendetanib (Te + Ra + Ve), Temozolomide + Radiation + Everolimus (Te + Ra + Ev). (A) Confusion; (B) Anxiety; (C) Insomnia. The adverse events are shown as percentages in the figures.

Confusion is a psychological illness that affects patients, and the prevalence of confusion among patients after having TMZ and radiation treatment can be seen in figure 20(A). People with (TMZ+ high dose radiation) and (TMZ + TSC + radiation) showed moderate levels of confusion at 7.69 % and 7.14 %, respectively. Figure 20(B) exhibits the presence of anxiety in individuals who have received several TMZ radiation treatments. In the case of the (TMZ+ PPX+ radiation) regimen, the highest rate of anxiety is 14.63%. Patients treated with (TMZ+ high dose radiotherapy) and (TMZ+ bevacizumab + radiation + erlotinib) regimens, on the other hand, had anxiety levels of 11.54% and 10.42%, respectively. Figure 20(C) illustrates the percentage of insomnia in patients who have the highest risk of insomnia when high-dose radiation and TMZ are used together. Patients treated with (TMZ+ radiation +PPX) and (TMZ+ radiation+ vandetanib) have substantial levels of sleeplessness.

# Chapter 5

# Discussion

12 different types of drug combinations are evaluated in this study based on their efficacy in the treatment of individuals with glioblastoma multiforme, including treatment outcomes and treatment-related adverse effects. The use of temozolomide and radiation is prevalent in all these therapeutic combinations. Temozolomide is a new oral alkylating drug that has performed admirably in the treatment of a wide range of solid tumors, including primary malignant brain tumors. Because of its unique chemical composition and pharmacokinetic features, TMZ has some advantages over other alkylating drugs. TMZ can be taken orally with no dietary restrictions, and about 100 percent of the dose taken orally enters the bloodstream. TMZ is also linked to a low rate of serious adverse effects. Unlike nitrosoureas and other alkylating drugs, which chemically cross-link DNA and cause severe, dose-limiting cumulative hematopoietic toxicity, TMZ causes only mild, non-cumulative myelosuppression (Koukourakis et al., 2009). TMZ efficiently crosses the blood-brain barrier and is effective against primary brain cancers due to its modest molecular weight (M,1995). Temozolomide was originally invented to treat malignant melanoma patients with brain metastases, but it also displayed activity in relapsed GBM patients, prompting additional exploration. Temozolomide has a fast, essentially full oral absorption rate. It transforms to MTIC (5-(3-methyltriazen-1-yl)imidazol-4-carboxamid) spontaneously, and the active metabolite reaches plasma peak concentration 30 to 90 minutes after uptake, with a plasma half-life of 2 hours (Dresemann, 2010).

This study compares the outcomes and efficacy of various treatment regimens by analyzing the findings of numerous clinical trials in which several medications are used in conjunction with TMZ and radiation to treat glioblastoma. It provides a thorough comparison of traditional treatment with TMZ and radiotherapy, as well as treatment with drug combinations in

conjunction with chemoradiation, to help establish which of these treatments is the most beneficial.

Everolimus [Afinitor, RAD-001 (40-O-(2-hydroxyethyl)-rapamycin)] is a rapamycin analog (rapalog) in development as an anticancer drug. Everolimus binds to the cyclophilin FKBP-12 in the same way that rapamycin does, and this complex attaches to the serine-threonine kinase mammalian target of rapamycin (mTOR) when it forms a complex (mTORC1) with raptor and mLST8, inhibiting signaling downstream. Everolimus and other rapalogs decrease the growth of a variety of human tumor cell lines, with up to 50% suppression in the sub nano-molar concentration range, limit the proliferation of human umbilical vein endothelial cells, and diminish HIF-1α and VEGF production in cultured tumor cells (Houghton, 2010). This mTOR signaling pathway blocker is commonly used to prevent rejection following kidney and heart transplants. Everolimus has been shown to inhibit the proliferation of cancer cell lines in vitro in breast cancer and pancreatic neuroendocrine tumors, and patients receiving TMZ treatment demonstrated good tolerability. (Dong et al., 2020).

The combination of everolimus with conventional chemoradiation resulted in mild toxicity. FLT-PET trials demonstrated a preliminary antitumor activity in a genetically different subgroup of tumors, but there was no discernible benefit in survival when compared to the historical control, which underwent standard therapy. A total of 100 participants were screened in the phase II segment of N057K. After a median follow-up of 17.5 months, patients on N057K had a median OS of 15.8 months and a median PFS of 6.4 months. The median age of patients was 61 years (range, 23-81). Substantial toxic effects were attributed to weekly treatment using 70 mg everolimus given consistently after and during conventional chemoradiation. When compared to historical controls, a combination of everolimus/chemoradiotherapy did not result in a longer survival time. Grade 3 or 4 hematologic adverse event was observed in twenty-five patients where thrombocytopenia (8.91%) and neutropenia (41.58%) were the most common

one. ("Everolimus, Temozolomide, and Radiation Therapy in Treating Patients with Newly Diagnosed Glioblastoma – Full-Text View - ClinicalTrials.gov", 2017). Non-hematologic incidents of grade 3 or 4 occurred in 45 individuals. The most common non-hematologic problems in patients were fatigue (44.55%) and hypercholesterolemia (1.98%). 22 patients stopped taking their protocol drugs early due to an undesirable incident. A grade 5 adverse reaction resulted in the death of one patient. During combination therapy, this patient experienced neutropenia and ended up dead due to sepsis immediately after radiotherapy ceased. Hypermethylation of MGMT was observed in 25% of cancer tissues, while the absence of MGMT methylation was found in 75% of tumor tissues. The cohort of patients who had completed the MGMT analysis had a median follow-up of 16.6 months. Patients with hypermethylated tumors had a much longer OS and PFS than those with unmethylated tumors. Prospective biomarkers for mTOR inhibition sensitivity were looked for after learning about the function of MGMT status in TMZ sensitivity (Ma et al., 2015).

