Institutional review board statement

Nineteen patients were enrolled in the institutional review board (IRB) of the Memorial Sloan-Kettering Cancer Center, New York, NY protocol titled "Dynamic Contrast Enhanced MRI and Magnetic Resonance Spectroscopy of Head and Neck Tumors" (IRB No. 06-007).

Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#: 06-007A(2)

Dynamic Contrast Enhanced MRI (DCE-MRI) and Magnetic Resonance Spectroscopy (MRS) of Head and Neck Tumors

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator: Amita Dave, PhD

Co-Principal Investigator(s): Jason A. Koutcher, MD, PhD

Investigator(s):
Nancy Lee, MD
Hilda Stambuk, MD
David Pfister, MD
Jatin Shah, MD
Dennis Kraus, MD
Ashok Shaha, MD
Richard Wong, MD
Sasan Karimi, MD
Bhuvanesh Singh, MD
Snehal Patel, MD
Howard Thaler, PhD
Diane Carlson, MD

Consenting Professional(s):
Jatin Shah, MD
Dennis Kraus, MD
Ashok Shaha, MD
Richard Wong, MD
Bhuvanesh Singh, MD
Snehal Patel, MD
Nancy Lee, MD
David Pfister, MD
Hilda Stambuk, MD
Sasan Karimi, MD
Maayan Korenblit, BS
Amita Dave, PhD
Jason A. Koutcher, MD, PhD

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

Memorial Sloan-Kettering Cancer Center
1275 York Ave.
New York, NY 10021

Amended: 12/12/06

IRB PB

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Our aim is to perform pretreatment dynamic contrast enhanced – magnetic resonance imaging (DCE-MRI) and proton magnetic resonance spectroscopy (^{1}H-MRS) on 200 patients with head and neck cancer eligible for surgery or chemo-radiation treatment. The pretreatment DCE-MRI and ^{1}H-MRS exam will add about 20 minutes of scanning time to the routine MRI study with contrast agent performed at MSKCC. Patients undergoing chemo-radiation will also have an additional followup DCE-MRI and ^{1}H-MRS exam between 10-14 days into the course of treatment. The followup DCE-MRI and ^{1}H-MRS exam will be about 30-35 minutes (the DCE-MRI images will take about 10 minutes, the ^{1}H-MRS images about 10 minutes and setup on the MRI table will require 10-15 minutes).

The DCE-MRI data will provide insight into the tumor pathophysiology. With proper compartmental modelling, the data will yield results on tumor-vessel permeability, tumor perfusion, and extracellular-extravascular volume fraction, i.e. data relating to the tumor microenvironment. In addition, MR spectroscopy data show the metabolic signature of the tumor and an elevated choline level (resulting from the enhanced phospholipid cell membrane turnover associated with tumor proliferation, increased cellularity, and growth) which may serve as an indicator of active tumor and a decrease in choline may reflect tumor response. These results will determine the potential of DCE-MRI and ^{1}H-MRS data as a priori or early markers of tumor response to chemo-radiation as well as long term disease-free survival after surgery or chemo-radiation therapy. The a priori DCE-MRI and ^{1}H-MRS data may ultimately help physicians in selecting patient specific therapy.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

The main objective of the study is to identify a priori prognostic markers for head and neck cancer patients using DCE-MRI and ^{1}H-MRS data, which may help in stratifying patients into "good risk" and "poor risk" categories to improve outcome and quality of life. The scientific aims are as follows:

1) To assess whether a priori or early dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) and proton magnetic resonance spectroscopy (^{1}H-MRS) changes can reliably predict early chemo-radiation clinical response (before apparent tumor regression) and/or long term disease-free survival in patients with head and neck cancer undergoing either chemo-radiation therapy (subset 1) or surgery (subset 2).

2) To determine if the a-priori DCE-MRI and ^{1}H-MRS results provide independent markers of tumor response and/or long term disease-free survival compared to clinical prognosticators.

3.0 BACKGROUND AND RATIONALE

Head and neck cancer is the sixth most common malignancy worldwide, with an anticipated yearly incidence of about 400,000 (1,2) and the survival rate of such patients has remained relatively unchanged over the past decade (3). Surgery is the historic corner stone of curative treatment, but may result in major functional loss and dysfunction. In an effort to improve the probability of disease control without surgery, chemotherapy has been incorporated with radiation therapy (XRT) into the initial nonsurgical management of newly diagnosed cases. A cisplatin or carboplatin based chemotherapy program is most commonly employed with XRT to treat head and neck cancers (4-9). Randomized trials have evaluated alternative treatments, among them chemotherapy before XRT (i.e. induction chemotherapy), chemotherapy concurrent with XRT, and altered fractionation XRT (10-14). Today, with many treatment options available, an early or a priori predictor of response is essential to allow the oncologist to intervene and modify the treatment plan if the chosen one is likely to fail. Similarly, in untreated patients to be managed by planned aggressive surgical resection, it would be important to know prior to surgery whether they could be spared a major and potentially debilitating procedure, or whether they might benefit from some alternative experimental therapy due to a high risk of failure. Reported tumor-based clinical prognostic factors for locoregional tumor control include the presence and extent of nodal metastases, T-stage, tumor site, total tumor volume, and tumor size (15-19). Despite the multiplicity of prognostic factors, considerable variance in outcome remains unexplained.

The relationship between microvascular blood flow, pO2, and radio- or chemo-resistance is of considerable interest (20,21), and DCE-MRI may provide a simple, readily available tool for probing the tumor microenvironment and possibly hypoxia and relate them to outcome. Several recent studies by Dewhirst et al. (22), Berezcki et al. (23) and others (24-31) have suggested that DCE-MRI data (i) are correlated with pO2 measured by Eppendorf probes, (ii) may predict rectal tumor response to treatment, and (iii) may be used to evaluate angiogenesis in carcinomas.

DCE-MRI data in tumors will evaluate the hypothesis that poorer perfusion is a marker for poor outcome. DCE-MRI has shown the ability to correlate with treatment outcome and provides data related to tumor cell hypoxia, perfusion and permeability (20,25,26,28,29,32-34). A study by DeVries et al (28) suggests that pre-treatment noninvasive perfusion index (PI) measurements by dynamic MRI are predictive of chemoradiation therapy outcome in rectal cancer patients. When the patients were grouped by treatment outcome, therapy responders showed a significantly lower mean PI value than nonresponders. Cooper et al (24) studied 30 patients with carcinoma of the cervix by performing pO2 histograph and DCE-MRI before and after (n=9 patients) treatment with external beam radiotherapy. Using these measurements, the data revealed a significant correlation between maximum enhancement over baseline obtained from the DCE-MRI time/signal intensity curve, and tumor oxygenation, as measured by the pO2 histograph. The study emphasized that DCE-MRI may be a method for measuring hypoxia in human tumors, although spatial correlation of pO2 and DCE-MRI was not demonstrated.

