

Biomarkers of Brain Damage Induced by Radiotherapy

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Abstract

Radiotherapy remains currently a critical component for both primary and metastatic brain tumors either alone or in combination with surgery, chemotherapy, and molecularly targeted agents, while it could cause simultaneously normal brain tissue injury leading to serious health consequences, that is, development of cognitive impairments following cranial radiotherapy is considered as a critical clinical disadvantage especially for the whole brain radiotherapy. Biomarkers can help to detect the accurate physiology or conditions of patients with brain tumor and develop effective treatment procedures for these patients. In the near future, biomarkers will become one of the prime driving forces of cancer treatment. In this minireview, we analyze the documented work on the acute brain damage and late consequences induced by radiotherapy, identify the biomarkers, in particular, the predictive biomarkers for the damage, and summarize the biological significance of the biomarkers. It is expected that translation of these research advance to radiotherapy would assist stratifying patients for optimized treatment and improving therapeutic efficacy and the quality of life.

Keywords

biomarker, cranial radiotherapy, radiation-induced brain damage, cognitive impairment

Introduction

Brain tumors are one of the leading causes of cancer-related death especially in children.¹⁻³ The metastatic brain tumors, generally from lung carcinoma, breast carcinoma, and melanoma, experienced by about 10% to 30% of adult patients with cancer and 6% to 10% of children with cancer, are the main reason of morbidity and mortality.⁴ Radiotherapy (RT) remains currently a critical component for both primary and metastatic brain tumors either alone or in combination with surgery, chemotherapy, and molecularly targeted agents. However, simultaneously it causes normal brain tissue injury which leads to serious health consequences. Previously it was considered that the brain was the major radioresistant part of the body but now it has been proved and accepted that the brain is one of the most radiosensitive organs in the clinical RT.⁵ Recent studies reported that cranial RT is the major cause of cognitive impairments and other complications of the brain.^{6,7} As a fact, radiation-induced detrimental effects on normal brain tissue limit the benefit of RT for the treatment of brain tumors.⁸⁻¹³

Due to the late health consequences of cranial RT, treatment of brain tumors has become more complicated in many aspects. For example, predicting individual radiosensitivity, which can differ from hypersensitivity to resistance depending on both

individual genotype and tumor type, exact delivery of the radiation dose, realization of the exposure mode, and clinical limitation for diagnosis of radiation-induced necrosis from continued tumor growth.¹⁴ Thus, to improve treatment outcome and the quality of life of the patient, understanding of the damage and the underlying mechanisms is essential for identifying potential opportunities to protect the patient from severe damage and/or

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mitigate the detrimental effects. In this context, biomarker studies introduce a novel era for early diagnosis and ensuring effective treatment. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.¹⁵ A biomarker can accurately indicate the actual biological, pathological, and therapeutic condition of the host. A predictive biomarker specifies the benefit or the outcome to the patient from the treatment, assessed to their condition at baseline.¹⁶ Studies of biomarkers, in particular predictive biomarkers, for radiation-induced brain injury and translation of the research advances to RT would enable stratifying patients for customized treatment and improving therapeutic efficacy and the quality of life.

In this minireview, we would give a brief overview on the current main cranial RT based on the latest literatures, analyze the documented work on the acute brain damage and late consequences induced by RT, try to identify the biomarkers, in particular, the predictive biomarkers for the damage, and summarize the biological and clinical significance of the biomarkers.

Cranial RT

Both primary and metastatic brain tumors are of the most combative and damaging forms of cancer. Although the exact etiology is still unknown, various genetic and environmental risk factors were identified.¹⁷ Treatment actions for brain tumors are mainly depend on the type, location, size, and grade of the tumor, and age and health conditions of the patient. Generally, surgery, chemotherapy, and RT are accepted as standard treatment procedures for brain tumors. Being effective for accessible and single area of tumor, surgery is usually the initial treatment step for most primary and malignant brain tumors, while it is ineffectual for all types of malignant tumors. Chemotherapy acts as an adjuvant with the combination of surgery and RT but an effective treatment procedure for brain tumors due to the drug restriction by the blood-brain barrier (BBB). Radiotherapy, as one of the standard treatment option for brain tumors, applying controlled high energetic ionizing radiation (IR) such as X-ray and γ -ray could either damage cancer cells directly or arrest cell cycle to limit their ability to grow.¹⁸ Ionizing radiation can be administered externally and internally, and external RT is an important way to treat brain tumors in many patients.¹⁹