N057K was created to see if using the mTOR blocker everolimus may help patients live longer when it is coordinated with RT and TMZ, but it did not reach the specified requirement for an appreciable survival endpoint (65% OS12), although it did have comparable survival to previous phase 2 trials. In comparison to another study, N0177 (chemoradiation + erlotinib) resulted in 15.3 months of overall survival rate and 7.2 months of progression-free survival rate. (Brown, 2008). Weekly consumption of everolimus was also accompanied by mild toxic effects, where 57% of patients reported having experienced one grade 3+ unexpected event and 23% reported a grade 4 adverse reaction. The fatality levels were also identical to those observed in prior prospective studies using TMZ and everolimus (Mason, 2012). Another study revealed that, everolimus inhibits glioma cell proliferation while also promoting autophagy (Dong et al., 2020). When TMZ and everolimus are used together, the sensitivity of TMZ to glioma cells is greatly increased, cell proliferation is inhibited, and autophagy is promoted more

effectively than when TMZ is used alone. In a randomized phase 2 study of everolimus in association with chemoradiotherapy, glioblastoma patients experienced higher treatment-related toxicities and their progression-free survival rate didn't get better. (Chinnaiyan et al., 2018). However, this study found that during the combination treatment of everolimus with TMZ and radiation, which has modest toxicity, total 31.68% of significant side effects occurred in the phase 2 portion.

In patients with newly diagnosed glioblastoma multiforme, the safety and efficacy of bortezomib in combination with conventional radiation therapy (RT) and temozolomide, followed by adjuvant bortezomib and temozolomide for up to 24 cycles, were evaluated (GBM) where unexpected adverse events did not occur. Bortezomib is a proteasome inhibitor approved for the treatment of multiple myeloma, mantle cell lymphoma, and GBM in early phase trials. It inhibits the 26S proteasome's chymotryptic activity, preventing the degradation of misfolded proteins or numerous short-lived proteins like transcription factors, which may be crucial in the differentiation, proliferation, and death of tumor and immune cells. In selected individuals, sequential Bortezomib +TMZ therapy is safe and increases Th1-driven immune responses with better clinical results (Mohummad A. Rahman et al., 2020).

The treatment plan of this phase 2 study where bortezomib is in conjunction with temozolomide and radiation included two phases which were: radiation therapy stage and maintenance treatment phase. This cohort included 11 female and 13 male patients with a median age of 57 years. Methylation of MGMT was assessed in 23 patients. 21.8 months was the average time for follow-up. The total serious adverse effects observed during this treatment was only 20.83%. Hematologic events including lymphopenia (58.33%), neutropenia (25%), thrombocytopenia (29.17%) and non-hematologic events such as headache (58.33%), fatigue (70.83%), skin rash (8.33%), injection site reaction (54.17%), seizure (20.83%), cognitive disturbances (8.33%) were the most common grade 2 toxicities. ("Temozolomide, Bortezomib

and Regional Radiation Therapy in Treating Patients with Newly Diagnosed Glioblastoma Multiforme or Gliosarcoma – Full-Text View - ClinicalTrials.gov", 2020). Median overall survival (OS) was 19.1 months (95% CI, 6.7-31.4) and median PFS was 6.2 months (95% CI, 3.7-8.8) from the time of diagnosis. Rates of PFS and OS proved to be favorable in comparison to historical standards. When MGMT methylated patients were compared to unmethylated patients, the median PFS was 24.7 months for methylation and 5.1 months of PFS was seen for unmethylated participants. Methylated individuals achieved 49.4 months of median OS and unmethylated individuals had 15.6 months of PFS (Kong et al., 2018). The combination therapy of bortezomib with TMZ and radiation was well tolerated. A patient was excluded from the research due to a grade iii skin irritation while on bortezomib, temozolomide, Bactrim, and later Mepron. Another patient was eliminated from the study after exhibiting persistent neutropenia despite receiving bortezomib and temozolomide. Some of the most common toxicities were attributable to TMZ/RT. The inclusion of bortezomib to RT+TMZ led to the prospect of enhanced patient survival. Bortezomib in combination with RT+TMZ therapy tends to help MGMT methylated participants more. The toxicity was generally controllable, and the life expectancies proved to be excellent. One study demonstrated that In vitro, pre-treatment with Bortezomib before temozolomide killed chemoresistant GBM cells with an unmethylated MGMT promoter by depleting MGMT mRNA and protein but had no effect on methylation. The chymotryptic activity was inhibited, NFkB/p65 processing to activated forms was decreased, and low MGMT levels were observed. Bortezomib penetrated the blood-brain barrier, inhibiting proteasome activity and extending animal survival considerably (Mohammad Aminur Rahman et al., 2019).