Hypoxia as a prognostic marker of outcome in HN cancers has shown its promises as well as challenges. The reference standard for measurement of hypoxia has been the Eppendorf electrode method due to its known correlation with outcome (35,36). However, it is not without problems and the most problematic factor is that it cannot distinguish between tumor tissue and necrosis, which can bias the relevant oxygenation values to spuriously low levels in tumors with extensive necrosis. Because of these problems with the Eppendorf electrode, there are a number of ongoing efforts to find alternative methods of estimating tumor oxygenation. The main candidates that have been used clinically over the past few years are nitroimidazole hypoxia markers (37,38) which can be imaged by PET (positron imaging tomography). However, PET imaging requires radioisotope, which is produced by a cyclotron. This would require in-house availability of both technologies, PET and cyclotron, which is not available in many centers. The above data, and the theoretical study of Wang et al using DCE-MRI (20), suggest that DCE-MRI, may also provide a qualitative measure of hypoxia which could correlate with treatment and outcome.

DCE-MRI has been applied to many clinical problems including detecting/diagnosing breast tumors and evaluating response to treatment (39-41). Knopp et al (25) studied 27 patients with breast lesions by dynamic MRI and compared the data to histologic analysis of the breast tissue. The data showed that the exchange rates from the dynamic MRI were significantly faster in malignant vs benign breast lesions. Among the malignant breast lesions, differences in vascularization between histologic types were demonstrated by dynamic MRI showing a more rapid enhancement and elimination of the contrast agent in invasive ductal carcinoma (IDC) than invasive lobular carcinoma (ILC). The authors suggest that DCE-MRI can potentially be used as a non-invasive prognostic tool analogous to VEGF expression and microvessel count.

Hawighorst et al (30) examined the relationship between DCE-MRI derived characteristics and histological microvessel density counts, a recognized surrogate of tumor angiogenesis, from primary or recurrent cancers of the uterine cervix. The data revealed that pharmacokinetic MRI-derived parameters increased with increasing histological microvessel density counts. Another study by the same group (29) compared histomorphological markers of tumor angiogenesis with dynamic MRI-derived pharmacokinetic analysis in 37 patients with biopsy-proven primary cervical cancer. The results suggested that DCE-MRI approach maybe better suited to assess angiogenesis activity in terms of patient survival than the current histomorphological-based markers of tumor angiogenesis.

Shapeero et al (31) discuss the role and limitations of different imaging modalities for evaluating the chemotherapy response in high-grade osteosarcoma and Ewing sarcoma. They summarized the role of DCE-MRI as “the most effective imaging modality for differentiating viable tumor from nonviable tumor, necrosis, and inflammation in these bone sarcomas, and thereby the poor responder from the good responder to chemotherapy”. Dyke et al from our group have also demonstrated a relationship between DCE-MRI data and tumor necrosis and angiogenesis (42,43). NCI (National Cancer Institute) workshop title “Expanding the use of MR in the assessment of tumor response to therapy” reported by Evelhoch et al (39), emphasized the utility

of DCE-MRI and consensus recommendations were made for standardizing DCE-MRI methodologies for studying tumor response. The National Cancer Institute (NCI) has included DCE-MRI study in protocols involved in evaluating new anti-angiogenic drugs in human trials. A MSKCC IRB protocol number 03-138, title "An Open Label, Long-Term, Safety and Tolerability Study of VEGF Trap Administered Intravenously in Patients with Advanced Solid Tumors or Lymphoma" is using DCE-MRI to correlate DCE-MRI changes with clinical response and to assess tumor blood flow and vascular permeability. The Co-PI in this study is a co-investigator in the above-mentioned protocol.

Our preliminary DCE-MRI data on 14 HNSCC patients with nodal disease was fit by linear regression to determine initial slope as well as analyzed with a two compartmental fit for the rate constants by software previously written (42). Follow up of HNSCC patients was done radiologically based on response at 3-6 months after the end of treatment; patients were grouped as complete responders (CR, no evidence of disease), partial responders (PR, 50% or greater response to treatment), or non-responders (NR, failed treatment). The data showed a rapid rise in the characteristic time intensity curves for the tumor that appeared viable whereas the necrotic area showed minimal signal change. For the whole tumor, the mean Ak_{ep} value was higher for complete responders (n = 7) than incomplete responders (partial responders plus nonresponders, n = 7) (12.29/min±4.09 vs 7.11/min±2.51) [P = 0.04]. The histogram analysis for the slope showed that the width and median were able to differentiate between complete responders versus the partial and non-responders, P=0.039 and P=0.013 respectively. The follow-up response data for these patients are being updated.

So far, few studies have described the characteristic enhanced patterns of tumors with DCE-MRI in the oral region (32,33). Konouchi et al have studied 30 patients with primary oral cavity and oropharyngeal squamous cell cancer with DCE-MRI and correlated the findings with PCNA (proliferating cell nuclear antigen) (32). They have calculated the signal intensity (SI) (as opposed to concentration) of a region of interest (ROI) from the mean pixel value on each acquired dynamic image. The contrast index (CI) was calculated from the equation: $CI(t)=SI(t)(\text{post-contrast})-SI_0(\text{pre-contrast})/SI_0(\text{pre-contrast})$. The time versus CI curve was obtained by plotting the CI on a time course. They evaluated the maximum CI and the maximum CI gain for the dynamic MRI parameters. The CI gain presumably indicates the maximum gradient on the upslope phase of the enhancement curve. The maximum CI presumably represent the maximum amplitude of enhancement. The CI gain indicates the difference in the CI between the 2 consecutive images. The time CI curves in all cases showed a rapid and high uptake pattern. The PCNA labeling index showed a significant correlation with maximum CI and maximum CI gain ($P<0.0001$, $r=0.866$ and $P=0.0019$, $r=0.544$, respectively). Hoskin et al found in 13 patients with advanced head and neck cancer that tumors with diminished tumor perfusion at the end of radiotherapy are those most sensitive to treatment and that tumors which show greater tumor enhancement after accelerated radiotherapy are likely to fail locally (33). This may reflect the persistence of viable perfused tumor at completion of radiotherapy. Nevertheless, DCE-MRI studies in head and neck cancers need to be confirmed in larger prospective trials. Most importantly, previous studies did not correlate the pretreatment contrast

enhancement index with long term disease-free survival and secondly they did not perform a quantitative analysis.