Whole-Brain Radiation Therapy

Whole-brain radiation therapy (WBRT) is externally delivered to the entire brain, which is considered a well-advised treatment option for multiple brain metastases. It is more effective than surgery and stereotactic radiosurgery (SRS), destroying both gross and microscopic tumors. It is also used simultaneously with surgery and SRS to ameliorate local control.²⁰ In addition, WBRT is applicable to treat patients with metastases invading important the part of the brain or patients ineffective from either surgery or SRS. Currently, the most practice radiation dose for

brain metastases is 30 Gy in 10 fractions over 2 weeks. It was reported that WBRT could achieve an average survival of 3 to 6 months,²¹⁻²⁴ decrease the recurrence incidence of metastases, reduce death from neurological damages,²⁵ and improve the quality of life in 75% to 85% of patients by controlling and upgrading neurological symptoms.²³ On the other hand, some studies showed that WBRT could retard tumor growth but eliminating the tumor, neither increasing the period of functional independence and overall survival rate.²⁶ Cognitive deficits are considered the side effects of WBRT that adversely affects the quality of life. As a fact, cognitive impairments were observed in 50% to 90% of adult patients with brain tumor 6 months after WBRT.²⁷⁻²⁹ In addition, delayed disintegration of cognitive function,³⁰ growth hormone deficiency, and motor dysfunction were also observed in laboratory and clinical studies.³¹

Stereotactic Radiosurgery

As an alternative option to neurosurgery, in SRS, high energy X-rays, γ -rays, or protons are delivered in a single large dose or a few large doses to a surgically inaccessible discrete tumor. Multiple convergent beams are used to attenuate high dose exposure of normal tissue. Stereotactic radiosurgery is applied to treat a single tumor or multiple tumors (usually up to 3) and can be effectively used to treat deep intercranial surgically inaccessible lesions. Retroactive studies showed that SRS seemed to be equivalent to surgery^{32,33} and highly potential in inhibiting progressive tumor growth.³⁴ From this aspect, studies exhibited survival value enhancement as well as progress in Karnofsky Performance Status using SRS after WBRT.^{32,35} The limitation of this noninvasive treatment technique is that it was only advised or suitable for small tumors less than 3 cm in diameter and radiographically well-defined tumors by computed tomography or magnetic resonance scans. Furthermore, the expected dosage of radiation may not be safely delivered to the cancerous brain tumor due to the close proximity to the sensitive and critical normal portion of the brain, such as the optic nerve, hippocampus, and spinal cord or bowel.

Radiation-Induced Acute Brain Damage and Late Health Consequences

Cranial RT is extensively used to treat tumor growth and propagation, and IR could simultaneously affect the normal tissue of the central nervous system (CNS) via direct action (hitting the biomolecule of the cell, disrupting the molecular structure, particularly DNA) and indirect action (producing highly reactive free radical atoms and interacting free radicals with brain molecules), causing damage or the structural alteration or even cell death.³⁶ Compared to early responding tissues such as bone marrow, the vascular tissues, nerves, and parenchyma in the brain, and spinal cord are late responding to radiation exposure and usually do not manifest instantly radiation-induced effects, for example, vascular abnormalities, demyelination, irreversible necrosis of the white matter (WM), permeability changes in the BBB, reduced amount of endothelial cells, injury of

oligodendrocyte precursor cells, and activation of astrocytes and microglia,^{14,37} leading to delayed neurological difficulties and neurocognitive shortages in long-term survivors.³⁸ The late neurological dysfunction includes functional and cognitive impairments, with deficits in learning, attention, working memory, verbal memory, executive function, vision, motor function, severe dementia, and eventually the quality of life of the patients. The occurrence of radiation-induced brain damage after conventional RT was 5% to 24%.³⁹ Of note, the cognitive impairments could occur without the appearance of any structural modifications in the brain tissue.⁴⁰

