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CLINICAL STUDY

Incidence of high grade gliomas presenting as radiographically non-enhancing lesions: experience in 111 surgically treated non-enhancing gliomas with tissue diagnosis

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Abstract

Purpose Although non-enhancing lesions suspicious for glioma are usually assumed to be low grade glioma (LGG), some high grade glioma (HGG) do not enhance, which may lead to a delay in biopsy and/or resection, diagnosis, and treatment initiation. Thus, there is a clear need for a large-sample study that quantifies the rate of malignant, non-enhancing gliomas.

Methods We retrospectively reviewed our series of 561 consecutive surgically treated gliomas with tissue diagnosis, 111 of which were non-enhancing, to determine the prevalence of high-grade histology in radiographically presumed LGG. Relative expression of tumor markers were also reported for non-enhancing lesions to investigate genetic correlates.

Results We identified 561 surgically treated gliomas with tissue diagnosis from August 2012 to July 2018 and found that 111 patients (19.8%) demonstrated non-enhancing lesions suspicious for glioma on preoperative MRI. Thirty-one (27.9%) of the non-enhancing lesions were classified as HGGs (WHO Grade III or IV). Non-enhancing lesions were four times more likely to be HGG in patients older than 60 years than patients younger than 35 years (41.2% vs. 11.4%, Pearson Chi^2 $p < 0.001$). Binomial logistic regression showed a significant inverse effect of age on the presence of IDH mutation in non-enhancing HGGs ($p = 0.007$).

Conclusion A clinically significant proportion (27.9%) of non-enhancing lesions were found to be HGG on final pathologic diagnosis. Thus, in patients with good functional and health status, especially those older than 60 years, we recommend obtaining tissue diagnosis of all lesions suspected to be glioma, even those that are non-enhancing, to guide diagnosis as well as early initiation of chemotherapy and radiation therapy.

Keywords Glioma · Glioblastoma multiforme · Enhancing · High grade glioma · Low grade glioma

Introduction

Gliomas represent the most common central nervous system neoplasm with an age-adjusted incidence of 5.4 cases per 100,000 people every year [1]. Low-grade gliomas (LGG, grade I–II) account for approximately 25.8% of all gliomas, and their diagnosis often involves a combination of factors including patient clinical presentation, histopathology, and imaging findings (enhancement, diffusion restriction, size, infiltration, etc.) [2, 3]. In general, gliomas with enhancement after the administration of gadolinium-based contrast are associated with malignant features, while non-enhancing lesions are typically presumed to be a lower histological grade [4].

Non-enhancing lesions suspicious for glioma are usually assumed to be LGG and thus may be observed without obtaining tissue diagnosis at some institutions [5]. However, management of patients presenting with non-enhancing, presumed LGG has been a continued subject of debate. This controversy is further complicated by the fact that not all non-enhancing gliomas are found to have low-grade histology on biopsy. Several studies within the past 20 years

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have demonstrated that 9–45% of non-enhancing lesions can be histologically malignant (HGG, grade 3–4) [5–11]. Scott et al. demonstrated in a sample of 314 patients that 9% of HGGs lacked enhancement while 48% of LGGs enhanced, almost equal to the proportion of LGGs that did not. However, not all of the patients in their sample underwent pre-operative MRI and several patients underwent stereotactic biopsy, which is more susceptible to errors in sampling and thus may have skewed tumor grading [11]. Another large sample study was conducted by Chamberlain et al., that showed absence of contract enhancement in 4% of glioblastoma multiformes (GBM) and 31% of highly anaplastic astrocytoma (HAA). However, this study was conducted over 20 years ago and findings presented may differ in light of current incidence rates for glioma [12–15]. The remaining studies provide similar evidence of histologically malignant gliomas presenting with non-enhancing MRI, but rates reported dramatically differ most likely owing to small sample sizes [6–10]. Indeed, there is a clear need for a large-sample study that addresses the rate of malignant, non-enhancing gliomas in the current patient population.

