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Palliative Radiation Therapy For Brain Metastases

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Introduction

Central nervous system (CNS) involvement by tumoral metastasis is a potentially life-threatening complication, representing the immediate cause of death in more than 50 percent of the cases.[1][2] Of note, brain metastasis represents the most common brain tumor in the United States (US).[3] The most common brain metastasizing tumors include primaries from the lungs, breast, colon, skin (melanoma), and kidney.[4] Two-year and five-year survival rates of 8.1 percent and 2.4 percent are noted for those with intracranial metastasis across various tumor types.[5] Moreover, it has been estimated that 10-40 percent of all patients with cancer will eventually develop brain metastasis.[6] The lack of reporting of the extent of metastatic spread at the time of enrolment into studies and follow-up in advanced cancer patients (who might go onto develop intracranial metastasis later) might be the reason underlying the underdiagnosis of this disease entity.[7]

The most common spread route is through the hematogenous route with the seeding of the brain tissue (microvasculature).[8] Interactions between the tumor and the microvascular niche, a neuroinflammatory cascade that aids the spread of tumor and neovascularization, have been postulated to underlie the primary tumor's spread.[9] Intertumoral heterogeneity within the metastatic deposits and a failure to fully understand the clonally selected molecular aberrations might underlie the consistently poor prognosis associated with the tumor's spread to the CNS.[10]

The brain ecosystem represents a unique microenvironment with the inherent ability to aid and limit tumor homing in equal measures. While the microvasculature promotes the spread of tumors, penetration of systemic therapies to the brain tissue is limited.[11] Understanding the various mechanisms predisposing to the homing of the tumor cells to the brain and basic knowledge of genetic alterations is necessary for planning optimum treatment.

Radiation therapy aims to mitigate the adverse impact of intracranial metastasis on survival and improve the health-related quality of life (HRQoL).[12] Recent research in the management of brain metastasis has focused upon using targeted therapies that have good local bioavailability, strategies to provide conformal radiation, limiting adverse effects of irradiation on neurocognitive, and outlining relevant indications for optimum use of immunotherapy.[13][14][15] Local therapy choice depends upon various parameters, namely patient factors (performance status, stage, and estimated survival), tumor factors (location of metastasis, type of tumor, number, size, and extracranial disease status), and prior treatment history.[16][17]

The first evidence of the utility of whole-brain radiotherapy (WBRT) in palliation of brain metastasis came from Chao et al.[18] Their paper was also significant for reporting a high incidence of recurrence in irradiated patients.[18] Subsequent studies by Borgelt et al. were designed to explore the equivalence between different dose fractionation regimens. Both a dose fractionation schedule of 30 Gray in 10 fractions and 37.5 Gray in 15 fractions were equally effective.[19]

This chapter aims to recall, analyze, and select appropriate indications and contraindications for the use of palliative radiotherapy in patients with intracranial metastasis. The clinical significance, technique involved, and recent advances in providing palliative radiotherapy in this clinical setting are also addressed.

Anatomy and Physiology

Blood Cerebrospinal Fluid Barrier

The choroid plexus epithelial cells connected via tight junctions form the blood-cerebrospinal fluid (CSF) barrier.[20] Fenestrations and gap junctions within the choroid plexus capillaries enable movement of particles to and fro between the extravascular compartment and CNS.[21] The C3 complement component's expression by the primary tumor cells has been shown to aid mitogenic stimulus entry within the CNS.[22] This complement component has been implicated directly in the pathogenesis of leptomeningeal seeding. Activation of the C3a receptor in the choroid plexus epithelium, indeed, has been linked to the disruption of the blood-brain barrier, which allows the entry of amphiregulin and other mitotic signals within the cerebrospinal fluid.[22]

Cancer Metastasis

The process of metastasis can be summarized into three steps:[23][24]

- Intravasation
- Extravasation
- Adhesive arrest [25]

Intravasation involves the breakage of tumor cells away from the primary tissue and invasion of the surrounding tissues, venules, capillaries, and lymphatic system. Tumor cells that intravasate into the circulation through the lymphatics or blood vessels interact with macrophages to form actin-rich degradative protrusions—these protrusions aid in clearing the extracellular matrix.