Incorporation of the drug trans sodium crocetinate with radiation and TMZ provided a unique and simple technique to address hypoxia in tumor tissues. Trans-sodium crocetinate, a carotenoid molecule, has been found to boost oxygen availability in several types of tissues,

including the brain, by increasing oxygen transport in plasma (Sheehan et al., 2009). The interactions between the hydrophobic TSC molecules and water are thought to be the mechanism for enhanced oxygen transport. As a result, it can be found in any aqueous solution (Stennett et al., 2006). TSC has previously been shown to radio-sensitize hypoxic C6 glioma cells in vivo and promotes oxygen transport. Trans-sodium crocetinate appears to modify serum hydrogen bonding patterns, resulting in a faster rate of oxygen diffusion across capillary membranes. (Sheehan et al., 2010). A single-arm of 59 individuals was included in this study. Overall survival was 71.2 percent for one year (95% Cl, 59.2, 83.1) and median PFS was 3.3 months, according to Kaplan-Meier analysis. The total percentage of serious adverse events in this trial was just 17.86%. Throughout this trial, 27(73%) of the 37 tumor-bearing patients saw their tumors regress. The full eradication (100% decrease) of tumors in 11 patients is perhaps the most noteworthy outcome (30%). Data from contrast MRI revealed that there had been a lot of pseudo-progression. Throughout the experiment, most patients had an excellent quality of life. TSC was not found to be the cause of any significant adverse events in the trial. When added to the Standard of care for GBM, the anti-hypoxia medication TSC looks to be advantageous. Overall survival in this experiment was higher at 1 and 2 years than in the trial that established the Standard of care for GBM. Patients who had only needle biopsies at first, a population anticipated to do worse than those who had resections, had higher survival rates. Pseudo-progression was observed in participants throughout the first 18 weeks of the experiment, as measured by tumor size changes. Furthermore, it was shown that a significant number of tumors shrank. Only 17.86% of serious adverse events were recorded among which constipation (28.57%), nausea (28.57%), vomiting (8.93%), diarrhea (5.36%), dry mouth (5.36%), headache (21.43%), alopecia (32.14%), erythema (10.71%), pain in extremity (7.14%), fatigue (42.86%), edema peripheral (12.50%), insomnia (16.07%), radiation skin injury (8.93%) were the most notable ones. ("Safety and Efficacy of Trans Sodium Crocetinate

(TSC) With Radiation and Temozolomide in Newly Diagnosed Glioblastoma – Full-Text View - ClinicalTrials.gov", 2017). This experiment had no negative effects on quality of life, and no significant adverse events were linked to TSC. In fact, in three clinical trials involving over 150 individuals, TSC has yet to cause a significant adverse event. (Gainer et al., 2017).

The phase 3 study explored the impact of integrating Avastin with TMZ+ bevacizumab for glioblastoma management. In people with glioblastoma, this combination therapy did not rise survival, but bevacizumab was initiated to boost PFS and maintain a normal standard of living and cognitive functioning; although, the occurrence of negative outcomes was larger with bevacizumab than it is with placebo. Anti-VEGF antibody bevacizumab is a humanized monoclonal IgG1 antibody. GBMs are highly vascularized tumors with a high level of VEGF expression. VEGF has long been considered to be the major growth factor involved in tumor angiogenesis (Ghiaseddin & Peters, 2015). Antiangiogenics such as bevacizumab have been regarded as one of the first promising steps toward targeted therapy in GBM, although resistance to antiangiogenics can develop in GBM, potentially leading to a disease that is very difficult to treat (Bergers,2008).

The bevacizumab in Glioblastoma research was an F. Hoffmann–La Roche-sponsored, randomized, double-blind, placebo-controlled trial. There were 458 patients in the bevacizumab group and 463 patients in the placebo group. The bevacizumab group had a median progression-free survival of 10.6 months compared to 6.2 months in the placebo group. Multiple subgroups of patients, including those with methylation and unmethylated MGMT status, saw a benefit with bevacizumab in terms of progression-free survival. Bevacizumab delivered substantially longer PFS than placebo, according to the independent review. Pseudo-progression was identified in 10 patients (2.2%) who received bevacizumab and 43 patients (9.3%) who received a placebo. The bevacizumab group had a median overall survival of 16.8 months, whereas the placebo group had a median overall survival of 16.7 months. At one year,

overall survival rates with bevacizumab and placebo were 72.4% and 66.3%. The median period of safety follow-up for the bevacizumab group was 12.3 months, while it was 8.5 months for the placebo group. Patients in the bevacizumab cohort had a higher rate of major side effects (38.83%) than patients in the placebo group (25.56%) ("A Study of Bevacizumab (Avastin®) in Combination with Temozolomide and Radiotherapy in Participants with Newly Diagnosed Glioblastoma – Full-Text View - ClinicalTrials.gov", 2013). The bevacizumab group had more cumulative and category 3 or higher arterial thromboembolic occurrences than the placebo group. In each group, there was one fatal arterial thromboembolism. Among the adverse reactions seen more frequently in the bevacizumab group were bleeding, tissue regeneration issues, gastrointestinal rupture, and heart disease. Disease progression was the cause of death in 309 of the 339 participants in the bevacizumab group (Chinot et al., 2014). Average adjustments from baseline did not accomplish a statistically significant difference across groups for the most part. Both arms' health-related quality of life (HRQOL) worsened as the study progressed. RT+TMZ with bevacizumab resulted in a meaningful increase in patient survival across all items. (Taphoorn et al., 2015).

A randomized phase 2 trial was conducted to compare the efficacy and safety of single-agent PPX with RT (PPX/RT) versus TMZ with RT (TMZ/RT) for glioblastoma without MGMT methylation. Paclitaxel (PTX) is an anti-microtubule medication that is used to treat a variety of cancers. For patients with breast cancer and non-small cell lung carcinoma, it has been the first-line treatment. In vitro, PTX was found to have a strong apoptosis-inducing effect on glioblastoma cells. Furthermore, PTX penetrated brain tumors at least two orders of magnitude better than carmustine and 5-fluorouracil, among other drugs (Xu et al., 2016).