Thus, to understand the prevalence of high-grade histology in radiographically presumed low-grade gliomas, we retrospectively reviewed a series of 561 consecutive gliomas biopsies, 111 of which were non-enhancing radiographically. Relative expression of methylation and tumor markers were also reported for non-enhancing lesions to investigate genetic correlates. Findings from this study may allow for a more informed assessment of the risk for malignancy in non-enhancing gliomas and direct future treatment paradigms.

Methods

Patient selection

After Institutional Review Board approval, we conducted an exploratory retrospective review of all non-enhancing lesions diagnosed as gliomas, undergoing surgical resection or biopsy at our institution from August 2011 to June 2018. Inclusion criteria comprised of the following: (1) patients older than 18 years old; (2) patients with newly diagnosed supratentorial non-enhancing lesions in the diagnostic MRI with gadolinium-contrast; and (3) patients with a histological diagnosis of either LGG or HGG. The histological diagnosis was confirmed by our institution's pathology department using standard histopathological criteria. All imaging studies were reviewed by a Board Certified Neuroradiologist.

Data gathering

Relevant demographic data including diagnosis, sex, and age at surgery were collected. In addition, the presence of contrast-enhancement in the diagnostic presurgical MRI and histological variables, such as tumor pathology, were recorded to examine the rates of non-enhancing but histologically malignant tumors. Presence or lack of enhancement was determined by a board-certified neuroradiologist. Finally, the presence of prognostic biomarkers *MGMT, IDH1,* and *1p19q* were also collected to determine any potential association between MRI contrast-enhancement and tumor malignancy. Patients without mutational marker data were excluded from analysis.

Surgical planning

Our surgical treatment paradigm is to perform a maximal safe resection of FLAIR hyperintense lesions when feasible, while minimizing new neurologic deficits. We resect FLAIR hyperintense regions up to either anatomic landmarks such as sulci, the falx, or the dura, or functional landmarks such as initiation of motor or speech arrest during awake surgeries.

For lesions entirely within eloquent regions, the thalami, or the basal ganglia, or when there is multifocal disease, we opt for an open biopsy or a steorotactic needle biopsy.

When we take an open biopsy or a stereotactic needle biopsy, we pick our target within a FLAIR hyperintense area that is as far away as possible from blood vessels and eloquent areas. For stereotactic needle biopsies, we take two core biopsies from one target site, although we rotate the window of the biopsy needle 180 degrees in between biopsies to target a slightly different area.

Radiographic analysis

A blinded board certified neurosurgeon evaluated the radiographic characteristics of all non-enhancing high grade gliomas. Lesions were characterized as multifocal if there were two or more noncontiguous areas of FLAIR hyperintensity. Lesions were characterized as diffuse if one contiguous FLAIR hyperintense lesion involved more than one lobe and/or more than one hemisphere.

Statistical analysis

Pearson's correlation coefficient was used to assess the relationship between mutational status and age, followed by binomial logistic regression analysis. All data was analyzed using IBM SPSS Statistics v. 24.0 (IBM, Armonk, NY). Correlations between age and tumor grading were assessed using Pearson's chi square test. Tumors were categorized by histological grade based on WHO standards and relative frequencies were calculated based on tumor type and grade. Incidence of non-enhancing LGGs expressing tumor biomarkers *MGMT, IDH1, 1p19q* was also calculated.

Results

We identified 561 gliomas from August 2012 to July 2018 and found that 111 patients (19.8%) demonstrated non-enhancing lesions on preoperative MRI. Median age at diagnosis was 46 years old (17–84) with a similar distribution between females and males (51.4% vs. 48.6%, respectively). Tissue diagnosis was obtained for all patients at the time of surgery; 19 patients underwent supramaximal resection, 47 patients underwent lesionectomy, 28 patients underwent subtotal resection, 8 patients underwent open biopsy, and 9 patients underwent stereotactic needle biopsy.

