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Diagnosis and Treatment Options of Anaplastic Oligodendroglioma

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Abstract: **Oligodendroglial tumors are the least typical of the gliomas, accounting for 3% to 20% of all glial growths [Class III] Of these, roughly 70% are low-grade OD and 30% are AOD. This systematic review study aimed to evaluate the diagnosis approaches and differential diagnosis of oligodendroglioma and specifically anaplastic type AOD. We also aimed to discuss the treatment options of this type of brain tumors through reviewing the evidence based trails. A literature search was conducted through December 2016. The following databases were searched: PubMed (MIDLINE), Embase, Cochrane, and ScienceDirect. For each database mesh of terms were used in searching included: "glioma" or "primary brain tumor" or "brain cancer" or "malignant brain tumor" or "anaplastic oligodendroglioma (AOD)" or "AOD;" Combined with Diagnosis AND Treatment. We also search the references of every included articles to find more relevant studies discussing the same topic as our study aimed to discuss. Oligodendrogliomas are amongst the most checked out tumors of the nerve system. Despite the considerable deadly potential of these tumors, a significant number has actually been revealed to react well to treatment. The positive effect of combined early radiotherapy and PCV chemotherapy for AO and blended kinds, anaplastic oligoastrocytomas with 1p/19q co-deletion, has just recently been clearly demonstrated. An equally considerable or more positive effect of often utilized temozolomide has actually not yet been proven.**

Keywords: **Oligodendroglial tumors, PubMed (MIDLINE), Embase, Cochrane, and ScienceDirect.**

1. INTRODUCTION

Anaplastic oligodendroglioma (AOD) was very first acknowledged as a chemosensitive glial tumor in 1988 [(1)]. In the 1990s, molecular hereditary studies demonstrated that allelic loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) was essential prognostic markers of chemosensitivity and longer survival [(2,3,4,5)].

Oligodendroglial tumors are the least typical of the gliomas, accounting for 3% to 20% of all glial growths [(6)] [Class III] Of these, roughly 70% are low-grade OD and 30% are AOD [(7)] [Class II] About 20 years earlier, it was acknowledged that growths with oligodendroglial components have improved actions to therapy and much better diagnosis than other malignant gliomas [(8,9)] [Class III] Because that time, the reported occurrence of oligodendroglial cancers has risen gradually, with a corresponding decline in the occurrence of astrocytic growths [(10)] [Class II] This modification is believed to be due in part to less rigid histologic criteria for oligodendroglial growths in the most current WHO classification scheme along with to a bias in favor of presenting the most beneficial medical diagnosis to patients whenever possible [(10)] [Class II; Class III] More just recently, however, the validation of genetic markers for recognizing oligodendroglial growths has actually suppressed the frequency of medical diagnosis of AOD [(10)].

Based upon morphologic functions, the World Health Organization (WHO) has actually categorized them into astrocytoma, oligodendroglioma (OD), and mixed oligoastrocytoma (MOA) [(11)]. Within each category, the growths are bought to show low grade (WHO grade II) or high grade (WHO grade III or IV) based upon histologic functions (consisting of high cellularity, the existence of mitotic figures, or irregular vasculature) and their preference for aggressive habits (TABLE1). Although this category plan is medically useful in most cases, the difference of the different subtypes and grades is subjective, with high interrater variability. Furthermore, it remains uncertain whether numerous phenotypes of glioma show unique diseases or heterogeneous expressions of neoplasia originated from a shared glial family tree

[Class III; Class II] [11,12]. Current discoveries in the molecular functions of gliomas have actually raised the possibility of more accurate classification of growths based on molecular diagnostics [Class III] [11]. The recognition of specific genetic markers of anaplastic oligodendroglioma (AOD) that correlate with response to treatment has actually been the most essential of these discoveries to date and has actually led to dramatically increased interest in AOD in the previous 15 years [Class II; Class III] [13,14].

TABLE 1. World Health Organization classification of tumors with oligodendroglial features [11]

Class	Grade
Oligodendroglial tumors	
A) Oligodendroglioma	II
B) Anaplastic oligodendroglioma	III
Mixed gliomas	
A) Oligoastrocytoma	II
B) Anaplastic oligoastrocytoma	III

This systematic review study aimed to evaluate the diagnosis approaches and differential diagnosis of oligodendroglioma and specifically anaplastic type AOD. We also aimed to discuss the treatment options of this type of brain tumors through reviewing the evidence based trails.

