Appendix 1: Grouping studies by subject, type, methodology and parameters (gold standards)

Subject	Type		Methodology	Parameters (gold standards)
	Review	Original		
Virus-mediated	2	16	*in vitro* studies	Safety and Survival probability (tumor removal or tumor size reducing)
Cell-mediated	4	4	*in vivo* studies	
Polymer-mediated	4	18	Statistical studies	
Chemotherapy	1	2		
Multiple-delivery	8	0		

Appendix 2: Evaluating studies by their results those considerate interested parameters of this study

Experimental model	Type	Main finding	Reference
Virus–mediated	Original	pdcs can produce IFN-α and have anti-tumor efficacy, thus they could be effective in GBM treatment	(10)
Virus- mediated	Review	Oncolytic viruses are useful vectors in the clinical trials because they are safe and don't have side effects.	(15)
Virus- mediated	Original	The recombinant Ad35 viruses are new vectors in GBM therapy.	(16)
Virus-mediated	Original	Viruses could be used as vectors for the treatment of Glioblastoma. When Eg5 siRNA and HVJ-E are used together, they represent a synergistic effect as anti-tumor.	(17)
Virus-mediated	Original	Gene therapy in combination with cell- mediated gene delivery as vectors could be a new strategy in GBM treatment. Also, the novel totk1/ AZT suicide gene is a useful gene for tumor therapy.	(18)
Virus-mediated	Original	Adenoassociated virus (AAV) vector encoding interferon-β (IFN-β) which transduced into the normal	(19)

		brain cells can totally prevent tumor growth.	
Virus-mediated	Original	In order to prevent tumor growth in brain we can use a systemic antiangiogenic therapy.	(20)
Virus-mediated	Original	Many viruses like Myxoma virus could be used as vectors for gene delivery in GBM.	(21)
Virus-mediated	Original	OV-ChaseM (Oncolytic virus secreted ChaseM) is a candidate for increasing the susceptibility and sensitivity to TMZ in glioma cells.	(22)
Virus-mediated	Original	Survival rate of mice bearing glioma xenograft with triple therapy (Ad-Egr-TNF, IR, and temozolomide) is more than dual treatment.	(23)
Virus-mediated	Original	The study suggests new paths for cancer genetics and functional tumor suppressors *in vivo*.	(24)
Virus-mediated	Review	Oncolytic adenoviruses in combination with chemotherapy revealed anti-tumor effects.	(25)
Virus-mediated	Original	Combination of Ad5-D24RGD and irradiation shows increased antitumor activity *in vitro* and *in s.c.*	(26)
Virus-mediated	Original	Combined treatment of MG with JX-594 and rapamycin enhances survival rate in several animals.	(27)
Virus-mediated	Original	VvDD-EGFP has a dramatic effect as an anti-tumor agent especially in combination with immunosuppressive agents.	(28)

Virus-mediated	Original	In case of Glioma gene therapy complement, Glioma-specific and cell cycle-dependent HSV-1 amplicon vector could be so useful.	(29)
Virus-mediated	Original	Using combination therapies like Ad-stTRAIL and BCNU is more effective than monotherapy methods.	(30)
Virus-mediated	Original	S-TRAIL is a potential agent for Glioblastoma treatment and combination of temozolomide and S-TRAIL may increase the therapeutic effects.	(31)
Cell-mediated	Original	MSCs-TK and VPA Combination therapy is more effective than single-treatment groups in survival of glioma-bearing mice.	(32)
Cell–mediated	Original	Neural stem cells as suicide gene vectors are useful therapeutics for brain metastases.	(33)
Cell-mediated	Original	Combination of cellular and gene therapy is a promising method for treatment of brain metastases.	(34)
Cell–mediated	Review	Stem cells are promising agents of cell-based approaches in GBM therapy.	(35)
Cell–mediated	Review	MScs or NScs are useful vectors for genes or drugs in treatment of Gliomas and survival enhancement *in vivo*.	(36)
Cell–mediated	Review	Explaining the complexity of TICs eradication in novel cancer therapy methods because of their difficulties, variability, plasticity and dynamic phenotypes.	(37)

Cell–mediated	Review	Many investigations are needed to establish the effects of MSCs on tumors especially on animal models.	(38)
Cell–mediated	Original	Combination of MK886 and MSC-based TRAIL is a new strategy in malignant Glioma's therapy.	(9)
Polymer-mediated	Original	Chitosan nanoparticle compare to electroporation and Lipofectamie act as potential vector to deliver genes into cells.	(39)
Polymer-mediated	Original	Super para magnetic nanoparticles coated with pullulan-spermine are more effective carrier for transfecting the therapeutical agents into cells on application of the magnetic field.	(40)
Polymer-mediated	Original	Apoptosis of the transfected cancer cells by Super para magnetic nanoparticles coated with pullulan-spermine is increased compare to control.	(41)
Polymer-mediated	Original	DNZ loaded on the chitosan nanoparticles could recover the Chemosensitivity in the cancer cells.	(42)
Polymer-mediated	Review	Liposomes and AuNPs are potential vectors in RNAi-based therapies.	(43)
Polymer-mediated	Original	Combination of PBAE/HSV-tk nanoparticles with ganciclovir administration as a prodrug increases the survival of Glioma models.	(44)
Polymer-mediated	Original	EGFR targeting using a boronated mAb alone or combined with BPA has therapeutic effects in brain tumors. Also, combination of high	(45)