We confirmed through histological grading that 80 (72.0%) of the non-enhancing lesions were classified as LGGs (WHO Grade I or II). Grade II Astrocytoma was the most common non-enhancing LGG, observed in 47 patients (42.3%), followed by Grade II Oligodendroglioma which were observed in 17 (15.3%) patients (Fig. 1). Malignant features (WHO Grade III or IV) were described in 31 (27.9%) of the non-enhancing tumors. Out of these HGG, we identified 17 (15.3%) patients with Grade III Anaplastic Astrocytoma, 4 (3.6%) patients with Anaplastic Oligodendroglioma, and 1 (0.9%) patient with Anaplastic Mixed Glioma. Lastly, we identified a total of 9 (8.1%) cases of pre-operative non-enhancing glioma in which Grade IV Glioblastoma Multiforme was the definitive diagnosis.

Non-enhancing lesions were four times more likely to be HGG in patients older than 60 years old than patients younger than 35 years old (41.2% vs. 11.4%, Pearson Chi^2 $p < 0{,}001$). A binomial logistic regression was performed to assess the effect of age on the probability of having a non-enhancing HGG, as opposed to non-enhancing LGG. The regression model was statistically significant ($p = 0.007$) and showed that with each additional year in age there was a 3.8% increase in the probability of having a non-enhancing lesion suspicious for glioma be histologically HGG instead of LGG (Fig. 2).

Regarding methylation and tumor markers, we found that in patients with non-enhancing LGG, IDH+ mutational status was significantly negatively correlated with age ($R^2 = -0.509$, $p = 0.002$) (Table 1). This correlation was not seen with non-enhancing HGGs ($R^2 = -0.131$, $P = 0.642$). There was no correlation between the incidence of MGMT