2. METHODOLOGY

Systematic review study was performed following the guideline of systematics reviews studies

SEARCH METHOD:

A literature search was conducted through December 2016. The following databases were searched: PubMed (MIDLINE), Embase, Cochrane, and ScienceDirect. For each database mesh of terms were used in searching included: "glioma" or "primary brain tumor" or "brain cancer" or "malignant brain tumor" or "anaplastic oligodendroglioma (AOD)" or "AOD;" Combined with Diagnosis AND Treatment. We also search the references of every included articles to find more relevant studies discussing the same topic as our study aimed to discuss. we limited our search for English Language Articles, and only human trails were included in this review.

3. RESULTS & DISCUSSION

DIAGNOSIS of AOD through CLINICAL PRESENTATION:

The WHO definition for AOD is ''An oligodendroglioma with focal or diffuse histological features of malignancy and a less favorable prognosis'' [1], AOD tumors occur most typically in adults. The peak age of onset is 35 to 44 years, with low-grade OD presenting in younger patients and AOD presenting in older patients [Class II] [7]. Oligodendroglial tumors are really uncommon in children, accounting for only 2% to 4% of primary pediatric brain tumors; the terrific majority of these are low-grade [Class II] [7]. The vast majority of all oligodendroglial tumors occur in the supratentorial brain, with the frontal lobe the most common site overall (50%–65%). The temporal lobe (47%) is the second most common location, followed by the parietal lobe (7%–20%) and occipital lobe (1%–4%). Other sites include the cerebellum (3%), brainstem, spinal cord (1%), leptomeninges, cerebellopontine angle, cerebral ventricles, retina, and optic nerve [2].

AOD take place in white matter and the cortex. Their place is most commonly supratentorial, particularly in the frontal lobes, but they can provide throughout the main nerve system, including the brainstem and spinal cord. When oligodendroglial tumors are found infratentorially or in the deep nuclei, they are generally thought to represent a more aggressive phenotype [Class III] [6]. AOD generally present as single sores. There are case reports of multifocal AOD, leptomeningeal spread of AOD, and extraneural metastases from AOD. However, these cases are unusual and might just reflect the nature of a glioma associated with prolonged survival [Class III] [6,15]. The medical presentation mainly depends on the tumor's location and grade. Seizures are the most common symptom at discussion for all OD (50%-90% of patients) [Class III] [6,16]. Seizures are especially common with low-grade OD, which grow gradually and trigger irritation prior to symptoms due to mass effect. AODs may also provide with seizures but are most likely to provide with acute to subacute start of neurologic symptoms such as headache, focal weakness, vision changes, or cognitive deficits due to mass effect from the tumor [6,15,16].

On both CT and MRI, many AODs have improvement after administration of exogenous contrast. This represents an unusual blood-brain barrier within the tumor and perhaps tumor angiogenesis. Since of its exceptional ability to evaluate the neuroanatomic place of tumor and the level of signal problem, MRI is the favored technique for examining AOD. T2-weighted MRI frequently shows a mixed-intensity central core with scattered surrounding signal hyperintensity [Class II] [17]. The T1-weighted sequence without gadolinium frequently reveals hypointensity, but hyperintensity may be seen if calcification is present. CT is frequently needed to validate calcification. The presence of calcifications on neuro-imaging is likely to be a marker of long-standing or chronic disease rather than a specific biologic result. The existence of calcification has actually been associated with 1p19q LOH [Class II] [17,18]. AODs might likewise be associated with spontaneous intratumoral hemorrhage, and some have actually suggested that this is most likely in AOD than in other gliomas [Class III] [19,20]. It is possible that hemorrhage is associated with the particular microstructure of OD vasculature, but this connection has actually not been confirmed [Class III] [20]. Unlike other deadly gliomas, oligodendroglial tumors are frequently kept in mind on MRI to have sharp demarcations between normal brain and tumor core. Just recently, this imaging function was associated with 1p19q status: patients with 1p19q LOH were more likely to have a diffuse tumor border on MRI, whereas patients with intact alleles had the appearance of a sharp border [Class II] [17,18] (**Table 2**). Functional MRI techniques have actually recently been applied to AOD. There seems increased thallium-201 uptake on MR single-photon emission computed tomography (SPECT) in AOD patients with LOH at 1p19q no matter grade [Class II] [21] (**Table 2**).