Radiation-induced brain injury could be classified into 3 phases: acute, early delayed, and late-delayed injury.³⁸ Acute brain injury occurs in days to weeks after WBRT and SRS, involving fatigue, hair loss, skin erythema, headache, nausea, and lethargy, which is unusual with the present RT techniques. Early delayed brain injury is observed within 1 to 6 months post RT, showing fatigue, somnolence, short-term memory loss, and temporary demyelination. Clinically late-delayed injury is associated with the symptoms of vascular abnormalities, demyelination, and eventually WM necrosis,⁴¹ commonly observed from 6 months to several years after RT, and these late-delayed damages are considered as irreversible and progressive. In most of the cases, the cognitive deficiency was the consequence of radiation-induced late delayed injury⁴² presently occurring in 50% to 90% of brain tumor survivors^{43,44} and amplifying with the improvement of RT techniques.^{45,46} The advancing degeneration affected the physical and mental health and declined the quality of life of the long-term survivors.^{47,48} It is well-documented that high radiation doses (>60 Gy) were responsible for permanent injury, while emerging analysis also exhibited that low radiation doses (<20 Gy) could also arise late delayed damage.⁴⁹ Of particular concern, both acute and early delayed symptoms and damages were typically reversible that could be solved automatically but late delayed injury, which was counted as permanent brain damage.^{47,48,50} Currently, our knowledge on the mechanisms underlying radiation-induced cellular and molecular brain injury was still limited, while cumulated data indicated that radiation-induced damage in cerebral tissues was an extremely complex and interactive way associated with various components of tissues.^{5,38,51} Studies showed that radiation-induced memory losses and attention deficits were associated with neuroinflammation, BBB alterations, and demyelination, in addition to decreased neurogenesis.⁵²⁻⁶⁰ Cerebral vascular tissue showed acute injury and resulted in subsequent development of demyelination, reactive astrocyte, and microglia. Primary effects after IR involved stimulating endothelial cells, increasing dilation and thickening of blood vessels, nuclear enlargement of endothelial cells, and increasing in size and growth of perivascular astrocytes.⁶¹ Ionizing radiation could induce over activation of inflammatory cytokines (eg, tumor necrosis factor α [TNF- α]), adhesion molecules (eg, intercellular adhesion molecule 1 [ICAM-1]), chemokine (eg, monocyte chemoattractant protein 1), and matrix metalloproteinases (MMP; eg, MMP-9) that were potential factors of endothelial injury¹⁸ and responsible for primary endothelial cell death and

apoptosis.⁶² Cerebral vascular injury was also developed by deteriorating and degenerating structural changes in WM.⁶¹ Furthermore, clinical studies showed that radiation-induced WM injury was incorporated with axonal injury, demyelination, neuroinflammation, and necrosis.⁶³⁻⁶⁵ In adult rat models, it was reported that after IR regenerative capacity of the oligodendrocyte type 2 astrocyte progenitor cells decreased in both brain and spinal cord causing demyelination.⁶⁶ Hippocampus was considerably the most radiosensitive and neuroinflammation sensitive area of the brain.⁶⁷ It was critical to damage the hippocampus which involved the generation of neurons from neural stem cells or progenitor cells throughout the life and cognitive processes such as demonstrative memory and spatial information processing,⁶⁸ and adverse effects by RT could play a vital role in radiation-induced cognitive impairments. In laboratory mouse models, hippocampus-dependent memory deficiency was observed in adult animals 3 months after cranial irradiation due to decreased hippocampal neurogenesis.^{69,70} In the same way, after whole-brain irradiation treatment, the numbers of neural stem cells and progenitor cells were declined from the subgranular zone of the hippocampus.^{56,71}