Extravasation involves the egress of these cells from the circulation into the tissue. Circulatory tumors cells, upon metastatic extravasation, undergo adhesive or circulatory arrest. Brain metastases tend to occur at areas with relatively longer mean transit times, such as the white and grey matter interface and watershed territories, which provide cells relatively longer times to egress from the circulation. Tumor cells may lie dormant at the target site of extravasation and arrest, or undergo apoptosis. Cells undergo adhesive circulatory arrest followed by extravasation either as single cells or a tumor embolus.

Factors that favor increased chances of homing to the brain include a dense microcapillary network and higher blood flow in proportion to other organs. Slowing of tumor cell movement at branch points in capillaries and the larger size of tumor cells compared to red blood cells favor the process of circulatory arrest. Specific interactions between tumor cells and endothelium have been shown to predispose to circulatory arrest. The upregulation of glycosyltransferase ST6GALNAC5 has been shown to lead to the homing of breast cancer tumor cells to the vascular endothelium.

Radiobiology

The selection of dosing of treatment depends upon the biological behavior of the tissue to radiation therapy. Late responding tissues are more susceptible to a single high dose of irradiation than early responding tissues. Most malignant tumors (brain metastasis, glioblastoma multiforme, low-grade glioma) behave as early responding tissues (meningioma, acoustic neuroma), while benign tumors behave as late responding tissues.[26][27]

Indications

The following factors need to be taken into consideration while deciding upon the treatment options in patients with brain metastasis:[16][28]

- Volume and number of metastasis
- Performance status
- Age
- Presence of extracranial disease and leptomeningeal disease
- Location of metastasis
- Site of the resection cavity

- Patient's preference
- Primary tumor site
- Type and molecular profile

Points favoring the continued use of whole-brain radiotherapy (WBRT) in the setting of intracranial metastasis include:[29][30]

- Improvement in CNS control
- Management of micrometastasis
- Reduction in the rate of recurrence
- Improvement in overall survival and HRQoL
- Prevention of the life-threatening and imminently fatal brain compression syndrome

Factors favoring the use of hypofractionation dosing include:[31][32]

- Presence of a large lesion (more than 30 mm)
- Proximity to a critical structure
- History of previous irradiation
- Presence of comorbidities such as stroke and vascular dementia

Whole-Brain Radiotherapy (WBRT)

WBRT is indicated in patients in whom stereotactic radiotherapy or stereotactic radiosurgery (SRS) cannot be performed, including those with leptomeningeal disease, numerous metastasis, low radiation therapy oncology group (RTOG) diagnosis-specific graded prognostic assessment (DS-GPA) scores, or medical contraindications.[6][33]

The presence of comorbidities, location of metastasis, tumor size, patient preference, and the extent of edema determine the choice of treatment in the presence of a single metastasis.[34][35]

Brain metastasis velocity may be used to determine patients who might benefit from WBRT who have distal brain failure after initial SRS.[36] Brain velocity is defined as the cumulative number of new metastasis developed per year after the receipt of SRS.[36]

The two main concerns that have persisted with the continued preference for the use of WBRT in this setting include:

- The limited impact on survival outcomes
- The potential to lead to neurocognitive decline [29][30][37]

Tumor regression after WBRT has been shown to correlate with improvement in neurocognitive function.[30] An increase in maximum dose delivered to the hippocampus has been associated with a greater decline in memory, which has provided a degree of credibility to the argument that the maximum dose of radiation that the hippocampus can safely be exposed might be lower than that presumed earlier.[38] Dose to 100 percent volume (D100) of 9 Gray and maximum dose (Dmax) of 16 Gray, delivered to the hippocampus during the standard fractionation schedule of 30 Gray in 10 fractions have been associated with an impairment in memory.[39][40]

Irradiation to neuro regenerative zone of the hippocampus has been postulated to be associated with neurocognitive deficits.[41] The hippocampus contains a reserve of neural stem cells (located in the subgranular layer of dentate gyrus), responsible for memory.[42] Hippocampal granule cells generated from the actively dividing neural stem cells migrate into the granular cell layer.[43] Neurogenesis within the dentate gyrus has been associated with neurocognition.[44] The neurogenic stem cell compartment is exquisitely radiosensitive.[45] Radiation-induced changes in the stromal microenvironment may lead to premature differentiation of neuronal progenitor cells into glial morphology.[46] Radiotherapy induced cell death has been attributed to an alteration in the NMDA to GABA ratio.[47]

