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Mini Review

Management of CNS Tumors: The Road Ahead

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Abstract

Central nervous system (CNS) tumours comprise a heterogeneous group of neoplasms with great histological diversity. These are the second most common neoplasms in children and the leading cause of death in this patient population. In majority of cases, these tumors pose a diagnostic and therapeutic challenge, warranting multimodal treatment, as determined by the site of primary disease and the histopathology. Historically, there has been significant mortality and morbidity associated with this malignancy and the patients who survive face the risk of post-irradiation neurocognitive dysfunctions and secondary tumors. Advanced imaging modalities have revolutionized the accuracy of tumor localization both for surgery as well as conformal radiotherapy planning. The latest Radiotherapy techniques allow precision in delivery of radiation, thereby ensuring better coverage of target volumes, dose scalation and sparing of normal critical structures. This article is aimed at sensitizing the neuro-clinicians with some of the latest developments in the field of neuro-oncology.

Keywords: *CNS Tumors; Management; Complications; Radiotherapy Techniques; Neuropathology*

Introduction

An increasing incidence of brain tumors has been reported from multiple studies [1]. Globally, the age-adjusted incident rate of brain tumors in 2012 was 3.4 per 100,000; more so diagnosed in developed countries due to availability of better imaging facilities, awareness among people and lifestyle and demographic factors [2]. There is some data suggesting that incidence may rise further in heavy mobile users due to the carcinogenic effect of radiofrequency electromagnetic fields [3]. The common challenges in management of brain tumors include difficulty in complete surgical resection in view of eloquent location, and limited penetration of most chemotherapeutic agents across blood-brain-barrier; thus, some of these patients are likely to get benefitted by local radiotherapy to the tumor bearing area. Though radiation therapy may be successful in local control of these tumors, many patients experience treatment-related delayed toxicities, like neurocognitive and endocrinological disorders.

Adequate imaging of brain tumors prior to surgical resection or radiotherapy, along with a definitive histopathological correlation is of paramount importance in management of CNS tumors. Molecular markers are increasingly playing an important role in diagnosis, management and prognostification of brain tumors, common markers studied include 1p/19q codeletion, IDH mutations and MGMT methylation [4]. Three-Dimensional conformal radiation treatment (3D-CRT) planning and delivery has the general goal of conforming the shape of a prescribed dose volume to the shape of a 3-dimensional target volume, thereby limiting dose to critical normal structures. 3-DCRT should include volumetric imaging study of the patient in the treatment; commonly by computed tomography (CT) and/or magnetic resonance imaging (MRI); which may be supplemented by functional MRI, MR spectroscopy, and positron emission tomography (PET) scans to visualize the clinically relevant volumes [5].

Neuropathological Aspects

The histopathological diagnosis of diffuse gliomas often lacks the precision that is needed for tailored treatment of individual patients. Evaluation of the molecular aberrations will enable further classification of these tumors and an individualized, targeted management. The markers which have gained popularity in the recent years are co-deletion of complete chromosome arms 1p and 19q, (hyper)methylation of the MGMT promoter and IDH1 mutations. Molecular diagnostics have gained widespread acceptance in diagnosis and management of glioma patients. However, this molecular information needs to be interpreted with caution, and should be correlated with radiological findings, histopathological features, age of patient, financial implications, availability of these tests etc. The treatment should not get delayed while waiting a molecular classification, and in case of equivocal results the patient should be treated empirically with an aggressive approach. The 2016 World Health Organization Classification of Tumors of the Central Nervous System is quite exhaustive and inclusive, based on molecular parameters in addition to histopathology, and will be of great help to the clinicians in this molecular era [4,6,7].

Newer Surgical Techniques

Extent of resection is believed to be a key prognostic factor in neuro-oncology. Image guided surgery has seen technical advancements and can be of great help in selected cases. Navigated 3D ultrasound is an intraoperative imaging tool which allows quick real-time inputs, thereby facilitating tumor resection. Diffusion tensor imaging (DTI)-based tractography is another increasingly important tool for planning brain surgery in patients suffering from brain tumours. Navigated transcranial magnetic stimulation (nTMS) is another imaging modality which facilitates preoperative localization of functional areas in patients with tumors in presumed motor eloquent areas. The use of functional localizer data such as nTMS or functional magnetic resonance imaging (fMRI) seem to improve fibre tracking data in conditions where anatomical landmarks are less informative due to tumour-induced distortions of the gyral anatomy. The neurosurgeons must familiarize themselves with image acquisition and interpretation techniques to keep themselves updated with the changing scenario [8-10].

Imaging for Radiotherapy Planning

Quite often, single imaging modality cannot provide sufficient information because of its inherent limitations of discriminating different brain soft-tissues or diseased tissues, and combination of different imaging modalities has to be utilized to get more comprehensive understanding of the disease and fulfill an accurate target volume delineation. Therefore, the radiation oncologist and medical physicist must correlate and integrate images from multiple resources for defining with precision the extent and location of disease [11]. As compared to dual-modality (CT/MRI) image acquisition; the tri-modality image fusion method integrating CT, MRI and 18F-FDG-PET images has revolutionized radiotherapy treatment planning with better dosage to target volumes and respecting the dose constrains of surrounding organs at risk. Integrating functional MRI (fMRI) information into the 3D-based planning process has the potential benefit of significant dose reduction for the critical organs, with no compromise in adequate target volume coverage [12]. Functional and molecular imaging techniques offer the promise of increased dose sparing to high functioning subregions of normal organs or dose escalation to selected subregions of tumor, as well as the potential to adapt radiotherapy to functional changes that occur during the course of treatment [13].

