

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6662

**SEMI-AUTOMATED CALCULATION OF VOLUMES OF ENHANCING TUMOR AND
TUMOR PLUS EDEMA FROM ROUTINE MR IMAGES IN PATIENTS WITH MALIGNANT
GLIOMAS**

In Collaboration with the New Approaches to Brain Tumor Therapy Group (NABTT)

***PARTIAL
PROTOCOL—
CONTACT ACRIN
PROTOCOL
DEVELOPMENT
AND REGULATORY
COMPLIANCE FOR A
COMPLETE
PROTOCOL***

Study Chair

Birgit B. Ertl-Wagner, MD
Institute of Clinical Radiology
University of Munich, Klinikum Grosshadern
Marchioninstr. 15
D-81377 Munich, Germany
+49-89-7095-3620
Fax # +49-89-70958832
B.Ertl-Wagner@t-online.de

Statistician

Jeffrey D. Blume, PhD
Center for Statistical Sciences
Brown University, Box G-H
Providence, RI 02912
(401) 863-9968
Fax # (401) 863-9182
jblume@stat.brown.edu

**Version Date: June 27, 2003
Including Amendments #1 & 2
Activation Date: May 2, 2003**

This protocol was designed and developed by the American College of Radiology Imaging Network (ACRIN). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by ACRIN, nor does ACRIN assume any responsibility for unauthorized use of this protocol.

INDEX

Schema

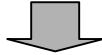
1.0	Abstract.....	1
2.0	Background and Significance	2
3.0	Specific Aims and Objectives.....	5
4.0	Case Selection.....	7
5.0	Site Selection	9
6.0	Patient Registration and Randomization System.....	10
7.0	Data Collection and Management.....	10
8.0	Data Collection Forms	13
9.0	Image Acquisition.....	15
10.0	Image Interpretation.....	17
11.0	Statistical Considerations REMOVED FROM WEB VERSION	25
	References.....	26
	Appendix I: Sample IRB Letter	29

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6662

SCHEMA

Identification of cases at the databases of Henry Ford Hospital (HFH) and Hospital of the University of Pennsylvania (HUP)



Scrubbing of patient identifying data



Submission of “scrubbed” cases to ACRIN



Installation of 5 training cases and 24 study cases at the workstations at ACRIN, Philadelphia



Assessment of reader’s level of expertise (form)
16 readers: 4 staff neuroradiologists, 4 neuroradiology fellows, 8 registered rad. technologists



Training of readers with 5 training cases
Determination of time to train (form and objective time assessment)

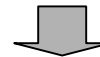


Assessment of study cases by readers
24 cases to be evaluated by 16 readers with both software systems
Randomization of order of cases to be assessed and of order of software systems
Determination of tumor volume, tumor plus edema volume, software preferences of the reader (form), ease of use (form) and time for assessment (form and objective time assessment)

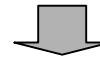


Data analysis (Center for Statistical Sciences, Brown University, Providence, RI)

Installation of Eigentool and 3DVIEWNIX-TV softwares at ACRIN Philadelphia office



Training of Anthony Levering of ACRIN, Philadelphia, by the software specialists from HFH and HUP



AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6662

Eligibility (see Section 5.0 for details)

- Histologically proven diagnosis of malignant glioma, including glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma (**WHO grade III or IV**).
- **Two subsequent post-operative scans demonstrating tumor recurrence must be available (first and at the second follow up imaging at 3 months and 6 months post surgery).**
- Imaged with standard protocol including axial short TR, short TE spin echo, before and after gadolinium administration, axial FLAIR, and axial long TR, long TE fast spin echo technique.

Required Sample Size: 24 cases and 16 raters

1.0 ABSTRACT

Calculation of tumor volumes is of crucial importance both for clinical practice and for clinical studies evaluating new brain tumor therapies. This retrospective multi-reader study is designed to explore and evaluate two semi-automated systems (Eigentool and 3DVIEWNIX-TV) for calculating brain tumor volume in tumor recurrence. Both the volume of the enhancing brain tumor after Gadolinium administration and the volume of the solid tumor plus the surrounding edema will be calculated. The two systems will be assessed on a variety of aspects including reliability, the average time required to produce a volumetric measurement, and the average time to train an operator.

A total of 24 cases with two respective time points will be assessed with both systems by a total of 16 readers. The readers will consist of four faculty neuroradiologists, four fellows training in neuroradiology, and eight radiologic technologists with a minimum of three years MR experience. Cases from two institutions will be included in the study. Case selection will be balanced on the magnitude of changes in tumor volume over time. Only cases with a histology-proven WHO grade III or IV brain tumor and a post-operative recurrence will be included.

The primary endpoints of the study will be the tumor volume and the tumor plus edema volume in cubic centimeters. Secondary endpoints include the time to train for the respective system, the time to estimate tumor volume with the respective system, and reader preferences regarding the systems. The inter-rater reliability, as measured by the Intraclass Correlation Coefficient, will be estimated for both systems. Moreover, the effect of reader expertise on reproducibility of tumor volume will be explored. The times required to train and to estimate tumor volumes will be assessed for both systems.

This study lays the groundwork for further evaluation of these two systems in prospective multi-center controlled studies on new therapeutic regimens for brain tumors. The study will be conducted in collaboration with the New Approaches to Brain Tumor Therapy Group (NABTT).

2.0 BACKGROUND AND SIGNIFICANCE

In the United States, approximately 17,000 patients are affected by primary brain tumors each year [1]. Approximately 60% of these are gliomas with the majority belonging to the high grade or WHO grade III and IV category [2].

The median survival rate of a patient diagnosed with a high-grade glioma is still under 12 months. Cure rates are exceedingly low [3]. Despite marked advances in surgery chemotherapy, radiation therapy, and diagnostic radiology, survival rates in patients with high-grade gliomas appear largely unaffected [4-6].

There is a pronounced need for new, effective therapeutic approaches to brain tumors. To this end, the New Approaches to Brain Tumor Therapy (NABTT) was founded in 1993. It is a nationwide cooperative groups funded by the National Cancer Institute to conduct Phase I and II clinical evaluations of promising new treatment strategies including surgery, radiation, chemotherapy, and biologic therapies in the treatment of primary malignancies of the central nervous system. It combines and focuses the experience, resources, and capabilities of nine outstanding medical institutions, including Emory University, Henry Ford Hospital, Johns Hopkins University, Massachusetts General Hospital, Moffitt Cancer Center, The University of Alabama at Birmingham, The University of Pennsylvania, The University of Texas at San Antonio, and Wake Forest University.