Various tools have been used to assess the neurocognitive dysfunction associated with receipt of radiotherapy to the brain (mainly WBRT). Psychometric tools that have been validated in this setting include Hopkins verbal learning test (HVLT), controlled oral word association, grooved pegboard test, trail making tests a, and b.[48] A mean 30 percent decline has been noticed on the HVLT with the use of WBRT.[49] Morris water maze test, which assesses spatial learning and memory (hippocampal function) in preclinical investigations, demonstrates a measurable decline following irradiation.[50] Impairment in working memory (as conceived in Baddeley model), thought to be independent of hippocampal functioning, has also been reported with cranial irradiation.[51] This led to the hypothesis that irradiation to other brain regions such as the prefrontal cortex or the striatum may also be responsible for the decline in neurocognitive function associated with cranial irradiation.[52][53] The use of cholinesterase inhibitors like donepezil has been a study subject in phase three trials in this setting. Benefit has been demonstrated in those with greater pretreatment cognitive deficits.[54] The use of memantine in addition to HA (hippocampal avoidance)-WBRT has been proposed as a standard of care in those with a good performance status with no metastases in the hippocampal region, who are candidates for WBRT.[55][41]

WBRT with hippocampus avoidance (HA-WBRT), use of SRS, and spatially partitioned adaptive radiotherapy (SPARE) have been used to mitigate the effects of WBRT on the neurocognitive decline. SPARE employs a technique of administering single-fraction SRS over multiple days, limiting the daily treatment time to less than 60 minutes in those with 10-30 brain metastases. This technique has been postulated to have the least possible off-target effects on the hippocampus.[56]

RTOG 933 criteria have described the dosimetric characteristics of dual-arc conventional volumetric modulated arc therapy (DAC-VMAT) in WBRT with hippocampal sparing. Dual arc conventional volumetric modulated arc therapy covers a large field to provide the requisite planned tumor volume.[57]

The following issues may be encountered:

- Reduction in gantry velocity from one angle to another
- Acquisition of limits prescribed for traveling distance for the MLC upon reaching the distal part of the planned target volume[57]

A wide jaw opening has been linked with suboptimal multileaf collimator function (due to interference with movements).[57] The multi-leaf collimator's failure to shield the organs at risk upon reaching the distal parts of the planned target volume has also been a cause of concern. Measures such as simple split arc technique and split arc partial field (SAPF) technique have been used to prevent suboptimal multileaf collimator movements (limit scatter radiation) and related radiation-induced toxicity to organs at risk. SAPF volumetric modulated arc therapy (VMAT) has been shown to reduce the dose of radiation delivered to the hippocampus and other organs at risk without compromising the planned target volume delivery.[57]

The role of WBRT has been mired in some controversy given the results of the QUARTZ trial, where 538 non-small lung cancer patients with brain metastasis were not eligible for SRS. These patient subgroups were randomized to either WBRT or best supportive care. No significant differences in overall survival, overall HRQoL, or dexamethasone dosing were noticed between the two arms.[58][59]

Though randomized control trials in this setting are lacking, the presence of extensive nodular or symptomatic linear leptomeningeal metastasis is also an indication for WBRT.[60][61]

The Choose Wisely Campaign orchestrated by the American Society for Radiation Oncology has advised against the addition of WBRT in the adjuvant setting to SRS for patients with limited intracranial metastasis.[62]

A continued deferral of WBRT with receipt of multiple SRS courses for progression of recurrent brain metastases (in those who have received initial courses of SRS) has led to higher rates of local control, lower toxicity, and favorable overall and neurological progression-free survival.[63]

Stereotactic Radiosurgery

Emerging randomized data demonstrate a potential beneficial effect on survival from the use of SRS.[64][65] Stereotactic radiotherapy/SRS is usually indicated in patients with multiple brain metastases with the controlled or uncontrolled extracranial disease along with a Karnofsky performance status of 70 or more.[65] There

have been suggestions that support a combination of surgery followed by SRS in the presence of a single large and multiple small lesions. After surgery, the sequencing of SRS is indicated to improve local control, reduce the incidence of radionecrosis, and leptomeningeal spread.[66][67][68]