MGMT was unmethylated in 86 of the 164 individuals who took part in the study. There were 63 patients in total, with 42 receiving PPX/RT and 21 receiving TMZ/RT. There was a total of 59 patients who could be studied. The PPX/RT group had a median PFS of 9 months, while

the TMZ/RT group had a median PFS of 9.5 months (hazard ratio in the PPX/RT group, 1.10; 95% CI, 0.79-2.08; P= 0.75). The median OS for the PPX/RT and TMZ/RT groups was 16 months versus 14.8 months, respectively (hazard ratio, 1.44; 95% CI, 0.75-2.77; P= 0.27). The study demonstrated that the addition of paclitaxel to radiation did not result in improved PFS or OS for glioblastoma patients and unmethylated MGMT. Considering PPX is such a big molecule, it's possible that the blood-brain barrier will prevent it from entering glioblastoma patients. The dysfunctional blood artery was thought to allow PPX entrance, although this was not studied before this work. (Elinzano et al., 2018).

31.71% serious adverse events occurred in the PPX arm. ("PPX and Concurrent Radiation for Newly Diagnosed Glioblastoma Without MGMT Methylation – Full-Text View - ClinicalTrials.gov", 2015). The BRUOG data safety monitoring board suspended enrollment in the study when three of the first 14 patients had grade 4 thrombocytopenia, and the protocol was changed to reduce the PPX dose to 40 mg/m2/wk. The treatment was permanently suspended to accrual after 4 of 11 additional patients developed grade 4 thrombocytopenia, and 3 patients died with persistent grade 4 cytopenia. Three of the seven patients with thrombocytopenia also had grade 4 neutropenia. Three of the individuals exhibited anemia of grade 4. Hematologic toxicity began 4 to 6 weeks after starting PPX with temozolomide and radiation, with quick, steep pancytopenia that lasted up to 5 months (Jeyapalan et al., 2013).

The phase II trial involving radiation and temozolomide with or without vandetanib in glioblastoma patients was prematurely stopped since the schedule did not significantly promote better survival in comparison to the control arm. ZD6474 (vandetanib) is a chemotherapeutic drug that inhibits angiogenesis and is now being evaluated in clinical trials for glioma and non-small cell lung cancer. ZD6474 is projected to outperform existing anti-angiogenic treatments by targeting both the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR) (Jo et al., 2012).

Before the trial's early discontinuation, 106 patients were enrolled. Participants were 55 and 59 years old. 16.6 months of median OS was seen for vandetanib + RT + TMZ, while the RT + TMZ had a median OS of 15.9 months. The median PFS in each arm was 6.2 months and 7.7 months. The rate of response (CP + PR) in the TMZ + RT group was 17.9% while it was 25.4% in RT+ vandetanib + TMZ group (Lee et al., 2015).

Total of 63.41% serious adverse effects were experienced by patients in the vandetanib arm, whereas 50% adverse effects were found in the control arm. ("Temodar With Zactima During Radiation Treatment for Newly Diagnosed Stage IV Brain Tumors – Full-Text View - ClinicalTrials.gov", 2015). Lymphopenia (52.44%), neutropenia (41.58%), ALT/SGPT elevation (3.66%), and thrombocytopenia were the most common grade 3 or higher adverse events (AEs) at least probably attributable to study treatment in the vandetanib arm. In the vandetanib arm, 23 patients (33%) were removed from the study due to unacceptable toxicity, compared to 3 patients (10%) in the conventional therapy arm. The rash appeared more frequently in the vandetanib arm. One patient had a colonic fistula, one patient had a colonic perforation, three patients had thrombosis/thrombus/embolism and one patient had a cerebrovascular ischemic event in vandetanib arm; none of these toxicities were reported as grade 3 or higher and were at least possibly related to study treatment in the standard therapy arm. In the vandetanib arm, there was one case of grade 5 pneumonia that was at least possibly related to study treatment. In the standard arm, there were no grade 5 toxicities that were at least probably related to study therapy. All these data indicate that most toxicities occurred due to the addition of vandetanib drug to this treatment regimen. In patients with newly diagnosed GBM or GS, adding vandetanib at a dose of 100 mg daily to conventional chemoradiation was related to potential pharmacodynamic biomarker changes and was well tolerated. However, when compared to the parallel control arm, the regimen did not significantly improve overall survival.

In patients with glioblastoma, a study anticipated that dose-intensified chemoradiation therapy targeting adversely prognostic hypercellular (TVHCV) and hyperperfused (TVCBV) tumor volumes would improve outcomes. In glioblastoma patients with significant tumor reduction 3 months after radiation therapy, dose intensification against hypercellular/hyperperfused tumor areas resulted in a promising OS with excellent outcomes for symptom load and quality of life. 26 patients were enrolled, the median age of the patients was 61 years (interquartile range [IQR], 56-66 years) and median follow-up time was 26 months. When compared to historical controls, patients treated with the combined hypercellular/ hyperperfused tumor volume had a significantly improved 12-month OS (92 percent; 95 percent CI, 78 percent -100 percent) (P Z .03). This cohort's median OS was 20 months, and the median PFS was 12 months (10-17 months). The median survival time for all 23 patients was 20 months (95 percent CI, 14-29 months) (Kim et al., 2021). Total of 30.77% serious adverse effects were observed due to this treatment regimen. Thrombocytopenia (26.92%), dizziness (26.92%), constipation (34.62%), diarrhea (7.69%), fatigue (76.92%), alopecia (23.08%), insomnia (26.92%), depression (15.38%) are some of the adverse effects found in this trial. ("A Study of High-Dose Chemoradiation Using biologically-based Target Volume Definition in Patients with Glioblastoma – Full-Text View - ClinicalTrials.gov", 2021).