MR imaging plays a key role in the evaluation of brain tumor patients both for the primary diagnostic assessment and for surgical planning and post-operative follow-up. Moreover, MR imaging is a decisive factor in the assessment of the efficacy of new therapeutic strategies and is therefore a paramount factor in the design of brain tumor therapy trials.

However, in order to enable both an efficient follow-up in the clinical setting and an accurate estimate of a tumor's susceptibility to a new therapeutic approach, quantitative assessment of the tumor volume is crucial. Publications have demonstrated quantitative

computer-assisted volume analysis to be widely superior to simple visual assessment in the assessment of the response of brain metastases to radiotherapy [7].

In the past, MR-imaging based tumor volume assessment with manual segmentation was cumbersome and frequently unreliable. It depended largely on the reader's expertise and there was wide inter-rater variability. In recent years, semi-automated systems for the assessment of brain tumor volumes have been developed.

The reader marks the area of interest, while the system automatically segments the various imaging contrasts and calculates the respective volume.

Among these are the system Eigentool, developed by the Department of Physics and Engineering of the Henry Ford Hospital, Detroit, MI, and the system 3DVIEWNIX-TV, developed by the Medical Image Processing Group, Department of Radiology of the Hospital of the University of Pennsylvania Philadelphia, PA [8-14]. These systems have previously been tested in several applications including the determination of lesion load in multiple sclerosis and in the assessment of the extent of stroke.

The two software packages both incorporate a variety of image processing tools that can be used for research. Both software packages have been tested in many research areas for years at their respective sites and now need an independent study to verify their use in a broader sense. A description of the software packages and processing steps is included in Section 10. The difference between the software packages is in the methodology that has been developed specifically for segmenting enhancing tissue on T1 weighted spin echo MRI and the hyperintense area on FLAIR MRI. The main difference is the Eigentool method utilizes all images acquired and segments pixels based on the combined contrast differences determined from all image sequences. 3DVIEWNIX-TV utilizes only the pre- and post-Gd T1 spin echo MRI to segment the enhancing tissue and only the FLAIR image to segment the hyperintense area seen on this image. Because the Eigentool software uses all contrast differences to "direct" the segmentation, it is speculated that pixels that have distinct contrast differences on the T2, T1 or FLAIR images may not be included in the same region segmented by 3DVIEWNIX-TV. In addition, the segmented images (i.e. enhancing tissue or FLAIR

hyperintensity) created by Eigentool are not a binary overlay but instead display pixel values based on their partial volume of each tissue or “feature” defined. Therefore the segmented images have a gray scale appearance similar to acquired MRI images, e.g. if the pulse sequence could be tailored to remove the normal tissue. This trait of the Eigentool software allows the operator to visualize the segmented tissue more clearly such that voxels at the edge of a tissue or those that contain a large amount of partial volume with the normal tissue are now more visible. This visualization of the partial volume voxels may result in differences in operator expertise and in the ease of use since the operator may have more information available to make the decision which voxels to include in the volume. This may result in the two software packages being considered superior for different research projects in the future, and this protocol may assist in determining which package would be most appropriate based on the desired outcome of a study.

These semi-automated systems now allow for a less operator-dependent tumor volume assessment. However, the extent of interobserver reliability for tumor volume assessment in a multi-institutional setting remains to be determined before these systems can be applied in large multi-center-trials. Moreover, the extent of the reader’s expertise on the reproducibility will need to be assessed in order to determine the training level of the reader required for adequate performance. This will aid in the design of multi-center studies, as the relevant level of reader training can be chosen beforehand. In addition, determining the intra- and inter-reader reliability for measurements for serial changes in tumor volumes is of crucial importance for the future design of trials on brain tumor therapy. Previous reports have demonstrated rather large inter- and intra-rater variations with other segmentation techniques and have reported a case dependency of the accuracy of measurements [15]. It is therefore indispensable to evaluate the coefficients of determination and of variation of semi-automated segmentation systems, before their application in brain tumor therapy trials becomes feasible.

In summary, large multi-center trials on brain tumor therapy require a method of objective assessment of tumor volume, which has high inter-rater and intra-rater

reliability and is independent of the acquisition site. Two software systems providing semi-automated segmentation and tumor-volume assessment will be tested and compared in this study regarding their suitability to provide an end-point in brain tumor therapy trials.

3.0 SPECIFIC AIMS AND OBJECTIVES

3.1 Objective

The overall goal of this study is to assess and explore the value of two semi-automated systems for calculating the volumes of enhancing tissue and of enhancing tissue plus perifocal edema as estimated by the two software systems, in patients with a postoperative status and with recurrent malignant gliomas.

3.2 Specific Aims

3.2.1 To estimate the intra- and inter-rater reliability for measurement of the volume of enhancing tissue and the volume of enhancing tissue plus the hyperintense volume on the FLAIR sequence as estimated by the software systems Eigentool, developed by the Henry Ford Hospital, and 3DVIEWS-NIX-TV, developed by the Hospital of the University of Pennsylvania. This study will employ datasets retrieved from Henry Ford Hospital (HFH) and from the Hospital of the University of Pennsylvania (HUP). To avoid overlap with radiation necrosis, only cases will be chosen in which tumor recurrence was substantiated either by clinical follow-up, histological evidence, or FDG-PET.

We believe that both techniques will produce estimates that are reliable enough to be used for routine estimates of tumor volumes both in the clinical setting and in multi-center trials on brain tumor therapy. We also believe that there will be no systematic differences in the volume of enhancing tissue and the volume of enhancing tissue plus the hyperintense volume on the FLAIR sequence, or precision of estimates, between the two systems.

3.2.2 To explore the effect of reader expertise on reproducibility of volume measurements. The levels of expertise will be faculty neuroradiologist (American Board of Radiology certified and Certificate of Added Qualification in neuroradiology),

neuroradiology fellow (American Board of Radiology certified), and radiologic technologist (American Board of Radiologic Technologist certified) with at least three years of experience in MR imaging.