Table 2: Clinical, genetic, and radiologic features of oligodendroglioma with and without 1p/19q clodeletion [21]

	1p/19q loss	**No 1p/19q loss**
Histologic features	In particular, classical oligodendroglial morphology	Presence of astrocytic elements
Localization	(Bi)frontal, parietal, occipital	Temporal, deep basal ganglia, diencephalon
MRI features	More indistinct borders and mixed signal intensity on T1- and T2-weighted images	Homogeneous T1 and T2 signal intensity, distinct borders
Behavior	Often presentation with indolent tumors and seizures only	More rapid clinical progression
Enhancement on MRI	Diffuse, patchy	Ring enhancement, necrosis
Genetic alterations	1p/19q loss, in anaplastic tumors p16 deletions	p53 mutations, EGFR amplification, 10 and 10q loss
Responsiveness to	80%–100% of tumors	Less frequent objective response
chemotherapy	responding, with relatively long duration of response	and of shorter duration
Median survival in anaplastic tumors	More than 6–7 years	Median 2–3 years

GENETICS background of AOD could help in DIAGNOSIS:

The recognition that codeletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) is a diagnostic marker for oligodendroglial tumors that is related to improved scientific result was a critical discovery [Class II] [22]. It has actually subsequently been validated in two prospective trials as a prognostic marker for patients with AOD and anaplastic MOA [Class I] [23,24]. 1p19q removal is the most typical chromosomal lesion in oligodendroglial tumors; it might be seen in as lots of as 60% to 90% of low-grade OD and 50% to 70% of AOD [Class III] [7,25]. It is also the earliest hereditary change in these tumors and continues at the time of tumor development or recurrence [Class II; Class III, Class II] [22,24,25]. These findings recommend that the codeletion may be a marker of a genetically clonal cancer cell population with distinct medical features. In support of this hypothesis, 1p19q codeletion has actually been reliably associated with timeless oligodendroglial histologic features; specific MRI findings; tumor locations, growth patterns, and action to therapies; and ultimately, survival [Class III, Class II, Class I, Class II] [6,14,21, 23,24,25] (**Table 2**).

TREATMENT OF ANAPLASTIC OLIGODENDROGLIOMA (AOD):

The standard treatment of oligodendrogliomas consists of neurosurgery and oncological treatment: radiotherapy and chemotherapy. Radiotherapy is administered to a total dosage of 54 to 60 Gy. Chemotherapy is administered in a triple combination of lomustine, vincristine and procarbazine (PCV) or temozolomide [28,29]. The level of sensitivity to

radiotherapy of oligodendrogliomas was found as early as the 1980s [1,2], and the positive effect of temozolomide, pcv and chemotherapy, was found later on [1].

Neurosurgery is fundamental to eliminate the tumor and get neoplastic tissue in order to make an accurate medical diagnosis. Overall resection of the tumor is thought about ideal. Sophisticated diagnostic preoperative and perioperative techniques (magnetic resonance imaging - MRI, use of 5-aminolevulinic acid, MRI tractography, perioperative ultrasound and MRI, awake surgical technique, hybrid positron emission tomography and calculated tomography - PET/CT) and browsed microsurgical techniques are necessary parts of surgical treatment (7,30). A postoperative MRI (24 to 72 h after surgical treatment) is required to confirm the degree of tumor resection, discovered to be an independent favorable prognostic factor [31]. Targeted-biopsy of the tumor is booked for cases where tumor resection is impossible [30,31].

A) Role of Surgery in management of AOD:

Neurosurgery is fundamental to remove the tumor and obtain neoplastic tissue in order to make a precise diagnosis. Total resection of the tumor is considered optimal. Several studies [31,32,33,34,35,36] revealed that the first method in AOD management is represented by optimum safe surgical resection. The objectives of a prolonged exeresis are manifold: to acquire an exact histopathology medical diagnosis; to carry out molecular analysis; and, often, to improve tumor-related scientific symptoms, such as intracranial pressure or compression. In particular, a resection of > 90% of the contrast-enhancing volume appears to enhance both progression-free survival (PFS) and OS, [31] therefore decreasing the occurrence of recurrence and the risk of malignant improvement [32,33,34,35]. In the literature, a potential study conducted on 560 patients with high-grade gliomas showed that resection is a strong prognostic factor (P<0.0001) compared with biopsy [36].