Another phase III trial where dose-dense temozolomide was administered for newly diagnosed glioblastoma, showed 33.81% of total serious adverse events. ("Radiation Therapy (RT) and Temozolomide (TMZ) in Treating Patients with Newly Diagnosed Glioblastoma or Gliosarcoma – Full-Text View - ClinicalTrials.gov", 2014). The purpose of this study was to see if Dose-dense temozolomide increases overall survival (OS) or progression-free survival (PFS) in newly diagnosed GBM patients. TMZ is an oral chemotherapeutic medication that stops the cell cycle, causing DNA methylation and tumor cytotoxicity. It also has linear pharmacokinetics with high bioavailability, enters the cerebrospinal fluid quickly, and does not

require hepatic metabolism to activate (Feng et al., 2017). Patients treated with surgery and radiation had a median survival of 12 months before (2000–2003) and after (2005–2008) the introduction of TMZ, while those treated with TMZ had a median survival of 14.2 months (DT, 2012).

Total of 833 participants were included in this trial and no significant disparity was observed in median OS or PFS among the two groups. The level of methylation did not affect efficacy. 219 subjects (20%) survived during the ultimate research investigation with a median follow-up length of 31.9 months. 16 months of PFS and 7.5 months of OS persisted from the time of registration.

652 deaths were observed with 22% still alive. The median time for follow-up was 31.5 months.

Patients with normal dosage arm had 16.6 months of median OS, while those in the DD arm had 14.9 months of median OS (Gilbert et al., 2013). During the study time 753 individuals developed progression of tumor or died. The median PFS for the normal dosage arm was 5.5 months while 6.7 months of PFS was recorded for the DD arm. The median OS was 21.2 months for tumors with methylated MGMT gene promoters and 14.0 months for tumors with unmethylated MGMT gene promoters, respectively. Anemia (1.19%), leukopenia (45.24%), lymphopenia (5.48%), fatigue (2.62%), nausea (2.62%) were some noticeable adverse effects. In comparison to the previous study where high dose radiation associated with TMZ was given to the patients, this study demonstrated a higher level of adverse effects. In this study, irrespective of methylation patterns, DD temozolomide did not exhibit improved efficacy for GBM. Nevertheless, it validated the predictive value of the methylation of MGMT (Gilbert et al., 2013).

In phase II prospective study, two different temozolomide schedules were explored in the adjunctive therapy of clinically diagnosed GBM. This study showed that an alternative

temozolomide dose schedules may improve survival in patients via boosting the therapeutic efficacy or eliminating typical temozolomide resistance. Eighty-five individuals were included, with 42 receiving dose-dense temozolomide and 43 receiving metronomic temozolomide. After six rounds of adjuvant temozolomide with no clinical or radiographic development, the patient's treatment was switched to single-agent 13-cis-retinoic acid. Maintenance therapy was continued until the tumor progressed, significant toxicity developed, or the patient withdrew consent. No unanticipated hazards were observed in both adjunct regimens ("Temozolomide & RT Followed by Dose Dense vs Temozolomide & Retinoic Acid in Pts w/Glioblastoma – Full-Text View - ClinicalTrials.gov", 2018). Patients in the dose-dense arm experienced more myelosuppression and exhaustion, whereas those on the metronomic arm saw more aminotransferase elevations. Degree 4 or 3 constipation, vomiting and nausea were not observed in individuals during the experiment. 16.4 months of median OS was shown for the entire cohort. At last, 39 participants were surviving where the time for a median follow-up was 18.8 months. The metronomic group had a median OS of 15.1 months, while the dose-dense cohort revealed 17.1 months of median OS. 5.0 months of median PFS was observed for the TMZ group and 6.6 months observed for the dose-dense arm. Metronomic arm while dose-dense arm revealed 6.6 months of median PFS. Metronomic and dose-dense administration of TMZ were considerably accepted in patients with minor toxicities. Encouraging results were found in the case of dose-dense TMZ where an 80% one-year survival rate was established (Clarke et al., 2009).

Bevacizumab combined with irinotecan (BEV+IRI) was investigated as a viable substitute to TMZ in the GLARUS research. Irinotecan, a first-line treatment for metastatic colorectal cancer and a high-activity drug against solid tumors of the gastrointestinal tract, is a topoisomerase I inhibitor, which suppresses DNA transcription. Irinotecan crosses the blood-brain barrier and has shown cytotoxic effect against central nervous system tumor xenografts

in preclinical studies. Its anticancer effect has also been observed in multidrug-resistant glioblastoma cells. Irinotecan has been studied in adults and children with recurrent, persistent malignant glioma as a monotherapy and combination with other medicines such as temozolomide, carmustine, thalidomide, and bevacizumab. Irinotecan in combination with other drugs, particularly temozolomide and bevacizumab, has shown promising effects in clinical trials (Vredenburgh et al., 2009). With BEV+IR, PFS increased from 5.99 months to 9.7 months with TMZ. The median OS with IRI+BEV was 16.6 months while it was 17.5 months for TMZ. The hazard ratio for mortality was 1.02 for IRI+BEV. Patients experienced 72% major adverse events with BEV+IRI and 84% with TMZ. 72.27% of total serious adverse incidents occurred in patients while receiving this combination treatment. ("A Study of Avastin (Bevacizumab) and Irinotecan Versus Temozolomide Radiochemistry in Patients With Glioblastoma – Full-Text View - ClinicalTrials.gov", 2015). In unstratified patient populations with newly diagnosed GBM, BEV treatment has no place in routine first-line therapy. With BEV+IRI, the rate of major adverse events in patients was 72%, while with TMZ, the rate was 84 percent. Severe vascular side effects were more common with BEV+IRI. During primary therapy, two brain hemorrhages and one minor systemic arterial ischemia episode appeared. High-grade hematotoxicity was controlled with TMZ. Due to IRI, vomiting and nausea were much more frequent with the addition of IRI to BEV, compared to TMZ but they were mostly moderate symptoms (Herrlinger et al., 2016).