SRS provides the advantages of delivering higher dose conformal radiation in a single session, without any inordinate delay in the provision of systemic chemotherapy or immunotherapy.[69] A very steep gradient dose falls off beyond the prescribed isodose line and adds to the favorable dosimetric characteristics, which lend themselves well to the delivery of dose to intracranial and skull base lesions.[70] SRS is a standard of care in patients with good performance status and a performance status of more than 70 percent.[71] SRS has also been more cost-effective than a combination of SRS and WBRT in patients with 1-3 brain metastasis (an oligometastatic disease with a limited metastatic burden), those with an expected median survival of fewer than six months and for those with a less than ten metastasis.[72]

Pre-operative SRS has also been proposed as an adjunct to surgery due to challenges associated with contouring the post-operative surgical cavity, higher local failure rates with the use of WBRT, risks of leptomeningeal spread (with the use of cavity SRS due to sterilization effect), and radiation-induced necrosis (smaller amount of non-malignant brain tissue irradiated, resection of a majority of irradiated tissue). Other potential advantages of pre-operative SRS include increased local control due to improved target delineation, sterilization effect, and improved oxygenation. Lack of pathological confirmation and impaired wound healing are potential disadvantages.[73]

It has been postulated that the decision to use WBRT or SRS should not be solely based upon the number of brain metastases (in those with the number of metastases limited to less than 15). A total cumulative volume of 12-13 cm3 may be considered to a better prognostic indicator of overall survival. More than ten lesions in the brain (have been) can be treated (successfully) using stereotactic radiosurgery.[74][75]

Several studies have demonstrated SRS's utility in brain metastasis due to tumors, traditionally considered to be radioresistant such as melanoma and renal cell carcinoma, with comparable local control rates (compared to non-radioresistant histologies).[76] SRS has achieved a steep fall off from the target tissues to surrounding normal structures by the use of multiple converging static or moving beams.[77] This has been able to reduce the risk of damage to the surrounding structures. The dose of radiation is inversely proportional to tumor size. The maximal tolerated doses of radiation derived from the RTOG 9005 study vary from 24 Gy for lesions 20 mm in size, 18 Gy for 21–30 mm, and 15 Gy for 31–40 mm, respectively.[78]

The risk of radiation necrosis needs to be weighed against the potentially unproven clinical benefit with reirradiation of a local recurrence with SRS, in those who have received SRS earlier.[79]

Fractionated Radiosurgery

Fractionated radiosurgery (with 2 -5 fractions) combines the use of steep dose gradients and closer treatment margins associated with SRS, with the radiobiological advantages of fractionation.[80][81] An improvement in the extent of local control, lower risk of complications, and its position as an alternative option to surgery have been listed as the potential advantages of this procedure. As SRS may fail to treat all microscopic disease and the treatment of choice in the salvage setting is yet to be determined, more studies have been suggested in this setting.

Prophylactic Cranial Irradiation

While prophylactic cranial irradiation is recommended in those with limited-stage small-cell lung cancer (SCLC), who show a good response to systemic therapy, it remains a controversial option for those with extensive-stage SCLC or other unfavorable prognostic factors such as advanced age and presence of multiple comorbidities.[82][83] Though dosing of 25 Gy in 10 fractions has been advised as the standard, the role of prophylactic intracranial irradiation needs to be re-visited in light of the changes in the treatment landscape brought about by immunotherapy.