Several reports suggest that radical tumor resection (> < 0.0001) compared to biopsy [36]. Numerous reports suggest that radical tumor resection (> 90 % of contrast-enhancing volume) results in enhanced progression-free survival (PFS) and OS in both grownups and children across all malignant gliomas [Class III] [37,38]. Nevertheless, all of these examinations are unchecked (and typically retrospective), and it is possible that tumor place, patient functions such as age and comorbid disease, and standard tumor biology account for the observed differences in survival after partial versus radical resection or biopsy alone [37,38].

B) Novel treatment of AOD:

As early as 1998, it was discovered that patients with 1p/19q co-deletion are more conscious Chemotherapy is administered in a triple combination of vincristine, lomustine and procarbazine (PCV) [3]. However, the evidence-based evidence of the substantially longer survival in patients with oligodendrogliomas and 1p/19q co-deletion treated with combined chemotherapy and radiotherapy did not exist for a long period of time. The long-lasting follow-up of 2 essential phase III randomized clinical trials with patients struggling with AO treated with PCV, particularly RTOG 9402 and EORTC 26951, is bringing considerable results and leading to a paradigm shift of the disease treatment [39,40]. The treatment paradigm of oligodendroglial tumors was just recently changed, reflecting on the long-term results of two big independent phase III scientific trials, The Radiation Therapy Oncology Group (RTOG) 9402 [39] and European Organisation for Research and Treatment of Cancer (EORTC) 26961 [40].

In the RTOG study 9402, [39] performed in between 1994 and 2002, 291 patients with AO and anaplastic oligoastrocytomas were consisted of and randomized into 2 treatment arms: PCV with follow-up radiotherapy, and radiotherapy-alone. In the EORTC, research study 26951 carried out from 1996 till 2002, 368 patients with AO and anaplastic oligoastrocytomas were randomized into 2 arms: radiotherapy-alone and RT followed by PCV chemotherapy. The 1p/19q status was identified through fluorescent in situ hybridization (FISH) in both research studies [39,40].

In RTOG 9402, 1p/19q co-deletion was discovered in 46% of the patients. During the study, 80% of the patients randomized for radiotherapy consequently received PCV treatment due to the progression of the disease. After a minimum three-year follow-up in 2006, the mean progression-free survival (PFS) was various for the radiotherapy-only arm and the pcv-plus-radiotherapy arm (2.6 and 1.7 years, p= 0.004), however the median OS was similar in both study arms (4.9 and 4.7 years, p= 0.26). The OS in patients with 1p/19q co-deletion was longer than in patients without co-deletion (> 7 and 2.8 years, p< 0.001), but the OS in both treatment arms was not substantially various based on the presence of 1p/19q co-deletion [39]. As a result, the favorable predictive significance of 1p/19q co-deletion in relation to PCV-plus-radiotherapy was not proven. The lack of a positive impact of combined treatment on the OS and the event of major negative effects of PCV in more than 65% of the patients led to hesitation in regard to PCV.

The EORTC 26951 study [40] offered comparable outcomes after an average five-year follow-up in 2006. 1p/19q co-deletion was found in 21% of patients. The patients in the arm that got PCV and radiotherapy benefited more than those getting radiotherapy-alone in PFS (typical of 23 and 13.2 months), however the mean OS was comparable (40.3 and 30.6 months, p= 0.23) [40]. Patients with 1p/19q co-deletion had longer OS than patients without co-deletion, irrespective of the treatment arm. The results of both studies were thought about rather negative in 2006. They did not prove the significance of 1p/19q co-deletion as a predictive biomarker in relation to chemotherapy, but rather showed the significance of 1p/19q co-deletion as a prognostic biomarker [39,40].