We believe that there will be not be a clinically substantial effect of reader expertise upon reproducibility of volume measurements. We have no reason to believe otherwise, as there is only minimal input required from the readers. However, we will examine our data to see if this is indeed the case. If our data suggest that such differences do indeed exist, then further investigation, most likely in future studies, will be required to determine the extent of these differences (with high precision) if one is unwilling to use the variance pooling assumption stated here.

- 3.2.3** To estimate the ease of use of the respective systems. Moreover, both the time required to train individuals to use the systems to produce volume measurements with adequate reliability and the time required for a trained operator to generate tumor volumes will be assessed.

We hypothesize that training to achieve adequate reproducibility will require less than 12 hours for readers at all levels of expertise and that measurement of volumes of enhancing tissue and of enhancing tissue plus the hyperintense volume on the FLAIR sequence will require at the most 30 minutes per case on modern workstations. In addition, we do not expect that there will be a noticeable effect of level of expertise or system on training or analysis time required.

- 3.2.4** To estimate the intra- and inter-rater reliability (coefficients of determination and of variation) for measurement of serial change in the volume of enhancing tissue and the volume of enhancing tissue plus the hyperintense volume on the FLAIR sequence in the same patient with both systems. Case datasets will be retrieved and provided by HFH and HUP.

We expect that the systems will be comparable in precision for measurement of serial changes in volume (they have already shown to be in limited individual testing of the

software). Again, we do not expect to see a substantial clinical effect of expertise on the precision (same comments apply here as discussed above).

- 3.2.5** To determine the inter- and intrarater reliability of manual measurements of the volume of enhancing tissue and of the volume of enhancing tumor tissue and edema and to explore the relationship between these estimates and those obtained with the two software systems.

We believe that there will be a significantly larger intra- and inter-rater variability of the manual tumor estimates as compared to the software systems. In fact, manual tumor estimates are known to be extremely variable, which translated into little reliability. Because of the volume estimating assumption used to compute manual measurements, we believe they will tend to overestimate the volumes as compared to the software systems because the systems can more “accurately” compute volumes for a variety of morphologies.

3.3 Confirmation Studies

We note that further prospective studies may be required to identify small subgroup effects (such as small effects of reader expertise or of case difficulty on the ICC) that cannot be identified by borrowing strength across the subgroups. In addition, we acknowledge that our retrospective case mix will include a higher proportion of difficult cases than most real-world settings and hence the effect of case difficulty may need to be studied further in a prospective trial. Hence it would be prudent to validate these results in a larger multi-center prospective therapeutic trial.

4.0 CASE SELECTION

The cases will consist of WHO grade III and IV malignant gliomas. We expect that the majority of cases will be glioblastomas. However, a minority may be anaplastic astrocytomas or anaplastic oligodendrogliomas.

4.1 Inclusion Criteria

- 4.1.1** Histologically proven diagnosis of WHO grade III or IV glioma, including glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, is required.

4.1.2 Two subsequent post-operative scans demonstrating tumor recurrence serial scan must be available. These must be acquired at the first and at the second follow up imaging (3 months and 6 months post surgery). Tumor recurrence must be monocentric to facilitate manual assessment. All cases included will be post-operative cases, in which tumor tissue had been removed with a macroscopically complete R0 resection. In all cases to be included recurrent, radiologically detectable, enhancing tissue will be present at the 3 months follow-up. Since an abundance of cases will be available at the sites, only cases in which tumor recurrence was substantiated either by clinical follow-up, histological evidence, or FDG-PET will be chosen. The cases will be chosen from a random sample of cases. Within this random sample, consecutive cases will be evaluated by a panel of three readers (advisory panel) regarding difficulty of assessment (i.e. presence or absence of necrosis and complexity of the shape) and amount of change of tumor volume. Regarding change in tumor volume, three strata will be formed with eight cases in each stratum: one with minimal to no change in tumor volume, one with moderate change in tumor volume, and one with a large change in tumor volume. The stratum with minimal to no change in tumor volume will consist of patients judged radiologically stable by the advisory panel.

4.1.3 Cases must include an axial short TR, short TE spin echo, before and after gadolinium administration, an axial FLAIR, and an axial long TR with long TE fast spin echo. All serial studies will be performed on the same vendor platform. The acquisition parameters will be kept the same for each time point; this includes the basic pulse sequences (e.g. spin echo, fast-inversion recovery - FLAIR, 2D verse 3D acquisition, etc.), slice thickness, FOV, frequency and phase encoding directions, signal averages, etc. Subtle differences in pulse sequence parameters, e.g. TE and TR, which occur in all centers when following patients over months to years, are not considered critical. Also, since the comparison is the volume results obtained between operators and software packages using the same data set, any variability inherent to the acquisition will be the same for both methods and should not affect the outcome or will affect the outcome in a systematic manner based on the processing method. Moreover, all images will be standardized to the

same gray scale by using the published standardization method prior to the study [22-23].

4.2 Exclusion Criteria

4.2.1 All cases in which serial studies are not available will be excluded. Moreover, all gliomas with a WHO grade less than III will be excluded.

5.0 SITE SELECTION

5.1 Image Requirements

All studies will include axial T-2-weighted acquisitions and pre- and post-contrast T1-weighted, and FLAIR MR images.

5.2 IRB Approval and Informed Consent

The institutions submitting images must have study-specific IRB approval. For this retrospective study, an expedited review is anticipated. A copy of the IRB approval will be on file at ACRIN headquarters (Fax 215-574-0300) prior to submitting case material. A sample letter for institutional IRBs is provided in Appendix I.

5.3 Patient Accrual Issues

The HUP images will be identified through the database of the University of Pennsylvania Brain Tumor Center (UPBTC). In the calendar year 2000, 450 cases of brain tumors were seen at the UPBTC. Approximately 400 were newly diagnosed malignant gliomas. Of these, approximately one half met the diagnoses required for this study and had an adequate set of follow-up scans at HUP.

Once applicable images have been identified through the UPBTC database, the availability of MR images at HUP will be confirmed through the Radiology Information System. The search of images will begin at 1/01/1999, and end at 12/31/2000. This should yield approximately 400 eligible cases. Confirmation of the availability of images may reduce the number by 30%.

The HFH images will be identified through the database of the Hermelin Brain Tumor Center (HBTC). In the calendar year 2000, 250 cases of brain tumors were seen at the HBTC. Approximately 150 of these were newly diagnosed malignant

gliomas. Of these, approximately one half met the diagnoses required for this study and had an adequate set of follow-up scans at HFH.