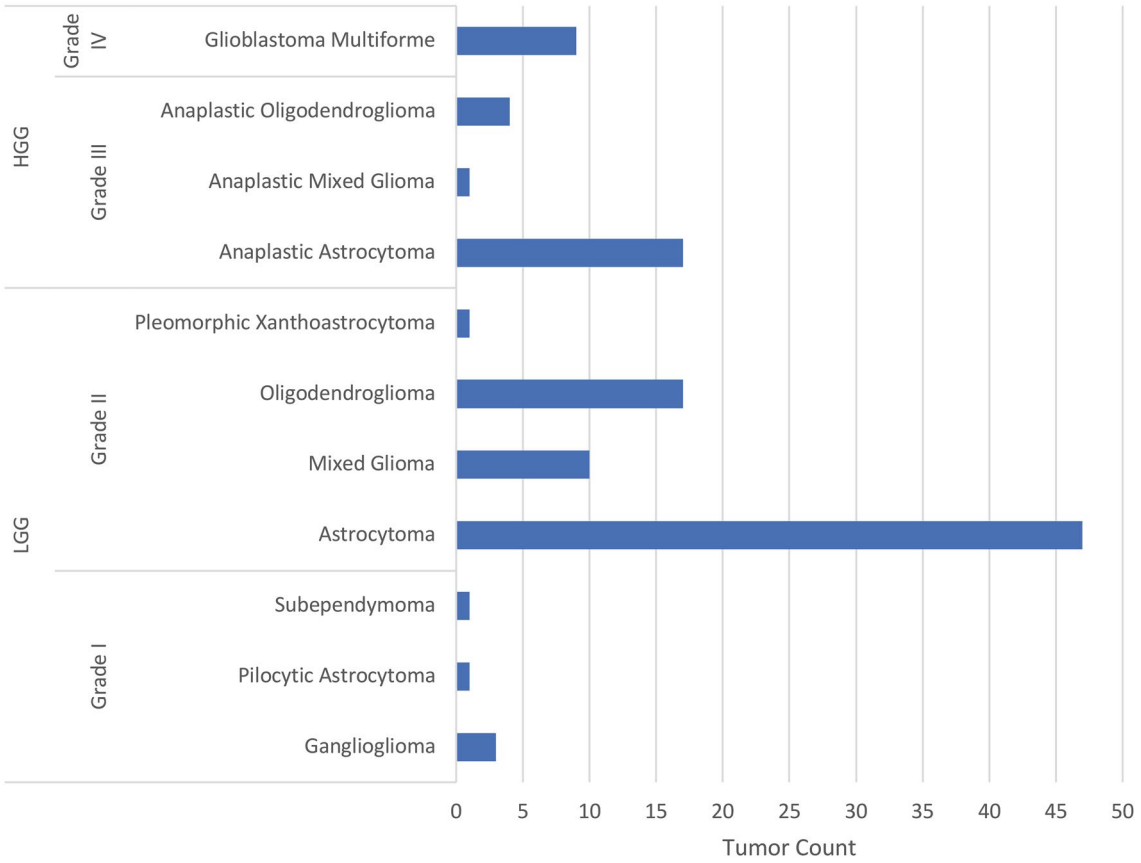

Fig. 1 Summary of histologic grading of tumor specimen without radiographic enhancement

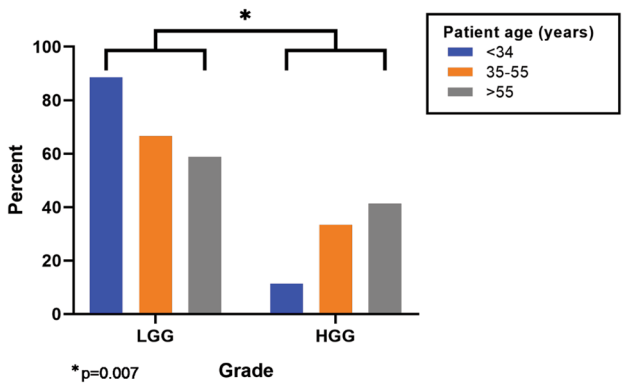

Fig. 2 Proportion of LGG and HGG after stratification by age. The proportion of non-enhancing LGGs decreases with age while the number of non-enhancing HGGs increase with age. The proportion of non-enhancing LGGs decreased from 88.6% in patients younger than 34 to 58.8% in patients older than 58.8. Contrarily, the proportion of patients with non-enhancing HGG increased from 11.4 to 41.2%. (Color figure online)

hypermethylation or 1p19q co-deletions and age in either non-enhancing HGGs or LGGs (Table 1, Fig. 3). Finally, binomial logistic regression showed a significant effect of age on the presence of IDH mutation (P = 0.007). With each increasing year in age, the presence of IDH+ mutational status becomes 0.922 times less likely.

Of 111 non-enhancing high grade glioma patients, 41 patients (36.9%) had diffuse lesions and 9 patients (8.1%) had multifocal disease, of which 4 patients (3.6%) had both diffuse and multifocal lesions. Of the 41 patients with diffuse lesions, twenty-five patients (61.0%) had lesions involving the insula. No patients had non-diffuse insular lesions.

Discussion

Surgical treatment of LGG and HGG

Although the routine evaluation of brain lesions compatible with low-grade gliomas include contrast-enhanced T1/T2 and FLAIR weighted sequences, our study provides contemporary data supporting the fact that there is a clinically significant percentage of non-enhancing gliomas that possess malignant histological characteristics at diagnosis (27.9%, n = 31). The probability of a non-enhancing high-grade glioma was higher in the older cohort compared to the

Table 1 Correlation among age groups, histological grading, and methylation/tumor marker expression in nonenhancing low grade gliomas and nonenhancing high grade gliomas

	Age	≤ 34 years	35–55 years	≥ 55 years
Low Grade (I-II)	# low grade tumors	31	28	20
	MGMT Hypermethylation			
	No	1 (3.2)	0 (0)	4 (20)
	Yes	0 (0)	1 (3.6)	0 (0)
	No data	30 (96.8)	27 (96.4)	16 (80)
	IDH-1 (+)			
	No	1 (3.2)	4 (14.3)	8 (40)
	Yes	9 (29.0)	10 (35.7)	4 (20)
	No data	21 (67.8)	14 (50)	8 (40)
	1p19q Co-deletion			
	No	7 (22.6)	5 (17.9)	3 (5)
	Yes	6 (19.4)	11 (39.3)	5 (25)
	No data	18 (58)	12 (42.8)	12 (60)
High Grade (III-IV)	# high grade tumors	4	14	14
	MGMT Hypermethylation			
	No	0 (0)	0 (0)	4 (28.6)
	Yes	1 (25)	2 (14.3)	1 (7.1)
	No data	3 (75)	12 (85.7)	9 (64.3)
	IDH-1 (+)			
	No	1 (25)	4 (28.6)	4 (28.6)
	Yes	1 (25)	2 (14.3)	3 (21.4)
	No data	2 (50)	8 (57.1)	7 (50)
	1p19q Co-deletion			
	No	0 (0)	2 (14.3)	3 (21.4)
	Yes	1 (25)	0 (0)	2 (14.3)
	No data	3 (75)	12 (85.7)	9 (64.3)

