BRACHYTHERAPY WORKSHOP

BRACHYTHERAPY OF MALIGNANT GLIOMAS DEFINITION OF TUMOR BOUNDARIES

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Introduction

Stereotactic interstitial irradiation delivers a controlled dose of radiation to a defined target volume.[4,6-8] The isodose envelopes produced by an array of radionuclide sources should have the same configuration as the three dimensional shape of the tumor and rapid dose fall off so that surrounding brain parenchyma receives minimal irradiation.[6-8] In order to accomplish this, we developed a computer program for simulation of Iridium^{192} source placements and display of aggregate isodose configurations which are superimposed on planar contours of a defined tumor volume.[4] However, this method depends on a histologically accurate definition of the tumor as a three dimensional volume in stereotactic space.

The following will briefly describe our methods for defining target volume by imaging and by stereotactic serial biopsy. In addition, a study which correlates histology and CT and MRI findings will be summarized. Finally, a structural classification of glial neoplasms, important for treatment planning, will be reviewed.

Definition of Tumor Volume:

Interactively defined tumor volumes are suspended in a computer image matrix by interpolation of stereotactically gathered CT and MRI data as follows: patients undergo stereotactic CT and MRI studies in imaging compatible stereotactic head holders to which localization systems are attached.[4,5] The localization systems consist of nine modality opaque reference rods arranged in the shape of the letter "N" on either side of the head and anteriorly which create nine reference marks on each CT slice and MRI image.[3] The CT slices and MRI images are viewed on an operating room computer display system. Using a cursor and trackball subsystem, the surgeon digitized the outlines of the lesion on each CT slice and MRI image. These are suspended in a three dimensional computer matrix in precise relationship to their stereotactic positions which are determined from calculations based on the localization systems' artifacts. The computer interpolates intermediate slices between the digitized contours at 1 mm intervals. The

digitized and interpolated slices are then filled in with 1 mm cubic voxels. The computer calculates the CT and MRI defined volumes in cubic millimeters.[5] Points within the tumor volumes are expressed in mechanical settings on the stereotactic frame. For simulation of stereotactic interstitial Ir^{192} placement, the CT and MRI defined tumor boundaries are sliced perpendicular to the intended implantation angles.[4] However, the following procedure is necessary in order to determine whether the CT or MRI defined volume more accurately reflects the actual histologic limits of the tumor for treatment planning purposes.

Stereotactic Serial Biopsy:

The patient is replaced in the same stereotactic head holder utilized for the CT/MRI data acquisition phase. A micrometer attaches to each fixation pin and insures precise replacement. An avascular trajectory is simulated on a video display terminal from stereotactically gathered digital angiographic information. This determines the arc (angle from the vertical plane) and collar (angle from the horizontal plane) stereotactic frame settings. A series of 1 cm long stereotactic biopsies are obtained along each trajectory. Biopsy specimens are studied by H & E stained smear preparations (which allow identification and study of single cellular elements) and by formalin and gluteraldehyde fixed sections.

Correlation of CT/MRI Defined Limits with Histology:

Histologic findings and CT and MRI defined abnormalities were correlated in one hundred seventy-seven (177) biopsy specimens obtained from thirty nine patients with previously untreated gliomas. A computer program displayed the spatial position of each biopsy on stereotactic CT slices T-1 and T-2 MRI images, and measured the display window level along the 1 cm range of each biopsy specimen.

A subroutine was then used to calculate mean and standard deviations for display screen intensity values of 30 normal gray and 30 normal white matter locations. Biopsy specimens were then classified as originating from isodense, hyperdense, or hypodense areas on contrast enhanced computed tomography and from regions having normal, short or prolonged signals on T-1 and T-2 weighted MR images. Table I demonstrates the origin of each of the 177 biopsy specimens in terms of the findings on CT and MRI.

TABLE I

ORIGIN OF 177 BIOPSY SPECIMENS IN 39 PATIENTS

	HYPODENSE	ISODENSE	HYPERDENSE
CT	98	45	34
MRI	Short	Normal	Prolonged
T_1	4	23	125
T_2	1	10	166

Histological categorization of each biopsy specimen was based on the predominant presence or absence of the following:

Tumor Tissue (33 specimens):

Tumor cells are coalescent with other tumor cells, vascular elements, or areas of necrosis. Intervening neural parenchyma is absent.

Isolated Tumor Cells (122 specimens):

Individual tumor cells having large abnormal nuclei and little or no cytoplasm can be found within intact parenchyma. Astrocytic processes, if present, are too short and numerous to be confused with gliosis on the smear preparations.

Necrosis (7 specimens):

Some specimens demonstrate necrotic tissue as the primary feature. All of these specimens were obtained from within tumor tissue proper.

Normal

Fifteen of the 177 specimens demonstrated no evidence of tumor tissue of infiltration. Histologic correlations with CT are revealed in Table II.