Contraindications

Collagen vascular diseases such as lupus, scleroderma, Sjogren syndrome, and inflammatory bowel syndrome are considered absolute contraindications, though it has been argued that these are not absolute contraindications.[84]

Inherited cancer predisposition syndromes such as ataxia telangiectasia, Nijmegen breakage syndrome, Fanconi anemia, Gorlin syndrome, Cockayne syndrome, Down syndrome, Gardner syndrome, Usher syndrome should be

carefully addressed.[85][86]

Equipment

Stereotactic Radiosurgery

Stereotactic radiation can be delivered by using a linear accelerator, gamma knife unit, and the use of charged particles.[87][88] The current version of the gamma knife uses 192 Cobalt 60 sources. An inbuilt MRI compatible, stereotactic headframe is used for the immobilization of the head. The headframe adapter has three gantry angles, which are attached to the new positioning system. The positioning system enables movement in the x, y, and z directions, which minimizes the time spent in changing the patient configuration. During SRS, the head frame is secured to the patient's skull bone using titanium pins. The X, Y, and Z coordinates and the gamma angle determine the positioning of the head frame relative to the gamma knife. These coordinates are determined based upon the target coverage required and the treatment planning parameters.

Treatment planning software uses digital imaging and communication in medicine, and the use of automatic radiation dose balancing algorithms are recent advances introduced with the advent of the gamma knife. The composite dose can be calculated by using a DICOM image and dose file, while the weighing of radiation doses at multiple targets is performed by the automatic dose balancing algorithm blocking of sectors to protect critical structures by the use of dynamic shaping has also been introduced. Prescribed radiation dose and isodose are determined by multiple factors, including target type, target size, and prior radiotherapy or SRS.

Personnel

Brain irradiation therapy is a multidisciplinary task; the following personnel is involved in it.

- Specialist providers qualified in the application of radiotherapy.
- Clinical oncologists qualified in the application of chemotherapy and hormone therapy in cancer treatment.
- Therapeutic radiographers specialized in the use of ionizing radiation for the localization and treatment of cancer.
- Physicist, clinical scientist/medical physicists responsible for supervision, delivery, commissioning, calibration, safe operation, and maintenance of radiotherapy equipment and close involvement in the planning of treatment and use of linear accelerators. Also, have a role in the maintenance of a safe environment and personal protection of individuals considered.
- Clinical technologists, including dosimetrists and medical technologists, are involved in maintaining radiotherapy equipment and instruments, who may also be responsible for treatment planning, provision of quality assurance measures, maintenance of equipment, and engineering support provision.
- Clinical engineer, technicians involved in the testing and design of tools and equipment used to carry out the planning of radiotherapy treatment and procedures.
- Support staff-Clerks, secretarial and administrative staff, clinic helpers, and support workers who play a role in ensuring smooth operation and services.[89][90]

Preparation

A particular issue with the planning of radiotherapy to the brain is the proximity to functionally significant structures, whose exposure to radiation can lead to significant morbidity. Efficient immobilization and accurate planning are essential to ensure that complications can be minimized.[91][92]

Technique

Immobilization

The type of material used, method of fixation employed, the percentage area of the material that comes in contact with the patient during the procedure, and technique used to support the patent all affect the procedure's reproducibility. Immobilization may require masks, which may be hazardous for patients with claustrophobia. Pretreatment

identification of the patients and setting up limits and appropriate margins, up to which irradiation can be provided in such scenarios, may be useful in achieving optimum results.[93]

Compliance of the Patient

The patient's inability to assume a posture for the duration of treatment may compromise the procedure. Anxiety, neurological deficit, and nausea due to raised intracranial tension may lead to movement.[94]

Accuracy of treatment delivered may also vary due to the uncertainty associated with using multiple images acquired through different techniques. Transfer errors associated with each imaging stage might attain significance and affect outcomes.

Reproducibility of the Setup

It depends upon the immobilization technique used. Set up errors in the region of 1.3 to 2 mm have been reported using stereotactic frames. The degree of setup errors encountered during immobilization also depends upon the material of the masks used, ranging from 3 mm with the use of high melting point thermoacrylic systems, 4-5.5 mm using low melting point thermoacrylic systems, and 3.27 mm when thermoplastics are used in combination with a bite block.[95]

Internal Organ Movement

The lack of movement of the brain within the cranium limits the effect of internal organ motion, thus, making the use of intrafraction analysis unnecessary.[96]

Radiotherapy Fields and Imaging

The timing and frequency of imaging to the brain need to be standardized.[97][98][99] First day images are accurate to identify gross and systematic data preparation errors. To account for the errors which may be introduced due to other factors, daily images for the first three days are advised. Weekly imaging may be required to account for the variations in the fit of the immobilization device due to the effects of steroid use.