Once applicable images have been identified through the HBTC database, the availability of a serial MR image at HFH will be confirmed through the Image Analysis Lab. The search of cases will begin at 1/01/1997 and end at 04/15/2001. This should yield approximately 1300 eligible cases. Confirmation of the availability of images may reduce the number by 30%. Consecutive cases will be selected from among those with complete inclusion criteria, beginning on 1/01/1997.

Since statistical analysis indicates a need for only 24 cases in total plus 5 training cases, there will be a generous excess of clinical material.

6.0 PATIENT REGISTRATION AND RANDOMIZATION SYSTEM

- 6.1** Eligible cases will be identified through the databases of the various NABTT sites. Consecutive cases will be selected from among those with complete inclusion criteria by the two submitting sites (HFH and HUP; compare section 6.3). The DMC will subsequently register submitted cases and randomly provide a centrally assigned unique ACRIN protocol case number for each case. This number will be used for the remainder of the study. Readers will be assigned a random order of systems and cases.
- 6.2** The submitting institutions will be compensated \$500.00 for each patient actually registered into the trial.

7.0 DATA COLLECTION AND MANAGEMENT

7.1 General

- 7.1.1** The ACRIN web address is www.acrin.org
- 7.1.2** Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences in Providence, RI, and the Data Management Center (DMC) is located at the American College of Radiology's Data Management Department in Philadelphia.

7.1.3 The BDMC uses screens on the ACRIN web site to schedule readers, and maintains calendars of data submission for each reader. By using the World Wide Web, ACRIN has made updated information available 24 hours a day.

7.2 Data Submission

7.2.1 Data will be collected on paper forms, and entered into the ACRIN database by personnel in the DMC. A validation system will check the record for accuracy and completeness. This validation system produces a log of errors that is sent to the DMC RA for resolution. This system is frequently updated to incorporate exceptions to rules so that subsequent, correctly entered data pass validity checks, minimizing the time the DMC RA needs to spend resolving problems. Once the data have been entered, they will be sent to the BC, where additional data review will take place. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in the data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC RA for resolution.

7.2.2 If the validation system and/or the BC detect missing or problematic data, the DMC RA will send a Request for Information (query letter) to the investigator (for queries on the Case Request and Submission form) or to the radiologist (for queries on either the Reader Experience form, the Software grading and preference forms or the tumor volume assessment form) specifying the problem and requesting clarification. The DMC RA then updates the reader's data submission calendar with the due date for the investigator's or reader's response.

7.3 Missing and Delinquent Data Submission

Due to the practical design of the study, delinquent data are not anticipated. However, the DMC will track form submission deadlines, and, if necessary, will contact readers and/or the RA at the central reading site to request submission of any overdue forms.

7.4 Data Quality Monitoring

7.4.1 The BC at Brown University will maintain a study database at its site for monitoring data quality. This analysis database will be maintained in permanent SAS (Statistical Analysis System software) format on the BC's ACRIN server. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

7.4.2 The BC, in conjunction with the DMC, will prepare a summary of the accrued data to be presented to investigators. This summary will assess the completeness and accuracy of the data, and discuss any trends that may impact the outcomes of the trial. Data Submission Institutions should keep copies of the MR imaging exams and the completed Case Request and Submission form. The RA at the central reading site should keep copies of all forms.

7.5.1 Submission of Case Material

Following notification by the BDMC, each institution will complete the Data Request form (LX Form, see Section 8.2), and prepare the requested case material for submission to the DMC. All attempts will be made to ensure patient confidentiality. No information will be provided that could reveal the identity of the patient. Prior to sending the hard copy MR imaging studies, all identifying information and headers will be scrubbed. The MR study and case numbers will be written on each tape. Each MR imaging exam will meet the minimum requirements as described in section 9.0. All image data will be in DICOM 3.0 format. Cases are to be submitted within three weeks of registration.

7.5.2 Completion of Reader Experience Form, Reader Training Form, Software Grading Form, Software Comparison Form, and Tumor Volume Assessment Form

Each participating reader is obliged to submit the Reader Experience Form (RX) with a current curriculum vitae (CV) attached within one week of receipt. The Reader Training Form (SP) must be filled out directly after the completion of training. One form must be filled out for each system.

7.5.3 Tumor Volume Assessment Forms

- E1 – One Month, Eigentool
- VI – One Month, 3DvVewnix-TV
- E3 – Three Month, Eigentool
- V3 – Three Month, 3DViewnix-TV

All the above forms need to be completed for each exam interpreted during the reader's session. ***Forms E1, VI, E3, and V3 are all the same data form but represent different time points.***

The Software Grading Form (SX) will have to be filled out once for each system by every reader. The Software Comparison Form (PX) needs to be filled out once by

each reader. The reader's obligations are completed when all data have been received and reviewed and no outstanding query exists for the reader.

7.5.4 Forms Submission

All data collection forms should be sent to:

American College of Radiology Imaging Network

ACRIN 6662

1101 Market Street, 14th Floor

Philadelphia, PA 19107

Fax: 215-717-0936

7.5.5 Image Submission

All MR imaging exams being submitted from HUP and HFH should be sent to the address noted above, labeled: ACRIN 6662 CASES. Data should be identified only by a study and case number. The time point at which the study was taken should be indicated (1 = first follow up exam postoperatively, 2 = second follow up exam postoperatively). Moreover, the study number assigned by the MR machine should be recorded. All identifying data should be scrubbed. The ACR will assign ACRIN case numbers to eligible cases once an MR imaging exam with two separate time points has been submitted. MR imaging exams for patients who will not be included in this study (e.g., errors in eligibility determination, surplus of submissions) will be returned to the submitting institution. All image data will be in DICOM 3.0 format. Cases are to be submitted within three weeks of registration.

8.0 DATA COLLECTION FORMS

8.1 Forms and Reports

The following forms will be used in the study. Unless otherwise noted, the forms are to be completed at ACRIN headquarters directly (electronically or on paper), although some may be completed on paper by the reader and checked at ACRIN headquarters for completeness and legibility. The RA reviews all forms at the time of completion for legibility and completeness, requesting any missing data elements before proceeding to other questionnaires.