Biomarkers

The term biomarker, a portmanteau of biological marker, generally used in a broad sense, is an indicator or a sign of normal and pathogenic biological processes. As an accusative attribute capable of objectively measuring and accurately evaluating any specific biological and pathological conditions with reproducibility, it has valuable medical applications in diagnosis, staging and prognosis of diseases, monitoring clinical response to therapeutic interventions, and predicting late health consequences. Biomarker is a characteristic, which could be measured reflecting fluctuation of or alteration in any substance, structure, process, or function, and predicting the incidence of outcome or disease, the effects of treatments, interventions, and even unintended environmental exposure. From the point of view on the validity of biomarkers in environment risk assessment, a true definition by World Health Organization of biomarkers includes almost any measurement reflecting an interaction between a biological system and a potential hazard.⁷²⁻⁷⁵ For example, a biomarker could be a cell or a molecule in a biological sample collected from the body (ie, complete blood count, circulating DNA, messenger RNA (mRNA), microRNA, and long noncoding RNAs, carcinoembryonic antigens, glucose, proteins, cytokines, growth factors, metabolites in the blood). It could be a result obtained from the imaging technique showing the fluctuation of a substance or alteration in structure and function.^{76,77} Thus, measurement of a biomarker is not necessarily subject to a biological sample which could be collected; noninvasive diagnostic method, that is, medical imaging techniques using near infrared spectroscopy, is also included.

The biomarker in RT could be grouped into the following categories: (1) the predictive biomarker, available before irradiation, which could predict the outcome and subsequent increased risk of RT, that is, interleukin-1 (IL-1), IL-6, and

Table 1. Biomarkers of Brain Damage Induced by Radiotherapy.^a

Physiological conditions	Biomarkers	References
Inflammation	Tumor necrosis factor α (TNF- α) Interleukin (IL-1 β , IL-4, IL-6, and IL-8) Inducible nitric oxide synthase Intercellular adhesion molecule 1 (ICAM-1) Matrix metalloproteinase 9 (MMP-9) Vascular cell adhesion molecule 1 Monocyte chemoattractant protein 1 Cyclooxygenase 1 and 2	9,18,81
Cell activation and damage	Glial fibrillary acidic protein Vascular endothelial growth factor (VEGF) Vascular cell adhesion molecule Intercellular adhesion molecule 1 (ICAM-1) Antiaquaporin-4 antibodies Neuron-specific enolase S100 calcium-binding protein B Myelin basic protein Cerebrospinal fluid oxysterols Proteolyzed N-methyl-D-aspartate receptor Anti-N-methyl-D-aspartate receptor antibodies Endothelial monocyte-activating Polypeptide-II cytokine Nitrotyrosine	14,82-85
Angiogenesis	Vascular endothelial growth factor (VEGF) Angiopoietin (Ang-1, Ang-2, Ang-3, and Ang-4) Tyrosine-protein kinase (Tie 2)	18,86-89
DNA damage and repair	p53-Binding protein 1 Gamma histone protein from the H2A family (γ -H2AX) Dicentric chromosomes Micronucleus (MicroRNA) O6-methylguanine DNA methyltransferase (MGMT)	14,90-93

^aPeripheral blood plasma was used to analyze biomarkers for inflammation, cell activation and damage and angiogenesis, and peripheral lymphocytes with complete DNA for DNA damage and repair.

micronuclei⁷⁸; (2) the prognostic biomarker, which can be detected at any time after IR and anticipate a consequent increased probability for recurrence or more severe disease, that is, transforming growth factor β 1 and fibroblast growth factor 2^{79,80}; (3) the diagnostic biomarker, which appears during the symptoms of radiation-induced damage; and (4) the dosimetric biomarker, present at some time point after IR, which is able to determine the radiation dose delivered to the organ. According to the presence of biomarkers in various radiation-induced physiological conditions of the brain, different types of biomarkers are listed in Table 1.

Biomarkers of Radiation-Induced Inflammation

It was identified that oxidative stress and inflammatory pathway were mostly responsible for radiation-induced brain injury.^{9,81}

Significant overexpression of cyclooxygenase 1 and 2 activity and subsequent generation of prostaglandin E2 synthesis lead to developing radiation-induced inflammation in CNS through the upregulatory activity of various proinflammatory mediators including TNF- α , IL-1 β , IL-4, IL-6, IL-8, inducible nitric oxide synthase, ICAM-1, and MMP-9. Upregulating adhesion molecules, such as ICAM-1 and vascular cell adhesion molecule 1, was also spotted in radiation-exposed brains. In the hippocampus and the cortical regions, highly overexpressed mRNA encoding cytokines (TNF- α , IL-1 β , IL-4, IL-6, IL-8, etc) and protein product of proinflammatory mediators such as TNF- α , IL-1 β , and monocyte chemoattractant protein 1 were detected. Area-specific cytokine activation process was observed: TNF- α levels were markedly higher in the cortex than hippocampus, and IL-1 β levels were significantly prominent in the hippocampus than the cortical area.¹⁸ All of these inflammatory markers were detected in the blood sample of patients after RT.⁹⁴ These studies suggested that all above-mentioned proinflammatory mediators may be recognized as potential biomarkers of RT-associated damage in CNS.