A review of the field edges and the isocentre, with the use of images that are representative of all treatment fields, may be required to preserve critical structures in the brain. Double exposures with asymmetrical fields may be required to prevent injury to critical structures when the anatomy of the intracranial structures is not evident in one image.

Measurement of fiducial surrogates might provide good information when clear images cannot be obtained, either due to the structure of immobilization devices or non-coplanar arrangement of the fields.

Concomitant exposure to vital structures needs to be reduced while treating benign tumors such as pituitary adenoma. An attempt may be made to target the site of interest while preserving target structures nearby, even at sites for which double exposure may be required.

Virtual planning CT scanning should be done before irradiation for planning. Virtual CT simulation when part of the brain is being irradiated.

Treatment Planning

Whole-brain Radiotherapy

- The use of parallel fields in WBRT enables coverage of the entire brain. Recent research has focused on reducing the dose of radiation delivered to the parotid gland (an organ at risk) by using WBRT with non-coplanar beams and four field box therapy, which is delivered with the patient's head bent forwards. While bilateral WBRT is delivered using parallel opposed beams, four field box therapy uses anterior, posterior, and bilateral beams. The parallel fields in WBRT include the brain parenchyma, skull, and the spinal cord (until the level of the second cervical vertebrae).[100][101][102][103]
- 3 D planning, which should use CT data fused with T1 weighed gadolinium-enhanced images. Gross tumor volume is defined by the contours of the gadolinium enhancement on T1 weighted image (after adding 2 mm to the contours/borders for adjustments due to MRI fusion uncertainties). The routine use of intensity-modulated treatment should be considered. Dose delivered in a single daily fraction may vary from 16 Gy.

- The field of irradiation includes the whole brain with a clearance of 1 cm from the outer table and the base of the skull extending up to the bottom of C2. This might be achieved with the use of lateral parallel opposed fields for virtual simulation.
- Fractionation schedules may include 30 Gy in 10 fractions, 20 Gy in 5 fractions, and 12 Gy in 2 fractions, in those with poor performance status.

Stereotactic Radiosurgery

Standard SRS is reserved for lesions less than 3 cm in diameter to reduce the risk of radiation necrosis in the surrounding brain parenchyma. Standard SRS places an isocentre target within individual brain metastases, following which each isocentre is set up and managed sequentially. There has been a move towards anointing a single isocentre within the brain, along with the use of helical tomography and volumetric modulated arc therapy to target multiple metastases at the same time.[104][105]

Hypofractionated Stereotactic Radiotherapy

Hypofractionated SRT allows increased time for recovery of surrounding parenchyma by allowing 3-5 fractions on successive or alternate days. The two most common regimens enable the delivery of 25 Gy in 5 fractions and 21 Gy in 3 fractions, respectively.[32]

Supratentorial Boost

Supratentorial boost optimization of 2-3 field plan may be achieved by using 3D planning using CT data along with MRI fusion. A boost delivering 10 Gy in 5 fractions may be delivered over the course of one week.[106][107]

Posterior Cranial Fossa Boost

Virtual simulation may use opposing lateral fields extending from the posterior fossa to the second cervical vertebrae. Adequate anatomical coverage can be achieved by using MRI fusion, which may aid in the outlining of the contours of the cerebellum and brainstem. A boost delivering 20 Gy in 5 daily fractions may be delivered over one week.[108]

Hippocampal Avoidance Region

Bilateral hippocampal contours can be generated on a thin slice MRI-CT fusion image set. The HA region is generated by expanding the hippocampal contour by 5 mm.[41]

Contouring of Brain Metastasis

MRI with gadolinium contrast has been advised for treatment planning. Fusion with axial CT is also advised. Gross tumor volume is defined upon gadolinium enhancement with a 1 mm margin. Planning tumor volume or the total treatment volume is calculated by adding a 1-3 mm margin to the gross tumor volume in geometrical form. The tolerance dose for critical structures, while using intensity-modulated radiotherapy treatment, is calculated using the planning at risk volume, which can be created by adding a 3 mm margin to the critical structure.[109]

Quality Assurance

Dose homogeneity (HI) values close to zero indicate superior homogeneity.[110][111]

Complications

Whole-brain Radiotherapy

Several issues can be associated with the use of WBRT.[112][113][114][115] Key risks with the use of radiotherapy include the risk of radionecrosis, which might require resection in the future. The increased propensity to cause seizures, especially in people with a history of epilepsy, the possibility of a long duration of steroids, problems likely to be encountered due to the immobilization of the head required for the receipt of treatment, has difficulties patients with claustrophobia.