When compared to TMZ, BEV+IRI had a higher PFS-6 rate and a longer median PFS. BEV+IRI, on the other hand, did not enhance OS, possibly because of the large crossover rate. When compared to TMZ, BEV+IRI did not affect QOL.

After completing RT and TMZ, a trial was performed combining erlotinib and bevacizumab in unmethylated GBM patients. The median age ranged from 29 to 75 years. With a median progression-free survival of 9.2 months, 41 patients either progressed or died. The median

overall survival was 13.2 months after 33 months of follow-up. There were no unanticipated side effects, and most observed side effects were classified as CTC grade 1 or 2. Patients treated with RT plus temozolomide without MGMT methylation had a median overall survival of 12.7 months and a median progression-free survival of 5.3 months. A total of 928 adverse events with a probable link to the bevacizumab plus erlotinib combo were recorded (Raizer et al., 2016).

Hypertension (2.08%), fatigue (60.42%), dehydration (2.08%), rash desquamation (75.00%), rash acneform (27.08%), dizziness (25%), abdominal pain (22.92%), diarrhea (20.83), hyperglycemia (39.58%), depression (18.75%) were the major side effects observed due to this combination treatment. 31.25% of total adverse effects are recorded in this trial. ("Bevacizumab and Erlotinib After Radiation Therapy and Temozolomide in Treating Patients With Newly Diagnosed Glioblastoma Multiforme or Gliosarcoma – Full-Text View - ClinicalTrials.gov", 2018). It appears to be lower than the previous study where irinotecan is corporated with TMZ, bevacizumab, and radiation. The combination of erlotinib and bevacizumab is tolerated, however, it did not achieve the primary goal of improving survival.

In a speculative clinical study, gene therapy to bestow the resistance of O6 Benzylguanine in hematopoietic stem cells was analyzed to identify if it enhanced chemotherapy tolerance and outcome. O6 -benzylguanine (O6 BG) coadministration can restore TMZ sensitivity, although it produces off-target myelosuppression. Seven newly diagnosed glioblastoma patients with MGMT tumors were included in this study. Following single-agent carmustine administration, patients received autologous gene-modified HSCs. Patients received O6 BG/TMZ treatment in 28-day cycles after hematologic recovery. Throughout the trial, blood samples and tumor pictures were gathered on a regular basis. The observed myelosuppression and recovery after each cycle were used to measure chemotherapy tolerance. Patient-specific biomathematical tumor growth modeling was carried out. The researchers looked at progression-free survival

(PFS) and overall survival (OS). PFS was 9 months and OS was 20 months on average. Gene therapy allowed for a substantial rise in the average scores of tolerated TMZ/O6BZ cycles when compared to historical controls. One individual was able to endure an exceptional nine rounds and had a lengthy PFS where no extra treatment was required (Adair et al., 2014). No severe toxicities were reported in this study. ("O6-Benzylguanine-Mediated Tumor Sensitization with Chemoprotected Autologous Stem Cell in Treating Patients With Malignant Gliomas – Full-Text View - ClinicalTrials.gov", 2018). These findings suggest the future expansion of chemoprotective gene therapy in conjunction with O6 BG and TMZ for the treatment of glioblastoma and other cancers with MGMT overexpression.

# Chapter 6

# Conclusion

The efficacy outcomes and safety assessment of several combination therapies related to temozolomide and radiation standard treatment were documented in this study's clinical trials. Based on the frequencies of adverse events in patients and a comparison of median overall survival rates and median progression-free survival rates, different conclusions were reached. According to the secondary endpoint, the efficiency of numerous drug combinations was investigated, and it was discovered that two studies had the highest median overall survival rate. One of these was a combination of high-dose radiation and temozolomide therapy given to the patient, which resulted in a median OS of 20 months and the greatest median PFS of 12 months among patients. It also had less toxicity than another study in which patients were offered TMZ and radiation simultaneously. Similarly, a combined treatment of (Temozolomide+ Radiation+ 06 Benzylguanine+ Carmustine+ Plerixafor) culminated in a median OS of 20 months. In addition, there were no substantial side effects for the patients in this trial. The dose-dense regimen appeared promising, with an 80% one-year survival rate (Clarke et al., 2009). Adding the medications bortezomib and trans sodium crocetinate to TMZ and radiation resulted in reduced toxicity than other trials. According to current trends, the treatment of recurrent GBM will continue to be multimodal. To develop more effective methods, a better understanding of the underlying cancer pathogenesis is required. Clinicians, researchers, and patients hope that, with continued innovations in treatments and imaging tools, GBM will become a controllable disease with a longer life span (Se, 2006).

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# Appendix

Supplementary Table 1: Efficacy of drug combinations used in the treatment of glioblastoma multiforme

| **Drug combination** | **Median OS** | **Median PFS** | **Serious Adverse effect** | **Citation** | **Clinical Trial ID** |
|---|---|---|---|---|---|
| TMZ+radiotherapy+ everolimus | 15.8 | 6.4 | 31.68% | (Ma et al., 2015) | NCT00553150 |
| TMZ+ radiation+ ZD6474 | 16.6 | 7.7 | 63.41% | (Lee et al., 2015) | NCT00441142 |
| Bevacizumab+ TMZ+ radiation | 16.8 | 10.6 | 38.83% | (Taphoorn et al., 2015) | NCT00943826. |
| TMZ + bortezomib+ radiation | 19 | 6.2 | 20.83% | (Kong et al., 2018) | NCT00998010 |
| TMZ+TSC+ radiation | 11.86 | 3.3 | 17.86% | (Gainer et al., 2017) | NCT01465347 |
| TMZ+radiation+ PPX (CT2103) | 16 | 9 | 31.71% | (Jeyapalan et al., 2013) | NCT01402063 |
| TMZ+ high dose radiation | 20 | 12 | 30.77% | (Kim et al., 2021) | NCT02805179 |
| TMZ+ irinotecan+ bevacizumab | 16.6 | 9.7 | 72.27% | (Herrlinger et al., 2016) | NCT00967330 |