4. CONCLUSION

Oligodendrogliomas are amongst the most checked out tumors of the nerve system. Despite the considerable deadly potential of these tumors, a significant number has actually been revealed to react well to treatment. The positive effect of combined early radiotherapy and PCV chemotherapy for AO and blended kinds, anaplastic oligoastrocytomas with 1p/19q co-deletion, has just recently been clearly demonstrated. An equally considerable or more positive effect of often utilized temozolomide has actually not yet been proven. The presence of 1p/19q co-deletion in oligodendroglial tumors is essential for diagnosis, and diagnosis, as well as forecast of treatment outcome. scientific trials for newly identified anaplastic oligodendroglioma are critical to examine brand-new treatment paradigms and to define proper methods to tailor treatment suggestions based upon molecular genetic details. Offered the relative deficiency of patients with newly identified anaplastic oligodendroglioma, global cooperation will be crucial to the effective conduct of planned trials.

REFERENCES

[1] Cairncross JG, MacDonald DR. Successful chemotherapy for recurrent malignant oligodendroglioma. Ann Neurol. 1988;23:360–364.

[2] Reifenberger G, Kros JM, Burger PC, Louis DN, Collins VP. Oligodendroglial tumours and mixed gliomas. Pathology and Genetics of Tumours of the Nervous System. In: Kleihues P, Cavenee WK, editors. World Health Organization Classification of Tumours. Lyon: IARC; 2000. pp. 55–70.

[3] Cairncross JG, Ueki K, Zlatescu C, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst. 1998;90:1473–1479.

[4] Smith JS, Perry A, Borell TJ, et al. Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. J Clin Oncol. 2000;18:636–645.

[5] Bauman GS, Ino Y, Ueki K, et al. Allelic loss of chromosome 1p and radiotherapy plus chemotherapy in patients with oligodendrogliomas. Int J Radiat Oncol Biol Phys. 2000;48:825–830.

[6] Van den Bent MJ. Anaplastic oligodendroglioma and oligoastrocytoma. Neurol Clin. 2007;25:1089–1109. ix–x.

[7] CBTRUS. Statistical report: Primary brain tumors in the United States, 1998–2002. Published by the Central Brain Tumor Registry of the United States 2005.; Available at http://www.cbtrus.org/reports//2005-2006/2006report.pdf.

[8] Cairncross JG, Macdonald DR. Successful chemotherapy for recurrent malignant oligodendroglioma. Ann Neurol. 1988;23:360–364.

[9] van den Bent MJ, Kros JM, Heimans JJ, et al. Response rate and prognostic factors of recurrent oligodendroglioma treated with procarbazine, CCNU, and vincristine chemotherapy. Dutch Neuro-oncology Group. Neurology. 1998;51:1140–1145.

[10] McCarthy BJ, Propp JM, Davis FG, Burger PC. Time trends in oligodendroglial and astrocytic tumor incidence. Neuroepidemiology. 2008;30:34–44.

[11] Louis DN, Holland EC, Cairncross JG. Glioma classification: a molecular reappraisal. Am J Pathol. 2001;159:779–786.

[12] Maintz D, Fiedler K, Koopmann J, et al. Molecular genetic evidence for subtypes of oligoastrocytomas. J Neuropathol Exp Neurol. 1997;56:1098–1104.

[13] Ino Y, Zlatescu MC, Sasaki H, et al. Long survival and therapeutic responses in patients with histologically disparate high-grade gliomas demonstrating chromosome 1p loss. J Neurosurg. 2000;92:983–990.

[14] Aldape K, Burger PC, Perry A. Clinicopathologic aspects of 1p/19q loss and the diagnosis of oligodendroglioma. Arch Pathol Lab Med. 2007;131:242–251.

[15] Mork SJ, Lindegaard KF, Halvorsen TB, et al. Oligodendroglioma: incidence and biological behavior in a defined population. J Neurosurg. 1985;63:881–889.

[16] Daumas-Duport C, Varlet P, Tucker ML, et al. Oligodendrogliomas. Part I: patterns of growth, histological diagnosis, clinical and imaging correlations: a study of 153 cases. J Neurooncol. 1997;34:37–59.

[17] Jenkinson MD, du Plessis DG, Smith TS, et al. Histological growth patterns and genotype in oligodendroglial tumours: correlation with MRI features. Brain. 2006;129:1884–1891.

[18] Megyesi JF, Kachur E, Lee DH, et al. Imaging correlates of molecular signatures in oligodendrogliomas. Clin Cancer Res. 2004;10:4303–4306.

[19] Kondziolka D, Bernstein M, Resch L, et al. Significance of hemorrhage into brain tumors: clinicopathological study. J Neurosurg. 1987;67:852–857.