Acute adverse effects include skin erythema, alopecia, fatigue, altered sense of taste and smell, and serous otitis media. Memory loss, confusion, and leukoencephalopathy are late adverse effects. A higher burden of brain metastasis, higher integral dose to the calvarium, and use of WBRT are associated with an increased risk of development of

leukoencephalopathy in long term survivors.

The benefits of whole-brain radiotherapy are conditional upon the fact that it may lead to a short term deterioration in the HRQoL, temporary hair loss, and fatigue, the potential for accelerated cognitive loss, and the requirement for multiple hospital visits. The possible risks of bone marrow toxicity, enteritis, and mucositis preclude the use of cerebrospinal radiotherapy in adult solid tumor patients with leptomeningeal metastasis, up to one-fifth of patients who received concomitant intrathecal methotrexate, dexamethasone, and focal radiotherapy presented with grade 3-4 adverse effects.

Stereotactic Radiosurgery

Concerning SRS, local effects must be distinguished by acute and late-onset toxicities.[116][117][118]

Local Effects

Pin site trauma, bleeding, and infection due to head frame placement.

Systemic Effects

Acute (within two weeks):

- Headache, nausea, vomiting, seizures, and worsening neurological deficits, etiologically related to edema, are usually responsive to steroids.

Late (months to years):

- Hemorrhage, necrosis, and treatment-related changes (increase in contrast enhancement, necrosis, edema, and mass effect). These may be difficult to distinguish from disease progression and require additional imaging techniques for diagnosis. Modalities used in the treatment of radiation-induced necrosis include steroids, hyperbaric oxygen, anti-vascular endothelial growth factor antibody (bevacizumab), and surgical resection.

Late effects also include the potential risk of cranial neuropathies, including optic neuropathy, radiation necrosis, and vascular injury. Serious late toxicities of SRS are low.

Clinical Significance

Prognostication Tools

Recursive partitioning analysis (RPA) developed by Gaspar et al. of the radiation therapy oncology group uses four different parameters: the Karnofsky performance status (KPS), the control of primary tumor, extracerebral disease, and age to classify patients into three different groups. While patients belonging to classes I and II are advised local control with either surgery, radiotherapy, or a combination of the two, those with RPA class III are advised best supportive care only. Disease-specific Gaspar analysis also uses the primary location of the tumor as an additional parameter in prognostication. While Karnofsky performance status and the number of metastasis remain constant across the disease spectrum, other factors differ across diseases. The presence or absence of extracellular matrix has been shown to impact prognosis in disease-specific graded prognostic assessment tools developed for use in gastric and colorectal adenocarcinomas and lung cancer.[119][120][7]

There have been recent attempts to include molecular alterations in the tumor, as can be evidenced by the development of RPA scores for lung cancer using molecular markers such as EGFR mutations or ALK rearrangement, in addition to age, KPS, presence of extracranial metastasis, and the number of brain metastasis. The molecular factors found to have prognostic significance in breast cancer and melanoma include the ER/PR and HER2/neu status and the presence of the BRAFV600E mutation, respectively.

Imaging and Response Assessment

A close assessment of the various criteria used in the assessment of response to treatment in those with CNS metastasis (WHO, RECIST, and Mac Donald criteria) reveals critical gaps in understanding of the definition of disease status and assessment of response to treatment. Issues that are relevant in assessing the extent of disease and response to treatment upon imaging include modality and frequency of assessment, choice of method of assessment (linear, two dimensional and volumetric), differentiation between tumor-related and treatment-related change, the definition of

quantum of change that defines treatment response or disease progression, the utility of corticosteroid use, degree of concordance between signs and symptoms and changes on imaging and the impact of systemic disease status on CNS disease progression.[121][122][123][124]

The response assessment in neuro-oncology brain metastases (RANO-BM) committee reported consensus criteria, which defined measurable metastases as contrast-enhancing lesions less than 10 mm in diameter, and are based on the sum of the longest diameter of the target lesions (up to five lesions).