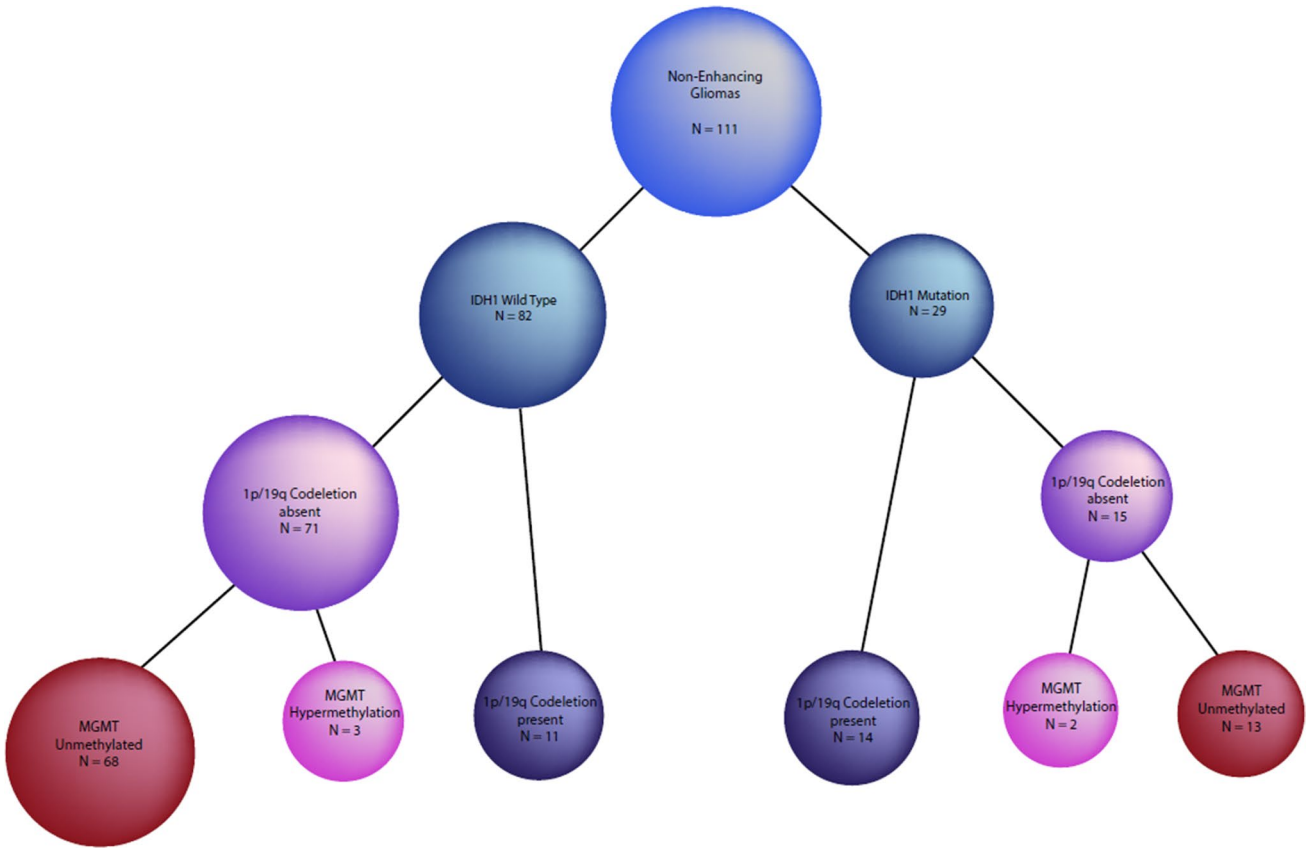

Fig. 3 Tree diagram of biomarkers expressed in non-enhancing high grade glioma lesions. 43 out of 111 non-enhancing HGG expressed at least one favorable biomarker such as MGMT hypermethylation, 1p19q co-deletion, IDH1 mutation, or a combination these. The majority (61.2%) of non-enhancing high grade gliomas were IDH-1 wildtype, non-1p19q codeleted, and MGMT non-hypermethylated

younger group (41.2%vs. 11.4%, Pearson Chi^2, $p < 0.001$). Despite the limitations of our study (retrospective study, single-surgeon series, selection bias), we found sufficient evidence to support the concept that non-enhancing high-grade gliomas may be relatively common; therefore, the absence of contrast-enhancement in these lesions may not be sufficient to accurately predict histology.

Whether non-enhancing, presumed low-grade, gliomas should be conservatively followed or treated with surgical resection remains a topic of debate. While some studies have shown a wait-watch approach may be a safe and effective initial strategy for the management of LGG, patients will often need to be treated for larger lesions once treatment is initiated following changes in lesion size or quality [16, 17]. This may prove ultimately disadvantageous as increased pre-surgical lesions size may complicate surgical resection and increase perioperative morbidity [18–20]. In a systematic review, Aghi et al. also described that, while conservative follow-up resulted in no negative impact, most cases of surgical resection for LGG resulted in positive benefit including improved seizure control and cognitive function [21]. Many authors advocate for early resection for both LGG and HGG in most circumstances, although the objective is mainly to obtain histologic confirmation, improve neurologic condition, reduce tumor growth, and prevent malignant transformation in cases of LGG as opposed to cytoreduction and alleviating mass effect in surgery for HGG [22, 23]. The invasive nature of LGG and frequent occurrence near eloquent areas of cortex often preclude complete resection. Thus, intraoperative stimulation brain mapping should be employed to prevent severe neurologic deficits while still achieving gross total resection [24]. Finally, Jakola et al. compared wait and watch versus surgical resection strategies for LGGs in a sample of 240 patients [25]. Of these, 153 patients underwent biopsy and "watchful waiting" while 87 underwent early resection. Surgical resection significantly improved overall survival (74% compared to 60%) with conservative treatment associated with a relative hazard ratio of 1.8. Thus, in situations where resection is possible, it is clear surgical intervention for LGG or HGG should be preferred.