There are two approaches to analyzing the data which include a quantitative modelling approach (44-47) and semiquantitative analyses (29,34,40,41,48-50). Parametric maps of the tumor can be obtained from these data which provide spatial information about physiologic parameters that can be calculated from the Gd-DTPA uptake data. DCE-MRI studies may also provide insight into underlying mechanisms and physiology that induce differences in tumor contrast uptake. In the quantitative methodology, accurate T1 (longitudinal relaxation time) values are critical for precise quantitation of Gd-DTPA (51,52). Semi-quantitative analyses are based on measuring changes in signal intensity (as opposed to concentration) and are not related to physiologic parameters, although it is important to note that they do provide clinically useful data (34,40).

There has been much interest recently in tumor hypoxia and tumor proliferation as prognostic indicators in human tumors. ^{1}H-MRS studies of brain tumors have shown elevated choline-containing compounds likely reflecting an elevated cell proliferation rate, low Nacetylaspartate and the presence of lactate or lipids (53-55), and have related decrease in choline metabolite to tumor response (56-59). Our studies in prostate cancer using proton 3D MR spectroscopic imaging (MRSI) have shown that MRSI is a predictor of tumor aggressiveness based on the Choline+Creatine/Citrate ratio, and that MRSI detection of cancer is related to tumor grade and volume (60). A study exhibited the significant role of a priori MRSI in predicting treatment outcome, especially in high risk prostate cancer patients treated with neo-adjuvant chemo-hormonal therapy as part of a clinical trial (61). *In vitro* 1D and 2D -1H MRS studies have been correlated with clinical studies in HNSCC (62-67). These studies and a recent study by Bisdas et al (68) have shown that the Cho/Cr ratio was elevated in the lymph node metastases of HNSCC. Our preliminary proton decoupled phosphorus MRSI study of HN cancers showed that the pretreatment PME/NTP metabolic ratio was able to differentiate between complete responders and not complete responders before the onset of therapy (69). Similar results have been published in Non-Hodgkin's Lymphoma (70). Our recent bone sarcoma study showed that pretreatment NTP/Pi was significant (P=0.003) in differentiating event-free survivors from those who died (71). Thus metabolic data has been linked with outcome.

In patients with head and neck cancer, early identification of patients likely to respond, or not to respond, to a specific treatment, would allow physicians to optimally match patients to a treatment approach and/or alter the treatment plan and thus avoid the morbidity and added costs of ineffective therapy. The anatomic location of these tumors, frequent superficial regional node involvement, and the availability of alternative treatment options with differing associated morbidities for a given clinical scenario, make this an ideal tumor for study by using DCE-MRI as a potential early predictor of outcome. The results of this study could have a direct clinical impact in addition to providing new scientific data. Additionally, the study will help to better identify patients whose cancers can be treated with standard therapies and be spared aggressive therapies; this would have major benefits for these patients' quality of life and would also benefit

society by decreasing the overall cost of treatment and the burden of treatment-induced morbidity.

Summary: If these studies are successful, they will provide a non-invasive early predictor of tumor response and/or long-term disease-free survival, which could allow for patient specific treatment.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Patients will undergo DCE-MRI and ^{1}H-MRS study prior to surgery or prior to chemo-radiation treatment. Those patients undergoing chemo-radiation therapy will have a second study 10-14 days after starting chemo-radiation. Due to side effects from chemo-radiation, some patients feel poorly and, in our experience, are at times unable to undergo the second study. We will contact the patient after start of chemo-radiation and if the patient is willing, the second study will be performed. The amount of time needed to complete the DCE-MRI part of the study will be about 10 minutes and for the ^{1}H-MRS part of the study, about 10 minutes. These studies are designed to determine if the DCE-MRI and ^{1}H-MRS data will provide an a priori or early prognostic marker of tumor response and/or long term disease-free survival. These data will be compared with clinical markers (presence and extent of nodal metastases, primary disease site, primary disease size (length and volume), stage). Data from the baseline study will be evaluated to see whether it is an a priori predictor of long-term disease-free survival. The 10-14 day study will be examined independently and together with the baseline study to determine response to treatment.

4.2 Intervention

After informed consent, patients will undergo DCE-MRI and ^{1}H-MRS as part of their initial staging prior to surgery or chemo-radiation therapy. Baseline MRI from outside institutions includes routine MRI sequences used for diagnostic purposes and does not include additional DCE-MRI and ^{1}H-MRS sequences. If a patient has an adequate baseline MRI from outside, then only the DCE-MRI and ^{1}H-MRS parts will be done here at MSKCC for research purposes and the study will not be billed to the patient. Patients who have not had a prior adequate staging MRI will undergo the routine pretreatment staging MRI including DCE-MRI and ^{1}H-MRS as part of their care. Patients who participate in chemo-radiation therapy protocols will undergo a second study after 10-14 days of starting treatment, if they feel well enough to do so.

DCE-MRI and ^{1}H-MRS studies will be acquired on a 1.5T GE (Milwaukee, WI) Excite scanner and a standard neurovascular phase array coil (General Electric, Milwaukee, WI). A full clinical staging exam includes T1-weighted images and T2-weighted fat saturated

images in the axial plane as well as the sagittal or coronal planes. DCE-MRI studies will be acquired using a fast multi-phase spoiled gradient echo sequence. The entire tumor will be covered contiguously with 5-8 mm thick sections yielding 4-6 slices depending on tumor extent. The first 6 images obtained during the study will be pre-contrast injection to assure accurate baseline signal intensity. A pre-contrast proton density weighted gradient echo sequence will be obtained.

During DCE-MRI, injection of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) intravenously is followed by the agent passing from the intravascular space to the interstitial space at a rate that depends on perfusion and tissue permeability. Gd-DTPA is administered into the right antecubital vein at a concentration of 0.1 mmol/kg resulting in a standard dose of 2 ml gadopentetate dimeglumine per 10 kg of patient weight. A saline flush is administered at the same flow rate with a volume of 20 ml following Gd-DTPA administration to insure complete mixing of the bolus upon delivery. A power injector delivery system (Medrad, Inc., Indianola, PA) is used to provide accurate flow rates. Patients with a central venous silastic catheter (Hickman/Broviac [HC/BC]) require a slower flow rate of 0.8-1.0 ml/s to prevent damage to the catheter. All other patients receive contrast at a rate of 2 ml/s. All patients receive contrast while at scan position in the magnet.