TABLE II

CONTRAST ENHANCED CT SCANNING

		ISODENSE	HYPODENSE	HYPERDENSE
HISTOLOGY	(No. of Specimens)			
Tumor Tissue	(33)	2	12	19
Isolated Tumor Cells	(122)	34	74	14
Necrosis	(7)	--	6	1
Normal/Edema	(15)	9	6	--

Tumor tissue was always found in biopsies obtained from contrast enhancing areas. Contrast enhancement is directly related to the degree of neovascularity noted most frequently in tumor tissue proper. However, in lower grade neoplasms, hypodensity of CT scanning can represent tumor tissue with no or mild neovascularity. Most commonly, hypodensity on CT usually corresponds to perilesional edema which is permeated by isolated tumor cells. In addition, biopsy specimens obtained from isodense areas outside the limits of CT hypodensity demonstrated abnormal cells in 34 specimens.

Magnetic Resonance:

Microscopic examination of the 177 biopsy specimens revealed the following correlations with MRI:

Histology (No. of Specimens)

	MRI T-1		
	Short	Normal	Prolonged
Tumor Tissue (29)	1	--	28
Isolated Tumor Cells (108)	3	16	89
Necrosis (5)	--	--	5
Normal/Edema (10)	--	7	3

TABLE III-A: HISTOLOGIC CORRELATION IN T-1 STUDIES PERFORMED ON 34 PATIENTS

	MRI T-2		
	Short	Normal	Prolonged
Tumor Tissue (33)	--	--	33
Isolated Tumor Cells (122)	1	4	117
Necrosis	--	--	7
Normal/Edema (10)	--	6	9

TABLE III-B: HISTOLOGIC CORRELATION IN T-2 EXAMINATIONS PERFORMED ON 39 PATIENTS

MRI relaxation times are greatly affected by unbound water (edema). Thus, abnormalities on MR images are more dramatic (usually 5 to 10 standard deviations beyond normal values) than the zone of hypodensity defined by CT scanning (usually 1 standard deviation beyond normal). In the vast majority of glial tumors, MRI uniformly detects much larger areas of involvement than CT scanning.[3] The abnormal volumes defined especially by the T-2 weighted sequence are considerably larger than those defined by hypodensity on CT. Our histologic findings indicate that tumor cell infiltration extends at least as far as the MRI abnormality indicates. Unfortunately, for ethical reasons, only a few specimens were obtained from normal T-1 and T-2 regions. However even some of these specimens demonstrated scattered isolated tumor cells.

Tumor Structural Types:

Based on the results of CT based stereotactic serial biopsy studies in 127 patients having intracranial gliomas and volume reconstructions derived from stereotactic CT scanning and MRI in 39 patients, we confirmed the following classification for glial neoplasms originally described by Daumas-Duport.[2] This is useful in patient selection for interstitial irradiation and for treatment planning.

Type I consists of circumscribed tumor tissue with no isolated tumor cell invasion into surrounding parenchyma. Neural parenchyma is absent within tumor tissue. On CT, tumor tissue is defined by contrast enhancement or intense hypodensity. Calculated volumes for the CT defined limits are equal to the volume defined by the T-1 and T-2 weighted sequences on MRI.

Type II. Tumors consist of solid tumor tissue surrounded by a zone of isolated tumor cells invading edematous but intact parenchyma. In grade 3 and 4 tumors, the histologic limits of tumor tissue proper are defined by contrast enhancement on CT scanning. The zone of isolated tumor cell infiltration is best defined by the T-2 weighted MRI sequences.

Type III. In these lesions, there is no solid tumor tissue component. The tumor is comprised of intact parenchyma infiltrated by isolated tumor cells. The parenchyma is usually functional. These tumors are hypodense or in some instances isodense on CT scanning. MRI shows moderate prolongation of T-1 and marked prolongation of T-2. As far as we can discern at this juncture, the T-2 weighted sequence usually defines the histologic limits of these lesions.

Planning for Interstitial Radiation:

Interstitial radiation is reasonable for treating type I tumors and for administering a lethal dose of radiation to the solid components of type II tumors. Radiation doses exceeding 7,000 rads at dose rates of 50 to 100 rads per hour can be safely administered to solid tumor tissue since no functional parenchyma exists within it. Isodose configuration produced by a finite number of radioactive sources can be neatly molded to encompass the solid tumor tissue volume, provided that it is not too geometrically complex.[4]

However, interstitial radiation dose delivery to intact parenchyma infiltrated by isolated tumor cells is limited by two major constraints. First, the volume defined by the T-2 MRI image not infrequently exceeds that recommended for safe implantation.[8] Secondly, even though a lethal dose level at a low dose rate can be delivered to the zone of tumor cell infiltration, the intact parenchyma may also sustain irreversible radiation damage which will affect the long term quality of survival. Therefore, at this juncture, infiltrative zones are probably best treated by supplemental external beam radiation therapy. The total accumulated radiation dose to surrounding parenchyma delivered by external beam radiation and interstitial radiation should not exceed 6500 rads.

External beam radiation therapy is the preferred treatment for patients with type III (infiltrative) tumors, unless they are located in expendible brain tissue. Here interstitial irradiation provides a mechanism for tissue destruction similar to surgical resection.

The spatial definition and treatment of solid tumor tissue components of type I and type II tumors are relatively straightforward. However, the presence of highly motile and mitotically active tumor cells in intact brain tissue which receives less than 6500 rads is the reason that all forms of focal therapy, including interstitial radiation therapy, ultimately fail.[1] Development of methods for the selective destruction of these isolated tumor cells which spares the involved parenchyma continues to be a significant challenge.

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