Our finding that non-enhancing lesions were four times more likely to be HGG in patients older than 60 years old than patients younger than 35 years old (41.2% vs. 11.4%, Pearson Chi^2 $p < 0{,}001$) suggest that older patients,

especially those over 60 years, found to have a non-enhancing lesion suspicious for glioma, undergo biopsy, as there is an increased probability of having high grade pathology, and thus adjuvant chemoradioterhapy may be initiated as early as possible.

Radiographic features of HGG

The improved outcome in patients with LGG receiving early surgical resection and recent advancements in treatment necessitate a firm understanding of the radiographic features of HGG and LGG for diagnosis, management and treatment. MRI with gadolinium-contrast has traditionally been used as an imaging assessment for glioma malignancy prior to biopsy. This increased contrast enhancement in malignant lesions has been attributed to greater microvascular proliferation and increased blood–brain-barrier permeability, allowing for enhanced extravasation of gadolinium into tumor tissue [26–28]. However, we have shown 27.9% of non-enhancing gliomas may be of high grade. Several other radiologic characteristics of HGG and LGGs may offer supplemental information to refine diagnoses and are worthy of discussion here. First, high-grade gliomas typically present with less distinct and irregular borders compared to other tumors, often with nodular enhancement. Glioblastomas are often seen crossing the mid-line in a characteristic "butterfly" appearance; these GBMs that cross the midline and with diameters greater than 5–6 cm have been associated with worse patient outcome [29]. Fluid attenuation inversion recovery (FLAIR) weighted MRI images of HGGs will often reveal significant surrounding vasogenic edema, often referred to as peritumoral edema [30]. This is often accompanied by hemorrhage, mass effect, and ventricular distortion as well as a hypointense center of necrosis [26]. Hemorrhage, necrosis, and cyst formation can result in heterogeneous signal intensity on both T1and T2 weighted imaging.