In patients with nodal disease, MR spectroscopy will be done after the DCE-MRI sequence. During ^{1}H-MRS, spectral data will be acquired on the tumor identified on T2-weighted images, and a volume of interest (≥1cc) will be placed over the node. Single voxel spectroscopy data (TR/TE=1600/136 and 256 or 512 averages, scan time ~5-10 min) will be obtained using Probe –P (64) or Press CSI sequence (GE, software for acquiring data). If the excitation box for the single voxel is <1cc, the ^{1}H-MRS part of the exam will not be performed. From our earlier experience, we know that for voxels less than 1cc, the data collected from single voxel spectroscopy has a poor signal to noise ratio. The amount of time needed to complete the DCE-MRI and ^{1}H-MRS parts of the study will be about 20 minutes.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS:

This study utilizes FDA approved equipment (MR scanner, 1.5 Tesla General Electric (GE) Milwaukee, WI), neurovascular phase array coil (GE) and drug (GD-DTPA). DCE-MRI studies will be acquired using a fast multi-phase spoiled gradient echo (FMPSPGR) GE sequence. ^{1}H-MRS images will be acquired using single voxel spectroscopy. Probe-P is a commercially available, FDA approved spectroscopy program based on the PRESS localization technique(64). PRESS-CSI is a research version of the program, provided by GE, that allows more flexibility in setting acquisition parameters. We have used PRESS-CSI extensively in the brain in over 40 patients (59) with no ill effects. Data will be exported to a Sun Ultra 10 workstation or a Dell

(Austin, TX) 1.4 GHz P4 system for analysis. Software to display and analyze the data was written with interactive data language (IDL, version 5.4; Research Systems, Boulder, CO).

Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) is the standard contrast agent used with MRIs.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

All patients with head and neck cancer, no prior treatment, undergoing surgery or chemo-radiation treatment are eligible for study. Anti-neoplastic therapy will be determined by the primary physician and will not be impacted upon by this study. Patients/guardians must provide written consent.

6.1 Subject Inclusion Criteria

1. Histologically proven diagnosis of head and neck cancer

2. No prior treatment

3. Will undergo surgery or chemo-radiation treatment

4. Presence of evaluable primary tumor

5. Patients must be 18 years or older and have the ability to give informed consent

6.2 Subject Exclusion Criteria

1. Claustrophobia

2. Absence of evaluable primary tumor

3. Known reaction to Gd-DTPA

4. Pre-operative radiation to primary tumor site

5. Contraindication to MRI

    a. Pacemaker

    b. Aneurysmal clips

c. Metal implants in field of view

d. Pregnant or nursing women

e. Age and mental status wherein he/she is unable to cooperate for MRI study

7.0 RECRUITMENT PLAN

Patients for this study will be referred by the Departments of Surgery (Drs. Shah, Shaha, Kraus, Wong, Patel, Singh), Radiation Oncology (Dr. Lee) and Medicine (Drs. Pfister). All patients, 18 years or older, regardless of sex or race will be approached for participation.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3)

handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.0 PRETREATMENT EVALUATION

Not applicable.

9.0 TREATMENT/INTERVENTION PLAN

Patients will undergo DCE-MRI and ^{1}H-MRS study prior to surgery or prior to beginning chemo-radiation therapy. Patients being treated with chemo-radiation therapy will undergo a second DCE-MRI and ^{1}H-MRS study between 10-14 days after initiation of treatment.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Subjects will be monitored visually during the study and constant communication will be maintained during the study between the patient and the investigators via a speaker system.

11.0 TOXICITIES/SIDE EFFECTS

Approximately 5% of patients are claustrophobic. Gd-DTPA has been shown to be a very safe contrast agent. Reactions to Gd-DTPA are rare but include headaches, rash and itching. An incident report will be filled out if one of these events occurs. Severe adverse reactions (ADRs) occurred in one in 350,000 – 450,000 injections (72). Death has been reported in one in 10 million cases (72). A recent large survey conducted by Murphy et al (73) with regard to the occurrence of adverse reactions to gadolinium – based contrast material has revealed a small rate of ADRs. Of 687,255 gadopentate dimeglumine injections, 314 (0.046%) non-allergic reactions and 107 (0.016%) mild, 28 (0.004%) moderate, and five (0.001%) severe allergy like reactions occurred. Of 64,005 gadoteridol administrations, 171 (0.267%) nonallergic reactions and 49 (0.077%) mild, 29 (0.047%) moderate, and 11 (0.017%) severe allergy-like reactions occurred (73).

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

DCE-MRI and ^{1}H-MRS exams will be done on the schedule noted above. The first study will be done prior to surgical treatment or prior to chemo-radiation treatment. For those patients undergoing chemo-radiation, a second study will be performed between 10-14 days after starting chemo-radiation treatment. We will assess whether the MR parameters measured at that time are predictive of tumor response as subsequently determined by standard clinical evaluation (i.e. by

routine radiological imaging assessments: CT (computed tomography) or MRI (magnetic resonance imaging), and/or PET (positron emission tomography)). We will consider both absolute levels of the parameters and changes relative to the baseline measurements for each patient. This will be done by logistic regression, again including relevant clinical prognostic factors to determine whether they provide independent prognostic information. The best outcome measure is clinical response as measured by disease-free survival. It has been shown that 2-year disease-free survival is a good marker of long-term response and this will be used as a surrogate marker of long-term clinical response. Disease-free survival will be determined by results of patients' periodic radiological and physical examinations, that are part of the standard of care, for two years following the completion of chemo-radiation or surgery. As part of the standard of care, patients usually have a CT (computed tomography) or MRI (magnetic resonance imaging) scan 2-3 months after completion of all planned therapy, a PET (positron emission tomography) and CT scan at 4 months post-therapy, and then an MRI or CT scan every 6 months thereafter for the first 2 years after finishing therapy. Chest x-rays are also performed annually. Other imaging will be done only if indicated by exam or symptoms. Standards for followup, after completion of treatment, by history and physical examination will be according to clinician's judgment, however patients are usually examined no less than every 3 months during year one, every 6 months during year two. DCE-MRI and ^{1}H-MRS results will be analyzed using survival analysis methods to assess the degree to which DCE-MRI parameters (Ak_{ep}, amplitude of the exchange rate constant and K^{trans}, transfer coefficient) and ^{1}H-MRS parameters, such as choline, provide independent markers of tumor response and/or long term disease-free survival when compared to clinical prognosticators (presence and extent of nodal metastases, stage, primary disease site, total tumor volume and tumor size). MR parameters will be considered to provide independent prognostic information if they remain statistically significant when adjusted for the other variables in the appropriate multiple regression analysis.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Claustrophobia or reaction to Gd-DTPA would constitute the reasons why the physician or PI would need to remove the subject from study. If at anytime the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study. The subject/guardians will have the right to withdraw from the study if they choose.

14.0 BIOSTATISTICS

We anticipate seeing 40 new head and neck cancer patients with per year; 15 patients will undergo chemo-radiation therapy (subset 1) and 25 patients will be treated by surgery (subset 2). Patients will be entered for five years, to an expected total of 75 in subset 1 and 125 in subset 2. If the total of 75 in subset 1 and 125 in subset 2 is not reached within five years, continued accrual will be dependent on extension of federal funding. In ^{1}H-MRS data, choline will be assigned and fitted by Marquardt algorithm assuming Gaussian line shape using SAGE software.

