Discussion

Central nervous system (CNS) tumors represent a major public health problem as they bear an unfavourable clinical prognosis merely by their localization (Dobec-Meic et al., 2006). They constitute about 1-2% of all human neoplasia (Jemal et al., 2006).

Gliomas are the most common intracranial neoplasm with astrocytomas, glioblastomas, and oligodendrogliomas accounting for more than 80% of them (Central Brain Tumor Registry of the United States (CBTRUS), 2010 and Merchant et al., 2010).

In Egypt, according to The National cancer institute, Cairo university registry, malignant CNS tumors account for 0.77% of total malignancy. Astrocytoma is the most common, it accounts for 67.1% of total CNS tumors, and 0.52% of total malignancy, most of them were classified as fibrillary astrocytoma( WHO grade II) (Mokhtar et al., 2007).

Glial tumors have known mutations in critical cellular pathways, including cell cycle regulation, proliferation, cellular metabolism, cell death and survival (Elsers et al., 2014).

The accelerated rate of vascular proliferation in glioblastomas suggests that tight regulation of angiogenesis is altered to favour neoplastic growth. One of the main triggers for tumoral angiogenesis is believed to be the physiological response to hypoxia (Brat and Mapstone, 2003).

HIF-1 consists of two sub-units HIF-1α and HIF-1β both of which belong to the basic loop-helix Per-Aryl hydrocarbon nuclear translocator-Sim (PAS) protein family. Of the two subunits of Hypoxia Inducible Factor-1,
HIF-1α plays a major role in determining its activity and increasing the survival of cell in the hypoxic environment by adaptive mechanisms (O’Donnell et al., 2006).

Most studies have shown that HIF-1 overexpression has been detected in several human cancers, (such as brain, bladder, breast, lung, esophagus, colon, ovary, pancreas, kidney, and prostate) (Yang et al., 2011). Furthermore, HIF-1 overexpression has been reported to be significantly correlated with highly aggressive disease, resistance to radiation therapy and chemotherapy, and poor prognosis in some cancer types (Wong et al., 2012).

According to immunohistochemical results HIF-1 was detected as strong nuclear brown granules.

The present retrospective study included 40 cases of astrocytoma. Eight cases (20%) were grade I, 9 cases (22.5%) were grade II, 10 cases (25%) were grade III and 13 cases (32.5%) were grade IV astrocytoma.

In the current study 87.5% of grade I, 44.4% of grade II, 20% of grade III and 15.3% of grade IV cases ranged in age from 10 to 30 years old, 12.5% of grade I, 44.4% of grade II, 70% of grade III and 46.2% of grade IV cases ranged from 31 to 50 years old while no cases of grade I, 11.1% of grade II, 10% of grade III and 38.5% of grade IV were more than 50 years old.

There was a highly significant statistical direct correlation between tumor grade and patient’s age (p value <0.01). This was in agreement with a study carried by Santi et al., (2003), Nomiya et al., (2007) and Reszec et al., (2013), who found a statistically significant positive correlation between the tumor grade and patient’s age (P value =0.0027).
In contrast to our study McGirt et al., (2008) found that there is no statistical correlation between tumor grade and age of studied group. This difference may be due to obtaining specimens from dissimilar population with two thirds of studied cases were of old age with high grade astrocytoma in his study.

As regard gender of studied cases in our study there was no statistical relationship between tumor grade and gender of studied cases (P value > 0.05).

These results were conflicted by Bouffet et al., (1998) and Adams et al., (2012) who found that there was a significant statistical relationship between gender of studied cases and grade of astrocytoma, this variation with the present study may be attributed to the nature of studied cases as most of cases in the his study were malignant astrocytoma and include cases of primary malignant astrocytoma of spinal cord (PMASC) and he stated that it is increasingly evident that data regarding intracranial astrocytomas cannot be generalized to those tumors affecting the spinal cord.

In this work all cases of grade I and grade II astrocytoma survived within 3 years of follow up while only 40% of grade III and 46.2% of grade IV survived within the same period.

There was a highly significant statistical inverse correlation between tumor grade and 3 years survival (p value < 0.01), these results were in line with McGirt et al., (2008) and Adams et al., (2012) who found that histological grade was strongly associated with survival (P value =0.02). This indicates that tumor grade can be used as a prognostic factor for astrocytoma.
In contrary with our study Merchant et al., (1999); Santi et al., (2003) and Raco et al., (2010) found that there is no statistically significant correlation between the histological grade of astrocytoma and survival.