8.1.1 RX Reader Experience Form

The Reader Experience Form documents the background of each reader. The form is to be completed at ACRIN headquarters prior to any training on either of the software packages.

8.1.2 *OX Reader Training Form*

The Reader Training Form documents the learning experience of each reader. The form is to be completed at ACRIN headquarters upon the completion of training. A separate form for each software system is to be completed.

8.1.3 *E1, V1, E3, V3 Tumor Volume Assessment Forms*

The Tumor Volume Assessment Forms assess the performance, ease of use and speed of each software package. The absolute tumor volume is also recorded. The form is to be completed at ACRIN during the time of each reading of each case. A separate form is to be completed for each case reviewed.

8.1.4 *SX Software Grading Form*

The SX Software Grading Form evaluates each software package at the time of a review session. The form is to be completed at ACRIN headquarters at the end of each day of image review.

8.1.5 *PX Software Comparison Form*

This form compares the two software packages. It is to be completed at ACRIN at the completion of the last day of the last reading session.

8.1.6 *LX Data Request Form*

This form documents the image data being requested/enrolled for protocol 6662 from each site. It is to be completed at the site, faxed to ACRIN headquarters for the assignment of case numbers and returned to the site via fax. The completed LX form is kept at the site and entered electronically into the ACRIN web site.

8.1.7 *IE, VX Image Pre-Registration Forms*

IE – Eigentool Registration Form

VX – 3Dviewnix-TV Registration Form

These forms document the time required for image pre-registration of the scans. Moreover, difficulties encountered during the image pre-registration process will be recorded.

These forms are to be completed by the pre-registering technologist at ACR headquarters. The completed forms are kept at ACR headquarters.

8.2 Data Collection Table

Forms		Timetable for submission
RX	Reader experience form. This form is to be submitted by each reader.	Submitted prior to training on either of the software packages.
QX	Reader Training form. This form documents reader training for each software package.	Completed at ACR at the time of each training session.
E1, V1, E3, V3	Tumor Volume Assessment forms. These forms capture software performance and ease of use.	Completed at ACR at the time of each image review session.
SX	Software Grading form. This form captures the subjective performance of each software package as perceived by the reader.	Completed at ACR at the time of each image review session.
PX	Software Comparison form. This form compares the 2 software packages.	Completed at ACR at the time of the last image review session.
LX	Data Request form. This form documents the cases obtained from each site.	Completed at the site and at ACR (ACR assigns case numbers).
IE, VX	Pre-registration forms. These forms documents the time needed for image pre-registration and potential difficulties encountered.	Completed by the technologist at ACR after image pre-registration.
C-1	Stratification form. This form documents a quality assessment of the images prior to reading and a grading of change in tumor volume and level of difficulty.	Completed by an advisory panel of three radiologists prior to stratification.

9.0 IMAGE ACQUISITION

All studies will include pre- and post-contrast T1 weighted, FLAIR, and T2 weighted MRI obtained in the axial plane. The image sets available will be restricted to cases that have at least 1 serial study. Stratification of the data will include cases with minimal changes in their tumor volume over 2 studies, cases with moderate changes, and cases with large changes of tumor volume.

Images will be obtained on 1.5 T MR systems. The standard protocol is to include axial imaging with short TR, short TE spin echo acquisitions, before and after Gadolinium administration, axial Fluid Attenuated Inversion Recovery (FLAIR), and axial long TR with long TE fast spin echo.

The following protocols will be employed:

HFH Tumor Volume Protocol
GE 1.5T system, using quadrature head coil
Localizer – Standard sagittal series

Axial Fast Spin Echo

- 2D, spin echo, Flow Compensation, Variable Bandwidth, Fast
- Echo Train Length = 8
- # echo = 2, TE1 = 22 ms, TE2 = 88 ms, TR = 3500 ms
- Bandwidth = 31.2 kHz
- FOV = 20 cm
- Slice Thickness = 3.0 mm, interleaved
- SAT = I
- Image Matrix = 256 x 192
- NEX = 2

Axial FLAIR

- 2D, Inversion Recovery, Variable Bandwidth, Fast
- TE = 145 ms, TR = 10000 ms, TI = 2200 ms
- Minimum number of acquisitions = 1
- Bandwidth = 32 kHz
- FOV 20 cm
- Slice Thickness = 3.0 mm, interleaved
- SAT = I
- Image Matrix = 256 x 192
- NEX = 2

Axial T1 - Pre-GD Injection

- 2D, spin echo
- # echo = 1, TE = Minimum Full, TR = 500 ms
- FOV 20 cm
- Slice Thickness = 3.0 mm, interleaved
- SAT = I
- Image Matrix = 256 x 192
- NEX = 2

Axial T1 - Post GD Injection

Same as Above Pre-Gd Axial T1

HUP protocol:

GE Signa 1.5T system

quadrature head coil

imaging parameters:

Axial T1-weighted:

TR 400-717, TE 8, NEX 1

without and with Gadolinium at a dose of 0.1mmol/Kg;

FLAIR:

TR 10000, TE 133-145, NEX 1;

FOV: 22cms;

Matrix size: 256 x 192 ; rest as above

Stratification of data will be done both regarding changes in tumor volume and regarding difficulty of cases. Consecutive cases will be provided by the sites (three times the cases needed, i.e. $(24+5) \times 3 = 87$ cases). These cases will be reviewed and graded by an advisory panel of three radiologists. Three strata of eight cases will be selected to be included in the study.

In addition to assessing the software systems, the readers will also do a manual estimate of the tumor volume. They will identify the cross sectional image with the largest linear tumor dimensions on the FLAIR and on the contrast enhanced short TR, short TE images for each case. The tumor dimensions will be measured in the orthogonal directions that produce the largest measures. The number of sections on which the tumor is identified will be measured, and the section spacing will be multiplied by this number. This method will produce an estimate of the maximal tumor dimension in three directions. Inter- and intra-rater reliability of these measurements will be determined and compared to the estimates provided by the two software systems.