Biomarkers of Radiation-Induced Cell Activation and Damage

The development of radiation-induced brain injuries became chronic through the activation of various cell subpopulations. Under cerebral pathologic conditions, several biomarkers presented in the peripheral blood indicating specific nerve cell activation or damage. Glial fibrillary acidic protein, vascular endothelial growth factor (VEGF), and vascular cell adhesion molecule were particularly for astrocyte activation, and ICAM-1 was also considered as the endothelium activating biomarker. Antiaquaporin-4 antibodies in blood serum by molecular diagnosis indicated the demyelination of brain cells in patients with tumor after cranial RT.¹⁴ Neuron-specific enolase, a neuroendocrine processing glycolytic enzyme, and S100 calcium-binding protein B, a nervous system specific cytoplasmic protein generated by astrocytes when the BBB was ruptured, were regarded as the prospective markers for screening endothelial and neuronal injury. As particular markers, increased neuron-specific enolase denoted brain metastases and predicted shorter survival,^{82,83} an elevated level of S100 calcium-binding protein B in the circulating blood indicated BBB damage,⁹⁵ brain metastasis,⁹⁶ and predicted melanoma brain metastases.⁹⁷ Demyelination of myelin basic protein was involved with damage of oligodendrocytes.⁸⁴ Increased cerebrospinal fluid oxysterols in plasma was a promising marker of acute radiation syndrome of CNS.⁸⁵ Studies also showed that neuron-specific enzyme ubiquitin C-terminal hydrolase, the fragment of proteolytic cleavage of the N-methyl-D-aspartate receptor or N-methyl-D-aspartate receptor antibodies, endothelial monocyte-activating polypeptide-II cytokine, and nitrotyrosine could correlate with brain injury following RT.¹⁴ These molecules could be regarded as potential biomarkers and a high level of these molecules in blood serum implied the severity of radiation-induced brain damage.

Biomarkers of Angiogenesis After Irradiation

Angiogenic factors were reported as promising tumor markers in various malignancies.⁹⁸ For example, VEGF was a key angiogenic factor which could effectively regulate vascular endothelium⁸⁶⁻⁸⁸ involving initiation of endothelial cell proliferation, migration, and propagation of new capillary sprouts, ultimately leading to enhanced vasculogenesis and angiogenesis.⁹⁹⁻¹⁰¹ Investigations confirmed that VEGF could promote the growth of tumor cells and protect endothelial cells from apoptosis.⁸⁸ In addition, all angiopoietin (Ang) families, such as Ang-1, Ang-2, Ang-3, Ang-4, and endothelial cells receptor tyrosine kinase Tie 2 were responsible for the development and integration of endothelial cells; Ang-2 could enhance endothelial cell death and eventually lead to rarefaction of vessels without activating signals from VEGF. Physiological angiogenesis was assisted by Ang-2 through the presence of a high level of VEGF.¹⁸ In the rat model for studying endothelial cell proliferation and apoptosis, and expression of various angiogenic factors after whole brain irradiation, it showed that substantially decreased mRNA and protein expression of VEGF, Ang-1, and Tie-2 but significantly upregulated Ang-2 expression were induced,⁸⁹ suggesting that these angiogenic factors could be used as biomarkers of radiation-induced endothelial cell damage in the brain.