In DCE-MRI data, the signal intensity versus time data for the tumor will be graphed. From these enhancement curves, parameters that will be calculated are K^{trans} (transfer coefficient) as well as Ak_{ep} (amplitude of the exchange rate constant). Simple relationships between MR data (Ak_{ep}, K^{trans}, and choline) will be assessed using correlation coefficients. We will determine which data transformations (such as logarithm of square root), if any, bring the statistical distribution of each of the quantitative measures into closer approximation with normal distribution before performing statistical tests. Prognostic significance will be assessed using survival analysis methods such as the Cox proportional hazards regression model. More detailed multivariate analysis will be used, such as multiple regression and analysis of covariance, to evaluate MR measures in the context of relevant clinical covariates, such as age, gender, and tumor site, type and stage. When assessing the relationships between parameters, there will be a > 80% chance of detecting a statistically significant correlation ($p<0.05$, two-sided) between the MR parameters, or changes in parameters, if the true correlation coefficient in subset 1 is $r=0.32$ or greater and in subset 2 if $r=0.25$ or greater. We will use power functions or polynomial regression to determine if the relationships are other than linear.

Tumor response will be assessed radiologically to determine the effect of chemo-radiation therapy. We will assess whether the MR parameters measured at that time are predictive of tumor response as subsequently determined by standard clinical evaluation (i.e. by routine radiological imaging assessments: CT (computed tomography) or MRI (magnetic resonance imaging), and/or PET (positron emission tomography)). We will consider both absolute levels of the parameters and changes relative to the baseline measurements for each patient. This will be done by logistic regression, again including relevant clinical prognostic factors to determine whether they provide independent prognostic information. However, the best outcome measure is clinical response as measured by disease-free survival. It has been shown that 2-year disease-free survival is a good marker of long-term response and this will be used as a surrogate marker of long-term clinical response. Estimated 2 year survival in head and neck cancer patients is 55-65% irrespective of the treatment they receive which may be surgery or chemo-radiation therapy. For illustration, we use 2-year disease-free survival as a long-term criterion for clinical outcome, because it is easier to estimate (approximately 70%) a priori than the full survival curve. Then for any MR parameter there will be approximately 80% chance of a statistically significant comparison between those patients who progress and those who do not, if the difference between the means is 0.72 times the within-group standard deviation in subset 1 and 0.56 times the within-group standard deviation in subset 2. The actual comparison will be done using survival-analysis methods such as Cox regression to make more efficient use of the data, adjust for clinical variables (tumor type, stage, age at diagnosis) that impact survival, and assess the degree to which parameters give independent prognostic information. All head and neck cancer patients will undergo essentially equivalent treatment with chemo-radiation therapy or surgery. The data will be stratified based on stage but not on likelihood of relapse. Patients will be followed for 2 years following the completion of chemo-radiation or surgery to obtain more complete disease-free survival follow-up.

For any parameter that can be studied in parallel in the two treatment groups, we will use the combined sample to improve power, adjusting for treatment as a possible covariate or stratifying in survival analysis. Wherever a one-sided test is appropriate, as when a correlation is only expected to be positive, statistical power will be enhanced. Results will be reported with consideration to issues of multiple statistical testing in this setting.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 RESEARCH PARTICIPANT REGISTRATION

The following person(s) can obtain informed consent:

Jatin Shah, MD
Dennis Kraus, MD
Ashok Shaha, MD
Richard Wong, MD
Bhuvanesh Singh, MD
Snehal Patel, MD
Nancy Lee, MD
David Pfister, MD
Hilda Stambuk, MD
Sasan Karimi, MD
Maayan Korenblit, BS
Amita Dave, PhD
Jason A. Koutcher, MD, PhD

Confirm in the electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written informed consent, by following procedures defined in section entitled Informed Consent Procedures.

All particpants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am - 5:30pm at (646) 735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the informed consent form, the completed signature page of the Research Authorization and a completed Eligibility Checklist must be faxed to PPR.

During the registration process registering individuals will be required to answer specific eligibility questions and provide the following information:

Registering Individual	[Last, First Name]
Notice of Privacy Status	[Yes, No, N/A]
Research Authorization	[Date]
MSKCC IRB Protocol#	
Attending of Record (if applicable)	[Last, First Name]
Consenting Professional	[Last, First Name]
Informed Consent Date	
Participant's Full Name	[Last, First Name]
Participant MRN	

16.0 DATA MANAGEMENT ISSUES

Clinical data (name, age, medical record number, pathology, dates of treatment, treatment regimen, date of surgery, date of chemotherapy, and date of radiation therapy) will be collected by the research study assistant (RSA). Imaging data will be analyzed by Drs. Dave and Koutcher. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol team. The data for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

All data and forms gathered for this study will be collected in a secure location in the facilities of the Department of Medical Physics. Data will be added and stored in the Clinical Research Database (CRDB).

Regular meetings, attended by the research assistant(s), investigators and the Principal Investigator will be held to review study progress and to manage any difficulties encountered.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extext and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation

17.0 PROTECTION OF HUMAN SUBJECTS

MRI is considered a minimal risk device. MRI with contrast is a standard diagnostic test utilized in the staging of subjects with head and neck cancers and the risk from exposure to the additional standard FDA approved sequence used in DCE-MRI and ^{1}H-MRS should not be considered any greater than conventional MRI sequences. Subjects will be responsible for all charges associated with the items that are part of the routine care, including the initial study if they do not have a previous adequate study. The subjects will not be compensated for their participation. Every effort will be made to keep study records private. No identifiers will be used in any reports or publications resulting from this study. All data obtained will be shared with the patients' physicians and will be considered by them in the clinical context but it is not expected to have impact on decision making processes.

During informed consent, it will be made clear to the patient that participation is voluntary. Participation in the study is not expected to convey any significant benefits to any patient enrolled. At the time of informed consent, potential subjects will be advised of alternatives to

the proposed study. All data will be maintained on a secure database to ensure patient privacy and confidentiality.

Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

17.1 Privacy

It is the responsibility of the Research Staff to ensure that protocol subjects received the Center's Notice of Privacy Practices. If the subject has not received one, MSK personnel must provide a Notice of Privacy Practices and obtain acknowledgment before the subject participates in the study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB as soon as possible but no later than 5 calendar days. The IRB requires a Clinical Research Database (CRDB) AE report to be delivered to the Institutional SAE Manager (307 East 63rd Street, 1st Floor) containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)

- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

18.0 INFORMED CONSENT PROCEDURES

The risks/drawbacks including the need for 1-2 MRI studies will be stated and explained. The risk of injection of Gd-DTPA (headaches, itchiness, and rash, one death has been reported) will be described and are minimal. The duration of the study (about 80 minutes for a full staging study and about 30-35 minutes for purely research studies) will be stated. There will be no payment for participation in the study. There will be three copies of the informed consent: one for the patient to keep, one for the medical record, and one for the research files.

