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Review article

Diagnosis and treatment options for sequelae following radiation treatment of brain tumors

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ABSTRACT

Radiation serves an important role in the treatment of metastatic and primary brain tumors. Radiation carries a risk of post radiation treatment effects, such as pseudoprogression and radiation necrosis. The ability to differentiate between radiation necrosis, pseudoprogression, and tumor recurrence remains a diagnostic conundrum with varying treatment options. In this review, we will discuss the pathophysiology, diagnostic imaging modalities, and treatments of these post-radiation treatment effects. We focus on the latest developments in magnetic resonance imaging (MRI) modalities including imaging biomarkers and the newest therapeutics such as VEGF inhibitors, Hyperbaric Oxygen Therapy, sensitized cytotoxic T cells, and Laser Interstitial Thermal Therapy (LITT).

1. Introduction

Radiation of malignant metastatic or primary brain tumors may serve as an upfront or adjuvant therapy, depending upon a patient's functional status and the extent of disease. The most common primary tumors to metastasize to the brain are lung (48%), breast (15%), melanoma (9%), and colon cancer (5%) [1]. Treatment options for patients with brain metastases include corticosteroids, surgery, chemotherapy, whole-brain radiation therapy (WBRT), and stereotactic radiosurgery. Patients with malignant primary gliomas have a median survival of 15 months [2]. The current treatment algorithm for malignant gliomas involves surgical resection, radiation therapy, and temozolomide chemotherapy (TMZ) [3]. Radiation has been demonstrated to improve survival in glioblastoma (GBM) up to 12 months [4]. Although medical advancements have increased overall survival in patients with malignant metastatic and primary brain tumors, post-radiation treatment effects (PTRE) including pseudoprogression and radiation necrosis are increasingly identified. As recurrent tumor and radiation necrosis may have different treatment algorithms, it is important to understand the diagnostic options to distinguish these entities, and therapeutic options once established.

2. Pathophysiology

Radiation therapy causes both immediate and delayed tissue damage [5]. Post-treatment radiation effects can be thought of as a spectrum of entities, which include pseudoprogression and radiation necrosis. Given the enhancement on MRI, pseudoprogression and radiation necrosis can both be falsely attributed to tumor recurrence (Fig. 1) [6]. The distinction between pseudoprogression and radiation necrosis can be based upon the timing of occurrence and clinical presentation.

Pseudoprogression appears weeks to months after radiation treatment, and presents as an enlarging contrast enhancing lesion that stabilizes with time [47,8]. Pseudoprogression is usually asymptomatic and may be seen in up to 20% of patients treated with radiation [9]. On the other hand, radiation necrosis may appear months to years after radiation treatment and involves a space occupying necrotic lesion with mass effect (Fig. 1) [6,10,11].

2.1. Molecular and histologic pathophysiology of radiation injury

Injury with radiation occurs through a combination of demyelination and vascular abnormalities [12]. As radiation injury usually involves white matter necrosis and demyelination, oligodendrocytes are thought to be the primary target of the injury. In the penumbra around the necrotic core, astrocytes, microglial cells and oligodendrocytes produce factors that encourage cytokine release and increase BBB permeability [13].

Radiation also causes injury to the endothelial cells leading to a reduction in the blood vessel density [14,15]. A reduction in the microvasculature leads to chronic ischemia and increased oxidative stress.