In the present study 63% of survived cases recurred within 3 years of follow up and there was a significant statistical direct correlation between tumor grade and tumor recurrence (P value <0.05), that was consistent with studies carried by Hou et al., (2006) and Stüer et al., (2007).

According to the current study 50% of cases were negative for HIF-1 expression, 37.5% of cases were scored as (+) and 12.5% of cases were scored as (++).

As regard age, 60% of studied cases that were negative for HIF-1 expression ranged in age from 10 to 30 years old while only 5% of this cases were >50 years old. There was a positive statistical correlation between HIF-1 extent of expression and age of studied cases (P value <0.05).

That was consistent with a study carried by Assimakopoulou et al., (2015) on 34 cases of astrocytoma ranging in age from 2 to 74 years old who reported that in patients >19 years old with glioblastoma the distribution of HIF-1 was significantly increased (P value <0.0001).

These results are supported by Kang et al., (2005) who found that aging process induces the activation of HIF-1 and its downstream-regulated proteins like Vascular Endothelial Growth Factor (VEGF).

In contrast to our study Isobe et al., (2013) found that there was no significant statistical correlation between the expression of HIF-1 and age of cases of gastric carcinoma.
In this work there was no significant statistical relationship between extent of HIF-1 expression and gender of studied cases (P value >0.05). This result is in agreement with Assimakopoulou et al., (2015) who found that no significant differences in HIF-1 expression based on gender of the patients of astrocytoma.

In this study 40% of cases that were negative for HIF-1 expression were grade I astrocytoma and 80% of cases showed score (++) for HIF-1 expression were grade IV astrocytoma.

In this study there was a highly significant statistical direct correlation between HIF-1 extent of expression and grades of astrocytoma as the extent of expression increases with progression from grade II to grade IV (P value < 0.01).

These results were consistent with Mashiko et al., (2011); Mayer et al., (2012); Ji et al., (2013) and Reszec et al., (2013) who observed a statistically significant correlation between HIF-1 protein expression and the grading of the astrocytoma (p value < 0.001).

This indicates that HIF-1 plays a critical role in progression of the tumor and it may be attributed to the oncogenic effect of HIF-1 in development of astrocytoma apart from hypoxia (Dreyfuss et al., 2009 and Mayer et al., 2012).

In the present study there was diffuse expression of HIF-1 in pseudopalisading cells around necrosis in glioblastoma group, the same finding was reported by Sondergaard et al., (2002); Hendriksen et al., (2009); Hong et al., (2009) and Reszec et al., (2013). This result is supported by Giannopoulou et al., (2006) and Soda et al., (2013) who
found that tumor cells palisading around necrosis express high levels of hypoxia inducible regulators of angiogenesis such as VEGF.

In the present study 80% of cases that were negative for HIF-1 expression survived within 3 years of follow up while only 40% of cases showed score (++) survived within the same period.

There was a statistically significant inverse correlation between extent of HIF-1 expression and 3 years survival of studied cases (P value <0.05).

These results were consistent with Korkolopoulou et al., (2004); Mashiko et al., (2011) and Ji et al., (2013) who found a positive statistical correlation between HIF-1 expression and survival of patients of astrocytoma and reported that HIF-1α is an independent factor for shorter overall survival in glioblastoma.

Reszec et al., (2013) also found a significant statistical correlation between HIF-1 expression and prognosis of astrocytoma (P value <0.001) and observed that almost all of gemistocytic astrocytomas, which are associated with worse prognosis were positive for HIF-1 protein.

These results may indicate that HIF-1 expression may be used to refine the prognostic information provided by grade in patients with astrocytoma.

In contrary Giannopoulou et al., (2006) found that there was no statistical correlation between the expression of HIF-1 and patient survival.

A positive statistical correlation between HIF-1 extent of expression and patient's survival was also detected in many other tumors as reported by Isobe et al., (2013) in gastric cancer, Kaya et al., (2012) in breast carcinoma, Feng et al., (2013) in endometrioid endometrial carcinoma and Ping et al., (2013) in non-small cell lung carcinoma (NSCLC).
In the current study all cases scored (++) for HIF-1 expression recurred within 3 years of follow up while only 50% of cases that were negative for HIF-1 expression recurred within the same period.

There was a positive statistical direct correlation between extent of HIF-1 expression and tumor recurrence (P value < 0.05).

That was in agreement with a study carried by Theodoropoulos et al., (2005) who stated that HIF-1 overexpression is combined with aberrant mutant p53 nuclear protein accumulation and seem to indicate an aggressive phenotype, suggesting a potential biological model predictive of future risk of disease progression and recurrence in patients with superficial urothelial bladder carcinoma.