18.1 Research Authorization

Procedures for obtaining Research Authorization: Before any protocol-specific procedures are carried out, investigators and/or designated staff will fully explain the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate set of signatures from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.

19.0 REFERENCE(S)

1. International Agency for Research on Cancer. GLOBOCAN 2002. Cancer incidence, mortality and prevalence worldwide (2002 estimates). http://www-dep.iarc.fr.
2. Shah JP, Singh B. Keynote comment: why the lack of progress for oral cancer? The lancet oncology 2006;7(5):356-357.
3. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. CA Cancer J Clin 2001;51(1):15-36.
4. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, Forastiere AA, Adams G, Sakr WA, Schuller DE, Ensley JF. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998;16(4):1310-1317.
5. Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Oudinot P, Bertrand P. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 1999;91(24):2081-2086.
6. Adelstein DJ, Li Y, Adams GL, Wagner H, Jr., Kish JA, Ensley JF, Schuller DE, Forastiere AA. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21(1):92-98.
7. Browman GP, Hodson DI, Mackenzie RJ, Bestic N, Zuraw L. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: A systematic review of the published literature with subgroup analysis. Head Neck 2001;23(7):579-589.
8. Chua DT, Sham JS, Wei WI, Ho WK, Au G, Choy D. Control of regional metastasis after induction chemotherapy and radiotherapy for nasopharyngeal carcinoma. Head Neck 2002;24(4):350-360.
9. Forastiere AA, Trotti A. Radiotherapy and concurrent chemotherapy: a strategy that improves locoregional control and survival in oropharyngeal cancer. J Natl Cancer Inst 1999;91(24):2065-2066.
10. Ang K, Weber R, Vokes E, Trotti A, Chapman D, Cooper J, Forastiere A, Fu KK, Hammond E, Khuri F, Leveque FS, Leupold N, Eisbruch A, Mack C, Mukherji S, Pajak TF, Ridge JA. Radiation Therapy Oncology Group. Research Plan 2002-2006. Head and Neck Cancer Committee. Int J Radiat Oncol Biol Phys 2001;51(3 Suppl 2):39-43.
11. Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, Geara FB, Klotch DW, Goepfert H, Peters LJ. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;51(3):571-578.
12. Flood W, Lee DJ, Trotti A, Spencer S, Murphy B, Khuri F, DeConti R, Wheeler R, Forastiere AA. Multimodality therapy of patients with locally advanced squamous cell cancer of the head and neck: preliminary results of two pilot trials using paclitaxel and cisplatin. Semin Radiat Oncol 1999;9(2 Suppl 1):64-69.

13. Forastiere AA. Induction and adjuvant chemotherapy for head and neck cancer: future perspectives. Acta Otorhinolaryngol Belg 1999;53(3):277-280.
14. Bernier J. Chemoradiation in locally advanced head and neck cancer: new evidence, new challenges. Expert Rev Anticancer Ther 2004;4(3):335-339.
15. Baatenburg de Jong RJ, Hermans J, Molenaar J, Briaire JJ, le Cessie S. Prediction of survival in patients with head and neck cancer. Head Neck 2001;23(9):718-724.
16. Chua DT, Sham JS, Kwong DL, Tai KS, Wu PM, Lo M, Yung A, Choy D, Leong L. Volumetric analysis of tumor extent in nasopharyngeal carcinoma and correlation with treatment outcome. Int J Radiat Oncol Biol Phys 1997;39(3):711-719.
17. Grabenbauer GG, Steininger H, Meyer M, Fietkau R, Brunner T, Heinkelmann P, Hornung J, Iro H, Spitzer W, Kirchner T, Sauer R, Distel L. Nodal CT density and total tumor volume as prognostic factors after radiation therapy of stage III/IV head and neck cancer. Radiother Oncol 1998;47(2):175-183.
18. Mukherji SK, O'Brien SM, Gerstle RJ, Weissler M, Shockley W, Castillo M. Tumor volume: an independent predictor of outcome for laryngeal cancer. J Comput Assist Tomogr 1999;23(1):50-54.
19. Rudat V, Dietz A, Schramm O, Conradt C, Maier H, Flentje M, Wannenmacher M. Prognostic impact of total tumor volume and hemoglobin concentration on the outcome of patients with advanced head and neck cancer after concomitant boost radiochemotherapy. Radiother Oncol 1999;53(2):119-125.
20. Wang Z, Su MY, Nalcioglu O. Applications of dynamic contrast enhanced MRI in oncology: measurement of tumor oxygen tension. Technol Cancer Res Treat 2002;1(1):29-38.
21. Maxwell RJ. Simultaneous measurement of gradient-echo 1H MR images and pO2 using a fiber-optic oxygen sensor in rodent tumours and their response to carbogen breathing. 1998; Sydney, Australia.
22. Dewhirst MW, Kimura H, Rehmus SW, Braun RD, Papahadjopoulos D, Hong K, Secomb TW. Microvascular studies on the origins of perfusion-limited hypoxia. Br J Cancer Suppl 1996;27:S247-251.
23. Bereczki D, Wei L, Otsuka T, Acuff V, Pettigrew K, Patlak C, Fenstermacher J. Hypoxia increases velocity of blood flow through parenchymal microvascular systems in rat brain. J Cereb Blood Flow Metab 1993;13(3):475-486.
24. Cooper RA, Carrington BM, Loncaster JA, Todd SM, Davidson SE, Logue JP, Luthra AD, Jones AP, Stratford I, Hunter RD, West CM. Tumour oxygenation levels correlate with dynamic contrast-enhanced magnetic resonance imaging parameters in carcinoma of the cervix. Radiother Oncol 2000;57(1):53-59.
25. Knopp MV, Weiss E, Sinn HP, Mattern J, Junkermann H, Radeleff J, Magener A, Brix G, Delorme S, Zuna I, van Kaick G. Pathophysiologic basis of contrast enhancement in breast tumors. J Magn Reson Imaging 1999;10(3):260-266.
26. Henderson E, Rutt BK, Lee TY. Temporal sampling requirements for the tracer kinetics modeling of breast disease. Magn Reson Imaging 1998;16(9):1057-1073.
27. Hulka CA, Edmister WB, Smith BL, Tan L, Sgroi DC, Campbell T, Kopans DB, Weisskoff RM. Dynamic echo-planar imaging of the breast: experience in diagnosing

breast carcinoma and correlation with tumor angiogenesis. Radiology 1997;205(3):837-842.