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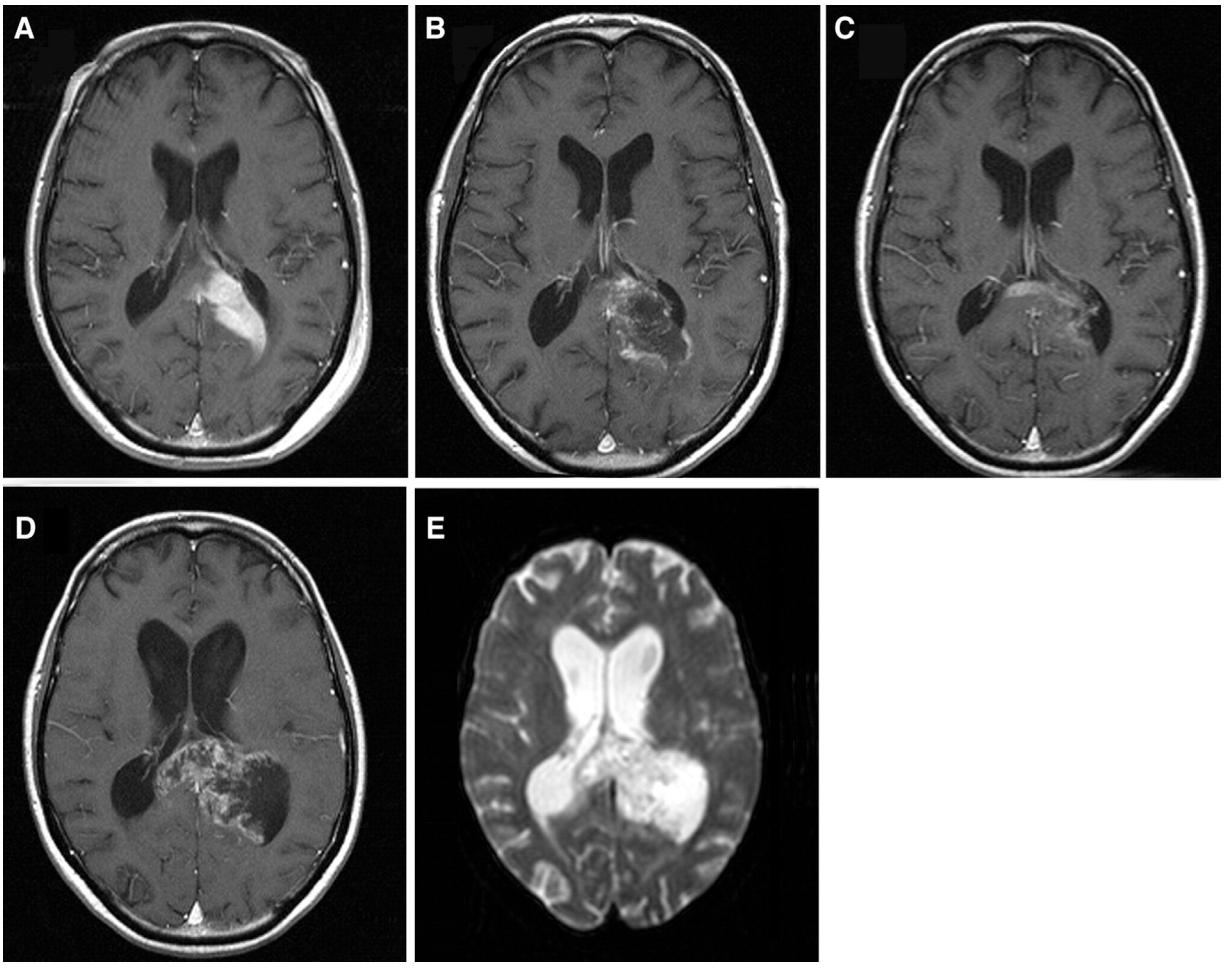

Fig. 1. MRI Demonstrating Evolution of GBM to Radiation Necrosis.
This image panel demonstrates the treatment course of a 52 year old man with a GBM – the patient initially had good response to Gamma Knife radiosurgery with subsequent development of radiation necrosis. After gross total resection, the patient was found to have recurrence of a lesion in the splenium of his corpus collosum. (A). He received 13Gy of radiation (total volume 6.2cc) with regression at 3 months (B) which also demonstrated increased regression at 6 months (C). However, the patient demonstrated expansion concerning for radiation necrosis (D), 9 months post radiosurgery (E).
Source: Image taken from: Elliott RE, Parker EC, Rush SC, Kalhorn SP, Moshel YA, Narayana A, et al. Efficacy of gamma knife radiosurgery for small-volume recurrent malignant gliomas after initial radical resection. World neurosurgery. 2011 Jul–Aug;76(1–2):128–40; discussion 61-2. PubMed PMID: 21839964. Epub 2011/08/16.

An increase in reactive oxygen species triggers secondary injury cascades [16]. Endothelial cell damage results in BBB breakdown and increased radiographic enhancement as seen in radiation necrosis. Histologic studies of brain tissue with radiation injury demonstrate coagulative and liquefactive necrosis with calcification, fibrinoid deposition, vascular hyalinization, and endothelial thickening [15,17].

Secondary injury occurs with chronic inflammation, microvascular restructuring leading to ischemia, chronic oxidative stress, and inhibition of neurogenesis [18–21]. These inflammatory changes are mediated through many different cytokines including tumor necrosis factor-alpha (TNF-α). TNF-α activates astrocytes, increases blood brain barrier permeability, and induces endothelial cell apoptosis [22–24]. Animal studies have shown that anti-TNF-α antibodies can partly abrogate the effects of radiation, which include astrogliosis, blood brain barrier damage, and microvascular changes [22]. In addition, increased vascular endothelial growth factor (VEGF) expression is also seen after radiation treatment. By increasing vascular permeability, VEGF promotes cerebral edema [25]. Although VEGF expression is seen in radiation necrosis, it is generally not seen with pseudoprogression.

The observed enhancement and edema seen after radiation injury are thought to be due to a transient breakdown of the blood brain barrier. In addition, there may be a correlation between MGMT methylation status and pseudoprogression as most MGMT methylated tumors demonstrate pseudoprogression [26]. As pseudoprogression is generally asymptomatic, for the remainder of the review, we will focus the diagnostic modalities and treatments of radiation necrosis that will aid in therapeutic decision making.

3. Imaging modalities

The goal of imaging is to provide a non-invasive means of differentiating pseudoprogression, radiation necrosis, and tumor recurrence, thereby obviating the need for histopathological diagnosis, which is the current gold standard [7,27–30]. Current MRI-based techniques can be categorized into conventional MRI, advanced MRI, and newer methodologies that employ biomarkers and T-cell mediated probes. Table 1 summarizes the various imaging modalities with respect to their application, findings, and sensitivity and specificity. In the following section, we evaluate each of these modalities in further detail and provide a critical assessment of their efficacy.

4. Conventional MRI

MRI is commonly used to monitor post-treatment responses. As such, the identification of a standard MRI method that could reliably distinguish tumor recurrence from radiation necrosis would be of

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