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|---|---|---|---|---|---|
| TMZ+ radiation | 16 | 7.5 | 33.81% | (Gilbert et al., 2013) | NCT00304031 |
| Radiation+TMZ adjuvant erlotinib+ bevacizumab | 13.2 | 9.2 | 31.25% | (Raizer et al., 2016) | NCT00720356 |
| TMZ+ RT+ dose dense TMZ & cis retinoic acid | 17.1 | 6.6 | 0% | (Clarke et al., 2009) | NCT00200161 |
| TMZ+ radiation+ O6 benzylguanine+ carmustine + plerixafor | 20 | 9 | 0% | (Adair et al., 2014) | NCT00669669. |

Supplementary table 2: Adverse effects of different temozolomide and radiotherapy combination treatment for glioblastoma multiforme

| Parameters | TMZ+ Radiation+ everolimus | TMZ+ Radiation+ ZD6474 | TMZ+ radiation+ Avastin+ placebo | Bortezomib+ TMZ+ radiation | TMZ+ radiation+ TSC | TMZ+PPX+ radiation |
|---|---|---|---|---|---|---|
| Anemia | 3/101 (2.97%) | 2/82 (2.44%) | 3/461 (0.65%) | 9/24 (37.50%) | --/-- | 1/41 (2.44%) |
| Thrombocyto penia | 9/101 (8.91%) | 4/82 (4.88%) | 17/461 (3.69%) | 7/24 (29.17%) | | |
| neutropenia | 10/101 (9.90%) | 7/82 (8.54%) | 4/461 (0.87%) | 6/24 (25.00%) | | 6/41 (14.63%) |
| Abdominal pain | 1/101 (0.99%) | 2/82 (2.44%) | 4/461 (0.87%) | | | 0/41 (0.00%) |
| Constipation | 5/101 (4.95%) | 17/82 (20.73%) | 178/461 (38.61%) | 8/24 (33.33%) | 16/56 (28.57%) | 9/41 (21.95%) |
| Vomiting | 1/101 (0.99%) | 1/82 (1.22%) | 5/461 (1.08%) | 6/24 (25.00%) | 5/56 (8.93%) | 1/41 (2.44%) |
| Diarrhea | 2/101 (1.98%) | 1/82 (1.22%) | 2/461 (0.43%) | 1/24 (4.17%) | 3/56 (5.36%) | 5/41 (12.20%) |
| Nausea | 3/101 (2.97%) | 1/82 (1.22%) | 0/461 (0.00%) | 11/24 (45.83%) | 16/56 (28.57%) | 2/41 (4.88%) |
| Dehydration | | 0/82(0.00%) | | 1/24 (4.17%) | | 5/41(12.20%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Hydroce-phalus | 1/101 (0.99%) | | 2/461 (0.43%) | 1/24 (4.17%) | 2/56 (3.57%) | |
| Headache | 2/101 (1.98%) | | 4/461 (0.87%) | 14/24 (58.33%) | 12/56 (21.43%) | 2/41 (4.88%) |
| Seizure | 1/101 (0.99%) | 6/82 (7.32%) | | 5/24 (20.83%) | | 2/41 (4.88%) |
| Cognitive disturbance | 1/101 (0.99%) | 0/82 (0.00%) | | 2/24 (8.33%) | 3/56 (5.36%) | |
| dizziness | 2/101 (1.98%) | 1/82 (1.22%) | 0/461 (0.00%) | | | 10/41 (24.39%) |
| Memory impairment | 2/101 (1.98%) | 20/82 (24.39%) | | 2/24 (8.33%) | | 7/41 (17.07%) |
| Tremor | 1/101 (0.99%) | 12/82 (14.63%) | | 2/24 (8.33%) | | 3/41 (7.32%) |
| Alopecia | 9/101 (8.91%) | 18/82 (21.95%) | 180/461 (39.05%) | 3/24 (12.50%) | 18/56 (32.14%) | 22/41 (53.66%) |
| Dry skin | 1/101 (0.99%) | 4/82 (4.88%) | 34/461 (7.38%) | 1/24 (4.17%) | 3/56 (5.36%) | 1/41 (2.44%) |
| Anorexia | 5/101 (4.95%) | 0/82 (0.00%) | | 6/24 (25.00%) | | |
| Hyperglycemia | 1/101 (0.99%) | 50/82 (60.98%) | 1/461 (0.22%) | 4/24 (16.67%) | | 2/41 (4.88%) |
| Muscular weakness | 3/101 (2.97%) | 1/82 (1.22%) | 2/461 (0.43%) | | 2/56 (3.57%) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Back pain | | 5/82 (6.10%) | 1/461 (0.22%) | 2/24 (8.33%) | 3/56 (5.36%) | |
| Pain in extremity | 1/101 (0.99%) | 6/82 (7.32%) | 48/461 (10.41%) | | 4/56 (7.14%) | |
| hypertension | 1/101 (0.99%) | 1/82 (1.22%) | 4/461 (0.87%) | 1/24 (4.17%) | 2/56 (3.57%) | 1/41 (2.44%) |
| hypotension | 1/101 (0.99%) | 1/82 (1.22%) | 1/461 (0.22%) | 1/24 (4.17%) | | |
| Pulmonary embolism | | | 13/461 (2.82%) | 1/24 (4.17%) | 2/56 (3.57%) | 1/41 (2.44%) |
| cough | 1/101 (0.99%) | 1/82 (1.22%) | 55/461 (11.93%) | 4/24 (16.67%) | | 1/41 (2.44%) |
| dyspnea | 1/101 (0.99%) | 2/82 (2.44%) | 26/461 (5.64%) | 1/24 (4.17%) | | 2/41 (4.88%) |
| Fatigue | 3/101 (2.97%) | 1/82 (1.22%) | 0/461 (0.00%) | 17/24 (70.83%) | 24/56 (42.86%) | |
| Death | 1/101 (0.99%) | 1/82 (1.22%) | 0/461 (0.00%) | | | |
| Urinary tract infection | 2/101 (1.98%) | 1/461 (0.22%) | | 1/56 (1.79%) | | |
| Insomnia | 6/101 (5.94%) | 20/82 (24.39%) | 53/461 (11.50%) | 4/24 (16.67%) | 9/56 (16.07%) | 10/41 (24.39%) |
| Anxiety | 3/101 (2.97%) | | 1/461 (0.22%) | | 4/56 (7.14%) | 6/41 (14.63%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Depression | 1/101 (0.99%) | | 43/461 (9.33%) | | 3/56 (5.36%) | 5/41 (12.20%) |
| Weight loss | 5/101 (4.95%) | | 36/461 (7.81%) | 3/24 (12.50%) | | 5/41 (12.20%) |
| Weight gain | 1/101 (0.99%) | | | 4/24 (16.67%) | | 3/41 (7.32%) |
| Thrombosis | 4/101 (3.96%) | 18/82 (21.95%) | 1/461 (0.22%) | | | |
| Urinary retention | | 2/82 (2.44%) | 1/461 (0.22%) | 1/24 (4.17%) | | |
| Vision blurred | 3/101 (2.97%) | 1/82 (1.22%) | | 1/24 (4.17%) | | |
| Clinical trial ID | NCT00553150 | NCT00441142 | NCT00943826 | NCT00998010 | NCT01465347 | NCT01402063 |
| Citation | (Ma et al., 2015) | (Lee et al., 2015) | (Taphoorn et al., 2015) | (Kong et al., 2018) | (Gainer et al., 2017 | (Jeyapalan et al., 2013) |