28. Devries AF, Griebel J, Kremser C, Judmaier W, Gneiting T, Kreczy A, Ofner D, Pfeiffer KP, Brix G, Lukas P. Tumor microcirculation evaluated by dynamic magnetic resonance imaging predicts therapy outcome for primary rectal carcinoma. Cancer Res 2001;61(6):2513-2516.
29. Hawighorst H, Knapstein PG, Knopp MV, Weikel W, Brix G, Zuna I, Schonberg SO, Essig M, Vaupel P, van Kaick G. Uterine cervical carcinoma: comparison of standard and pharmacokinetic analysis of time-intensity curves for assessment of tumor angiogenesis and patient survival. Cancer Res 1998;58(16):3598-3602.
30. Hawighorst H, Knapstein PG, Weikel W, Knopp MV, Zuna I, Knof A, Brix G, Schaeffer U, Wilkens C, Schoenberg SO, Essig M, Vaupel P, van Kaick G. Angiogenesis of uterine cervical carcinoma: characterization by pharmacokinetic magnetic resonance parameters and histological microvessel density with correlation to lymphatic involvement. Cancer Res 1997;57(21):4777-4786.
31. Shapeero LG, Vanel D. Imaging evaluation of the response of high-grade osteosarcoma and Ewing sarcoma to chemotherapy with emphasis on dynamic contrast-enhanced magnetic resonance imaging. Semin Musculoskelet Radiol 2000;4(1):137-146.
32. Konouchi H, Asaumi J, Yanagi Y, Shigehara H, Hisatomi M, Matsuzaki H, Kishi K. Evaluation of tumor proliferation using dynamic contrast enhanced-MRI of oral cavity and oropharyngeal squamous cell carcinoma. Oral Oncol 2003;39(3):290-295.
33. Hoskin PJ, Saunders MI, Goodchild K, Powell ME, Taylor NJ, Baddeley H. Dynamic contrast enhanced magnetic resonance scanning as a predictor of response to accelerated radiotherapy for advanced head and neck cancer. Br J Radiol 1999;72(863):1093-1098.
34. Mayr NA, Yuh WT, Magnotta VA, Ehrhardt JC, Wheeler JA, Sorosky JI, Davis CS, Wen BC, Martin DD, Pelsang RE, Buller RE, Oberley LW, Mellenberg DE, Hussey DH. Tumor perfusion studies using fast magnetic resonance imaging technique in advanced cervical cancer: a new noninvasive predictive assay. Int J Radiat Oncol Biol Phys 1996;36(3):623-633.
35. Brown JM, Le QT. Tumor hypoxia is important in radiotherapy, but how should we measure it? Int J Radiat Oncol Biol Phys 2002;54(5):1299-1301.
36. Olive PL, Banath JP, Aquino-Parsons C. Measuring hypoxia in solid tumours--is there a gold standard? Acta Oncol 2001;40(8):917-923.
37. Van de Wiele C, Lahorte C, Oyen W, Boerman O, Goethals I, Slegers G, Dierckx RA. Nuclear medicine imaging to predict response to radiotherapy: a review. Int J Radiat Oncol Biol Phys 2003;55(1):5-15.
38. Rasey JS, Koh WJ, Evans ML, Peterson LM, Lewellen TK, Graham MM, Krohn KA. Quantifying regional hypoxia in human tumors with positron emission tomography of [18F]fluoromisonidazole: a pretherapy study of 37 patients. Int J Radiat Oncol Biol Phys 1996;36(2):417-428.
39. Evelhoch J, Garwood M, Vigneron D, Knopp M, Sullivan D, Menkens A, Clarke L, Liu G. Expanding the use of magnetic resonance in the assessment of tumor response to therapy: workshop report. Cancer Res 2005;65(16):7041-7044.

40. Kaiser WA, Zeitler E. MR imaging of the breast: fast imaging sequences with and without Gd-DTPA. Preliminary observations. Radiology 1989;170(3 Pt 1):681-686.
41. Degani H, Gusis V, Weinstein D, Fields S, Strano S. Mapping pathophysiological features of breast tumors by MRI at high spatial resolution. Nat Med 1997;3(7):780-782.
42. Dyke JP, Panicek DM, Healey JH, Meyers PA, Huvos AG, Schwartz LH, Thaler HT, Tofts PS, Gorlick R, Koutcher JA, Ballon D. Osteogenic and Ewing sarcomas: estimation of necrotic fraction during induction chemotherapy with dynamic contrast-enhanced MR imaging. Radiology 2003;228(1):271-278.
43. Hoang BH, Dyke JP, Koutcher JA, Huvos AG, Mizobuchi H, Mazza BA, Gorlick R, Healey JH. VEGF expression in osteosarcoma correlates with vascular permeability by dynamic MRI. Clin Orthop Relat Res 2004(426):32-38.
44. Brix G, Semmler W, Port R, Schad LR, Layer G, Lorenz WJ. Pharmacokinetic parameters in CNS Gd-DTPA enhanced MR imaging. J Comput Assist Tomogr 1991;15(4):621-628.
45. Hoffmann U, Brix G, Knopp MV, Hess T, Lorenz WJ. Pharmacokinetic mapping of the breast: a new method for dynamic MR mammography. Magn Reson Med 1995;33(4):506-514.
46. Tofts PS, Kermode AG. Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1. Fundamental concepts. Magn Reson Med 1991;17(2):357-367.
47. Larsson HB, Stubgaard M, Frederiksen JL, Jensen M, Henriksen O, Paulson OB. Quantitation of blood-brain barrier defect by magnetic resonance imaging and gadolinium-DTPA in patients with multiple sclerosis and brain tumors. Magn Reson Med 1990;16(1):117-131.
48. Verstraete KL, Dierick A, De Deene Y, Uyttendaele D, Vandamme F, Roels H, Kunnen M. First-pass images of musculoskeletal lesions: a new and useful diagnostic application of dynamic contrast-enhanced MRI. Magn Reson Imaging 1994;12(5):687-702.
49. Lang P, Honda G, Roberts T, Vahlensieck M, Johnston JO, Rosenau W, Mathur A, Peterfy C, Gooding CA, Genant HK. Musculoskeletal neoplasm: perineoplastic edema versus tumor on dynamic postcontrast MR images with spatial mapping of instantaneous enhancement rates. Radiology 1995;197(3):831-839.
50. Daniel BL, Yen YF, Glover GH, Ikeda DM, Birdwell RL, Sawyer-Glover AM, Black JW, Plevritis SK, Jeffrey SS, Herfkens RJ. Breast disease: dynamic spiral MR imaging. Radiology 1998;209(2):499-509.
51. Parker GJ, Suckling J, Tanner SF, Padhani AR, Revell PB, Husband JE, Leach MO. Probing tumor microvascularity by measurement, analysis and display of contrast agent uptake kinetics. J Magn Reson Imaging 1997;7(3):564-574.
52. Parker GJ, Tofts PS. Pharmacokinetic analysis of neoplasms using contrast-enhanced dynamic magnetic resonance imaging. Top Magn Reson Imaging 1999;10(2):130-142.
53. Negendank W, Sauter R. Intratumoral lipids in 1H MRS in vivo in brain tumors: experience of the Siemens cooperative clinical trial. Anticancer Res 1996;16(3B):1533-1538.