Response Assessment in Target Lesions

- Complete response: The disappearance of all lesions, which is sustained for at least four weeks, with no appearance of new lesions, without the use of corticosteroids, with stable clinical status or clinical improvement in the patient's condition.
- Partial response: 30 percent reduction in the sum of the longest diameter of target lesions from the baseline, which is used as a reference, which is sustained for at least four weeks with no new lesions, with stable corticosteroid use, stable clinical status, or clinical improvement.
- Progressive disease: At least a 20 percent increase in the sum of the longest lesion diameter, with the smallest sum on the study taken as reference. A single lesion should increase by a diameter of at least 5 mm to constitute progression.

Response Assessment for Non-target Lesions

These lesions include metastases with the longest diameter of less than 10 mm, lesions with borders that cannot be measured accurately, dural metastases, bony metastasis in the calvarium, cystic lesions only, and leptomeningeal metastasis has also been defined. These were not based upon measurement of individual lesions, but on qualitative measurements of evidence of disease progression on follow up imaging. Unequivocal progression of non-target lesions may constitute a basis for discontinuation of treatment. Pseudoprogression may be related to treatment response and requires advanced imaging investigations (in addition to routine MRI imaging).

Chemical exchange saturation transfer (CEST) imaging is a novel quantitative MRI technique that quantifies compounds, such as amide protons, amine protons, and fast exchanging hydroxyl protons, considered undetectable during structural MRI or even conventional MR spectroscopy. The principle underlying that technique involves the transfer of magnetization from aliphatic protons to labile protons known as the relayed nuclear Overhauser effect (rNOE). Reduced CEST signals and changes in the width NOE tumor peak and amplitude of peak on normal-appearing white matter, which predicted subsequent alterations in tumor volume, have been used to predict SRS response. CEST metrics involving rNOE and amide tumor magnetization ratios have been used to differentiate treatment-associated changes from tumor progression and assess treatment responses in areas such as the brainstem (which are not amenable to biopsy).

A major challenge to the inclusion of patients in clinical trials is the lack of standardization in measuring the extent of response assessment. According to RANO-BM criteria, patients in whom the metastases' size is less than 10 mm or 5 mm in diameter may be deemed to have an unmeasurable disease. Standardization of techniques involved in MRI acquisition parameters, including optimization of signal to noise ratios and specific contrast to noise ratios is necessary.

Definitions of survival which have been proposed by the RANO-BM consortium in relation to radiological response assessment in clinical trials include bicompartmental progression-free survival (includes CNS lesions, distant CNS lesions, and non-CNS lesions), CNS progression-free survival, which involves local and distant CNS lesions, non-CNS progression-free survival includes non-CNS lesions only and CNS local progression-free survival which includes CNS lesions only. The inclusion of other parameters that measure the HRQoL, the quantum of corticosteroid use, the progression of clinical neurological symptoms, and neurocognitive function also constitutes important parameters for judging response assessment in clinical trials.

Enhancing Healthcare Team Outcomes

With the advent of systemic approaches targeting the tumor and advances in radiotherapy techniques, patients' careful selection has assumed greater importance. The use of disease-specific prognostication systems with molecular

parameters has put the focus squarely on prognostication. Although it is important to avoid treating those with limited prognosis, it is equally important to provide up to date management to deserving patients. While SRS becomes the standard of care, prevention of neurocognitive decline with HA-WBRT and neuroprotective agents' use holds the promise of improved HRQoL. An interdisciplinary approach that includes a disease management group consultation to provide patient-centered care remains the need of the hour.

The demarcation between tumor recurrence and radiotherapy related changes remains a subject of further research and demands closer integration of radiologists and nuclear medicine specialists within the multidisciplinary team. Autosegmentation for precise contouring, model-based automated target delineation, automatic generation of treatment plans, and use of omics driven radiation therapy (incorporating omics derived information for treatment planning) are recommended treatment approaches for the future.

Continuing Education / Review Questions

- Earn continuing education credits (CME/CE) on this topic.
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