10.0 IMAGE INTERPRETATION

10.1 Processing of Image Data

All images will be registered using 3DVIEWNIX-TV or Eigentool before further analysis is performed. After registration, volumetrics will be performed using the routine protocols for Eigentool and 3DVIEWNIX-TV. For volumetrics with Eigentool, registration of all images is required. For volumetrics with 3DVIEWNIX-TV, registration of only the pre- and post-contrast T1 images and axial FLAIR images is necessary. Since registration is largely operator independent, pre-registration will be performed by a technologist prior to image analysis in order to reduce reading time. Several registration algorithms are available for use in this project [17-21]. The Eigentool software package has several methods incorporated to provide the registration, or other registration software can be “called” and used by the Eigentool software (e.g. AIR 3.0). The registration methods used by the UPenn approach have been published. These are methods based on correlation of image intensities and maximization of mutual information. They have been shown to provide subpixel accuracies in brain image registration. Separate studies conducted to evaluate these methods for registering brain MRI have come to similar conclusions [20]. The

advisory panel will review all data sets and at that time the requirement for registration will be noted. The registration method will be done prior to the data being put into the trial. Therefore any effects the registration method has on the volume determination will be similar to acquisition variables.

No changes in the software systems will be allowed after the opening of the study.

10.2 Image Processing Details with 3DVIEWNIX-TV

All images are processed on a 600 MHz Pentium PC utilizing the 3DVIEWNIX-TV software system. Processing consists of the following steps for each data set.

10.2.1 Step 1: MRI Intensity Standardization

Inter-case and intra-case scanner-dependent MR image intensity variations cause considerable difficulties in MR image segmentation and analysis. To mitigate this problem, an intensity standardization method is applied to the acquired image data [17; 18]. This method maps the input intensities into intensities on a standard scale, so that the mapped intensities in images acquired as per the same protocol for the same body region will have the same tissue meaning independent of the scanner and the patient. The map is achieved by deforming the histogram of the volume image to match as best as possible a standard histogram for that protocol and body region. It has been proven in previous work that this transformation, when performed properly, retains the relationship of the intensities in the input image and never merges distinct input intensities into a single intensity. All images acquired for each of the protocols mentioned above—non contrast short TR, short TE (T1), post-contrast short TR, short TE (T1e) and FLAIR—are independently transformed so that the images within the same protocol have the same tissue-specific intensity meaning.

From this point on, the processing steps for the FLAIR images are different from those for T1 and T1e images. For further reference, we will use the following notation: I_F - the standardized FLAIR volume image; I_{T1} - the standardized T1 volume image; I_{T1e1} - the standardized T1e volume image for the first axial acquisition.

10.2.2 Step 2: Segmentation of FLAIR Images

On one slice of I_F , an operator indicates a rectangular box large enough to completely enclose the tumor and edema volume to be segmented. This is not an attempt to trace the borders of the lesion, but it simply serves to limit the 3D region in which the

subsequent analyses are performed. The range of the slices in I_F covering the tumor is also specified. In this fashion, a rectangular box is specified in 3D within I_F . All subsequent operations are confined to the part of the volume image within this box. This restriction is not necessary for the method to work, but by limiting the region to be analyzed, processing time is reduced considerably. The region of high signal on FLAIR images includes both tumor and edema, and these cannot be distinguished on the FLAIR images. For the purposes of this study, we refer to the region of abnormal high signal on the FLAIR images as the “FLAIR volume.” Next, seed points are specified within the tissue of interest. Although typically one point is sufficient, we specify several points sprinkled in different slices so that even weakly connected parts of the tumor are detected. At this time, the tumor is delineated in 3D as a fuzzily connected 3D object containing the specified points automatically in a few seconds. The system then displays the delineated tumor region as a colored overlay over I_F in a slice-by-slice fashion for operator verification. Any extraneous segments, such as scalp or orbital enhancement, which are occasionally picked up if the tumor is close to these areas, are deleted interactively. False negative regions rarely occur. At the end of the process, the volume of the fuzzy connected object is reported as the FLAIR volume.

Step 2 can be completed in approximately 2 minutes, including editing.

10.2.3 *Step 3: Segmentation of Enhancing Tumor*

To enable distinguishing hemorrhage from enhancing tumor, I_{T1e1} is first registered with I_{T1} using an intensity correlation method implemented in 3DVIEWSNIX-TV [19] that has been demonstrated to have an accuracy of up to a voxel. The registered I_{T1e1} is then re-digitized via interpolation to obtain slices that match with those in I_{T1} . This results in new volume images I'_{T1e1} . The difference image $I'_{T1e1} - I_{T1}$ is then computed.

The procedure described in Step 2 above is repeated on this difference image to compute the enhancing tumor volume. The enhancing tissue includes viable tumor, reactive inflammatory changes and variable amounts of necrosis. We refer to the region of abnormal signal as “enhancing volume.”

For segmentation in Steps 2 and 3, the values of the parameters of the affinity relation for the fuzzy connectedness algorithm were determined via the training facility available in 3DVIEWNIX-TV. Training is done by painting the tumor and edema regions on one slice in one patient study using a “paint brush” attached to the mouse cursor. The required parametric values were then estimated automatically and fixed for all subsequent studies. To ensure that the standardized intensities in T1 and T1e images are on the same scales, which is a prerequisite for subtraction, they are standardized, treating them within the same group as if coming from the same protocol.

Subjectivity in this system for volume estimation stems from the required operator interaction in segmentation.

10.3 Image Analysis Details with the Eigentool Software

All images are processed using a SUN SPARC Workstation running Solaris 2.7 or above using the Eigentool software package. Processing consists of the following steps for each data set.

10.3.1 Step 1: Registration

The eigenimage filter is a linear transformation that uses the contrast differences in all images acquired to segment tissues. Therefore, the 2-dimensional axial images for all acquisitions must be registered prior to any processing. The registration is required only if movement occurs between acquisition of each sequence. Therefore, the time required can be reduced by determining the minimum number of sequences to register. The determination of the sequences to register is done by loading one location for all sequences into Eigentool. The image sequences used at HFH are pre- and post-Gd T1 weighted spin echo images, FLAIR, and long TE T2 weighted images. By scrolling or looping through the sequences those that require registration can be found.

In most studies the post-Gd T1 weighted image must be registered with the other sequences. In some studies, approximately 20% at HFH, the Flair and T2 weighted images must also be registered. The registration is accomplished by loading all locations from one sequence to use a basis set into Eigentool. Contours of the outer surface of the skin are created by selecting a gray level range for the image background

and placing a seed point outside the head in the background. A multiresolution algorithm then determines the skin contour automatically from the seed point. For some locations the seed point or gray level range may need to be redefined to create the contour. The contours do not have to be exact, and minimal operator interaction is required to create acceptable contours. Once the contour is created on the basis sequence, the procedure is repeated on the sequences to register. During the registration all locations that contain the lesion should be noted, so further processing is done only on these locations to reduce the total processing time. Since registration is largely operator independent, pre-registration will be performed by a technologist prior to image analysis in order to reduce reading time.