Supplementary Table 3: Adverse effects of different temozolomide and radiotherapy-based combination treatment for glioblastoma multiforme

| Parameters | High dose radiation+ TMZ | TMZ+ irinotecan+ Avastin+ radiation | TMZ+ radiotherapy | Radiation + TMZ adjuvant erlotinib+ bevacizumab |
|---|---|---|---|---|
| anemia | 2/26 (7.69%) | | 16/420 (3.81%) | 10/48 (20.83%) |
| Lymphopenia | 2/26 (7.69%) | | 23/420 (5.48%) | 25/48 (52.08%) |
| Thrombocytopenia | 7/26 (26.92%) | 4/119 (3.36%) | 16/420 (3.81%) | 10/48 (20.83%) |
| headache | 1/26 (3.85%) | 2/119 (1.68%) | 7/420 (1.67%) | 2/48 (4.17%) |
| dizziness | 7/26 (26.92%) | 1/119 (0.84%) | 3/420 (0.71%) | 12/48 (25.00%) |
| dyspnea | 1/26 (3.85%) | 1/119 (0.84%) | 7/420 (1.67%) | 3/48 (6.25%) |
| Vision blurred | 2/26 (7.69%) | | 1/420 (0.24%) | |
| Ataxia | 1/26 (3.85%) | | 4/420 (0.95%) | 3/48 (6.25%) |
| Abdominal pain | 1/26 (3.85%) | 1/119 (0.84%) | 2/420 (0.48%) | 11/48 (22.92%) |
| nausea | 1/26 (3.85%) | 1/119 (0.84%) | 11/420 (2.62%) | 1/48 (2.08%) |
| cough | 1/26 (3.85%) | | 3/420 (0.71%) | 10/48 (20.83%) |
| constipation | 9/26 (34.62%) | | 0/420 (0.00%) | 11/48 (22.92%) |
| Diarrhea | 2/26 (7.69%) | 2/119 (1.68%) | 3/420 (0.71%) | 39/48 (81.25%) |
| fatigue | 20/26 (76.92%) | | 11/420 (2.62%) | 29/48 (60.42%) |
| Weight loss | 1/26 (3.85%) | | 1/420 (0.24%) | 11/48 (22.92%) |
| anorexia | 2/26 (7.69%) | | 5/420 (1.19%) | 14/48 (29.17%) |
| pruritus | 3/26 (11.54%) | | 53/420 (12.62%) | 18/48 (37.50%) |
| alopecia | 6/26 (23.08%) | | 191/420 (45.48%) | |

| | | | | |
|---|---|---|---|---|
| insomnia | 7/26 (26.92%) | | 0/420 (0.00%) | |
| anxiety | 3/26 (11.54%) | | 0/420 (0.00%) | 5/48 (10.42%) |
| confusion | 2/26 (7.69%) | | 10/420 (2.38%) | |
| depression | 4/26 (15.38%) | 0/119 (0.00%) | 4/420 (0.95%) | 9/48 (18.75%) |
| thrombosis | 2/26 (7.69%) | 2/119 (1.68%) | 19/420 (4.52%) | 2/48 (4.17%) |
| Muscular weakness | 2/26 (7.69%) | 1/119 (0.84%) | | 1/48 (2.08%) |
| hyperglycemia | | 2/119 (1.68%) | | 19/48 (39.58%) |
| Clinical trial ID | NCT02805179 | NCT00967330 | NCT00304031 | NCT00720356 |
| Citation | (Kim et al., 2021) | (Herrlinger et al., 2016) | (Gilbert et al., 2013) | (Raizer et al., 2016) |