[20] Liwnicz BH, Wu SZ, Tew JM., Jr The relationship between the capillary structure and hemorrhage in gliomas. J Neurosurg. 1987;66:536–541.

[21] Walker C, du Plessis DG, Fildes D, et al. Correlation of molecular genetics with molecular and morphological imaging in gliomas with an oligodendroglial component. Clin Cancer Res. 2004;10:7182–7191.

[22] Cairncross JG, Ueki K, Zlatescu MC, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst. 1998;90:1473–1479.

[23] van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. J Clin Oncol. 2006;24:2715–2722.

[24] Cairncross G, Berkey B, Shaw E, et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group trial 9402. J Clin Oncol. 2006;24:2707–2714.

[25] Reifenberger G, Louis DN. Oligodendroglioma: toward molecular definitions in diagnostic neuro-oncology. J Neuropathol Exp Neurol. 2003;62:111–126.

[26] Fallon KB, Palmer CA, Roth KA, et al. Prognostic value of 1p, 19q, 9p, 10q, and EGFR-FISH analyses in recurrent oligodendrogliomas. J Neuropathol Exp Neurol. 2004;63:314–322.

[27] Van den Bent MJ, Looijenga LH, Langenberg K, et al. Chromosomal anomalies in oligodendroglial tumors are correlated with clinical features. Cancer. 2003;97:1276–1284.

[28] Roth P, Wick W, Weller M: Anaplastic oligodendroglioma: A new treatment paradigm and current controversies. Curr Treat Options Oncol *14*: 505-513, 2013.

[29] Weller M, Stupp R, Hegi ME, van den Bent M, Tonn JC, Sanson M, Wick W, Reifenberger G: Personalized care in neuro-oncology coming of age: Why we need MGMT and 1p/19q testing for malignant glioma patients in clinical practice. Neuro-Oncol *14*(Suppl 4): iv100-108, 2012.

[30] Phillips C, Guiney M, Smith J, Hughes P, Narayan K, Quong G: A randomized trial comparing 35Gy in 10 fractions with 60Gy in 30 fractions of cerebral irradiation for glioblastoma multiforme and older patients with anaplastic astrocytoma. Radiother Oncol J Eur Soc Ther Radiol Oncol *68*: 23-26, 2003.

[31] Polivka J, Jr, Polivka J, Rohan V, et al. New treatment paradigm for patients with anaplastic oligodendroglial tumors. Anticancer Res. 2014;34(4):1587–1594.

[32] Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. Neurosurgery. 2008;62(4):753–764. discussion 264–266.

[33] Smith JS, Chang EF, Lamborn KR, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol. 2008;26(8):1338–1345.

[34] Brandes A. Linee Guida Neoplasie Cerebrali. Milano: Associazione Italiana di Oncologia Medica (AIOM); 2012.

[35] Brandes A. Linee Guida Neoplasie Cerebrali. Milano: Associazione Italiana di Oncologia Medica (AIOM); 2014.

[36] Roth P, Wick W, Weller M. Anaplastic oligodendroglioma: a new treatment paradigm and current controversies. Curr Treat Opt Oncol. 2013;14(4):505–513.

[37] Devaux BC, O'Fallon JR, Kelly PJ. Resection, biopsy, and survival in malignant glial neoplasms. A retrospective study of clinical parameters, therapy, and outcome. J Neurosurg. 1993;78:767–775.

[38] Laws ER, Parney IF, Huang W, et al. Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. J Neurosurg. 2003;99:467–473.

[39] Intergroup Radiation Therapy Oncology Group Trial 9402, Cairncross G, Berkey B, Shaw E, Jenkins R, Scheithauer B, Brachman D, Buckner J, Fink K, Souhami L, Laperierre N, Mehta M, Curran W: Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol Off J Am Soc Clin Oncol *24*: 2707-2714, 2006.

[40] Van den Bent MJ, Carpentier AF, Brandes AA, Sanson M, Taphoorn MJ, Bernsen HJ, Frenay M, Tijssen CC, Grisold W, Sipos L, Haaxma-Reiche H, Kros JM, van Kouwenhoven MC, Vecht CJ, Allgeier A, Lacombe D, Gorlia T: Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: A randomized European Organisation for Research and Treatment of Cancer phase III trial. J Clin Oncol Off J Am Soc Clin Oncol *24*: 2715-2722, 2006.