Biomarkers of Radiation-Induced DNA Damage and Repair Processes

Lymphocytes are important cells with complete DNA for screening the effects from exposure to radiation.⁹⁰ Ionizing radiation could cause various types of chromosomal aberrations, for example, translocations, terminal deletions, ring chromosomes, and dicentric chromosomes.⁹¹ Radiation-induced DNA double-strand breaks (DSBs) could activate ataxia telangiectasia mutated (ATM) and ATM- and Rad3-related (ATR) protein kinase, and alter phosphorylation of many cell cycle proteins and DNA repair enzymes,¹⁰² leading subsequently to cell cycle arrest or apoptosis.¹⁰³ Although only a few numbers of lymphocytes were in the brain, lymphocytes collected from peripheral blood with chromosomal aberrations and altered repair proteins accumulated in the area of DSBs, such as p53-binding protein 1 and γ -H2AX involving phosphoinositide 3-kinase and ATM,^{92,93} could be detected by such as immunofluorescence and flow cytometry microscopy technique for quantitative assessment of IR exposure.¹⁰⁴ Studies showed that dicentric chromosomes, micronucleus, and over-expression of some microRNAs including miR-212 could be recognized as valuable biomarkers for both measuring chromosomal damage caused by IR and predicting the progress of radiation injury and outcome for survival.⁹¹ Identification of altered repair proteins in the blood with advanced biochemical methods is also an approach to assess the effects of IR on the brain. For example, the repair enzyme O₆-methylguanine DNA methyltransferase (MGMT) could enable to protect DNA against alkylating agents (ie, temozolomide) that enhance the risk of radiation-induced injury while transcription of promoter

methylation inhibitory enzyme could increase the sensitivity of brain tissue to RT. Therefore, the technique for measurement of MGMT methylation process could determine radiosensitivity and radiation-induced necrosis development.¹⁴

Biomarkers of Radiation-Induced Brain Damage Used in Imaging Technology

Radiation-induced detrimental effects generally appeared late and occurred in the closed cranial cavity of the brain,⁴⁷ making the identification of biomarkers for radiation-induced brain damage, especially the predictive or prognostic ones, more challenging. Novel noninvasive methods are needed to overcome these limitations. Imaging techniques could be considered potential noninvasive biomarkers due to the capability to interrogate metabolic, physiologic, and functional characteristics of the brain and providing significant information for specific areas of normal and tumor tissue.⁴⁷ The use and validation of both established and new techniques in the context of monitoring early and late brain damage induced by RT in the healthy tissues currently are minimal at best.^{105,106} In this section, the performance and limitations of existing imaging techniques and the relation of these findings with key clinical parameters were summarized.

Diffusion tensor imaging, as the most sensitive imaging technique, can visualize and evaluate WM integrity and histopathological alterations, distinguish infiltrative growing tumors from bounded tumors and properly specify the tumor grade with conventional magnetic resonance imaging (MRI).¹⁰⁷⁻¹⁰⁹ Based on anisotropic diffusion, the value of fractional anisotropy could be used to monitor and detect the early radiation-induced WM injury, that is, alterations in density and orientation of fiber tracts, demyelination or necrosis, and distinguish between demyelination and axonal injury following brain RT.^{47,110,111} Magnetic resonance imaging is used for the exact screening of tumor, greatly sensitive to pathologic alterations of parenchyma¹¹² but not to low-grade glioma¹¹³ and infiltrative tumor growth.^{114,115} Typical scan includes T1/T2-weighted, fluid-attenuated inversion recovery, and post-contrast T1-weighted images, showing anatomical features, cerebrospinal fluid, pathological conditions, and lesions.¹¹² Functional MRI is mainly to measure blood flow in the region of interest. It could evaluate tumor grade specification, hypoxic, and tumor invasive area by using a T2-weighted signal.¹¹⁶⁻¹¹⁸ Magnetic resonance imaging can detect radiation-induced acute vascular injury involving blood vessel dilatation, endothelial cell enlargement, capillary loss, astrocyte hypertrophy, BBB disruption, increased permeability, and edema prior to the appearance of radiation-induced demyelination and WM necrosis.^{119,120} Alteration of BBB permeability after RT, the consequence of endothelial cell damage¹²⁰ could be monitored with the contrast-enhanced technique using K-trans values.¹²¹ Magnetic resonance spectroscopy could provide biochemical and metabolic information of tumors and adjacent tissues evaluate RT-induced necrosis and tumor recurrence, differentiate tumor from lesions¹²² and recurrent tumor progression from