		and low molecular weight vectors for BNCT is a new method in GBM treatment.	
Polymer-mediated	Original	Peptides-modified liposomes are as effective as vectors of siRNA and DTX delivery into glioma cells with having synergistic manner in tumor growth inhibition.	(46)
Polymer-mediated	Original	The chemosensitivity of tumor will increase when amphiphilic star-branched copolymer are used as hydrophobic therapeutants for delivery.	(47)
Polymer-mediated	Original	Nano-conjugate system could be effective in removing the tumor and also has protective effects in metastasis or recurrence.	(48)
Polymer-mediated	Original	Nano-carriers are useful for destroying the cancer mass.	(49)
Polymer-mediated	Review	The bioactive materials are like nanoparticles with different diameters, and for *in vivo* transportation the area is protective and effective in circulation of the chemotherapeutic drugs.	(50)
Polymer-mediated	Original	When VD3NPs and DOX, EPI, and DTX are used together, their cytotoxic effects did not increase on C6 cell line, but the cancerous characteristics increased somehow.	(51)
Polymer-mediated	Review	Liposomes could shield and carry different molecules to CSCs as Nano-carriers in order to targeting therapy.	(52)
Polymer-mediated	Original	The cellular uptake efficiency, cytotoxicity and cell apoptosis of	(1)

		Choline-derivate modified co delivery system is higher than unmodified co-delivery system both *in vitro* and *in vivo*.	
Polymer-mediated	Original	Combined curcumin and the HSV-tk gene showed high effect on tumor growth suppression in GBM model, increased the therapeutic effect on the xenograft Glioblastoma model.	(53)
Polymer-mediated	Original	Immunogenic therapy, which means combination of IL-12 and gene showed promising effects in brain tumor treatment.	(54)
Polymer-mediated	Review	When subcutaneous vaccination and i.m. Poly-ICLC administration were used together, they induced antigen GAA-specific Tc1s, which express VLA-4 in CNS tumors. Also improved the survival rate *in vivo* without any autoimmunity response.	(55)
Polymer-mediated	Original	The Chemosensitivity of GBM against TMZ was increased with siRNA-based down regulation of MGMT.	(56)
Polymer-mediated	Original	DOX have synergetic effects with plasmid pORF-hTRAIL and they could better in accumulate in tumor site, induce apoptosis in tumor cell, reduce toxicities and enhance survival rate in tumor-bearing mice.	(57)
Polymer-mediated	Original	The life expectancy improved after radiosurgery because of enhancement in tissue factor treatment, also more thrombosis induced in glioblastoma vasculature with lipopolysaccharides.	(58)

Polymer-mediated	Original	A new method in GBM gene therapy is the combination of BCNU-loaded wafer implantation and intra-carotid perfusion of BCNU-loaded nanoparticles.	(59)
Multiple-delivery	Review	Gene therapy is one of the flexible and robust methods of GBM therapy.	(60)
Multiple-delivery	Review	Besides using viral and non-viral delivery systems in gene therapy, CRISPR/Cas system could highly improve survival rate in GBM patients.	(61)
Multiple-delivery	Review	Cytotoxic therapy has synergistic effects with immunotherapy in destroying the tumor and they can reduce neurotoxicity so this combination could be a promising method in GBM treatment,	(62)
Multiple-delivery	Review	There are some new useful methods in GBM therapy like direct delivery into the brain, immunotherapy, genomics, and nanotechnology.	(63)
Multiple-delivery	Review	In order to understand the molecular pathways of oncogenesis, major genetic alterations are needed.	(64)
Multiple-delivery	Review	Genes and proteins could be affected by many different molecular agents in brain tumors. So, it is hard to molecular targeting of these tumors. For gathering this aim combined molecular therapy with cytotoxic agents is needed.	(65)
Multiple-delivery	Review	Drugs have different toxicities and to balance their acceptable efficacy it is suggested to optimize the usage of altered TMZ schedules, use new drug delivery approaches, targeted	(4)

		therapies and combine multiple drugs or modalities.	
Multiple-delivery	Review	Mechanisms, effects and limitations of therapy such as temozolomide, viral gene transfer, and biomarker-based vaccines or even engineered T cells for more specific responses were discussed. Eventually, biomarkers are suggested to have a high value as drug targets.	(66)
Chemotherapy	Review	PCV or TMZ showed similar survival rate and time-to progression outcomes in Chemotherapy-naive patients with HGG at first recurrence.	(67)
Chemotherapy	Original	Cilengitide helps TMZ delivery to brain tumor cells and had beneficial clinical effects *in vivo* which may be because of its altered perfusion.	(68)
Chemotherapy	Original	When TMZ and Herceptin were used together, the anti-tumor effect and survival rate of GBM bearing mice increased when compared to using each one alone.	(69)

Appendix 3: Excluded studies based on the methodology

Studies	**Methodology**
Brouwer, et al. (2007) (16)	*in vitro*
Ningaraj, et al. (2009) (69)	*in vitro*
Maurer, et al. (2009) (68)	Clinical trail
Mohamed, et al. (2014) (48)	*in vitro*
Maleklou, et al. (2016)(51)	*in vitro*
Eslaminejad, et al. (2016) (40)	*in vitro*
Eslaminejad, et al. (2016) (70)	*in vitro*
Erkoc, et al. (2017) (49)	*in vitro*
Eslaminejad, et al. (2017) (41)	*in vitro*
Zokaei, et al. (2019) (42)	*in vitro*