Radiographic features of LGG

Despite being classified as WHO Grade II or lower, LGGs have the propensity to undergo malignant transformation which can be unpredictable and rapid [28]. This insidious progression is suspected to occur in up to 70% of LGGs within 5–10 years of diagnosis [27]. Routine MR imaging is the current modality of choice for patient monitoring and thus a knowledge of the radiographic features of LGG is essential. LGGs typically present with low and high signal on T1 and T2 weighted MR respectively. FLAIR sequences may also show high signal indicating cerebral edema which may be useful in differentiating between non-neoplastic masses. Still, conventional imaging is not highly specific and further differentiation of LGGs from other non-neoplastic, non-enhancing lesions (developmental anomalies, tumefactive multiple sclerosis, bacterial abscesses) should be supplemented with histological confirmation and clinical correlates [31]. Worthy of note are pilocytic astrocytomas which, despite being categorized as a Grade I glioma, may display imaging features of higher-grade neoplasms, such as intratumoral hemorrhage and intense enhancement. In these cases, PAs may be distinguished by their slow growth, cystic character, and distinctive enhancing mural nodule [32].

In addition, previous studies have been conducted associating imaging findings with the presence of gene mutations in hopes that imaging correlates may serve as noninvasive biomarkers. In the current study, we examined the relative incidence of *MGMT, IDH-1, and 1p19q* biomarkers in our population of non-enhancing LGGs. *IDH1* mutations and *MGMT* promoter methylation have both been associated with longer survival [33]. In a study of 202 patients, Carrillo et al. found that non-contrast enhancing tumors (nCET) significantly correlated with presence of *IDH1* mutations but not *MGMT* methylation [34]. In addition, nCET was able to predict *IDH1* mutational status with 97.5% accuracy but poorly predicted *MGMT* promoter methylation. Presence of a smooth, non-enhancing tumor margin has also been associated with presence of a *1p19q* co-deletion subtype [35]. Similarly, we found that, of the non-enhancing LGGs expressing one of our relevant biomarkers, most were either *IDH-1* mutants, *1p19q* subtypes, or both. Of note, we found that 43 of 111 (38.7%) of non-enhancing high grade gliomas had at least one favorable biomarker such as 1p19q co-deletion, IDH-1 mutation, and/or MGMT promoter methylation (Fig. 3). Such prognostic and potentially therapy directing information would benefit this clinically significant proportion of patients with non-enhancing high grade gliomas. While these findings are interesting, further radiogenomic studies are needed to characterize the diagnostic and prognostic value of these associations.

Current approaches at grade-based glioma imaging

Our data on the prevalence of non-enhancing, malignant gliomas underscore a need for novel methodologies with improved predictive value that correlate radiological findings with tumor grade. Although contrast-enhancement alone may not be a powerful enough differentiator of tumor grade, Asari et al. used a combine score of nine MRI criteria including contrast enhancement, flow-void, edema, and necrosis/cyst formation, that correlated positively with tumor grade [36].

Another approach may be through examining the motion of water molecules as an inverse correlate of tumor cellularity through diffusion weighted imaging (DWI). Implied increases in cellular density and impaired free water diffusion may result in a lower apparent

diffusion coefficient (ADC) correlating with degree of malignancy in glioblastoma and anaplastic astrocytomas [37]. A recent histogram analysis conducted by Kang et al. showed ADC maps to be a promising predictor of tumor grade with sensitivity and specificities of 85.7% and 100% respectively [38].