radiation necrosis,¹²³ but less effective to detect the mixed tumor and necrosis.¹²⁴ Human brain metabolites, such as N-acetyl aspartate, creatine and choline that remained relatively constant¹²⁵ and were the key marker of the neuronal density and activity, indicator for cellular metabolism and membrane stability, respectively, were most important usable indexes.¹²⁶ Magnetic resonance spectroscopy could determine the pathological progression process at the biochemical level prior to any conventional techniques.^{122,125,127} For example, the concentration of N-acetyl aspartate, choline, choline compounds, and choline/creatine ratio significantly decreased after IR, choline/N-acetyl aspartate and choline/creatine ratios are comparatively high in the area of recurrent tumors than the area of radiation injury. Decreased N-acetyl aspartate/creatine ratio indicates neuronal damage, cell death, dysfunction due to apoptosis, and brain irradiation.⁶¹ Magnetic resonance spectroscopy was an effective prognostic tool for tumor treatment,¹²⁸ monitoring response to RT¹²⁹ and evaluating late-delayed radiation-induced injuries.¹³⁰ Two-dimensional multivoxel or 3-dimensional spectroscopic imaging technique was used in interval follow-up of RT-treated patients.¹³¹ Positron emission tomography (PET) imaging technique could be used in neuro-oncology as an essential tool for grading of primary brain tumors; identifications of neoplastic tissue with delineation of tumor extent for future diagnosis, tumors progression follow-up, and assessment of anticancer treatment response; prognostication; detection of tumor part with a malignant progression; and prediction of biomarkers.^{132,133} Positron emission tomography can discriminate late-delayed radiation injury from a recurrent brain tumor with 80% to 90% of sensitivity and 50% to 90% of specificity.⁶¹ [¹⁸F]2-fluoro-2-deoxy-D-glucose was considered as the most important PET modality for the detection of radiation-induced changes in normal brain tissue and neurocognitive impairment.¹³⁴ With the broad application of radiolabeled amino acid tracers, in addition to significant predicting the outcome of survival,¹³⁵ PET could precisely differentiate recurrent tumor from radiation-induced necrosis,¹³⁶ accurately distinguish RT-induced early and late injury from tumor progression.¹³⁷

Conclusions and Perspectives

Various types of biomarkers have been identified with a variety of measuring techniques in biological and clinical studies. The valuable biomarkers are identified on the basis of some important criteria such as easy collection, instant availability, inexpensiveness, easy detection process, and in particular, of predictive or prognostic ability to specify a disease. Clinical application of a particular and potential biomarker can prevent and mitigate the severity of unbeaten diseases like cancer.

Radiation-induced brain damage is a major dose-limiting adverse event of RT. The incidence varies with the RT modality, dose and its delivery, and the nature of the lesion being targeted and genetic factors of the patients. Biomarkers of brain damage induced by RT are the most objective, quantifiable biological or medical indicators and signs, allowing

measurement, evaluation, and prediction of the acute injury and late health consequences with reproducibility. Currently, numerous types of biomarkers are available in the clinical medicine, while biomarkers of radiation-induced brain damage are not available in large quantities. For example, there is no validated biomarker to measure the absorbed dose of the brain after deliberate IR exposure or nuclear accident event.⁹¹ As a key issue that innovative approaches to the research, development, and refinement of biomarkers are urgently needed to rapidly advance the research work on the decisive relationship between any biomarker and the relevant clinical consequences, and research and development of the new candidate biomarkers, that is, the endocrine hormones in peripheral blood that have not yet been documented. For imaging biomarkers, though multiple structural and functional imaging modalities exist, each technique independently is not efficient enough, and biochemical indicators combined with imaging techniques will be the development direction of the biomarker application. In addition to the prediction, early detection, and diagnosis of brain injury, research and development of biomarkers could also produce major benefits for monitoring, prognosis, and prediction of therapeutic response of the brain injury, and surveillance of late health consequences after treatment. Although the practical application of biomarkers is moderately new, it is expected that translation of this research advance to RT would assist stratifying patients for optimized treatment, minimizing side effects, and improving therapeutic efficacy and the quality of life.

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