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Review Article

Glioblastoma Surgery: Technology for Gross Total Resection. A Review

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Abstract

Current technologies used for glioblastoma resection seems to improve accuracy in achieving gross total resection but overall survival has been similar in the last decades with only minimal improvement. Non-enhancing areas on contrast enhanced T1-weighted MRI images has the highest density of viable malignant cells and MRI sequences are not tumor specific, making complete resection of the tumor and obtaining better survival very difficult despite the current combination of treatments. In this article we review the latest technological advances that attempt to improve tumor resection to prolong survival time.

Keywords: Gross Total Resection (GTR); Glioblastoma Multiform (GBM); Blood Brain Barrier (BBB)

Introduction

Glioblastoma multiform (GBM) is the most common primary malignant intracranial neoplasia, with an incidence of 12,390 new cases each year (USA) [1]. Current therapy incorporates careful resection followed with radiation and chemotherapy and afterward chemotherapy. Its well-known that extent of resection (EOR) is an important prognostic factor in GBM and 5-Aminolevulinic acid (5-ALA) fluorescence–guided resection may improve surgical accuracy and prolong survival [2]. Gross total resection (GTR) of 98% of GBM mass improves outcome, and removal of at least 77% show increase survival [3]. Infiltrative GBM cells makes excision of neoplastic cells difficult to achieve with the current technology [4].

Non-enhancing areas on contrast enhanced T1-weighted MRI images has the highest density of viable GBM cells and MRI sequences are not tumor specific. Enhancement usually only reflects opening of blood brain barrier (BBB) [5]. T2-weighted MRI-hyperintensities are caused by numerous conditions with low specificity for GBM cells [6].

Despite GTR and adjuvant therapy, molecular and cellular heterogeneity makes complete eradication impossible, due to surrounding tumor-associated microenvironment and GBM cells invading the parenchyma not otherwise seen on routine image [7]. Current neurosurgical GTR fails to prevent recurrence and progression of GBM.

Currently we only have low evidence that with these modern and advanced technical tools [8]. There is enthusiasm for investigating supratotal resections in the non-enhancing areas (STR). Be that as it may, there is as of now no agreement on the potential endurance advantage of STR contrasted with GTR.

Current technologies used for glioma resection seems to improve accuracy in achieving GTR but overall survival (OS) has been similar in the last decades with only minimal improvement [9].

Advanced magnetic resonance imaging

Current radiographic examination for the diagnosis and control of GBM is magnetic resonance imaging (MRI). Usual diagnostic MRI modalities for GBM are T1 and T2 with and without contrast including T2-FLAIR, T2 gradient echo (GRE) and diffusion weighted im-

aging (DWI). More MRI advanced imaging modalities in the most recent years incorporate multi-parametric sequences, such as dynamic susceptibility contrast (can measure blood flow), dynamic contrast enhancement (to evaluate microcirculature), diffusion tensor imaging (DTI), spectroscopy (to evaluate chemical metabolism) or functional imaging (eloquent areas) [10].

Dynamic contrast-enhanced-Magnetic resonance imaging (DCE-MRI) evaluates vascular permeability through BBB and differentiate high from low-grade gliomas. It also detects recurrent GBM and is a potential tool for classifying gliomas [11].

Dynamic susceptibility enhanced-Magnetic resonance imaging (DSC-MRI) estimates the relative cerebral blood volume within GBM and has been useful in determining prognosis and early treatment GBM response [12].

Special attention has been done to T2-FLAIR hyperintense abnormality beyond the boundaries of contrast-enhanced T1 MRI images. Recently has been reported that non-enhancing tumor area (hyperintense on FLAIR/T2WI), when hypoperfused values was associated with vasogenic edema, but when hyperperfused was associated with GBM cells. GBM cells can also infiltrate on non-hyperintense FLAIR images. Some authors have reported that resection ≥ 53.21% of the T2 MRI or FLAIR hyperintense region increased the survival from 15.5 months (GTR of only contrast-enhanced T1 MRI) to 20.7 months [13,14]. In fact, some authors suggest that supramaximal resection by anatomic lobectomy ought to be considered as a promising treatment in select patients if achievable [15].

Diffusion-weighted imaging (DWI) is an interesting MRI technique that can elucidate malignant areas of GBM in non-enhancing areas. Hyperintense lesions in a nonenhancing peritumoral area on DWI has been very specific for GBM and has inverse relationship with tumor cellularity. Combined with other MRI sequences improves diagnostic sensitivity [16].

Apparent diffusion coefficient (ADC) sequence of tumor regions on preoperative MRI can discriminate between low and high-grade gliomas. In a similar way than DWI can assist in tumor biopsy accuracy [16].

Intra-operative magnetic resonance imaging (iMRI) has been reported to achieve complete resection in three trials, Willems 2006, Senft 2011 and Kubben 2014, but all of them with very low-quality evidence. However, a combined use of iMRI and 5-ALA fluorescence–guided resection might be a good way to achieve GTR in non-eloquent GBM areas. Unfortunately, only low quality of evidence exists for this combined technology [17].

5-Aminolevulinic acid (5-ALA) fluorescence–guided resection

5-ALA fluorescence–guided resection is a standard surgical tool for GBM approved by FDA in 2017 https:/www.accessdata.fda.gov/drugsatfda_docs/label/2017/208630s000lbl.pdf. Is associated with a better extent of resection and gives real-time visualization during surgery of GBM but there is no difference in overall survival when compared with classical resection. Recent studies suggest the combination of (5-ALA) fluorescence–guided resection and iMRI as a promising technology but there is no current evidence of it [18,19].

PET-guided MR spectroscopy (MRS)

Positron emission tomography (PET) provides additional information MRI for GBM planning of surgery. PET imaging with 11C-methionine (MET) combined with MRS has been suggested as another expensive novel diagnostic tool to improve GBM diagnosis accuracy through brain biopsy. Amino acid tracers (MET) compared with ^{18}F-FDG show better delineation and accuracy of GBM extent. Interestingly, PET imaging of non-enhancing T2/FLAIR hyperintense GBM regions can detect malignant cells [20]. More investigations will be needed to indicate PET-MET in the usual clinical practice.

Intraoperative ultrasonography

Is another real-time low-cost technology that helps GTR. It Is a precise tool for differentiate neoplasm from ordinary brain parenchyma. Some author report 81% of GTR using this technique. Has been useful and safe for intraoperative GBM localization and visualize the extent of resection in real-time image guidance. Same authors encourage to study the combination with 5-ALA to improve results of GTR [21,22].

Raman spectroscopy probe technique

With this promising noninvasive modality intraoperatively prove normal brain can be differentiate from cancer cells giving accuracy in GBM margin assessment with a sensitivity of 83 % and a specificity of 90%. Raman probe obtains spectroscopic measurements with photodetection technology in real time analyzing the molecular nature of the brain. It may improve GBM diagnosis accuracy through brain biopsy or tumor resection [23,24].

Conclusion

The unenhanced areas on MRI images have not only the highest density of viable malignant glial cells, but also glioblastoma stem cells that stimulate growth and regulate the tumor microenvironment. Current advanced imaging techniques such as magnetic resonance imaging are not specific for locating these tumor areas, making complete tumor resection difficult. Some amino acid tracers have improved the detection of these areas by PET imaging of non-enhancing T2/FLAIR hyperintense. Although some results have been positive, the current scientific evidence for improved survival using advanced technology is very low, level IV.

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