Perfusion weighted imaging (PWI) may be another approach to radiological assessment of tumor grade. Diagnostic imaging for PWI relies on the ability of malignant gliomas to aggressively invade brain parenchyma and induce profound angiogenesis. In the past, small studies using PWI to create cerebral blood volume maps as an assessment for tumor vascularity correlating with tumor grade have been relatively successful [39–42]. Though promising, the sensitivity and specificity of this approach should be further investigated and confirmed in a large patient population.

In all patients with suspected glioma (both suspected high grade and low grade) on MRI, we favor a maximal safe resection without creating new neurologic, when feasible. While Perfusion Weighted Imaging (PWI) is a valuable tool to noninvasively predict tumor grade before surgery, this information would not affect our surgical decision making. Additionally, PWI is not routinely reimbursed at our hospital. Therefore, because PWI does not affect our surgical decision making and because it increases health care expenditures, we do not order it routinely.

Finally, MR spectroscopy is a well-studied technique that examines metabolic differences between neoplastic and normal brain tissue as well as metabolic inhomogeneity within the glioma itself [43]. Through the detection of various metabolites such as choline (Cho), creatine (Cr), and myo-inositol (MI), and N-acetylaspartate (NAA), MRS is able to differentiate between various tumor grades by quantifying varying metabolite ratios. HGGs have generally been correlated with increased Cho/ NAA and Cho/ Cr ratios while LGGs have generally shown elevated MI/ Cr ratios [44–48]. Hourani et al. reported the sensitivity and specificity of their approach to be 72.25% and 91.7% respectively with a cut-off ratio of NAA/Cho of 0.61. While this approach is approach is promising, adoption into clinical practice has been slow due to lack of large-sample, multi-center studies [43].

In the current study, we found no radiographic features common among all non-enhancing high grade gliomas, or specific to non-enhancing high grade gliomas that were not found in enhancing high grade gliomas. Diffuse lesions were found in 36.9% of patients, multifocal disease was found in 8.1% of patients, and 3.6% of patients had both multifocal and diffuse disease. Future studies with emerging imaging sequences such as MR spectroscopy will hopefully detect high grade gliomas non-invasively.

A treatment algorithm for suspected LGG and HGG

Finally, a treatment paradigm for suspected LGG and HGG should be discussed. First, when imaging suspected LGG or HGG, one should not solely rely on the presence or absence of gadolinium-enhancement for an assessment of tumor grade. A gross assessment of peritumoral edema, degree of necrosis, and evidence of hemorrhage among other distinguishing characteristics should be considered as a holistic assessment of malignancy. If deemed necessary, DWI, PWI, or MRS may provide supplemental radiologic information. Second, early surgical resection should be the principal approach to treating both low-grade and high-grade gliomas. While some centers may adopt a wait-and-watch approach for suspected LGG, we believe this is a suboptimal approach to care for three reasons: (1) this will inevitably result in an increased lesion size when surgery becomes necessary and may increase the risk of malignant transformation [16]; (2) as has been shown in previous studies, including our own, there is a considerable possibility that lesions appearing “low-grade” may, in fact, be malignant; and (3) there is a clear benefit to early tumor resection in terms of overall patient survival [25]. Thus, we believe that aggressive surgical resection should be the principal approach to treating both low-grade and high-grade gliomas. Third, extensive intraoperative mapping and awake-surgeries may allow for the greatest degree of tumor resection with minimal post-operative neurologic deficits. In cases where tumors that are highly disseminated, located in eloquent cortex, show extensive invasion of the dominant lobe, or are seen in patients with Karnofsky scores < 70 or with significant medical comorbidities, surgical resection should be deferred for biopsy and medical and/or radiologic treatment.

Conclusion

In the largest series of its kind, we have shown that the presence of non-enhancing gliomas of high-grade may be relatively common. Particularly in patients older than 60 years, we have found a clinically significant probability that non-enhancing lesions radiographically suspicious for glioma may be HGG, and thus early biopsy may be warranted in patients with minimal medical comorbidities and good functional status. Lack of enhancement should not be the sole factor that precludes biopsy and diagnosis, and thus early initiation of adjuvent chemoradiation therapy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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