54. Dowling C, Bollen AW, Noworolski SM, McDermott MW, Barbaro NM, Day MR, Henry RG, Chang SM, Dillon WP, Nelson SJ, Vigneron DB. Preoperative proton MR spectroscopic imaging of brain tumors: correlation with histopathologic analysis of resection specimens. AJNR Am J Neuroradiol 2001;22(4):604-612.
55. Shukla-Dave A, Gupta RK, Roy R, Husain N, Paul L, Venkatesh SK, Rashid MR, Chhabra DK, Husain M. Prospective evaluation of in vivo proton MR spectroscopy in differentiation of similar appearing intracranial cystic lesions. Magn Reson Imaging 2001;19(1):103-110.
56. Preul MC, Caramanos Z, Villemure JG, Shenouda G, LeBlanc R, Langleben A, Arnold DL. Using proton magnetic resonance spectroscopic imaging to predict in vivo the response of recurrent malignant gliomas to tamoxifen chemotherapy. Neurosurgery 2000;46(2):306-318.
57. Wald LL, Nelson SJ, Day MR, Noworolski SE, Henry RG, Huhn SL, Chang S, Prados MD, Sneed PK, Larson DA, Wara WM, McDermott M, Dillon WP, Gutin PH, Vigneron DB. Serial proton magnetic resonance spectroscopy imaging of glioblastoma multiforme after brachytherapy. J Neurosurg 1997;87(4):525-534.
58. Ng SH, Ko SF, Chen WC, Tang LM, Chang CN, Wai YY, Wan YL. Proton magnetic resonance spectroscopy of cerebral glioma after irradiation. Chang Gung Med J 2001;24(11):708-716.
59. Raizer JJ, Koutcher JA, Abrey LE, Panageas KS, DeAngelis LM, Lis E, Xu S, Zakian KL. Proton magnetic resonance spectroscopy in immunocompetent patients with primary central nervous system lymphoma. J Neurooncol 2005;71(2):173-180.
60. Zakian KL, Sircar K, Hricak H, Chen HN, Shukla-Dave A, Eberhardt S, Muruganandham M, Ebora L, Kattan MW, Reuter VE, Scardino PT, Koutcher JA. Correlation of proton MR spectroscopic imaging with gleason score based on step-section pathologic analysis after radical prostatectomy. Radiology 2005;234(3):804-814.
61. Pucar D, Koutcher JA, Shah A, Dyke JP, Schwartz L, Thaler H, Kurhanewicz J, Scardino PT, Kelly WK, Hricak H, Zakian KL. Preliminary assessment of magnetic resonance spectroscopic imaging in predicting treatment outcome in patients with prostate cancer at high risk for relapse. Clinical prostate cancer 2004;3(3):174-181.
62. Walenta S, Salameh A, Lyng H, Evensen JF, Mitze M, Rofstad EK, Mueller-Klieser W. Correlation of high lactate levels in head and neck tumors with incidence of metastasis. Am J Pathol 1997;150(2):409-415.
63. Mukherji SK, Gerstle RJ. In vitro 1H MR spectroscopy of squamous cell carcinoma of the extracranial head and neck. Neuroimaging Clin N Am 1998;8(4):835-847.
64. Mukherji SK, Schiro S, Castillo M, Kwock L, Muller KE, Blackstock W. Proton MR spectroscopy of squamous cell carcinoma of the extracranial head and neck: in vitro and in vivo studies. AJNR Am J Neuroradiol 1997;18(6):1057-1072.
65. Star-Lack JM, Adalsteinsson E, Adam MF, Terris DJ, Pinto HA, Brown JM, Spielman DM. In vivo 1H MR spectroscopy of human head and neck lymph node metastasis and comparison with oxygen tension measurements. AJNR Am J Neuroradiol 2000;21(1):183-193.

66. Brizel DM, Schroeder T, Scher RL, Walenta S, Clough RW, Dewhirst MW, Mueller-Klieser W. Elevated tumor lactate concentrations predict for an increased risk of metastases in head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;51(2):349-353.
67. Adalsteinsson E, Spielman DM, Pauly JM, Terris DJ, Sommer G, Macovski A. Feasibility study of lactate imaging of head and neck tumors. NMR Biomed 1998;11(7):360-369.
68. Bisdas S, Baghi M, Huebner F, Mueller C, Knecht R, Vorbuchner M, Ruff J, Gstoettner W, Vogl TJ. In vivo proton MR spectroscopy of primary tumours, nodal and recurrent disease of the extracranial head and neck. Eur Radiol 2006.
69. Shukla-Dave A, Poptani H, Loevner LA, Mancuso A, Serrai H, Rosenthal DI, Kilger AM, Nelson DS, Zakian KL, Arias-Mendoza F, Rijpkema M, Koutcher JA, Brown TR, Heerschap A, Glickson JD. Prediction of treatment response of head and neck cancers with P-31 MR spectroscopy from pretreatment relative phosphomonoester levels. Acad Radiol 2002;9(6):688-694.
70. Griffiths JR, Tate AR, Howe FA, Stubbs M. Magnetic Resonance Spectroscopy of cancer-practicalities of multi-centre trials and early results in non-Hodgkin's lymphoma. Eur J Cancer 2002;38(16):2085-2093.
71. Zakian KL, Shukla-Dave A, Meyers P, Gorlick R, Healey J, Thaler HT, Huvos AG, Panicek DM, Koutcher JA. Identification of prognostic markers in bone sarcomas using proton-decoupled phosphorus magnetic resonance spectroscopy. Cancer Res 2003;63(24):9042-9047.
72. James JS. Contrast agents in Neuroradiology. In: Orrison WW, editor. Neuroimaging. Philadelphia: WB Saunders; 2000. p 479-483.
73. Murphy KP, Szopinski KT, Cohan RH, Mermillod B, Ellis JH. Occurrence of adverse reactions to gadolinium-based contrast material and management of patients at increased risk: a survey of the American Society of Neuroradiology Fellowship Directors. Acad Radiol 1999;6(11):656-664.