Advances in Radiotherapy

Recent advances in radiation oncology are based on improvement in dose distribution and improvement in target definition through new diagnostic imaging such as spectroscopic or functional MRI or PET [14]. The radiation oncologist must make all attempts to precisely define and adequately cover various target volumes to attain better tumor control with sparing of organs at risk to address the quality of life issues [15]. Conventional 3DCRT has been gradually replaced with intensity-modulated radiotherapy (IMRT) which is a highly sophisticated treatment technique that requires precise definition and optimisation of local setup errors and, finally, of the irradiated volumes [16]. Recent studies have shown promising results of helical tomotherapy (HT)-based IMRT for tumors of varying size, shape and location, specially for large, complex shaped tumors [17]. However, patient setup margins and geometric uncertainities may occur during treatment decreasing the benefit of such optimization. Image-guided radiotherapy (IGRT) reduces these uncertainties occurring during treatment and therefore should reduce dose delivered to healthy tissues and enable dose escalation to enhance tumour control [14].

Stereotactic radiosurgery (SRS) is currently a well-established, non-surgical treatment option for many functional abnormalities, benign lesions as well as malignant tumors, though judicious patient selection is required, mainly guided by tumor size, number of lesions, location and radiobiological properties [18]. This technique is fast replacing whole-brain irradiation in the treatment of intracranial lesions, which leads to better preservation of brain functions, and therefore a better quality of life for the patient. There are several available forms of linear accelerator (LINAC)-based SRS; like dynamic conformal arcs (DCA), intensity-modulated radiosurgery (IMRS), and volumetric modulated arc radiotherapy (VMAT) [19]. All techniques include multiple noncoplanar beams or arcs with or without intensity-modulated delivery. SRS by VMAT has shown good dosimetric conformity and homogeneity with less time consumption and less potential for intrafraction organ and patient motion [20].

Focused, highly targeted radiosurgery and fractionated radiotherapy using the Gammaknife or Cyberknife are useful treatments for multiple or large metastases. The Cyberknife provides the advantage of allowing for fractionated treatment to multiple or large-size tumors for performing frameless stereotactic irradiation with improved patient comfort, increased treatment degrees of freedom, and the potential to target extracranial lesions [21,22]. Whole-brain radiation therapy (WBRT), SRS, or both are commonly employed in the treatment of brain metastases in the initial or recurrent setting. Tomotherapy-based hypofractionated radiotherapy to a limited number of metastatic lesions has shown encouraging results in the primary and recurrent setting with acceptable control and favorable toxicity profile. Helical tomotherapy (HT) for WBRT with integrated boost (IB) to multiple brain metastases has been found to deliver highly conformal, uniform doses to the target volume [23,24].

Craniospinal irradiation (CSI) is used for patients who have, or are at risk for, disseminated disease throughout the CNS that is not sufficiently responsive to chemotherapy. Apart from CSI on a conventional lineac, newer techniques like proton beam therapy, tomotherapy etc. has been tried with encouraging results. Protons for CSI have the distinct advantage of minimal dose deposition beyond the Bragg peak, thus sparing the normal tissues. This allows adequate dose to craniospinal axis with minimal scatter to surrounding normal tissues and sparing the brain stem, especially in pediatric population, and has been shown to have less acute and delayed toxicities as compared to conventional photon beam CSI [25-27].

Imaging for Surveillance after Radiotherapy

Differentiating radiation necrosis (RN) after radiotherapy from progression of glioma and pseudoprogression poses a dilemma for many clinicians. As RN may mimic the radiological picture of disease progression, the results must be interpreted with caution and supplemented with supplementary metabolic and functional scans, as both these entities have different course of management. Several MR techniques have used in establishing the characterization of the status of post-treatment radiation effects, and include contrast administration, diffusion weighted imaging (DWI), diffusion tensor imaging (DTI), dynamic contrast enhancement (DCE-MRI), and magnetic resonance spectroscopy (MRS). Multi voxel dynamic susceptibility contrast perfusion MRI (DSC) and MR spectroscopy (MRS) provide specific physiological information that may allow distinction between recurrent glioma and progression from stable disease. Progressing tumors exhibit increased amino acid transport, and therefore, amino acid analogs, such as ^{18}F-FDOPA, ^{18}F–FET, and ^{11}C-MET have also been explored in addition to SPECT as potential tracers for differentiating between treatment necrosis and tumor recurrence [28-30].

Conclusion

CNS tumors continue to be therapeutic challenge for the clinicians. These tumors are generally not completely surgical resectable owing to eloquent location, most chemotherapy agents cannot cross the blood brain barrier, and radiotherapy has its own acute and delayed morbidity. However, diagnosis and prognosis is likely to improve in days to come due to better imaging facilities, improvement in neuropathology, and advancements in the field of radiotherapy.

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