10.3.2 Step 2: Noise Suppression

To enhance the performance of any segmentation routine, additive noise should be reduced. Eigentool uses an adaptive filter to reduce noise while maintaining partial volume information. The adaptive filtering is performed by loading one location for all sequences into Eigentool. Note that the sequences must be registered before applying the adaptive filter. After the images for one location are loaded, the standard deviation from a region of interest (ROI) of white matter within the brain is found. The ROI can be a simple box drawn on one of the images. The standard deviation is used to specify the amount of noise suppression and preservation of partial volume information that is to be done. For the sequences acquired at HFH, two times the standard deviation is used. This value may need to be changed if other acquisition sequences or variations in the number of image sequences used changes. Once the filter has performed noise suppression on the initial location it can be automatically run without any operator interaction (i.e. in the background of the computer processor) on all locations that contain the lesion by selecting the repeat function in Eigentool.

10.3.3 Step 3: Segmentation

To segment the FLAIR and Gd components of the lesion, one location for each of the sequences following noise suppression is loaded into Eigentool. The location selected should include both Gd enhancement and FLAIR hyper-intensity visible in the images. The eigenimage filter is run by the operator's selecting points within all known tissue or features. The term feature will be used since the Gd enhancement and FLAIR hyper-intensity may not be considered a tissue but can be considered a trait or feature of the

acquisition. The features that must be defined are white matter, gray matter, cerebrospinal fluid (CSF), Gd enhancement, and FLAIR hyper-intensity. A feature is defined by selecting a point within each tissue (i.e. feature) from the images displayed. Once these points are selected the filter will create a separate image segmenting each feature. If the points selected for two or more features are similar, the segmented images may appear noisy. This can occur when points contain substantial amount of partial volume averaging of tissues so the contrast between features is reduced. In this case, new points must be selected for these features. Once the segmented images appear acceptable, the segmentation is run on all locations that contain the lesion by selecting the repeat function in Eigentool. The repeat function is run in the computer background, so no operator interaction is required. In addition to the segmentation of the features selected by the operator, an additional segmentation can be performed that will display all voxels that contain tissues or features that were not selected by the operator. This image is termed an orthogonal image. In the orthogonal image, any tissue not selected by the operator (e.g. fat, skin and other extracranial tissues) will be displayed. This may include other intra-cranial features as well as possible lesion components. This image is not required, and any tissue segmented by this image will not be included in the volume analysis.

10.3.4 Step 4: Volume Determination

The images created by the eigenimage filter may include some tissue/feature that was not selected by the operator. As mentioned above, these pixels may be displayed in the orthogonal image if it is created, but these pixels must not be included in the volume determination. In order to limit the volume determination to the Gd enhancement and FLAIR hyper-intensity, a volume of interest (VOI) is determined that includes only these features on each segmented image.

This is done by loading the segmented feature image for all locations into Eigentool. Then a ROI is selected inside the normal tissue area away from the feature segmented. The mean and standard deviation from this ROI is used to determine a threshold value that will exclude the normal tissue. For the sequences acquired at HFH, a threshold value of three standard deviations above the mean is used. Note that the normal tissue will appear black, i.e. with a zero value, in the segmented image. This determination of

the threshold value and creation of the volume ROI (i.e. VOI) is done automatically. Once the VOI is created, the operator must decide if any pixels should be removed based on features being included that are not the feature segmented. This decision can be assisted using the orthogonal image if it was created. This procedure is performed on the images segmenting the Gd enhancement and then on the FLAIR segmented images. Once a VOI for each feature on all locations is created, the volume for each feature and the overlapping pixels, i.e. partial volume pixels, between features is determined automatically. In most cases the FLAIR and Gd enhancement overlap and therefore this partial volume is computed separately. The operator can add this overlap volume to either feature, divide it between features, or keep it as a separate volume.

10.4 Linear Measurement Comparison

HUP and HFH data will be analyzed also with a simple method in common use in brain tumor studies. For each lesion, each reader will identify the cross sectional image with the largest linear tumor dimensions on the FLAIR and on the contrast enhanced short TR, short TE images. The tumor dimensions will be measured in the orthogonal directions that produce the largest measures. The number of sections on which the tumor is identified will be measured, and the section spacing will be multiplied by this number. Thus, this method will produce estimates of the maximal tumor dimension in three directions. For measurement in instances in which the tumor appears discontinuous, the largest dimension will be employed, including areas of necrosis or resection cavity. Thus, this method will overestimate the residual or recurrent tumor when there are intervening regions of non-neoplastic tissue. Although this is a limited method, it has the advantage of simplicity. The reproducibility may be compromised by subjectivity in selection of the dimensions to measure, as well as in determination of the tumor boundaries. Inter- and intra-rater reliability of these manual measurements and the calculated volume estimates will be determined. Volume estimates of the software systems will be compared to these manual volume approximations. However, since a large inter- and intra-rater variability is expected, these measurements will not be used as a gold standard.

10.5 Performance Site Training

All analyses will be conducted at ACRIN in Philadelphia. An ACRIN representative (Anthony Levering) will be trained on both Eigentool and 3DVIEWNIX-TV. Mr.

Levering will then train the readers in both techniques. Each reader will come to Philadelphia both for training and for image analysis.

10.6 Criteria For Adequate Performance

In order to enter the data generation phase of the study, each reader will have to complete five training cases with Eigentool and 3DVIEWSNIX-TV with adequate accuracy. For the purposes of training only, accuracy will be defined with the gold standard of the mean tumor volume produced from measurement with that technique at the source site. Therefore, HFH will measure the HFH data with Eigentool, while HUP will assess the HUP data with 3DVIEWSNIX-TV.

In order to control for the learning curve, the reading order will be reversed between readers. Moreover, readers will reread training cases after the reading.

10.7 Reader Population

Three different reader populations will be studied: Radiology Technologists with at least three years experience in MRI, neuroradiologists in training (ABR certified fellows in neuroradiology), and staff neuroradiologists. At least four members of each group will participate in the reader study. In the subgroup of technologists, eight readers will be included. Readers will be solicited by invitation to candidate readers at local radiology departments (Philadelphia area). The first 4 readers to respond positively in each category will be chosen for the study. The qualifications for each reader group are described below.

10.7.1 Technologists

Technologists must be certified by the American Board of Radiology Technologists. They must have at least three years of experience working with MR imaging.

10.7.2 Neuroradiologists in training

Neuroradiology fellows must be certified by the American Board of Radiology and currently be enrolled in an accredited neuroradiology fellowship.

10.7.3 Neuroradiologists

Staff neuroradiologists must be certified by the American Board of Radiology and hold a Certificate of Added Qualification in neuroradiology.

10.7.4 Case Distribution

Each reader will read 24 cases, including one interval study per case, on each system. It is estimated that the reading time will be approximately 2 ½ days for each system.

11.0 STATISTICAL CONSIDERATIONS

REMOVED FROM WEB VERSION

REFERENCES

1. Landis SH, Murray T, Bolden S, et al: Cancer statistics, 1998. *Ca-A Cancer Journal for Clinicians* 48:6-29, 1998.
2. Ries LAG, Hankey BF, Miller BA et al: Cancer statistics review 1973-88. National Cancer Institute. NIH Pub No. 91-2789, 1991, I.31 VI. 4.
3. Curran WJ, Scott CB, Horton J, et al: Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst* 85:704-710, 1993.
4. Walker MD, Alexander E Jr, Hunt WE, MacCarty CS, Mahaley MS Jr, Norrell HA, et al: Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. *J. Neurosurg.* 333-343, 1978.
5. Walker MD, Green SB, Byar DP et al: Randomized comparison of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery *N Engl J Med* 303:1323-1329, 1980.
6. Fine H.A., Dear B.G., Loeffler, J.S., et al: Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 71:2285-97, 1993.
7. Taphoorn MJ, Potman RA, Barkhof F, Weerts JG, Valk J, Karim AB, Heimans JJ. Quantitative computer-assisted analysis vs. visual estimation of MR imaging response of brain metastases to radiotherapy. *Magn Reson Imaging.* 1997;15(1):99-106.
8. Peck DJ, Windham JP, Soltanian-Zadeh H, Roebuck JR. A fast and accurate algorithm for volume determination in MRI. *Med Phys* 1992; 19(3):599-605.
9. Peck DJ, Windham JP, Emery LL, Soltanian-Zadeh H, Hearshen DO, Mikkelsen T. Cerebral tumor volume calculations using planimetric and eigenimage analysis. *Med Phys* 1996; 23(12):2035-2042.
10. Jacobs MA, Knight RA, Windham JP, Zhang ZG, Soltanian-Zadeh H, Goussev AV, Peck DJ, Chopp M. Identification of cerebral ischemic lesions in rat using Eigenimage filtered magnetic resonance imaging. *Brain Res* 1999; 837 (1-2):83-94.

11. Udupa, J.K. Odhner, D., Samarasekera, S., Goncalves, R., Iyer, K., Venugopal, K., and Furuie, S.: 3DVIEWNIX: An open, transportable, multidimensional, multimodality, multiparametric imaging software system, SPIE Proceedings, 2164:58-73, 1994.
12. Udupa, J.K., Samarasekera, S., Fuzzy connectedness and object definition: Theory, algorithms, and applications in image segmentation, Graphical Models and Image Processing, 58(3):246- 261, 1996.
13. Udupa, J.K., Wei, L., Samarasekera, S., Miki, Y., van Buchem, M.A., Grossman, R.I.: Multiple sclerosis lesion quantification using fuzzy connectedness principles, IEEE Transactions on Medical Imaging, 16(5):598-609, 1997.
14. Liu, J.-G., Udupa, J.K., Hackney, D., Moonis, G.: Brain tumor segmentation in MRI using fuzzy connectedness method, SPIE Proceedings, 4322:1455-1465, 2001.
15. Vaidyanathan M, Clarke LP, Velthuizen RP, Phuphanich S, Bensaid AM, Hall LO, Bezdek JC, Greenberg H, Trotti A, Silbiger M. Comparison of supervised MRI segmentation methods for tumor volume determination during therapy. Magn Reson Imaging 1995; 13(5):719-728.
16. Fleiss JL. Measuring agreement between two judges on the presence or absence of a trait. Biometrics. 1976; 31 (3):651-659.
17. Chen, G. T., Pelizzari, C. A., and Levin, D. N. Image correlation in oncology, Important Advances in Oncology 131-41, 1990.
18. Pelizzari, C. A. Image processing in stereotactic planning: volume visualization and image registration, Medical Dosimetry. 23: 137-45, 1998.
19. Woods, R. P., Grafton, S. T., Holmes, C. J., Cherry, S. R., and Mazziotta, J. C. Automated image registration: I. General methods and intrasubject, intramodality validation, Journal of Computer Assisted Tomography. 22: 139-52, 1998.
20. Nyul, L.G., Udupa, J.K., Saha, P.K., Task-specific comparison of 3D image registration methods. SPIE Proceedings, 4322: 237-243, 2001.
21. Woods, R. P., Grafton, S. T., Watson, J. D., Sicotte, N. L., and Mazziotta, J. C. Automated image registration: II. Intersubject validation of linear and

nonlinear models, *Journal of Computer Assisted Tomography*. 22: 153-65, 1998.

22. Nyul, L.G., Udupa J.K., On standardizing the MR image intensity scale. *Magnetic Resonance in Medicine*, 42: 1072-1081, 1999.
23. Nyul, L.G., Udupa J.K., Zhang, X., New variants of a method of MRI scale Standardization. *IEEE Trans Medical Imaging*, 19(2): 143-150, 2000.

APPENDIX I

ACRIN 6662

Sample Letter For IRB Permission

To Whom It May Concern:

I would like permission to share _____ MRI images of glioblastoma, anaplastic astrocytoma, or anaplastic oligodendrogliomas (WHO grade III or IV) with the American College of Radiology Imaging Network (ACRIN). Patient identifiers will either be removed from the images before they are sent to ACRIN, or ACRIN will scrub all patient identifiers from the data set prior to image review to ensure patient confidentiality.

Principal Investigator's Signature: _____ Date: _____